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Interaction between neuropsychiatry and sleep disorders: From mechanism to clinical practice

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Interaction between neuropsychiatry and sleep disorders: From mechanism to clinical practice

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Editorial: Interaction between neuropsychiatry and sleep disorders: From mechanism to clinical practice

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Editorial on the Research Topic
Interaction between neuropsychiatry and sleep disorders: From mechanism to clinical practice

Sleep is a basic physiological need for human survival. While sleep problems are often the main reasons that drive an individual to seek medical treatment, conventionally, sleep problems have only been considered as symptoms of certain neuropsychiatric disorders, such as depression. However, increasing evidence suggests that sleep problems can also be a trigger for other neuropsychiatric disorders (1). Sleep is a physiological function that involves comprehensive regulating between the central neurological, metabolic, and immunological systems. Sleep disorders present as chronically interrupted quality, timing, amount of sleep, and impaired daytime functioning and may lead to neuropsychiatric illnesses (2). However, the mechanisms connecting sleep disorders and neuropsychiatric illnesses remain unclear. The current Research Topic represents a collection of papers that investigate the relationship between sleep disorders and neuropsychiatric illnesses, as well as studies analyzing the effects of some treatments for sleep disorders, particularly in the context of the COVID-19 pandemic.

As we all know, the COVID-19 pandemic has persisted for almost 3 years worldwide, and has increased stress, impacted mental health, and disrupted sleep for many people (3). During the COVID-19 pandemic, the prevalence of insomnia also increased (4). Specifically, situational insomnia, also called acute insomnia/short-term insomnia disorder, become more common in people who had no previous sleep problems (5). The article by Wu et al. finds that at 3 months post-COVID, those who had shorter rapid eye movement (REM) sleep

latency and fragmented REM or NREM (non-REM) sleep also had more depressive symptoms (measured with Beck depression inventory score). Their findings indicate that REM sleep fragmentation may be a biomarker for depressive episodes in patients with short-term insomnia. Similarly, Qiao et al. find that impaired sleep quality and efficiency may be risk factors for depression and can predict the severity of depressive symptoms in 1,631 older Chinese adults.

Consistent with these studies that show sleep problems lead to mental health issues, Xie et al. find that those who had childhood trauma had poorer mental health during the pandemic, which is partly driven by their poorer sleep quality. Therefore, they suggest that mental health providers should pay more attention to individuals with childhood trauma, as childhood trauma is usually also associated with greater life stress and poor sleep. In a study conducted among college students, Wang, Liu et al. evaluate the association between chronotype and mental health. They find that compared to "early birds" or morning types, individuals defined as "night owls" or evening type were more likely to have long sleep compensation on weekends, insomnia symptoms, and depressive/anxiety symptoms. This study emphasizes that evening-type individuals should receive screening or intervention early due to their vulnerability to sleep or mental health problems.

The relationship between sleep disturbances and depressive/anxiety symptoms is further discussed in the articles by Xiao et al., Liang et al, and Wang, Liu et al. Using data collected from 12,178 college students in western north China, Xiao et al. find associations between depressive symptoms and insomnia were partly mediated by rumination. Whereas Liang et al. performed polysomnography (PSG) assessments and find that sleep perception affects sleep quality. In addition, they find that individuals with sleep misperception have common personalities and social behaviors, therefore, certain behavior treatments that target sleep misperception may help to improve their sleep and related anxiety symptoms. Last, immunologic (e.g., cytokine levels) and neurotransmitter systems (e.g., serotonin 2A receptor, 5-HTR2A) have important roles in the sleep-wake process (6, 7). The article by Wang, Gao et al. investigates the effects of cytokines and 5-HTR2A polymorphisms on sleep quality in non-manual workers in China. The results show that cytokines and 5-HTR2A polymorphisms not only have independent effects on sleep but may also cumulatively affect sleep quality.

Regarding treatments for sleep disorders, many studies used non-invasive brain stimulation techniques to reduce physiological arousal, a key component of insomnia (8, 9). Ma et al. perform a meta-analysis to evaluate the effectiveness of transcranial electric stimulation (TES) and repetitive transcranial magnetic stimulation (rTMS) in improving sleep quality. They find that rTMS shows a larger effect size than TES on improving objective measures of sleep including arousal, as well as on ameliorating subjective sleep complaints. Furthermore, Li et al. combine transcranial direct current stimulation (tDCS) and electroencephalogram (EEG) techniques to study sleep EEG complexity in patients with depression. They find that tDCS decreased intrinsic multi-scale entropy (which indicates improved sleep quality) during REM sleep without altering sleep structural integrity. The findings from Li et al. suggest daytime tDCS may be an effective method to improve sleep quality in depressed patients.

Acupuncture may be a safe alternative therapy for sleep problems, but the underlying mechanisms are unclear (9). In the systematic review and meta-analysis conducted by Zhao et al., acupuncture by itself or adjuvant to conventional pharmacotherapy (such as antidepressant and/or hypnotic) has low to moderate levels of evidence in treating insomnia patients with current depression. However, the benefit of acupuncture on residual insomnia in patients with remitted or partially remitted depression is limited. Also focusing on acupuncture treatment, Li et al. designed a randomized controlled trial to investigate the effectiveness of electroacupuncture in improving cognition after acute sleep deprivation and publish their protocol in this special issue.

CBTI remains the first-line treatment option for treating insomnia. In the article by Feng et al., one-week self-guided internet cognitive-behavioral treatments for insomnia (CBTI) improve insomnia symptoms and prevent situational insomnia from progressing to chronic insomnia during the COVID-19 pandemic. Xin et al. use bibliometric and visualization analysis to elucidate the trends of CBTI publication and show that the field of CBTI is maturing, with great study potential and broad prospects. They suggest future research should focus on creating new delivery models for CBTI that emphasize the prevention of insomnia and the scalability of treatments.

Obstructive sleep apnea (OSA) is a sleep disorder that characteristics by frequent arousal during sleep and excessive daytime sleepiness. Prajsuchanai et al. find that individuals with attention deficit hyperactivity disorder (ADHD) are prone to develop high-risk OSA. High-risk OSA was also associated with childhood obesity and affects children's quality of life, hence screen for high-risk OSA in children with ADHD may be cost-effective.

Primary restless legs syndrome (RLS), a less common sleep disorder, causes an intense, often irresistible urge to move your legs (sometimes arms or body) during sleep. The causes of PLS are still unknown. Liu et al. find that the patients with RLS have lower Vitamin D levels than healthy controls. Furthermore, they find that PLS patients with lower serum Vitamin D levels had worse sleep quality and more severe depressive symptoms. This study suggests a strong association between vitamin D and RLS that sheds light on developing more effective treatments for RLS.

Last but not least, sleep disorders have been well-established to be the early symptoms of neurodegenerative diseases, especially Parkinson's disease (PD). As described in the research

by Yuan et al., REM behavior disorder (RBD) is not only a highly specific marker of PD but also one of the prodromal symptoms of PD. Yuan et al. studied the mechanisms that link RBD to PD and hypothesize that the TNF-α pathway might not be involved in disease progression from isolated RBD (iRBD) to PD by regulating the orexin system, although their results need to be verified further. Multiple system atrophy (MSA) is another neurodegenerative disorder characterized by both motor symptoms (Parkinsonism-like) and non-motor symptoms (excessive daytime sleepiness, EDS). Wang, Tang et al. find that in MSA patients, EDS mainly predicted mood and sleep-related breathing problems. For example, they find the severity of EDS is positively correlated with anxiety, depression, fatigue, and apnea-hypopnea index level. In addition, Yang et al. find that enlarged perivascular spaces (EPVS), an MRI marker of cerebral small-vessel disease, are associated with PD syndrome. EPVSs both in basal ganglia and in white matter contributed to poor sleep quality. This article also reviews the association between EPVS dynamic regulation, sleep-related neurotransmission, synaptic cleft metabolites clearance, and sleep-wake transition.

In summary, this Research Topic covers important aspects of sleep disorders and their connections with neuropsychiatric illnesses. We aim to update readers on the latest research findings in this field. These selected articles will provide insights for researchers in different fields into cutting-edge study methods in sleep medicine, thereby motivating multidisciplinary collaborations on elucidating underlying links between sleep disorders and neuropsychiatric illnesses, and ultimately, developing effective therapeutic strategies for both conditions.

Author contributions

All authors have contributed intellectual content to the actual writing of the editorial. 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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ORIGINAL RESEARCH
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REM Sleep Fragmentation in Patients With Short-Term Insomnia Is Associated With Higher BDI Scores

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Objective: To observe the changes in sleep characteristics and BDI scores in patients with short-term insomnia disorder (SID) using a longitudinal observational study.

Methods: Fifty-four patients who met the criteria for SID of the International Classification of Sleep Disorders, third edition, were recruited. Depression levels were assessed using the Beck depression inventory (BDI) at enrollment and after 3 months of follow-up, respectively. Sleep characteristics were assessed by polysomnography.

Results: After 3 months of follow-up, the group was divided into SID with increased BDI score (BDI >15) and SID with normal BDI score (BDI ≤15) according to the total BDI score of the second assessment. The differences in rapid eye movement (REM) sleep latency, REM sleep arousal index, and NREM sleep arousal index between the two groups were statistically significant. The total BDI score was positively correlated with REM and NREM sleep arousal index and negatively correlated with REM sleep latency, which were analyzed by Pearson correlation coefficient. Multiple linear regression was used to construct a regression model to predict the risk of depression in which the prediction accuracy reached 83.7%.

Conclusion: REM sleep fragmentation is closely associated with future depressive status in patients with SID and is expected to become an index of estimating depression risk.

Keywords: polysomnography, REM fragmentation, acute insomnia, sleep arousal, depression

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BACKGROUND

Insomnia disorder is the most common sleep disorder worldwide. It is an important public health problem not only because of its high rate of prevalence and disability, but also because insomnia has been found to be an important risk factor for various psychiatric disorders (1–3), especially major depression disorder. Studies show that people with insomnia are two to three times more likely to develop depression than those without insomnia (4, 5), and other researchers believe that the core problem of insomnia involves an overactive arousal system. During sleep, frequent arousals can lead to unstable or fragmented sleep architecture (6–8). Because *rapid eye movement (REM)* sleep represents a state of high brain arousal during sleep, it plays a key role in insomnia (9–11). At the same time, REM sleep is shown to play an important role in the reprocessing and consolidation

of emotional experiences in the limbic system (12). A previous study (13) finds that changes in REM sleep are frequently observed in patients with major depression, for example, shorter REM sleep latency, increased REM sleep duration, and REM density. Excessive arousal and REM sleep fragmentation play an important role in the mood regulation of insomnia and depression by affecting the elimination of negative emotions. The bidirectional relationship between these two disorders may also suggest that instability of REM sleep has a particular impact on insomnia and depression and may be a key factor in the common mechanism of action of insomnia and depression (11, 14). The concept of instability of REM sleep is based on evidence showing increased micro- and macro-arousals during REM sleep in insomnia patients (15). REM sleep is involved in processes that affect emotional homeostasis in the brain. Prolonged and sustained disturbance of REM sleep through arousal or wake intrusion leads to decreased REM stability during sleep (16). REM sleep fragmentation is one of the pathological bases of depression in patients with chronic insomnia (17, 18). Therefore, stability of REM sleep is important for insomnia patients.

In our study, polysomnography (PSG) was used to analyze and assess the sleep architecture of patients with short-term insomnia, to explore the effects of REM sleep segments and REM-related sleep architecture on the mood of patients with short-term insomnia disorder (SID), and to try to construct regression models that can better predict the risk of depression.

MATERIALS AND METHODS

Patients

Patients attended the sleep clinic and psychological consultation clinic of Ningbo First Hospital from January 2019 to September 2020. They met the diagnostic criteria for SID of the International Classification of Sleep Disorders, third edition (19): age >18 years, male and female, total duration of illness <3 months, able to cooperate with the completion of questionnaires and PSG monitoring, and could comply with study requirements for follow-up. Exclusion criteria were untreated physical disease; a previous history of epilepsy, depressive disorder, schizophrenia, bipolar disorder, anxiety disorder, neurodevelopmental delay, or cognitive disorder; shift workers; travel across three or more time zones within 14 days prior to enrollment; a previous history of other sleep disorders or PSG monitoring revealing the following conditions: sleep apnea hypopnea syndrome, apnea hypopnea index (AHI) >15 breaths/h, REM AHI (RAHI) >5 times/h; oxygen saturation <90%; periodic leg movement syndrome: periodic leg movement index (PLMI) >5 times/h; heterogeneous sleep. All subjects did not receive any psychological, physical, and/or pharmacological treatment between 7 days prior to admission and 3 months of follow-up.

Methods

Phase I: Clinical Interview, Psychological Assessment, and Baseline Data Collection

We recorded baseline data on subjects' age, sex, body mass index, smoking, and alcohol consumption by telephone and clinic visits. After subjects were enrolled, psychological evaluations included the Pittsburgh Sleep Quality Index (PSQI) (20), a 19-item questionnaire that assesses sleep quality and disorders over a 1-month interval. The first four items are open-ended questions, and items 5–19 are scored using a 4-point Likert scale. Scores for the seven components were obtained, and the scores were summed to obtain a total score ranging from 0 to 21. A score >5 indicates poor sleep quality. The Beck Anxiety Inventory (BAI) (21), developed by 21, contains 21 self-administered anxiety questionnaires that reflect the severity of anxiety, and a BAI ≥45 is used as a criterion for positive anxiety. The Beck Depression Inventory (BDI) (22) was developed by 22. The whole scale is divided into 21 groups, which are divided into 0–3 levels. After completing the sum of the parts, the total score was divided into four levels with total scores as follows: ≤10: healthy and no depression, 10–15: bad mood and attention, and 15–25: depression. A total score >25 indicates that depression is severe, and the patient must be seen by a psychiatrist. Subjects were followed up for 3 months, and then depression was assessed again using the BDI.

A trained psychometrician administered the questionnaire to the patients, informing them of the purpose of the study, the protocol, and precautions. The subject gave informed understanding and consent and then began to fill out the questionnaire. After completion of the questionnaire, the participant returned it, and the staff checked the completeness of the content.

Phase II: Sleep Laboratory Tests

Subjects who met the enrollment criteria underwent PSG within 1 week, and patients were given a sleep diary record to determine their resting patterns while waiting for PSG. The specific information of the polysomnograph used in the study is as follows: model and specification: Grael, medical device registration certificate number: 20172210823, manufacturer: Compumedics Limited. Sleep lab tests include one night of PSG monitoring. The PSG monitoring consists mainly of six leads of EEG activity (EEG: F3-M2, F4-M1, C3-M2, C4-M1, O1-M2, O2-M1), electromyographic activity of the jaw and tibialis anterior muscles (EMG), bilateral electro-ocular activity (EOG), electrocardiogram (ECG), oral and nasal airflow, chest and abdominal movements, oxygen saturation, and snoring. The measured parameters include stage REM sleep latency (RL): sleep onset to first epoch of Stage REM in minutes; number of REM sleep cycles (RC); total sleep time (TST) in minutes; REM sleep arousal index (REM-ArI): number of arousals in stage REM × 60/TST; NREM sleep arousal index (NREM-ArI): number of arousals in stage NREM × 60/TST; REM sleep duration (RD): time in stage REM; percentage of TST in stage REM (REM%): (time in stage REM/TST) × 100; percentage of TST in stage NREM (NREM%): (time in stage NREM/TST) × 100; and sleep efficiency (SE): (TST/time in bed) × 100. The installation of the PSG equipment and the analysis of the PSG were performed by professional PSG technicians under the technical guidance of a physician licensed as a registered PSG technician in the United States. The

TABLE 1 | Baseline characteristics of 54 SID patients (BDI score classification after 3 months of follow-up).

Baseline data	BDI score* ≤15 ($n = 43$) Mean or %	BDI score* >15 ($n = 11$) Mean or %	χ^2 or *T*-value	*p*-value
Age	47.23 ± 12.71	37.27 ± 16.17	2.192	0.033
Female (%)	20 (47%)	6 (55%)	0.226	0.634
Smoking history (%)	4 (9%)	3 (27%)	2.507	0.113
Drinking history (%)	5 (12%)	3 (27%)	1.699	0.192
BMI(kg/cm^2)	22.63 ± 2.78	22.82 ± 2.6	−0.202	0.841
BDI score at the time of enrollment	5.98 ± 3.93	6.91 ± 2.84	−0.737	0.465
BAI score	10.33 ± 5.64	10.55 ± 7.09	−0.109	0.913
PLMI (times/hour)	0.27 ± 0.93	0.14 ± 0.45	0.474	0.372
AHI (times/hour)	2.60 ± 4.12	1.48 ± 3.41	0.824	0.413
REM-AHI (times/hour)	1.02 ± 1.47	0.53 ± 1.18	1.022	0.311
NREM-AHI (times/hour)	2.89 ± 4.72	1.67 ± 3.81	0.788	0.434
PSQI score	12.79 ± 3.91	15.91 ± 3.70	−2.383	0.809

BDI score: BDI score at the second assessment after 3 months of follow-up. BMI, Body Mass Index; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; PLMI, periodic limb movement index; AHI, Sleep apnea index; PSQI, Pittsburgh Sleep Quality Index; REM, rapid eye moment; NRME, non-rapid eye moment.*

TABLE 2 | Independent sample *t*-test of sleep structure of the two groups of patients (BDI score classification after 3 months of follow-up).

Sleep structure	BDI score ≤15 ($n = 43$)	BDI score >15 ($n = 11$)	*F*-value	*T*-value	*P*-value
RL (min)	167.64 ± 80.85	86.15 ± 33.40	13.399	4.877	0.003
RCs	2.79 ± 1.57	2.18 ± 1.08	3.174	1.213	0.231
TST (min)	370.32 ± 114.81	397.14 ± 102.11	0.187	−0.706	0.484
REM-ArI	4.13 ± 2.04	11.01 ± 6.21	15.948	−3.627	0.004
NREM-ArI	4.25 ± 2.42	6.60 ± 3.32	2.257	−2.662	0.010
RD	51.99 ± 34.80	45.41 ± 28.48	0.305	0.578	0.566
REM (%)	12.78 ± 6.81	11.40 ± 6.37	0.030	0.606	0.547
NREM (%)	86.99 ± 6.83	87.69 ± 6.69	0.006	−0.305	0.762
SE (%)	70.96 ± 17.27	77.44 ± 16.21	0.639	−1.123	0.266

RL, REM sleep latency; RCs, Number of REM cycles; TST, total sleep time; REM-ArI, REM sleep arousal index; NREM-ArI, NREM sleep arousal index; RD:REM sleep duration; REM (%), REM Sleep time/TST; SE, sleep latency.

rules, terminology, and technical specifications of the American Association for Sleep Research Manual of Interpretation of Sleep and Associated Events version 2.6 (AASM) were used (23) as the interpretation criteria to determine sleep staging and sleep events.

Statistical Methods

Statistical analysis was performed using SPSS 26.0. Measured data were expressed as mean ± standard deviation ($x \pm s$), count data were expressed as percentages, mean values between groups were compared using independent samples *t*-test and chi-square (χ^2) test, and Levene's homogeneity of variance test was used for independent samples *t*-test to test the difference in *t*-distribution of each index between two groups. If $P > 0.05$, there is a statistical difference. Both *t*-test and chi-square test (χ^2) were used as two-sided tests, and $P < 0.05$ was considered statistically significant. Pearson analysis was performed to analyze the correlation between multiple variables. Regression models were created using multiple linear regression, and their correlation was assessed using covariance diagnostics in linear regressions between multiple variables to determine whether these variables could be modeled. The Durbin-Watson (D-W) test was used to determine whether the independence conditions for linear regression were met. Analysis of variance was used to determine that the constructed regression model was statistically significant in the range of $P < 0.05$. Regression coefficients were used to indicate the degree of influence between the four constants of the REM arousal index, the number of REM cycles, REM latency, the number of REM arousals, and the dependent variable of depression score, and the regression coefficient $P < 0.05$ was statistically significant.

RESULTS

Overall

A total of 54 patients with SID were included, 28 (52%) of them were male and 26 (48%) were female. The mean age was (45.20 ± 13.92) years, and body mass index was (22.67 ± 2.73). The BDI score at admission was (6.17 ± 3.73). After 3 months of follow-up, BDI score was (10.07 ± 7.66); insomnia symptoms were relieved in 36 subjects and persisted in 18 subjects. Eleven of these patients (20%) had a BDI score >15, which implies 20% risk of depression in patients with SID after 3 months of follow-up. In the group with persistent insomnia symptoms, the probability of having a BDI score >15 was 50%, whereas in the group with recovery from SID, the probability of having a BID score >15 was only 6%. We define recovery from SID as subjects having 7 or more weeks of good sleep after an episode of SID at a 3-month follow-up, of which the last 4 weeks must be designated as good sleep. Good sleep: five or more nights per week requiring a sleep latency of 30 min or less with 5% TST or less time awake after sleep during the night. Total sleep duration is 6–10 h without daytime symptoms (19, 24).

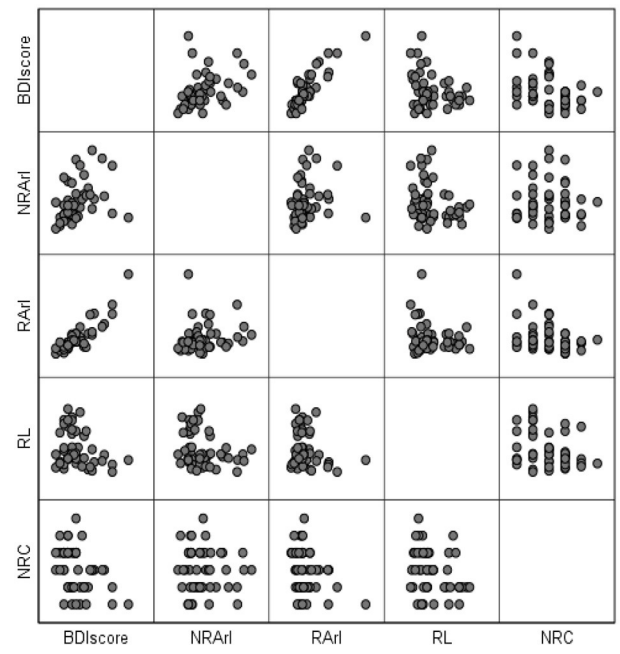

FIGURE 1 | Matrix scatterplot between BDI scores (after 3 months of follow-up) and structural variables of rapid eye movement sleep after 3 months of follow-up. BDI, Beck Depression Inventory; RL, REM sleep latency; REM-ArI, REM sleep arousal index; NREM-ArI, NREM sleep arousal index; RCs, Number of REM cycles.

Baseline Characteristics

After 3 months of follow-up, the group was divided into SID with increased BDI score (BDI >15) and SID with normal BDI score (BDI ≤15) groups according to the BDI score of the second assessment. There was no statistical difference in baseline levels between the two groups except for age differences (**Table 1**).

Sleep Characteristics

The statistical method of independent samples *t*-test was used to compare the differences between the two groups of indicators (**Table 2**): the REM sleep latency ($t = 4.877$, $P = 0.003$), the REM sleep arousal index ($t = -3.627$, $P = 0.004$) and the NREM sleep arousal index ($t = -2.662$, $P = 0.010$) with statistically significant differences.

Relationship Between Sleep Characteristics and Depression

In linear regression and Pearson correlation analyses (**Figure 1**; **Table 3**), it is shown that the BDI score is positively correlated with the REM-ArI and NREM-ArI (significant at the 0.01 level, $P = 0.000$, $P = 0.002$) and negatively correlated with REM sleep latency (significant at the 0.05 level, $P = 0.046$).

TABLE 3 | Correlation analysis between the BDI score and various indicators of sleep structure after 3 months of follow-up.

		BDI (score)	RL	REM-ArI	NREM-ArI
BDI (score)	Pearson correlation	1	−0.287*	0.825**	0.416**
	Sig. (Two-tailed)		0.046	0.000	0.002
	Number of cases	54	49	54	54
RL	Pearson correlation	−0.287*	1	−0.229	−0.285
	Sig. (Two-tailed)	0.046		0.114	0.047
	Number of cases	49	49	49	49
REM-ArI	Pearson correlation	0.825**	−0.229	1	0.252
	Sig. (Two-tailed)	0.000	0.114		0.066
	Number of cases	54	49	54	54
NREM-ArI	Pearson correlation	0.416**	−0.285	0.252	1
	Sig. (Two-tailed)	0.002	0.047	0.066	
	Number of cases	54	49	54	54

*BDI, Beck Depression Inventory; RL, REM sleep latency; REM-ArI, REM sleep arousal index; NREM-ArI, NREM sleep arousal index. *p < 0.05, **p < 0.01.*

TABLE 4 | Summary of regression models for predicting the risk of depression in patients with short-term insomnia.

Mode	*R*	R^2	Adjusted R^2	Standard estimation error	Durbin-Watson (*D-W*)
	0.915[a]	0.837	0.822	3.21662	1.924

[a]*Predictors: (constant), RCs, RL, RArl, NRAr.*

TABLE 5 | Analysis of variance of the regression model for predicting the risk of depression in patients with short-term insomnia.

Mode	Sum of squares		Degree of freedom	Mean square	*F*	*P*
	Regress	2340.993	4	585.248	56.564	0.000[a]
	Residual	455.252	44	10.347		
	Total	2796.245	48			

[a]*Dependent variable: depression score.*

TABLE 6 | Predictive regression model coefficients of depression risk in patients with short-term insomnia.

Model	Unstandardized coefficient		Standardization coefficient	*T*	*P*
	B	Standard error	Beta		
(constant)	2.504	2.646		0.947	0.349
RL	−0.008	0.007	−0.089	−1.261	0.214
REM-Arl	1.438	0.128	0.772	11.206	0.000
NREM-Arl	0.609	0.177	0.220	3.436	0.001
RCs	−0.860	0.418	−0.144	−2.058	0.046

RL, REM sleep latency; REM-Arl, REM sleep arousal index; NREM-Arl, NREM sleep arousal index; RCs, Number of REM cycles.

Regression Prediction Model

We constructed a regression model to further explore the relationship between REM sleep characteristics and BDI scores in patients with SID. Using the diagnosis of covariance in linear regression (**Table 4**), the correlation between multiple variables in this study was not significant. The D-W test value of 1.924 can be considered to satisfy the independence condition for linear regression. The results of the statistical tests of the model are presented in the analysis of variance (**Table 5**): the regression model ($F = 56.564$, $p = 0.000 < 0.05$), indicates that the constructed regression model is statistically significant. Therefore, a statistically significant model was constructed in this study, which had a good explanatory power ($R^2 = 0.837$). The accuracy of the model in predicting the risk of depression was 83.7%. **Table 6** shows the coefficients of the regression model used to predict the risk of depression in patients with SID: the standardized coefficient of the REM = ArI was $\beta = 0.772$, $p = 0.000$, indicating that the REM-ArI had the greatest effect on the risk of depression across the four variables.

DISCUSSION

The challenge of the link between insomnia and depression is that insomnia disorder may be both a risk factor for and a consequence of depression. The comorbidity of depression and insomnia disorder did not first attract the attention of researchers, and at first, attention was focused on the latter proposition: that insomnia was a clinical symptom accompanying depressive disorders and that insomnia symptoms would resolve with improvement of depressive symptoms as long as we treated them with antidepressant therapy. Until the early 1990s, several studies showed that preexisting or persistent insomnia symptoms not only failed to resolve with improvement in depressive symptom but instead, increased the risk of depressive episodes and were a risk factor for depressive disorders (25, 26). Therefore, one of our aims in this study was to investigate whether the presence or persistence of insomnia symptoms increases the risk of depressive episodes. By measuring depression in 54 patients with SID using the BDI depression scale, it was found that the probability of having a BDI score >15 was found to be 50% in the group with persistent insomnia symptoms after 3 months of follow-up, and the probability of having a BID score >15 was only 6% in the group with remission of insomnia symptoms. This result suggests that patients with persistent insomnia symptoms are more likely to experience depressive mood. Insomnia is an important marker of depression, which is consistent with the results of many foreign studies (5, 6, 27).

Although we observed that the chronic presence of insomnia symptoms is a risk factor for the development of depression, no studies have been able to explain the specific mechanisms underlying the association between insomnia and depression, and there is a lack of corresponding physiological features or biological characteristics that can predict the risk of depression (28). The quantitative electroencephalogram (EEG) studies show that there are characteristic changes in depression, consisting of disturbed sleep continuity, inductions of REM sleep. Of all the changes, abnormalities in REM sleep are key to the EEG changes in depression (29). It was shown as early as 2009 that REM sleep facilitates the reactivation of previously acquired emotional experiences in the limbic system of the brain and their integration with semantic memory, leading to a decrease in amygdala activity and traces of emotional memory over time (30). This finding suggests that changes in the structure of REM sleep results in blocked reactivation of previously acquired emotional experiences in the limbic system of the brain, leading to diminished amygdala activity and elimination of traces of emotional memory. Studies on how eye movements in REM sleep cause transient, time-specific activation of the amygdala also confirm the role of the limbic system in the reprocessing and consolidation of emotional experiences in REM sleep (12). As observed through several studies (13): changes in the structure of REM sleep, such as shortened REM

latency, increased REM sleep duration, and increased density of REM, are frequently observed in people diagnosed with depressive disorders.

Recently, it was found that depression may be related to the dysfunction of a network of structures that regulate REM sleep, such as the limbic system, including the hippocampus, amygdala, and medial pre-frontal cortex. The reward network is dysfunctional and associated with depression symptoms in patients with chronic insomnia disorder (31). Furthermore, the subregions of the medial pre-frontal cortex (mPFC) show great changes in neural activity in depressed patients (32). Anatomic tracing studies show that the mPFC projects to the pontine REM-off neurons in the ventrolateral periaqueductal gray and adjacent lateral pontine tegmentum, which interacts with REM-on neurons in the dorsal pons. Therefore, the ventral mPFC may be a critical area for regulating both depression and sleep, and it is suggested as a critical site for REM sleep abnormalities and other behaviors in depression (33). Depression is reported to be associated with a reduction in 5-hydroxytryptamine neurotransmission, which may explain why depression is characterized by a short REM sleep latency (the 5-hydroxytryptamine system is off-line during REM sleep). That said, the role of 5-hydroxytryptamine neurotransmission between insomnia and depression may be much more complex and may be better characterized by an overall dysregulation of the system (i.e., the system is online when it should be off-line and off-line when it should be online) (28, 34).

Expanding upon traditional ways of looking at REM alterations, recent studies examine REM sleep fragmentation (i.e., the number and duration of short arousals that disrupt the continuity of the REM period). Thus, REM sleep continuity may function to depotentiate emotional load: a function that is disrupted when REM is fragmented by brief arousals (13, 35). The possibility exists that REM sleep fragmentation is linked with less efficient regulation of negative affect. The results of our study found that 54 patients with SID were divided into SID with increased BDI score (BDI >15) and SID with normal BDI score (BDI ≤ 15), and the total BDI score was positively correlated with REM-ArI and NREM-ArI and negatively correlated with REM sleep latency after a 3-month follow-up observation. This structural sleep characteristic could suggest that the presence of shortened REM latency and REM sleep fragmentation (increased microarousal index) in patients with clinical insomnia disorder would increase the risk of depressive episodes. We further developed a regression model to predict the risk of depression to explore the relationship between REM sleep characteristics and depression in patients with SID. The model uses four independent variables, REM-ArI, REM cycle number, REM sleep latency, and NREM-ArI, to predict the risk of subsequent depression with 83.7% accuracy. Further analysis of the regression coefficients revealed that their REM-ArI had the greatest effect on depression. The results suggest that REM sleep fragmentation has an extremely important role in depressive mood changes, there are relatively few studies on specific REM structural characteristics in previous studies, and the study of the relationship between changes in REM structure and depressive mood may further refine the explanation and description of the mechanism that there are many studies reporting that insomnia disorder increases the risk of depressive episodes.

This may also indirectly suggest that insomnia may act on emotion regulation mechanisms by disrupting the structure of REM sleep, thus affecting the reprocessing and consolidation of emotions and leading to a weakening of the effect of eliminating negative emotions. Excessive arousal and REM sleep fragmentation play an important role in emotion regulation in insomnia, depression, and PTSD by affecting the elimination of negative emotions (36). Our study suggests that changes in the structure of REM sleep, especially REM sleep fragmentation, may be a characteristic marker for assessing the risk of depressive episodes and that these patients with short-term insomnia disorders presenting with REM sleep fragmention should be alerted to appropriate interventions to reduce the risk of developing depression.

Study Limitations

Our study used primarily one night of sleep monitoring data, and therefore, there is some controversy as to whether the results are affected by first-night effects. Although several previous studies show no statistical difference in sleep structure data between subjects on the first and second night (37–39). Another limitation of the study is that in the present study, we mainly assessed depression levels using the BDI scale in patients with SID with a 3-month follow-up without further clarifying the diagnosis according to the diagnostic criteria of depression.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

This study was reviewed and approved by the ethics committee of Ningbo First Hospital (No. 2018-R048). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DW: conceptualization, methodology, software, data curation, writing-original draft, visualization, investigation, and formal analysis. MT: writing-original draft, writing-review and editing, investigation, and validation. YJ: validation, investigation, and supervision. LR: project administration and validation. ZL: data curation and visualization. HG: investigation and formal analysis. QY: resources and investigation. All authors contributed to the article and approved the submitted version.

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The Association Between Depressive Symptoms and Insomnia in College Students in Qinghai Province: The Mediating Effect of Rumination

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Background: This study investigates the mediating effect of rumination on the associations between depressive symptoms and insomnia.

Methods: This is a cross-sectional study. Insomnia Severity Index (ISI), Ruminant Response Scale (RRS) and Beck Depression Inventory (BDI) were determined in 12,178 college students in Qinghai province by a questionnaire network platform.

Results: The prevalence of insomnia was 38.6% in the participants. Insomnia symptoms [interquartile range: 6 (3, 9)], depressive symptoms [interquartile range: 5 (1, 9)], and rumination [interquartile range: 22 (20, 26)] were positively correlated ($r = 0.25$–0.46, $p < 0.01$). Mediation effect analysis showed that the depressive symptoms affected insomnia directly and indirectly. The direct effect and the indirect effect through rumination account for 92.4 and 7.6% of the total effect, respectively.

Conclusion: The study shows that insomnia, depressive symptoms, and rumination are related constructs in college students in Qinghai province. It demonstrates the direct effects and the rumination-mediated indirect effects between depressive symptoms and insomnia; the direct effects seem to be dominant.

Keywords: depressive symptoms, insomnia, college students, mediation effect, ruminative thinking

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INTRODUCTION

For Sleep plays a critical role in health and well-being of a human. It is reported that various populations are experiencing sleep disturbance frequently and suffering from its consequences. In Chinese college students, the prevalence of sleep disturbances and insomnia are reported to be 25.7% (1) and 18.5% (2), respectively.

Depression in youth has been shown to be associated with distinct sleep dimensions, such as timing, duration, and quality (3). Shochat et al. reported that those students with fewest depressive symptoms had moderate sleep time, shorter sleep onset latencies, and fewer arousals (4). In addition, depression can exacerbate the severity of insomnia in college students (5). Depression has been shown to be the most important risk factor for insomnia (6, 7). However, it is unclear if a depressive mood can lead to insomnia directly or indirectly through some mediating factors.

There may be some mediating factors between depressive symptoms and insomnia (8), such as lying awake at night (9), cognitive inflexibility (10), worry (11), social support (12), and internet addiction (13). Rumination is considered a possible mediator in relation between the depression and insomnia. It was well-known that individuals who have chronic insomnia worry about a range of topics while in bed, including "What about tomorrow's work?" (14). Rumination tends to engage in preservative and non-constructive thoughts and negative reflection on the problems and feelings in the past or present. Although previous studies have focused almost exclusively on the role of anxiety in the development of insomnia, it appears that rumination is more critical for eliciting sleep difficulties (15). Rumination about adverse events and self-reflection have been shown to heighten the levels of physiologic arousal (16), lengthen the sleep latency (17), and decrease the sleep efficiency (17). A clinical study showed that a high level of depressive symptoms significantly predicted a higher level of rumination (18). However, only a few studies have explored the mediating effect of rumination on the association between depressive symptoms and insomnia (19, 20). It has been shown that ruminative thoughts mediated the relationship between depressive symptoms and insomnia in the population of healthy young adults (20) and adolescents (19).

It has been reported that the sleep quality of students from high altitude areas is worse than that of students from plain areas, and the sleep quality of the ethnic minority students is worse than that of the Han students (21, 22). Qinghai province is located in the Qinghai-Tibet Plateau, with an average altitude of more than 3,000 meters. Many ethnic minority groups live in Qinghai province. The population of the Tibetan, Hui, Tu, Mongolian and Salar ethic groups accounts for 47.7% of the total population in Qinghai province (23). There is a lack of research on the relationship between insomnia and depressive symptoms in the population in this multi-ethnic area in Qinghai-Tibet Plateau. In this study we investigated the association between insomnia and depressive symptoms, and determined the mediating effect of rumination on the association between depressive symptoms and insomnia in college students in Qinghai province.

MATERIALS AND METHODS

Participants and Procedures

The study was approved by the Ethics Committee of Nanfang Hospital of Southern Medical University and the Third People's Hospital of Qinghai Province. The study was conducted in accordance with the Declaration of Helsinki. Students from three universities (Qinghai University, Qinghai Normal University, and Qinghai Nationalities University) in Qinghai province were recruited using convenient sampling in November 2019. The inclusion criteria were: (1) Undergraduate students studying in the above three universities; (2) Wechat users; and (3) students participated in the study voluntarily. The exclusion criteria were: students on the campuses of the three aforementioned universities located outside Qinghai Province.

We conducted a cross-sectional survey on the online platform of Questionnaire Star. The purpose and significance of the survey were introduced to all participants, and the participant consent form was obtained from all participants prior to the study. The data were recorded and stored automatically. To protect the respondents' privacy, the survey was conducted anonymously. We put a total of 33 parameters into the model, including 30 observed variables or indicator variables and 3 latent factors. The sample size was required to be 5 or 10 times of the parameter, or 15 times of the observed or indicative variable (24). The minimum sample size in our study was 450.

Measures

Socio-Demographics and Lifestyle Practice

Data of socio-demographics were collected from all participants, including gender, age, grade, ethnicity (Han, Tibetan, Hui, Tu, Mongolian, Salar, etc.), body weight, height, household monthly income (range: <5,000 RMB/month, 5,000–10,000 RMB/month, 10,000–20,000 RMB/month or >20,000 RMB/month), and being an only child in the family or not. Lifestyle and health conditions included chronic medical conditions, alcohol drinking, study stress (no, mild, or high), and boarding or commuting during school days.

Insomnia

Insomnia Severity Index (ISI) was used to evaluate the severity of insomnia during the past 2 weeks for each participant, as described previously (25). ISI consists of seven items. Each item is rated on a 5-point Likert scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = extremely severe), with higher total scores indicating more severe insomnia. The scoring system is defined as follows: <8: no insomnia symptoms; 8–14: mild insomnia; 15–21: moderate insomnia; and 22–28: severe insomnia. The Cronbach's alpha of ISI is 0.83, and the 2-week test-retest reliability is 0.79 in Chinese adolescents (25).

Rumination

The 10-item Ruminative Responses Scale (RRS-10) was used to assess the severity of rumination. The Ruminative Responses Scale (RRS) was compiled by Nolen-Hoeksema, to assess the severity of depressive rumination (26). Treynor et al. removed 12 depression-related items from the RRS and developed a simplified scale called RRS-10 (27). The RRS-10 contains two

subscales that reflect pondering and brooding, using a 4-point Likert scale. The Cronbach's α coefficient of this scale in Chinese college students is 0.90, and the test-retest reliability is 0.82 (28).

Depressive Symptoms

Beck Depression Inventory (BDI) (29) was used to assess depressive symptoms over the past week. BDI includes 13 items, and each item is rated on a scale from 0 to 3 (0: none, 1: mild, 2: moderate, and 3: severe). The scoring system for depressive symptoms is as follows: 0–4: no depressive symptoms; 5–7: mild depressive symptoms; 8–15: moderate depressive symptoms, and ≥16: severe depressive symptoms. The BDI has been shown to be a valid tool for a college student population (30). It has been found that the split-half coefficient of BDI in Chinese samples is 0.879, and the Cronbach's alpha is 0.890. The whole scale and each item group of the scale have good validity (31).

Statistical Analysis

Analysis of structural equation structure (AMOS, version 24.0) and SPSS 21.0 software were used to analyze the data. Continuous variables (scale scores) with non-normal distribution are reported as the median [Interquartile range [IQR]]. The variables with normal distribution are reported as mean and standard deviation (mean ± SD). Categorical variables are reported as percentages. The direction and degree of correlation among factors were analyzed using Spearman's correlation analyses. The Bootstrap method of bias correction was used to test the mediating effect, and the parameter was set at 5,000 times. For the indirect effect, significance was considered at the level of $p < 0.05$, when the confidence interval did not contain zero. In the structural equation modeling (SEM), full information maximum likelihood was used to confirm interrelationships and parameters among the variables. The overall model fit was evaluated by using the likelihood ratio ($\chi 2$/df), the goodness of fit index (GFI), the Tucker-Lewis index and root (TLI), the comparative fit index (CFI), the root mean square error of approximation (RMSEA), and the root mean square residual (RMR). The Chi square (χ^2) statistic was non-significant in the model, but it was highly influenced by sample size (32). Values of RMSEA $\leq$ 0.08 and RMR $\leq$ 0.05 were considered adequate model fit. The rest of the indices (e.g., GFI, TLI and CFI) $\geq$ 0.90 are indicative of an adequate model fit (33, 34).

RESULTS

Demographic Characteristics of Participants

The demographic characteristics of participants are shown in **Table 1**. A total of 13,075 questionnaires were collected, and 12,178 (93.1%) participants responded with valid data. Among them, 8,065 participants (66.2%) were female. The mean age of participants was 20.2 ± 1.5 (range 16–30) years. The Han and Tibetan ethnic groups are the majority of the participants, accounting for 51.5% and 23.5% of the total population, respectively.

TABLE 1 | Socio-demographic characteristics, health condition, mental distress and lifestyle practice of college students in Qinghai province ($N = 12,178$).

Socio-demographics	*N* (%) or Mean ± SD
Age (years)	20.2 ± 1.5
BMI (kg/m²)	20.3 ± 2.5
Gender	
Male	4,113 (33.8)
Female	8,065 (66.2)
Ethnicity	
Han	6,258 (51.5)
Tibetan	2,866 (23.5)
Hui	1,730 (14.2)
Tu	674 (5.5)
Mongolian	322 (2.6)
Salar	108 (0.9)
Others	220 (1.8)
Grade	
Freshman	5,705 (46.8)
Sophomore	3,549 (29.1)
Junior	1,984 (16.3)
Senior	940 (7.7)
Only child (Yes)	2,697 (22.1)
Family income	
<¥5,000/month	7,639 (62.7)
¥5,000–10,000/month	3,404 (28)
¥10,000–20,000/month	903 (7.4)
>¥20,000/month	292 (1.9)
Lifestyle practice and health conditions	
Alcohol use (Yes)	3,748 (30.8)
Chronic medical conditions (Yes)	321 (2.6)
High study stress (Yes)	2,935 (24.1)
Boarding in school (Yes)	12,099 (99.4)

One Chinese Yuan (¥) equals 0.15 US Dollar. BMI, Body mass index.

Descriptive Statistics and Bivariate Correlations Between Measured Variables

The cross-sectional associations of insomnia, depressive symptoms, and rumination are presented in **Table 2**. The insomnia symptoms measured by the ISI scale revealed a sample median (IQR) score of 6 (3, 9). A total of 4,703 (38.6%) participants were considered insomniacs. Based on the BDI total score, a total of 6,250 participants (51.3%) suffered from depressive symptoms over the past week. Insomnia symptoms were significantly and positively correlated to depressive symptoms, brooding, and reflective pondering ($p < 0.01$), respectively.

Structural Equation Modeling Results

The mediating effect of rumination on the relationship between insomnia and depressive symptoms is described in **Figure 1**. Measurement models of latent variables were created for each measure of rumination and insomnia. The model fit was satisfactory for depressive symptoms, rumination, and insomnia

TABLE 2 | Descriptive statistics and bivariate correlations between insomnia symptoms, depressive symptoms, and rumination ($N = 12,178$).

	Median (quartile)	ISI Total score	BDI Total score	RRS Total score	RRS Brooding	RRS Reflective pondering
ISI total score	6 (3, 9)	1	–	–	–	–
BDI total score	5 (1, 9)	0.46*	1	–	–	–
RRS total score	22 (20, 26)	0.25*	0.36*	1	–	–
RRS-Brooding	11 (10, 14)	0.23*	0.37*	0.92*	1	–
RRS-Reflective pondering	10 (9, 13)	0.23*	0.30*	0.92*	0.72*	1

ISI, Insomnia Severity Index; BDI, Beck Depression Inventory; RRS, Ruminative Responses Scale.
**Indicates significant correlation ($p < 0.01$).*

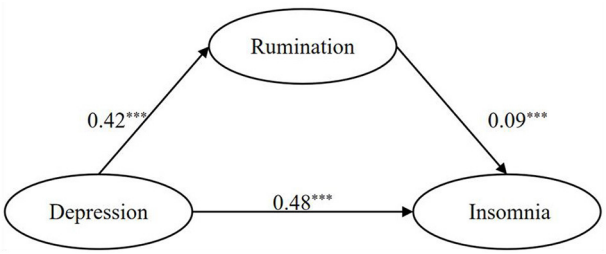

FIGURE 1 | Model of mediating effect of rumination on insomnia symptoms and depressive symptoms. *** indicates path coefficients are significant ($p < 0.05$).

($\chi^2/df = 35.215$, RMSEA = 0.053, TLI = 0.903, GFI = 0.918, CFI = 0.910, RMR = 0.022).

The Bootstrap method with bias correction was used to test the mediating effect between insomnia symptoms and depressive symptoms. As shown in **Table 3**, in the groups of Han, Tibetan, Tu, Mongolian, the 95% confidence interval did not contain 0, indicating that an indirect effect existed in these groups. The indirect effect mediated by rumination appeared to be higher in the groups of Tibetan (10.8%), Tu (9.6%), and Mongolian (15.7%) compared to that of the Han group (5.8%). In the group of Hui and Salar, the 95% confidence interval of standardized indirect effect contained 0, indicating that an indirect effect did not existed. In Group Others (**Table 3**), including ethnic minorities Zhuang, Miao, and Man groups, the 95% confidence interval did not contain 0, indicating that an indirect effect existed; the indirect effect accounted for 16.7%. For the total samples, the 95% confidence interval of standardized indirect effect did not contain 0, indicating that an indirect effect existed. In the process from depressive symptoms to insomnia, the direct effect and indirect effect accounted for 92.4 and 7.6% of the total effect, respectively (**Table 3**).

DISCUSSION

Our study showed that rumination mediated in the association between depressive symptoms and insomnia in college students in Qinghai province, a multi-ethnic and high-altitude area. However, the mediating impact is small.

In our study, 38.6% of college students reported that they suffered from insomnia in the past 2 weeks. Luo et al. demonstrated that the prevalence of insomnia among Chinese teenager in Guangzhou (average altitude: 21 meters) was 28.9% (35), which was lower than what we found. One reason may explain the difference is that nearly half of the participants in our study were ethnic minorities and lived in area with an average altitude of more than 3,000 meters. It has been shown that people who live at high altitudes have poorer sleep quality, which may be due to hypoxia-induced arousal and hypoxia-induced periodic breathing (35–37). Yip and Cheon reported that the prevalence of insomnia was high in ethnic minorities, which may be related to acculturation (38).

The results of the structural equation model display that depressive symptoms directly affect insomnia, and the direct effect accounted for 92.4% of the total effect. The results are consistent with previous studies that linking depressive symptoms to insomnia (8, 39). The youth with depressive symptoms demonstrate increased activity in extended medial network regions (40). Studies have shown that people with depressive symptoms have increased cortisol levels (41), hypothalamic pituitary adrenal (HPA) axis dysregulation (41), changes in inflammatory cytokines (42), and changes in sleep architecture (43). These changes can lead to insomnia. Beck's cognitive model of depression describes how people's thoughts and perceptions influence their emotional, behavioral, and physiological reactions. The elements of this model include biased attention, biased processing, biased thoughts and rumination, biased memory, and dysfunctional attitudes and schemas (44). These psychological processes may extend to the pre-sleep period, resulting in unpleasant intrusive thoughts, dysfunctional beliefs and attitudes about sleep, selective attention and monitoring to sleep-related threat, and misperception of sleep deficit. They may cause difficulty in initiating sleep and delayed sleep phase (45). Depressive symptoms are characterized by social withdrawal (46), poor interpersonal skills (47) and difficulty in coping with peer/family stressors (48). Such vigilance following social stressors may induce wakefulness before asleep.

In our study the structural equation model results display that rumination had mediating effects on the association between depressive symptoms and insomnia. Three possible mechanisms may explain our results. Firstly, depressive symptoms are considered the failure of emotion regulation. People with depressive symptoms may elaborate negative information. The

TABLE 3 | Bootstrap test of mediating effect of rumination between insomnia symptoms and depressive symptoms.

Ethnic Groups	N	Pathways	Estimates	Standard Error	Bias-corrected CI (95%)	
					Lower	Upper
Han	6258	Indirect effects	0.030 (5.8%)	0.006	0.019	0.042
		Direct effects	0.484 (94.2%)	0.015	0.454	0.514
		Total effects	0.514	0.013	0.488	0.539
Tibetan	2866	Indirect effects	0.054 (10.8%)	0.011	0.033	0.076
		Direct effects	0.448 (89.2%)	0.022	0.404	0.492
		Total effects	0.502	0.019	0.465	0.538
Hui	1730	Indirect effects	0.024 (4.7%)	0.016	−0.008	0.055
		Direct effects	0.491 (95.3%)	0.032	0.428	0.550
		Total effects	0.515	0.025	0.462	0.561
Tu	674	Indirect effects	0.048 (9.6%)	0.019	0.011	0.087
		Direct effects	0.451 (90.4%)	0.047	0.359	0.543
		Total effects	0.499	0.040	0.421	0.576
Mongolian	322	Indirect effects	0.081 (15.7%)	0.033	0.022	0.155
		Direct effects	0.434 (84.3%)	0.078	0.281	0.582
		Total effects	0.515	0.062	0.395	0.632
Salar	108	Indirect effects	0.087 (17.4%)	0.095	−0.020	0.324
		Direct effects	0.414 (82.6%)	0.140	0.099	0.653
		Total effects	0.501	0.106	0.292	0.704
Others	220	Indirect effects	0.098 (16.7%)	0.036	0.037	0.179
		Direct effects	0.489 (83.3%)	0.085	0.325	0.656
		Total effects	0.587	0.077	0.426	0.726
Total	12178	Indirect effects	0.039 (7.6%)	0.005	0.030	0.049
		Direct effects	0.476 (92.4%)	0.011	0.455	0.498
		Total effects	0.515	0.009	0.497	0.533

reactivation of these memories during the pre-sleep period (i.e., ruminating) may exacerbate the difficulty in falling asleep (49). Secondly, ruminative thinking is considered invasive thinking. Individuals with excess rumination tend to focus on negative emotions continuously and repeatedly. This may further increase their selective attention to adverse events (50) and stimulate more cognitive awakening, leading to the delay of sleep initiation (8). Thirdly, rumination can cause psychological arousal and autonomic excitation, such as elevated heart rate, elevated body temperature, increased basal metabolic rate and electrodermal activity (51). Such changes in the body may cause insomnia.

Our results are consistent with previous studies (19, 20, 52) showing that rumination is a mediating factor between depressive symptoms and insomnia. However, there are some differences between our results and others. Firstly, the mediating effect by rumination in our study is smaller than that in the previous studies. Previous studies have reported that rumination fully mediated the relationship between depression and insomnia (19, 20). However, we found that rumination only plays a relatively limited role on the association between depressive symptom and insomnia. Secondly, previous studies included some other mediators, such as perfectionism (19), neuroticism (52), and self-reported health (20). Incorporating other factors into the model may change the indirect effects. Thirdly, about half of the participants in our study were from multiple ethnic minority groups. It has been shown that ruminative thinking from different cultural backgrounds is bound to have differences in content, form and function (53). For example, the everyday worship and

annual Ramadan of the Hui Muslim group, including meditation and social networking, may promote psycho-physical well-being (54).

The present study has several strengths. Firstly, we applied a complex structural equation model to perform path analysis and quantify these paths. Secondly, the large sample size is a highlight of our study. Thirdly, the present study is the first sleep study conducted in the population of Qinghai-Tibet Plateau. It is also one of the few large-scale surveys conducted in the minority/multi-ethnic areas. However, several limitations should be noted when interpreting our findings. Firstly, due to the cross-sectional nature of the study, we cannot determine the causality among depressive symptoms, rumination, and insomnia. A longitudinal study will be designed to define the causality of these variables. Secondly, although rumination mediated the association between depressive symptoms and insomnia, the contribution of its effect was much less than that of the direct effect. Other unmeasured variables, such as attentional biases, self-control or social support (12), may play a role on the relationships among depressive symptoms, rumination, and insomnia. Thirdly, all the questionnaires in this study were self-reported. Although the self-report questionnaires provide a rapid access to a large number of college students' mental health status data via the Internet (45), the data may be prone to social desirability bias (55).

In summary, this study shows that insomnia, depressive symptoms, and rumination are related constructs in college students in Qinghai province. It demonstrates the direct effects and the rumination-mediated indirect effects between depressive symptoms and insomnia; the direct effects seem to be dominant.

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 Ethics Committee of Nanfang Hospital of Southern Medical University and the Third People's Hospital of Qinghai Province. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

SX and BZ: conceptualization. SX, ZX, and BZ: methodology. SX: writing—original draft. SX and SL: formal analysis. SL, PZ, JY, HA, HW, FZ, YX, NM, XiuZ, XM, JL, XW, XS, WL, XiaZ, WW, LW, RW, YH, LC, and BZ: investigation and resources. SL and BZ: writing—review and editing. PZ, JY, HA, HW, FZ, YX, NM, XiuZ, XM, JL, XW, XS, WL, XiaZ, WW, LW, RW, YH, LC, and SD: data curation. SL and BZ: funding acquisition. BZ: supervision and project administration. All authors have approved the final manuscript.

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Effectiveness of TES and rTMS for the Treatment of Insomnia: Meta-Analysis and Meta-Regression of Randomized Sham-Controlled Trials

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Objectives: Transcranial electric stimulation (TES) and repetitive transcranial magnetic stimulation (rTMS) have experienced significant development in treating insomnia. This review aims to examine the effectiveness of randomized sham-controlled trials of TES and rTMS in improving insomnia and examine potential moderators associated with the effect of the treatment.

Methods: Nine electronic databases were searched for studies comparing the effects of TES/rTMS with sham group on insomnia from the inception of these databases to June 25, 2021, namely, Medline, Embase, PsycINFO, CINAHL, Cochrane Library, Web of Science, PubMed, ProQuest Dissertation and Thesis, and CNKI. Meta-analyses were conducted to examine the effect of TES and rTMS in treating insomnia. Univariate meta-regression was performed to explore potential treatment moderators that may influence the pooled results. Risk of bias was assessed by using the Cochrane Risk of Bias Tool.

Results: A total of 16 TES studies and 27 rTMS studies were included in this review. The pooled results indicated that there was no significant difference between the TES group and the sham group in improving objective measures of sleep. rTMS was superior to its sham group in improving sleep efficiency, total sleep time, sleep onset latency, wake up after sleep onset, and number of awakenings (all $p < 0.05$). Both TES and rTMS were superior to their sham counterparts in improving sleep quality as measured by the Pittsburgh Sleep Quality Index at post-intervention. The weighted mean difference for TES and rTMS were −1.17 (95% CI: −1.98, −0.36) and −4.08 (95% CI: −4.86, −3.30), respectively. Gender, total treatment sessions, number of pulses per session, and length of treatment per session were associated with rTMS efficacy. No significant relationship was observed between TES efficacy and the stimulation parameters.

Conclusions: It seems that TES and rTMS have a chance to play a decisive role in the therapy of insomnia. Possible dose-dependent and gender difference effects of rTMS are suggested.

Keywords: insomnia, transcranial electric stimulation, repetitive transcranial magnetic stimulation, meta-analysis, meta-regression

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INTRODUCTION

As one of the most commonly reported sleep complaints, insomnia affects approximately 10–35% of the general population (1). According to the diagnosis criteria described in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders and the third edition of the International Classification of Sleep Disorders, insomnia disorder is a predominant complaint of dissatisfaction with sleep quantity or quality, associated with one (or more) of the following symptoms: difficulty initiating sleep, difficulty maintaining sleep, and early-morning awakening. The symptom is presented for at least three nights per week for at least 3 months. It is associated with distress or impairments in daytime function (2, 3). Insomnia could exist alone or be comorbid with other physical or psychiatric disorders, such as chronic pain, Parkinson's disease, cancer, anxiety, or depression (4–7). It decreases the psychological wellbeing and quality of life in people suffering from it and is frequently associated with mood disorders, driving accidents, and a greater prevalence of physical impairment (7, 8).

The cortical hyperarousal plays a central role in the etiology of insomnia. Many studies reported that people with insomnia have a higher level of physiological arousal (9, 10). Therefore, reducing the arousal level may facilitate sleep. Various therapeutic approaches have been used and investigated to improve the sleep of people with insomnia. Pharmacological treatments are proven to be effective and available but related to abuse, dependence, and adverse effects (11). Psychological and behavioral therapies, such as cognitive behavior therapy, targeting somatic and cognitive arousal, have demonstrated promising efficacy for relieving insomnia (12, 13) but remained underutilized due to highly demanding resources (14).

In recent years, non-invasive brain stimulation (NIBS) techniques have experienced significant development and gained increasing attention from researchers. Transcranial electric stimulation (TES) and repetitive transcranial magnetic stimulation (rTMS) are the two most popular types of NIBS. They share common characteristics of being relatively painless, safe, and well-tolerated with different mechanisms (15). TES is a neuromodulation approach that applies a low-intensity electrical current to the cerebral cortex of the brain. It includes cranial electrotherapy stimulation (CES), transcranial direct current stimulation (tDCS), transcranial alternative current stimulation (tACS), and transcranial random noise stimulation (tRNS). CES is a portable device that usually applies pulsed and low-level micro-current ($<$1 mA) stimulation to the brain *via* electrodes clipped onto the earlobes. It was approved by the US Food and Drug Administration for the treatment of insomnia, anxiety, and depression (16). tDCS modulates cortical activity by employing a constant, low-intensity current (0.5–2 mA) to the scalp over a pair of saline-sponge electrodes (17). The two electrodes are placed according to the international 10–20 electrode placement system (18). Generally speaking, anodal stimulation increases cortical excitability, while cathodal stimulation induces an opposite effect, i.e., reducing the cortical excitability (19). tACS and tRNS are relatively new TES techniques, which aim to increase the cortical excitability in a way similar to tDCS. However, instead of giving a steady and constant current between the two sites, tACS delivers a non-constant current to the brain so as to modulate the neural oscillations (20), and tRNS gives random frequencies between 0.1 and 640 Hz with a random noise distribution (21, 22). Currently, the mechanism of the effect of TES on insomnia is not well-established. It is hypothesized that TES could interfere with slow oscillation in the brain, which could increase the slow wave activity and enhance the low-frequency electroencephalogram (EEG) activity (i.e., a marker of arousal) (23–25). Due to its portable features and convenience to use, TES is suitable for self-administration at home (26, 27). However, TES is not free of limitations, and it has been criticized for poor spatial accuracy (28).

rTMS, on the other hand, is another appealing approach that combines both neurostimulation and neuromodulation techniques (29). It was developed in the 1980s and had shown therapeutic potential in improving insomnia (30, 31). Unlike TES, which stimulates the brain by delivering a weak current, rTMS utilizes electromagnetic induction. During rTMS stimulation, an electromagnetic coil is placed over the scalp. The coil could generate rapidly changing focal magnetic pulses that induce an electrical current to stimulate the neurons (29, 32, 33). rTMS has been classified into high (fast) frequency ($>$1 Hz) and low (slow) frequency ($\leq$1 Hz) (34). rTMS at high frequency tends to have an excitatory effect, while rTMS at low frequency appears to have an inhibitory effect on the cortex (35). rTMS is regarded as a parameter-dependent technique. Its therapeutic effect could be influenced by the characteristics of the participants and a range of stimulation parameters, such as frequency, number of sessions, number of pulses/session, length of treatment/session, total number of pulses, and stimulation site (36, 37). Regarding the mechanism of rTMS on insomnia, it has been suggested that rTMS may reduce the state of hyperarousal and regulate brain plasticity by increasing the release of sleep-related hormones, such as brain-derived neurotrophic factor and gamma-aminobutyric acid (38, 39). rTMS is usually delivered in clinical settings. Compared to TES, rTMS has a better focality of stimulation and time resolution. Meanwhile, rTMS has significant limitations in terms of cost and poor portability. It also requires constant attention from the therapist during the treatment (40).

Although several reviews have been conducted to summarize the effectiveness of NIBS techniques for insomnia (15, 41–45), they were either narrative summaries on available evidence without meta-analysis (15, 41) or merely focused on one form of NIBS (42–45). Moreover, the moderators of the therapeutic effect of TES and rTMS on insomnia have not been extensively studied. Therefore, we aimed to review the therapeutic effects of TES and rTMS for the treatment of insomnia and investigate differences between them and the potential moderators associated with the treatment while restricting our review to randomized sham-controlled trials.

METHODS

Search Strategy

Nine electronic databases were searched from the inception of these databases to June 25, 2021, including Medline, Embase, PsycINFO, CINAHL, Cochrane Library, Web of Science, PubMed, ProQuest Dissertation and Thesis, and CNKI. The retrieved abstracts and full-text articles were screened according to the PICOS framework.

The included studies should meet the following criteria: (1) Population: people with insomnia according to clinical diagnosis or had insomnia secondary to or comorbid with other physical or mental diseases or had a subjective complaint of insomnia without a clinical diagnosis; (2) Intervention: TES/rTMS techniques being employed as monotherapy or augmentation therapy for insomnia, such as TES/rTMS plus usual care or other types of intervention, were both eligible if the main aim of the study was to examine the effect of TES/rTMS and the sole difference between intervention and control was TES/rTMS. The search terms included transcranial electric stimulation or TES or cranial electrical stimulation OR CES OR cranial electric stimulat* OR electrotherap* OR fisher wallace stimulat* OR alpha-stim OR Neuroelectric therapy OR Transcerebral electrotherapy OR Transcranial stimulation OR tDCS OR Brain Polarization OR Electric Stimulation OR Electric Polarization OR transcranial alternative current stimulation OR tACS OR transcranial random noise stimulation OR tRNS OR transcranial magnetic stimulation OR TMS OR non-invasive brain stimulation OR NIBS; (3) Comparison: studies compare TES/rTMS with a sham group; (4) Outcome: each study must have reported at least one of the following objective or subjective measurements of insomnia: sleep onset latency (SOL), total sleep time (TST), wake after sleep onset (WASO), sleep efficiency (SE), number of awakenings (NA), or subjective sleep quality—for example, polysomnography (PSG) is considered a "gold standard" for the diagnosis of sleep disorders. The Pittsburgh Sleep Quality Index (PSQI) and Insomnia Severity Index (ISI) are popular subjective instruments of sleep quality and severity of sleep disturbance; and (5) Study design: only randomized controlled trial (RCT) was included. The search was limited to articles in English and Chinese languages. Studies which failed to meet the abovementioned inclusion criteria were excluded.

Two authors (JL and DL) independently screened the title, abstract, and full text of the studies and determined the study eligibility. Any disagreement was resolved by consensus through a discussion or further consultation with a third author (HX) if needed.

Data Extraction

Two authors independently extracted data from the included articles. The characteristics of the study were extracted and tabulated according to authors, year of publication, country, types of insomnia, diagnosis, age, percentage of males, sample size, attrition rate, treatment parameters, sham procedure, main instruments used for outcome measurements, and assessment time point. The treatment parameters included electrode/coil position, current intensity, stimulation frequency, magnetic field strength, (resting) motor threshold, number of pulses per session, duration of the treatment per session, and total number of sessions.

Assessment of the Risk of Bias

The risk of bias of the included study was assessed using the Cochrane Risk of Bias Tool. The assessment was done across seven domains of bias: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of care providers, (5) blinding of outcome assessment, (6) incomplete outcome data, and (7) selective reporting. Each study was ranked as having low, high, or unclear risk of bias for each of the potential sources of bias. Discrepancies were discussed until a consensus was reached.

Statistical Analysis

The data was analyzed using the Review Manager (version 5.4). Changes in the continuous outcome were expressed as weighted mean difference (WMD) when the outcome was measured with the same scale. Otherwise, standard mean difference was used. Changes in dichotomous outcomes were expressed as relative risks (RR). The corresponding 95% confidence interval (CI) was calculated. To estimate the statistical heterogeneity of the intervention effects among studies, the I^2 statistic was used, in which $I^2 < 25\%$, 25–50%, and >50% were considered low, moderate, and high heterogeneity, respectively. Fixed-effects model was performed to calculate the pooled mean difference if $I^2 < 50\%$. Otherwise, random-effects model was performed. When data was available, immediate, short-term, and long-term effects were also analyzed and compared. In this review, the immediate follow-up was defined as 0 to <1 week post-intervention, the short-term follow-up was defined as 1 to 4 weeks post-intervention, and the long-term follow-up was defined as >4 weeks post-intervention. To further explore the heterogeneity of the results, sensitivity analyses were limited to studies among participants with primary insomnia and having a lower or unclear risk of bias.

To explore potential treatment moderators that may influence the pooled results, univariate meta-regression of continuous moderators was performed using Comprehensive Meta-Analysis software (version 3.0). The analyses were restricted to studies with at least six effect sizes for a continuous variable and four effect sizes per group for a categorical variable (46). The following possible moderators were considered: mean age of the participants, percentage of males, stimulation intensity (milliampere), frequency (Hz), number of pulses per session, total number of sessions, number of weekly sessions, length of each session, and stimulation site. Multivariable meta-regression analyses were not conducted to avoid exceeding the power of the pooled studies (47). All p-values were set at 0.05 level (two-tailed).

In the presence of potential publication bias, funnel plots and Egger's regression test were applied using Comprehensive Meta-Analysis software (version 3.0). The funnel plots were analyzed when at least 10 studies were included in the meta-analysis.

RESULTS

A total of 843 citations were identified from the databases, and 129 duplicates were removed. After screening the title and abstract, 44 full-text articles were retrieved for further assessment. Of these, eight studies were excluded for the following reasons: abstract without full text ($n = 2$), ongoing trial without outcome data ($n = 2$), completed RCT without reporting data ($n = 2$), duplicated publication with data from the same source of study ($n = 1$), and research proposal ($n = 1$). Besides these, seven additional studies were identified from the hand search of the reference lists. In total, 43 studies were included in this review, including 16 TES studies and 27 rTMS studies (see **Figure 1**).

Among the TES studies, eight of them used CES (49–56), seven applied tDCS (57–63), and one examined tACS (64). No study was identified to have examined the effectiveness of tRNS in insomnia. A summary of the characteristics of TES and rTMS is described in the following section.

Characteristics of TES Studies

Participants

The groups of individuals treated by TES were heterogeneous, including people with cancer, fibromyalgia, post-polio, HIV, substance abuse, or women after menopause. The diagnosis of insomnia varied across studies. Of nine studies that reported a diagnosis of insomnia, three used DSM, ICSD, or International Statistical Classification of Diseases and Related Health Problems (ICD-10) criteria, and three studies used the cutoff scores of PSQI, ISI, and General Sleep Disturbance Scale (GSDS). One study employed the diagnosis of neurotic and personality disorders combined with insomnia, and one study adopted sleep parameters to determine insomnia. The sample size in each study ranged from 10 to 167, with a median number of 32. The mean age of all participants was 52.5 (SD = 7.36) years. There were considerably more female subjects than male subjects, with the male-to-female ratio being 1:3.2. The attrition rate ranged from 0.0 to 19.3%.

Electrode Position

Usually, most CES studies used ear-clip electrodes attached to the earlobes ($n = 5$). All tDCS studies applied one anode and one cathode, except that one study (57) used two anodes and one cathode. The anode was located according to the International 10–20 EEG system. Four studies applied the anode over the C3/C4 area. Three tDCS studies located the anode at the right or left dorsolateral prefrontal cortex (DLPFC) area, and one study placed the anode at the right inferior frontal cortex near F10. The cathode locations also varied. Three studies located the cathode at the contralateral supraorbital region, two studies chose the right/left DLPFC area, one study put it on the left shoulder, and another study placed it on the contralateral upper arm. The tACS study was composed of three electrodes; one was placed over the forehead, and two others were placed over the mastoid area (see **Supplementary Table 1**).

Stimulation Parameters

A low current of 0.1 mA was used in the majority of CES studies. The current intensity ranged from 1.5 to 2 mA in the tDCS studies and was 15 mA in the tACS study. The dosage and follow-up frame of the intervention varied widely. The duration of each session lasted from 5 to 90 min, with the majority of CES studies lasting for 60 min and of tDCS studies lasting for 20 min. The majority of TES was administered once daily for a duration of 5 days to 4 weeks. The majority of the studies only measured the outcome immediately after the end of the intervention. Five studies collected follow-up assessment at 1–4 weeks post-intervention, and one study investigated the effect of CES at 2 years of follow-up (see **Supplementary Table 1**).

Sham TES Procedure

All TES studies used a similar type of sham procedure, which involved no electrical current or gave a few seconds of electrical stimulation at the beginning/end of the intervention.

Characteristics of rTMS Studies

Participants

As summarized in **Supplementary Table 2**, a total of 27 studies applied rTMS technique (65–91). The diagnosis of insomnia also differed. Of 25 studies that reported the diagnosis of insomnia, 14 studies used the DSM or ICD criteria, six studies used the Chinese Classification of Mental Disorders, three studies adopted the diagnosis and treatment of adult insomnia in China, and two studies employed the cutoff score of PSQI. Most rTMS studies include patients with primary insomnia ($n = 18$). The sample size in each study varied from 19 to 160, with a median number of 78. The mean age of all participants was 47.5 (SD = 10.26), and the male-to-female ratio was 1:1.3. The attrition rate ranged from 0.0 to 13.3%.

Stimulation Site

Regarding rTMS trials, the majority of them targeted the right DLPFC ($n = 19$). Other sites included the left prefrontal cortex (PFC) ($n = 2$), the right lateral and middle PFC ($n = 1$), the vertex ($n = 1$), the right posterior parietal cortex (P4 electrode site) ($n = 1$), the raphe nuclei ($n = 1$), the middle of the bilateral frontal/occipital/temple cortex ($n = 1$), and certain acupoints ($n = 1$). One rTMS study did not describe the stimulation site (see **Supplementary Table 2**).

rTMS Stimulation Parameters

The intensity of the rTMS studies also varied. The stimulation frequency in most studies ranged from 0.5 to 1 Hz, the stimulation intensity ranged from 80 to 130% motor threshold, and the number of pulses per session ranged from 1,100 to 2,400. The duration of each session lasted from 10 to 90 min, with the majority of interventions lasting for 20 min ($n = 15$). The majority of rTMS was administered on consecutive days or 5 days per week for a duration of 2 to 4 weeks. Most studies measured the outcome immediately after the intervention. Seven studies also collected data at 1–22 weeks of follow-up (see **Supplementary Table 2**).

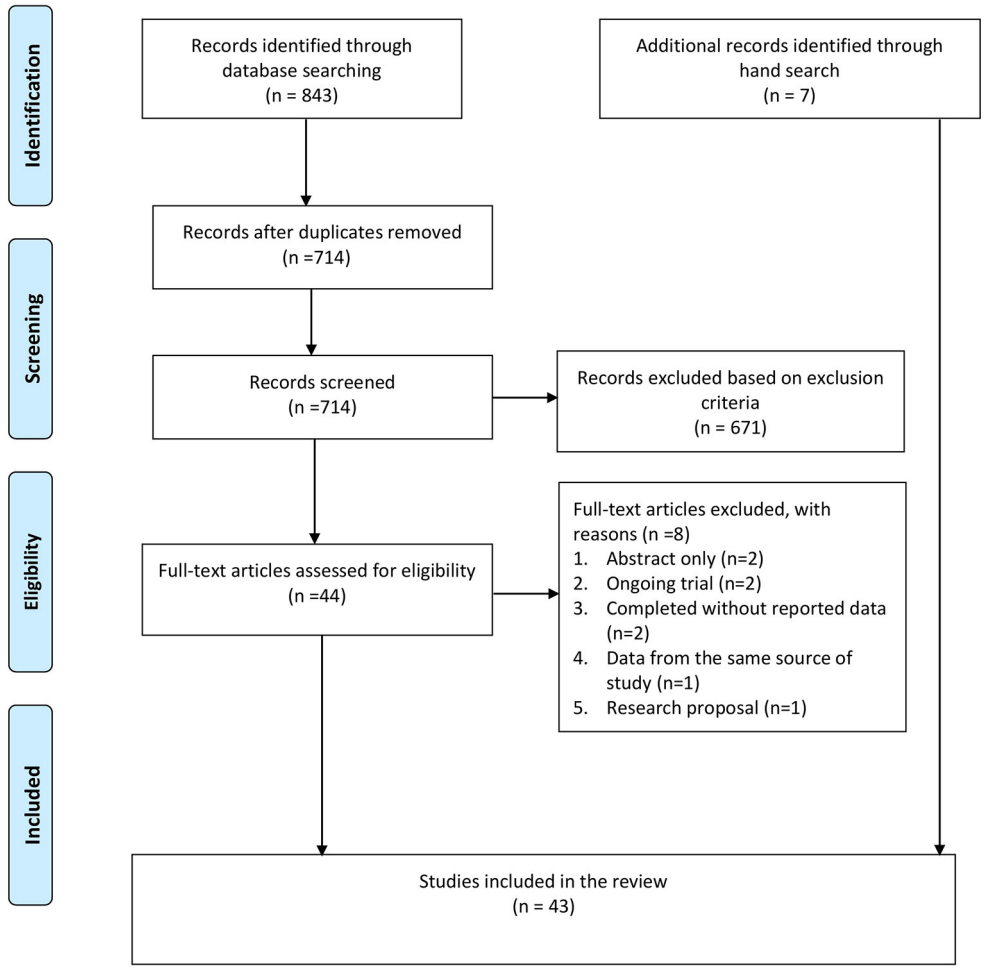

FIGURE 1 | PRISMA flow chart. Adapted from Moher et al. (48).

Sham rTMS Procedure

The common sham methods applied in rTMS studies were using a 90°/180° tilted coil ($n = 13$) or an inactive coil with/without a sound effect ($n = 11$).

Outcome Measurements of TES and rTMS Studies

Various measures have been applied in the included studies. Laboratory-based PSG, sleep diary, EEG, and actigraphy provided an objective evaluation of the sleep parameters. The most popular objective measurement was PSG-measured SOL (n =13), followed by PSG-measured WASO ($n = 10$), PSG-measured SE ($n = 9$), PSG-measured TST ($n = 9$), and PSG-measured NA ($n = 6$). Among the subjective measurements of sleep, the PSQI was the most frequently used measurement ($n =$ 33), followed by the GSDS ($n = 3$), ISI ($n = 2$), and Krakow Sleep Score ($n = 1$) (see **Supplementary Tables 1, 2**).

Quality Assessment

Overall, the risk of bias of the included studies was considered mediocre. The majority of the studies failed to report a detailed methodology. Moreover, 23 of them did not report an adequate method of random sequence generation. Only three studies described the allocation concealment. All studies were rated as having a low risk of bias in blinding the participants because of the sham procedure. However, it was difficult to blind the practitioner of the assigned intervention in most of the RCTs. Only one study blinded the practitioner *via* adopting pre-set sham devices provided by a device manufacturer. A total of 14 studies reported blinding of outcome assessment, while the rest of the 29 studies did not. Regarding the outcome data, 39 studies were considered as having a low risk of attrition bias (dropout rate <10%, used intention-to-treat analysis). In comparison, a high risk of attrition bias was reported in the remaining four studies (dropout rate >10%). All studies, except one, reported complete outcome data (see **Supplementary Figures 1, 2**).

Synthesis of Results

TES Studies

1) Objective Measures of Sleep Parameters

Supplementary Table 3 presents the results of a meta-analysis on PSG and EEG measures of sleep parameters in TES studies. Two RCTs evaluated the effectiveness of TES on SE and total TST, and three RCTs reported the results of TES on SOL. The findings from the random-effects model indicated that there was no significant difference between the TES group and the sham group in improving SE (WMD: −4.86, 95% CI: 17.29, 7.57, $p = 0.0003$), TST (WMD: −7.75, 95% CI: −42.25, 26.74, $p = 0.66$), or SOL (WMD: 1.24, 95% CI: −10.05, 12.52, $p = 0.83$). Between studies, substantial heterogeneity among these sleep parameters existed, which ranged from 79 to 95%.

2) Subjective Measurement of Sleep Quality—PSQI

A total of seven studies reported that the results of TES contrast with those of sham TES in terms of changes of the PSQI total score immediately after the intervention. Findings from the fixed-effects model showed that active TES were superior to their sham counterparts in improving the PSQI total score. The WMD for TES was −1.17 (95% CI: −1.98, −0.36) (**Figure 2**). Nevertheless, moderate heterogeneity existed among TES studies ($I^2 = 42\%$).

Supplementary Table 4 displays the results of univariate analyses of moderators for effects of TES on sleep quality as measured by PSQI. The results of the meta-regression of TES studies revealed that age, percentage of males, current intensity, total number of treatment sessions, number of weekly sessions, and duration of each session were not significant moderators for the effects of TES on sleep quality as measured by the PSQI.

rTMS Studies

1) Objective Measures of Sleep Parameters

The results of the meta-analyses on PSG and the actigraphy measures of SE, TST, SOL, WASO, and NA in rTMS studies are shown in **Supplementary Table 5**. Eight studies reported on the effectiveness of rTMS on SE and TST. The pooled results indicated that rTMS was superior to the sham group in improving SE (random-effects model: WMD −7.91; 95% CI −3.70, 12.12; $p < 0.00001$) and TST (random-effects model: WMD −37.25, 95% CI −21.51, 52.98). A total of 12 studies reported the effect of rTMS on SOL, and the WMD for rTMS was −9.78 (95% CI: −13.25, −6.31). Eleven studies examined the effect of rTMS on WASO. The findings from the random-effects model indicated that rTMS was superior to the sham counterpart in improving WASO (random-effects model: WMD: −27.86; 95% CI: −38.70, −17.02; $p < 0.00001$). However, the pooled data on SE, TST, SOL, and WASO had substantial heterogeneity, and the I^2 ranged from 80 to 96%. In addition, seven studies evaluated the effect of rTMS on NA. According to the fixed-effects model, rTMS significantly reduced the NA (WMD: −1.06; 95% CI:−1.53, 0.59; $p < 0.00001$). Mild heterogeneity between studies was found ($I^2 = 22\%$).

2) Subjective Measurements of Sleep Quality—PSQI

A total of 22 rTMS studies provided data on the PSQI total score after the completion of the intervention. The meta-analysis showed the evidence of a positive effect of rTMS on sleep quality compared to the sham group (WMD: −4.08; 95% CI: −4.86, −3.30, $p < 0.00001$). However, pronounced heterogeneity was also recorded between studies ($I^2 = 94\%$; **Figure 3**).

Four studies provided data on the PSQI total score in the short term (1–4 weeks post-intervention). rTMS, as compared to sham rTMS, resulted in a statistically significant improvement in the PSQI total score (WMD: −3.41; 95% CI: −5.70, −1.13; $p = 0.003$). Significant heterogeneity existed ($I^2 = 94\%$; **Figure 4**).

Supplementary Table 6 displays the results of the univariate analyses of moderators for the effects of rTMS on insomnia. The results of the meta-regression of rTMS studies showed that a greater number of total treatment sessions was associated with a greater improvement in SE and PSQI score (both $p < 0.05$). The results also indicated a significant inverse relationship between the length of rTMS treatment per session and the improvement in the TST and PSQI scores (both $p < 0.05$). Male gender and a greater number of pulses per session were associated with a significant improvement in the PSQI total score at post-intervention (all $p < 0.05$), whereas age and stimulation site were insignificant.

Sensitivity Analysis

Regarding the high level of heterogeneity in the studies, especially in TES studies, we restricted the meta-analysis to participants with primary insomnia and the results of the sensitivity analysis by removing five TES studies that confirmed the findings of the entire dataset of seven TES studies (see **Supplementary Figure 3**). The results of the sensitivity analysis by removing four rTMS studies also confirmed the findings of the entire dataset of 22 rTMS studies (see **Supplementary Figure 4**). Furthermore, the sensitivity analysis, by excluding one TES study and two rTMS studies with a high risk of bias, did not change the overall estimate of the effects of TES and rTMS (see **Supplementary Figures 5, 6**).

Publication Bias

Egger's test was used to assess the publication bias for the effect of rTMS on the objective and subjective measures of insomnia. Egger's test indicated that there was no evidence of significant publication bias in rTMS studies that reported WASO (intercept = −12.90; two-tailed 95% CI, −32.89, 7.09; $p = 0.18$) (**Supplementary Figure 7**), while potential publication bias was found in rTMS studies that reported SOL (intercept = −10.02; two-tailed 95% CI, −19.69, −0.34; $p = 0.04$) (**Supplementary Figure 8**) and PSQI score (intercept = −11.77; two-tailed 95% CI, −14.99, −8.56; $p = 0.000$) (**Supplementary Figure 9**).

Adverse Events

Mild and temporary adverse events were reported in tDCS and rTMS studies. The most frequently observed adverse events in tDCS studies were dizziness, discomfort, or itching at the stimulation site. The frequently reported adverse events in

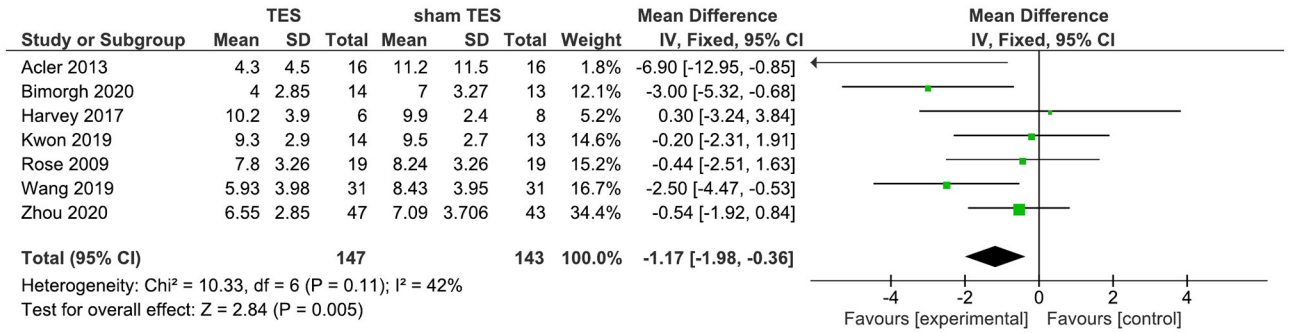

FIGURE 2 | TES vs. sham TES on PSQI at the post intervention.

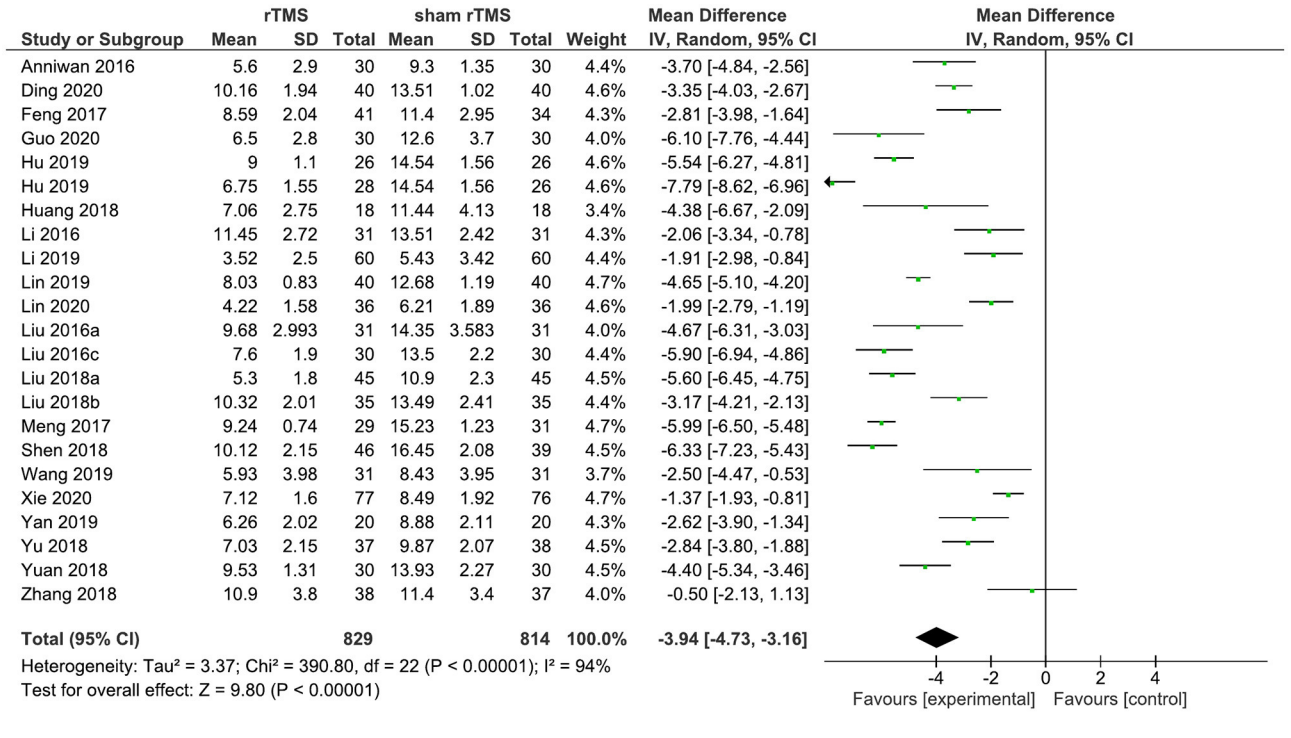

FIGURE 3 | rTMS vs. sham rTMS on PSQI at the post intervention.

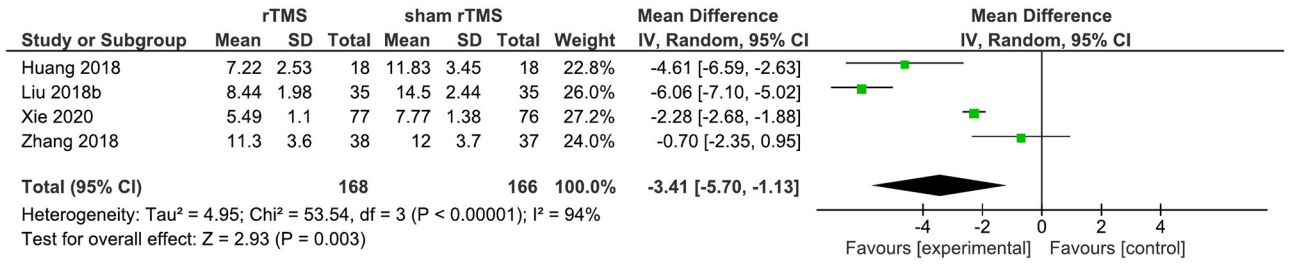

FIGURE 4 | rTMS vs. sham rTMS on PSQI at 1–4 weeks follow up.

rTMS studies were headache, dizziness, pain at the stimulation site, discomfort, itchiness, muscle spasm, and constipation (see **Supplementary Table 7**).

The meta-analyses of the safety outcomes are summarized in **Supplementary Table 8**. The occurrence of any adverse events, dizziness, or headache did not differ significantly between the NIBS group and the sham NIBS group and in their subgroup analysis. However, a marginally significant association was found between NIBS and the complaints of discomfort by the participants (RR = 5.00; 95% CI: 0.89, 27.97; $p = 0.07$, $I^2 = 0\%$). Furthermore, pain was a common side effect of rTMS and was reported in six studies. The participants in the rTMS group were significantly more likely to experience more pain at the stimulation site than those in the sham rTMS group (RR = 2.58; 95% CI: 1.14, 5.84; $p = 0.02$, $I^2 = 0\%$).

DISCUSSION

This review extends and improves previous reviews on the effectiveness of NIBS on insomnia. It examined the effects of TES and rTMS using a meta-analytical approach in treating insomnia and examining the potential moderators associated with the treatment. Overall, both techniques could be, respectively, considered as an effective and safe approach for insomnia, while the data suggested a greater effect size with rTMS than TES in improving SE, SOL, TST, and PSQI total score. In the following section, the possible explanations of differences in the treatment effectiveness between TES and rTMS, the dose-dependent effect of rTMS, and the gender difference in the effect of rTMS are discussed.

Findings from our review support the use of TES for insomnia. TES was superior compared to their sham counterparts in improving PSQI total score. However, it failed to demonstrate superiority in objective measures of sleep parameters. Compared to rTMS, TES also showed less strong evidence in improving sleep-related outcomes. The differences in effectiveness may be explained by a number of factors. Firstly, given the differences in the characteristics of the participants and the intervention, clinical heterogeneity should be considered. Secondly, the analysis was based on a relatively small number of TES studies. More TES studies should be conducted to confirm the superiority of either approach. Thirdly, the underlying mechanism of the two techniques could be another possible explanation for the difference in the therapeutic outcomes. For TES, it was assumed that only some fractions of the current could pass through the scalp. For rTMS, the magnetic field generated by stimulating the coil could pass through the scalp directly and reach the deep cortex cortical without energy loss (37, 92). The mechanism underlying the therapeutic effects of TES and rTMS need further exploration, while the findings from this review are still encouraging since TES devices have many advantages and have the potential to be easily promoted in the community—for example, most TES devices are portable and wearable, and they could even be self-administered at home by people with sleep problems. With the portable character, their effect on facilitating sleep could be enlarged.

The results of this review are in line with the prior meta-analysis that rTMS is effective in improving PSQI (43). Furthermore, the results from this review extend our knowledge of rTMS in improving objective sleep parameters, including SE, SOL, TST, WASO, and NA. Regarding the stimulation parameters, the included studies ranged from 10 to 30 sessions, with each session consisting of 1,100 to 2,000 pulses for 10 to 30 min. The finding from this review suggests a potential dose-dependent effect of rTMS in treating insomnia. A greater number of treatment sessions is associated with better SE and sleep quality as measured by PSQI, and a greater number of pulses per session is associated with an improved PSQI. These findings are consistent with many previous studies among people with other mental disorders (93–97). Meanwhile, the inverse associations between the length of treatment per session and TST and PSQI are also noteworthy. There is evidence that the rTMS technique could induce a cumulative effect on cortical excitability that outlasts the stimulation period (98). However, prolonged rTMS stimulation could have a reversed after-effect (99, 100). The abovementioned findings raise several interesting questions about designing an optimal rTMS treatment protocol for people with insomnia: What is the optimal number of pulses per session/duration of stimulation per session/total number of sessions? Does the cumulative number of pulses show the same relationship with the therapeutic outcome as the cumulative number of sessions? How long will the cumulative effect last?

Previous studies on gender differences have reported that gender, age, and menopausal status could predict rTMS response (101, 102). This review also showed that male subjects had a higher response to rTMS treatment in insomnia as measured by the PSQI. We speculate that such differences may be attributed to age and the associated level of sex hormones. As significant confounding factors for the association between gender and rTMS response, older age and the menopausal status of females could predict worse rTMS response (101, 102). In general, the average age of menopause is approximately 52.5 years (103), and the average age of the participants in our pooled analysis was 50.59 (SD = 11.05) years. It is thus plausible that a significant number of women were in the stage of perimenopause or menopause, resulting in a decreased rTMS response in females. However, due to the lack of a detailed description of the clinical characteristics of the participants, especially the age of male and female subjects, the gender ratio in the active rTMS group compared to the sham group, and menopausal status, future studies are recommended to explore the influence of confounding factors, such as age, gender, and sex hormones level, on rTMS response among people with insomnia.

Strengths and Limitations

One of the strengths of this review is that it examined two forms of NIBS technique with more RCTs and more participants. Furthermore, it described the trends in outcomes across the immediate post-intervention and short-term follow-up and considered the moderators of effects of TES and rTMS.

There are also some limitations in this review. Firstly, due to the poor reporting of random sequence generation and allocation concealment in most of the included studies, it was difficult

to evaluate the methodology quality. Secondly, substantial heterogeneity existed, which may partially be explained by the differences in the characteristics of the participants, diagnosis of insomnia, and stimulation parameters. This review also included participants with insomnia comorbid with other chronic conditions without control by the use of medication. The results should be interpreted with caution. Thirdly, due to the lack of studies evaluating the long-term effect of TES and rTMS in treating insomnia, only the short-term effect could be examined. The small number of studies may also limit the generalization of the findings. To further elucidate whether the effects could be sustained over time, future studies are suggested to adopt a longer follow-up period. The ideal follow-up period may be 3 months as insomnia is characterized by the sleep difficulty symptom that lasts for at least 3 months.

CONCLUSION

Overall, TES and rTMS are promising approaches in improving the symptoms of insomnia. rTMS was better studied and showed a larger effect size than TES in both the objective and subjective measures of sleep, with therapeutic effect maintained at 1–4 weeks of follow-up. Individual characteristics and stimulation parameters, such as gender, number of pulses per session, total number of treatment sessions, and length of treatment per session, were associated with the effect of rTMS and should be considered when developing optimal treatment protocols. This review highlighted the paucity of research on TES study. Future research with a longer follow-up period is also recommended.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

HT initiated the idea and conceptualized the framework for the article. JH and DL performed the literature search and data extraction. HM conducted the data synthesis and wrote the first draft of the manuscript. JL and HT commented on previous versions of the manuscript. All authors have read and approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.744475/full#supplementary-material

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Childhood Trauma and Mental Health Status in General Population: A Series Mediation Examination of Psychological Distress in COVID-19 Pandemic and Global Sleep Quality

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Background: Coronavirus-2019 (COVID-19) has been coexisting with humans for almost 2 years, consistently impacting people's daily life, medical environment, and mental health. This study aimed to test the series mediation model triggered by childhood trauma, in which perceived psychological impact of COVID-19 pandemic and sleep quality mediated the path sequentially and led to adverse mental health outcomes.

Methods: A cross-sectional design involving 817 participants were enrolled *via* WeChat online survey. Participants completed questionnaires, including demographic features, the Childhood Trauma Questionnaire, Impact of Event Scale-Revised (IES-R) questionnaire, Pittsburgh Sleep Quality Index (PSQI) questionnaire, and Depression, Anxiety, and Stress Scale (DASS-21). Pearson correlations and hierarchical multiple linear regression were employed to examine the association of childhood trauma and psychological stress of COVID-19, sleep quality, and mental health status. In addition, a series mediate analysis was carried out to examine sequence mediating effects of psychological impact of COVID-19 and sleep quality between childhood trauma and mental health status.

Results: The results showed that childhood trauma is positively and significantly related to psychological distress of COVID-19 pandemic, sleep quality, and mental health status ($p < 0.05$). Hierarchical multiple linear regression analysis shown that demographic features explained 4.4, 2.1, and 4.0% of the total variance in DASS-21, IES-R, and PSQI total scale scores, respectively. Adding childhood trauma significantly increased the model variance of DASS-21 ($\Delta R^2 = 0.129$, $F = 126.092$, $p = 0.000$), IES-R ($\Delta R^2 = 0.062$, $F = 54.771$, $p = 0.000$), and PSQI total scale scores ($\Delta R^2 = 0.055$, $F = 48.733$, $p = 0.000$), respectively. Moreover, the series mediation model showed that the perceived impact of the COVID-19 pandemic and sleep quality were sequential mediators between childhood trauma and mental health status (proportion explained: 49.17%, $p < 0.05$).

Conclusion: Amid the ravages of COVID-19, childhood trauma predicts poor mental health status, in part because of greater psychological impact related to COVID-19 and poorer global sleep quality. In order to improve mental health, future researchers should pay more attention to individuals with childhood trauma, for its association with greater stress related to life events and poorer sleep quality.

Keywords: coronavirus disease 2019, sleep quality, childhood trauma, depression, anxiety

INTRODUCTION

Globally, 2019 coronavirus disease (COVID-19), a highly infectious and potentially fatal disease, has been coexisting with humans for almost 2 years. Previous studies found that COVID-19 has a sudden and massive impact on freedom of movement, daily activity, and medical environment, which could significantly ruin mental health of medical staff, patients with mental disorder, and the general population (1–5). What is more, one meta-analysis found that the overall prevalence of sleep disturbances, depression, and anxiety among COVID-19 patients is 34, 45, and 47%, respectively (6). One study across geographic regions worldwide reported that events related to COVID-19 were more likely to be associated with mental health symptoms, especially symptoms of post-traumatic stress disorder (PTSD), insomnia, depression, and anxiety in the general population (7).

Childhood trauma, emotional or physical adverse experiences in one's early life, was associated with increased risk for developing almost all mental disorders, including sleep disorders, depression, anxiety, bipolar disorder, PTSD, and schizophrenia (8–10). The extant literature suggests that stress exposure during early life may lead to excessive glucocorticoid release, dysfunction of hypothalamic-pituitary-adrenal (HPA) axis, abnormal development of brain trajectories, and changes of epigenetics regulation (11–14). The trauma-psychosis cycle proposed that individual exposures to environmental stressors during early life further impaired their adaptive coping strategies and thus increased the vulnerability to future stressors (15). Stress-sensitization model proposed that dysregulation of stress response caused by exposure to childhood trauma may render an individual more susceptible to psychosis triggered by later stressors (16).

Some previous studies have reported that historical trauma (physical and emotional trauma over the life span and across generations), childhood abuse, and social support were closely related to psychological stress, sleep quality, and emotion regulation during the COVID-19 outbreak (17–19). One study found that psychological stress of COVID-19 mediated the association between childhood trauma and Pittsburgh Sleep Quality Index (PSQI) global sleep quality (18). Another study found that the relationship between childhood trauma and the severity of depressive/anxiety symptoms was partly mediated by insomnia symptoms in severe mental disorders (20). However, our understanding of how traumatic stress symptoms related to COVID-19 and global sleep quality mediate the association between early life trauma and mental health symptoms is currently limited. So, we aim to (1) examine the association between childhood trauma and psychological impact related to COVID-19, sleep quality, and the mental health condition in the general population and (2) explore whether there are mediating effects of traumatic symptoms related to COVID-19 and global sleep quality between childhood trauma and mental health status.

METHODS

Design and Participants

A cross-sectional survey-based study was conducted from August 20, 2021 to September 5, 2021. All participants in this study were recruited *via* WeChat, the most widely used social media platform in China, and all data were collected using electronic questionnaires *via* online survey tool, Wenjuanxing platform (https://www.wjx.cn/app/survey.aspx). In order to obtain more participation from different regions of China, direct online and snowball recruitment methods through "Circle of Friends" of WeChat were used. There were 948 participants who voluntarily filled in and submitted the questionnaire, among which 52.89, 9.15, 8.83, 5.68, 4.31, 2.84, 2.63, and 2.52% were from Sichuan, Chongqing, Henan, Hebei, Liaoning, Beijing, Jiangsu, and Guangdong, respectively. Our inclusion criteria were as follows: (1) aged from 16 to 60 years old and (2) were able to use smart phones and complete questionnaires. Invalid and incomplete questionnaires were excluded. The childhood trauma questionnaire has seven reverse-scored items, five of which constitute the subscale of emotional neglect (EN). Based on the comparison between the scores of reverse-scored items and the forward-scored items, we can better exclude invalid questionnaires (21). The questionnaires included general demographic characteristics (age, gender, BMI, education level, income level), childhood trauma, mental health (sleep quality, depressive symptoms, and COVID-19 related traumatic stress symptoms), and mental disorders (anxiety, depression, bipolar disorder, and schizophrenia) diagnosed by psychiatrists.

Measures

The education was divided into nine levels, including illiteracy (1), primary school (2), middle school (3), vocational high school (4), senior high school (5), junior college (6), bachelor's degree (7), master's degree (8), and doctor's degree/Ph.D. (9). The income levels were collected as self-reported incomes compared with those of local people. It was divided into five categories: 1 = Low income level; 2 = Low-Middle income level; 3 = Middle income level; 4 = Middle-High income level; and 5 = High income level. Education and income level were covariates

in the subsequent hierarchical linear regression analysis and mediation analysis.

Childhood Trauma Questionnaires

Childhood trauma questionnaires-short form (CTQ-SF) was adopted to assess participants' experience from emotional abuse (EA), physical abuse (PA), sexual abuse (SA), EN, and physical neglect (PN) before 16 years old (21). A five-point Likert scale (1 = not at all, 5 = very often) was used to indicate the trauma severity about certain events or situations occurring during the childhood. Childhood trauma questionnaires-short form consisted of 25 clinical items and 3 validity items. The 25 clinical items incorporated five dimensions: EA, PA, SA, EN, and PN. Sum score of five subscales were CTQ total score ranging from 25 to 125, which indicated the severity of trauma exposure during childhood. Chinese version of CTQ-SF has good reliability and validity among Chinese undergraduates and depressive samples (22).

The Pittsburgh Sleep Quality Index Questionnaire

Pittsburgh Sleep Quality Index questionnaire, a self-rated questionnaire, was used to assess sleep quality and disturbances over 1 month (23). This scale consisted of 19 individual items which generate seven component scores: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sedative-hypnotic drugs, and daytime dysfunction. The sum of the scores for these seven components ranges from 0 to 21, with a score $\leq$5, 6–10, 11–15, and 16–21 indicating very good, fairly good, fairly poor, and very poor sleep quality, respectively.

Impact of Event Scale-Revised

Impact of Event Scale-Revised (IES-R), a self-administered questionnaire, was used to assess psychological impact of the COVID-19 epidemic on all participants. The IES-R included 22 items and consisted of three components: avoidance, intrusion, and hyperarousal. The total IES-R score was the sum score of the three components, with scores 0–23, 24–32, 33–36, and >37 indicating normal, mild, moderate, and severe psychological impact, respectively (24). The Chinese version of IES-R has been well-validated in the Chinese population, with high Cronbach's alpha coefficients for subscales [0.89 (intrusion), 0.85 (avoidance), and 0.83 (hyperarousal)] (25).

Depression, Anxiety, and Stress Scale

The Depression, Anxiety, and Stress Scale (DASS-21) was used to evaluate individual's mental health status in the last week. Depression, Anxiety, and Stress Scale included 21 items and could be divided into subscales of depressive, anxiety, and stress symptoms. The DASS-21 subscales were scored as follows: normal (0–9), mild (10–13), moderate (14–20), severe (21–27), and extremely severe (28+) for depression; normal (0–7), mild (8,9), moderate (10–14), severe (15–19), and extremely severe (20+) for anxiety; normal (0–14), mild (15–18), moderate (19–25), severe (26–33), and extremely severe (34+) for stress (26). The Cronbach's alpha for Chinese version of DASS-21 was 0.95 for total scale, demonstrating a good internal consistency in the assessment of mental health in Chinese population (27).

Statistical Analysis

Pearson correlation analysis was conducted to calculate correlation coefficients between the total scale and five subscales of CTQ, perceived psychological impact of COVID-19 pandemic, and adverse mental health symptoms. Then, we applied a hierarchical linear regression to estimate the role of CTQ toward DASS-21, IES-R, and PSQI global sleep quality by sequentially adding predictors into two blocks within each model. The variables were added into models *via* the following steps: Step 1: input the demographic characteristics of age, sex, BMI, and education level; Step 2: add CTQ. Finally, a series mediation analysis was carried out to examine the mediated effects of perceived impact of the COVID-19 pandemic and PSQI global sleep quality in the relationship between childhood trauma and mental health status. The series mediation analysis was conducted by Process 3.5 for SPSS version 24.0 (model 6). The significance levels of direct, indirect, and mediated effects among the four factors [i.e., childhood trauma (X), the psychological impact of events (M1), PSQI global sleep quality (M2), and mental health parameters (Y)] were determined as two-tailed p-values < 0.05, such figure being considered statistically significant in all other tests of this study. All continuous variables were standardized and then included in regression and mediation analyses performed on SPSS 24.0.

RESULTS

Demographic Information, Childhood Trauma, COVID-19 Related Psychological Impact, Sleep Quality, and Mental Health Status

After excluding invalid and incomplete questionnaires, 817 (86.18%) of 948 participants were enrolled in this study. The mean age (± SD) was 27.77 (± 8.68) years old. The average education level and income were junior college and Low-medium income level, respectively. The mean scores of CTQ total scale and subscales of EA, PA, SA, EN, and PN were 37.03, 6.92, 6.12, 5.55, 9.77, and 8.66, respectively. The mean scores of DASS-21 total scale and subscales of anxiety, depression, and stress were 14.56, 4.15, 4.96, and 5.38, respectively. The mean scores of IES-R total scale and subscales of avoidance, intrusion, and hyperarousal were 9.04, 3.23, 3.40, and 2.40, respectively. The mean score of PSQI total score was 4.27. Of all subjects, there were 19.51, 20.73, and 9.76% individuals reporting mild to extremely severe anxiety, depressive, and stress symptoms, respectively. There were 25 (3.06%), 38 (4.45%), 10 (1.22%), and 6 (0.73%) subjects who were diagnosed by psychiatrists as depression, anxiety, bipolar disorder, and schizophrenia, respectively (**Table 1**).

Correlations Among Childhood Trauma, COVID-19 Related Psychological Impact, Sleep Quality, and Mental Health Status

Correlations of total scale scores of CTQ, PSQI sleep quality, DASS-21, and IES-R and subscales of those are displayed in **Table 2**. After Bonferroni correction, all the variables were

TABLE 1 | Descriptive statistics, $N = 817$.

	Mean	SD	Min	Max
Age	27.77	8.68	16	59
Gender (M/F)	431/386			
BMI	22.22	3.46	14.43	37.30
EDU level	6.27	1.52	1	9
Income level	2.44	0.85	1	5
Childhood Trauma Questionnaire (CTQ)				
Mean CTQ score	37.03	11.15	25	97
EA	6.92	2.89	5	25
PA	6.12	2.55	5	25
SA	5.55	1.82	5	25
EN	9.77	4.67	5	24
PN	8.66	3.42	5	21
Depression, Anxiety, Stress and Stress Scale-21 (DASS-21)				
Mean DASS-21 total score	14.56	20.78	0	126
DASS-21 (anxiety)	4.15	6.47	0	42
No (0–7)	657 (80.42)			
Mild (8,9)	35 (4.28)			
Moderate (10–14)	76 (9.30)			
Severe (15–19)	18 (2.20)			
Extremely severe (20+)	31 (3.79)			
Mean DASS-21 depression score	4.96	7.61	0	42
No (0–9)	647 (79.19)			
Mild (10–13)	66 (8.08)			
Moderate (14–20)	67 (8.20)			
Severe (21–27)	14 (1.71)			
Extremely severe (28+)	23 (2.82)			
Mean DASS-21 stress score	5.38	7.26	0	42
No (0–14)	737 (90.21)			
Mild (15–18)	27 (3.30)			
Moderate (19–25)	30 (3.67)			
Severe (26–33)	16 (1.96)			
Extremely severe (34+)	7 (0.86)			
Impact of event scale-revised (IES-R)				
Mean IES-R score	9.04	10.49	0	88
Mean IES-R avoidance score	3.23	4.19	0	32
Mean IES-R intrusion score	3.40	4.13	0	32
Mean IES-R hyperarousal score	2.40	3.39	0	24
PSQI global sleep quality score	4.27	2.95	0	17
Self-reported diagnosed mental disorders by psychiatrists				
Depression, *n* (%)	25 (3.06)			
Anxiety, *n* (%)	38 (4.65)			
Bipolar disorder, *n* (%)	10 (1.22)			
Schizophrenia, *n* (%)	6 (0.73)			

BMI, body mass index; CTQ, childhood trauma questionnaires; DASS-21, depression, anxiety, stress and stress scale-21; EA, emotional abuse; EDU, education; EN, emotional neglect; IES-R, impact of event scale-revised; PA, physical abuse; PN, physical neglect; PSQI, Pittsburgh sleep quality index; SA, sexual abuse.

significantly correlated ($p < 0.05$) except for SA with DASS-21 total scale, stress and depression subscales, IES-R total scale, avoidance, intrusion, and hyperarousal subscales, and PSQI total scale ($p > 0.05$); except for EN with IES-R avoidance subscale ($p > 0.05$); and except for PN with IES-R avoidance subscale ($p > 0.05$). The total score of childhood trauma was positively and significantly associated with the perceived psychological impact of the pandemic, sleep quality, as well as DASS-21 anxiety, depression, and stress scores ($p < 0.001$). The PSQI total scale score was positively and significantly associated with the psychological impact of the pandemic, DASS-21 total score, and subscales of anxiety, depression, and stress scores ($p < 0.001$). Moreover, the IES-R total scale score was positively and significantly associated with DASS-21 total scores and all subscale scores ($p < 0.001$).

The Hierarchical Linear Regression Analysis of Psychological Impact Related to COVID-19, Mental Status, and Sleep Quality

Table 3 shows the results of hierarchical linear regression analysis between childhood trauma and self-reported health status in all respondents, with adjustment to age, gender, BMI, and education level. In the hierarchical linear regression analysis, socioeconomic status, such as income level and educational level of parent(s), was incorporated into the model, but such model was not significant, thus excluding the socioeconomic factors from covariates in step 2. The final regression model (model 2) explained 17.3, 8.3, and 9.5% of the total variance in DASS-21, IES-R, and PSQI total scale scores, respectively.

Total score of childhood trauma was a significant predictor for COVID-19 related psychological impact, mental status, and PSQI global sleep quality ($p < 0.001$).

Series Mediation Effects of COVID-19 Related Psychological Impact and Sleep Quality Between Childhood Trauma and Mental Health Status

Figure 1 shows the series mediating effect of psychological impact related to COVID-19 pandemic and PSQI global sleep quality in the association between childhood trauma and self-reported mental health status. All the paths in this model were significant ($p < 0.001$). First, the direct effect of childhood trauma on mental health status was explored, and the results showed that the model fitted well with $R^2 = 0.173$, $F = 33.840$, and $p < 0.001$. Specifically, childhood trauma can directly and positively predict mental health status ($\beta = 0.362$, $p < 0.001$). Second, considering childhood trauma as a independent variable, mental health status as the dependent variable, and psychological impact related to COVID-19 pandemic and PSQI global sleep quality as mediating variables, model (childhood trauma → psychological impact → sleep quality → mental health, see **Figure 1**) was thereby established. The mediation model exhibited acceptable goodness of fit ($R^2 = 0.504$, $F = 116.845$, $p < 0.001$). This study further conducted the bootstrapping method for 5,000 times to test the significance of the mediating effect. The mediating effect was significant if the 95% confidence interval did not include 0. The mediating effects of psychological impact and sleep quality on the

TABLE 2 | Bivariate Pearson correlations with Bonferroni correction between main variables of interest.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
CTQ	1														
EA	0.772[c]	1													
PA	0.671[c]	0.659[c]	1												
SA	0.551[c]	0.483[c]	0.490[c]	1											
EN	0.778[c]	0.398[c]	0.236[c]	0.173[c]	1										
PN	0.753[c]	0.379[c]	0.300[c]	0.256[c]	0.568[c]	1									
DASS-21-T	0.353[c]	0.417[c]	0.228[c]	0.121	0.286[c]	0.174[c]	1								
DASS-21-A	0.347[c]	0.418[c]	0.245[c]	0.137[b]	0.264[c]	0.162[c]	0.959[c]	1							
DASS-21-D	0.359[c]	0.414[c]	0.213[c]	0.113	0.302[c]	0.187[c]	0.959[c]	0.879[c]	1						
DASS-21-S	0.313[c]	0.374[c]	0.202[c]	0.100	0.256[c]	0.152[b]	0.963[c]	0.894[c]	0.876[c]	1					
IES-R-T	0.240[c]	0.272[c]	0.166[c]	0.104	0.160[c]	0.157[c]	0.601[c]	0.608[c]	0.521[c]	0.607[c]	1				
IES-R-A	0.160[c]	0.210[c]	0.125[a]	0.077	0.078	0.105	0.477[c]	0.480[c]	0.417[c]	0.480[c]	0.890[c]	1			
IES-R-H	0.301[c]	0.327[c]	0.192[c]	0.111	0.235[c]	0.180[c]	0.673[c]	0.677[c]	0.593[c]	0.673[c]	0.864[c]	0.653[c]	1		
IES-R-I	0.201[c]	0.209[c]	0.138[c]	0.095	0.132[a]	0.144[b]	0.490[c]	0.501[c]	0.415[c]	0.501[c]	0.917[c]	0.734[c]	0.711[c]	1	
PSQI	0.215[c]	0.250[c]	0.095	0.073	0.191[c]	0.119	0.549[c]	0.521[c]	0.523[c]	0.537[c]	0.393[c]	0.269[c]	0.487[c]	0.325[c]	1

CTQ, childhood trauma questionnaire; DASS-21, depression, anxiety, stress and stress scale-21; DASS-21-A, DASS-21 anxiety score; DASS-21-D, DASS-21 depression score; DASS-21-T-S, DASS-21 stress score; DASS-21-T, DASS-21 total score; EA, emotional abuse; EN, emotional neglect; IES-R, impact of event scale-revised; IES-R-A, IES-R avoidance score; IES-R-H, IES-R hyperarousal score; IES-R-I, IES-R intrusion score; IES-R-T, IES-R total score; PA, physical abuse; PN, physical neglect; PSQI, Pittsburgh sleep quality index; SA, sexual abuse.

[a]$p < 0.05$; [b]$p < 0.01$; [c]$p < 0.001$.

TABLE 3 | Hierarchical regressions between CTQ total scale scores and DASS-21, IES-R, and PSQI global sleep quality scores.

	DASS-21			IES-R			PSQI global sleep quality		
	β	*SE*	*P*	*β*	*SE*	*P*	*β*	*SE*	*P*
Step 1	**$R^2 = 0.044$, $F = 8.030$, $p = 0.000$**			**$R^2 = 0.021$, $F = 4.039$, $p = 0.003$**			**$R^2 = 0.040$, $F = 8.743$, $p = 0.000$**		
Age	−0.085	0.035	0.014	−0.029	0.041	0.471	0.009	0.037	0.810
Sex	0.220	0.087	0.000	0.151	0.082	0.000	0.106	0.079	0.007
BMI	0.075	0.043	0.086	0.113	0.041	0.006	−0.014	0.039	0.727
Education	0.026	0.024	0.480	−0.009	0.024	0.812	0.150	0.023	0.000
Step 2	**$R^2 = 0.173$, $\Delta R^2 = 0.129$, $F = 126.092$, $p = 0.000$**			**$R^2 = 0.083$, $\Delta R^2 = 0.062$, $F = 54.771$, $p = 0.000$**			**$R^2 = 0.095$, $\Delta R^2 = 0.055$, $F = 48.733$, $p = 0.000$**		
Age	−0.083	0.032	0.009	−0.028	0.039	0.475	0.010	0.035	0.776
Sex	0.189	0.080	0.000	0.129	0.078	0.001	0.086	0.076	0.024
BMI	0.076	0.042	0.073	0.114	0.040	0.004	−0.013	0.039	0.738
Education	0.064	0.022	0.058	0.018	0.023	0.603	0.174	0.022	0.000
CTQ	0.362	0.046	0.000	0.251	0.045	0.000	0.236	0.038	0.000

CTQ, childhood trauma questionnaire; DASS-21, depression, anxiety, stress and stress scale-21; IES-R, impact of event scale-revised; PSQI, Pittsburgh sleep quality index; SE, standard error.

association between childhood trauma and mental health status were significant (95% confidence intervals were 0.095 [0.059, 0.136] and 0.051 [0.028, 0.078], respectively), and the series mediating effect was also significant 0.031 [0.020, 0.045]. The total mediation effect and the direct effect between childhood trauma and mental health were 0.178 [0.128, 0.228] and 0.184 [0.133, 0.235], respectively (**Tables 4**, **5**). Overall, the association between childhood trauma and mental health status was partly mediated by psychological impact and sleep quality (proportion explained 49.17%).

DISCUSSION

To our knowledge, this is the first study using series mediation model to examine whether the association between childhood trauma and mental health status could be partly explained by COVID-19 pandemic related psychological impact and sleep quality. There were two findings worth highlighting. First, childhood trauma was a risk factor for COVID-19 related psychological distress (avoidance, intrusion, and hyperarousal), sleep quality, and mental health status

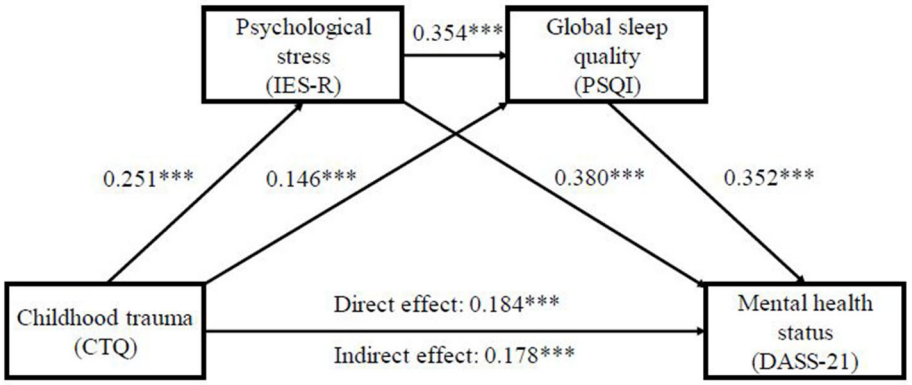

FIGURE 1 | Series mediation effects of psychological stress and sleep quality between childhood trauma and mental health status. CTQ, childhood trauma questionnaire; DASS-21, depression, anxiety, stress and stress scale-21; IES-R, impact of event scale-revised; PSQI, Pittsburgh sleep quality index. ***$p < 0.001$.

TABLE 4 | Results of mediation analysis.

	Fit index							%95 CI	
	R	***R^2***	***F***	***B***	***SE***	***T***	***p***	**LLCI**	**ULCI**
Dependent variable: IES-R									
CTQ	0.289	0.083	146.88	0.251	0.034	7.400	0.000	0.185	0.318
Age				−0.028	0.036	−0.775	0.439	−0.099	0.043
Sex				0.260	0.076	3.44	0.000	0.111	0.408
BMI				0.114	0.038	3.02	0.003	0.040	0.188
Education				0.012	0.023	0.521	0.602	−0.033	0.056
Constant				−0.456	0.171	2.665	0.008	−0.792	−0.120
Dependent variable: PSQI global sleep quality									
CTQ	0.458	0.210	35.697	0.162	0.033	4.494	0.000	0.082	0.210
IES-R				0.354	0.033	10.846	0.000	0.290	0.418
Age				0.020	0.034	0.593	0.553	−0.046	0.086
Sex				0.080	0.071	1.128	0.260	−0.059	0.218
BMI				−0.053	0.035	1.514	0.131	−0.122	0.016
Education				0.110	0.021	5.253	0.000	0.069	0.152
Constant				−0.811	0.159	5.090	0.000	−1.123	−0.498
Dependent variable: DASS-21									
CTQ	0.710	0.504	116.845	0.184	0.026	7.029	0.000	0.133	0.235
IES-R				0.380	0.028	13.692	0.000	0.325	0.434
PSQI				0.352	0.028	12.576	0.000	0.297	0.407
Age				−0.078	0.027	2.921	0.004	−0.131	−0.026
Sex				0.221	0.056	3.945	0.000	0.111	0.331
BMI				0.037	0.028	1.328	0.185	−0.018	0.092
Education				−0.003	0.017	−0.154	0.878	−0.036	0.031
Constant				−0.307	0.129	2.386	0.017	−0.560	−0.054

B = unstandardized coefficient (the continuous variables included in the mediation analysis were standardized). BMI, body mass index; CTQ, childhood trauma questionnaire; DASS-21, depression, anxiety, stress and stress scale-21; IES-R, impact of event scale-revised; PSQI, Pittsburgh sleep quality index; SE, standard error.

(depressive, anxiety, and stress symptoms). Moreover, after the effect of psychological impact related to COVID-19 pandemic was incorporated into the model, the impact of childhood trauma on mental health status was partly mediated by psychological distress for COVID-19 and global sleep quality.

The links between childhood trauma and poor sleep, depression, and anxiety were well-documented. One study found that severer childhood trauma was associated with poorer sleep health, including sleep quality, sleep efficiency, sleep duration, and daytime sleepiness (28). On the other hand, some cross-sectional studies found that childhood trauma was not only

TABLE 5 | Results of the series mediating effects after bootstrapping test.

	Indirect Effect			
	β	Se	LLCI	ULCI
CTQ → IES-R → DASS-21	0.095	0.020	0.059	0.136
CTQ → PSQI → DASS-21	0.051	0.013	0.028	0.078
CTQ → IES-R → PSQI → DASS-21	0.031	0.006	0.020	0.045
Total mediation effects	0.178	0.026	0.128	0.228

CTQ, childhood trauma questionnaire; DASS-21, depression, anxiety, stress and stress scale-21; IES-R, impact of event scale-revised; PSQI, Pittsburgh sleep quality index; SE: standard error.

associated with depression and anxiety symptoms in the clinical samples and general population but also related to the onset and recurrence of depressive and anxiety disorders (29–31). Previous studies reported that dysfunction of HPA axis, cognitive emotion dysregulation, epigenetic regulation of the stress response, and abnormal change of brain structural and functional plasticity may create a barren climate for the development of mental health (16, 29, 32, 33).

This study highlighted that childhood trauma was associated with COVID-19 related psychological distress. A few studies strongly supported that severer childhood trauma prior to the COVID-19 pandemic predicted greater risks of occurring psychological symptoms (17–19, 34, 35). One prospective study identified that childhood adverse experiences increased the risk of both psychological distress (ORs = 2.00–2.66) and probable acute stress reaction (ORs = 2.23–3.10) (5). Research evidence suggested that childhood trauma was associated with increased vulnerability to the stressful effect of the COVID-19 outbreak. Several potential mechanisms could interpret the association between the two. First, stress-vulnerability model assumes that childhood trauma, as chronic stress in the early life, could lower one's threshold of tolerance to acute stress, such as the outbreak of COVID-19 (16). Second, systemic inflammation may be an important mediator between childhood maltreatment and mental health in adulthood. Adults with exposure to childhood maltreatment exhibited a stronger inflammatory response under a standardized psychosocial stressor (36). Third, childhood trauma may change neuroendocrine responses to stress and increase vulnerability to acute events. One study found that limbic-medial temporal lobe regions, including amygdala and hippocampus, were sensitized in individual's exposure to life trauma. These regions could accommodate stress regulation/regulate stress and HPA axis function, and increase risk for negative stress-related mental health (37).

The results of the mediating effect test reveal that childhood trauma can affect adults' mental health through multiple mediating effects exerted by psychological impact of COVID-19 pandemic and sleep quality. Psychological impact of COVID-19 pandemic played a mediating role in the association between childhood trauma and mental health. To put it in another way, childhood trauma can predict mental health not only in a direct way but also in an indirect way through COVID-19 related psychological impact and sleep quality. It was suggested by a previous study that insomnia symptoms partly mediate the relationship between childhood trauma and the severity of depressive and anxiety symptoms in patients with psychosis (20). This is also similar to the conclusion drew by John-Henderson that psychological stress mediated the association between childhood trauma and sleep quality (18). Childhood trauma is mainly related to the adaptive dimension of stress. This shows that people who experience severer childhood trauma are more likely to suffer a high degree of psychological impact. This result indicates that early intervention in children's exposure to trauma may reduce the occurrence of event-related trauma symptoms (38). Therefore, childhood trauma can lead to greater COVID-19 related psychological impact and, thus, poorer mental health status. The results of this study confirmed the series mediating roles of COVID-19 related psychological impact and PSQI global sleep quality in the association between childhood trauma and mental health.

There are several limitations in this study that should be noted. First, this study was based on self-reported questionnaires, which could lead to self-awareness and reporting bias. Second, due to the cross-sectional design in this study, the causal relationships between childhood trauma and mental health may be weakened. Third, the COVID-19 related changes of people's life (e.g., family conflicts and unemployment) were not included in our study. Therefore, the impact of these confounding factors on sleep quality and mental health could not be controlled. Fourth, the associations between childhood trauma and mental health are also affected by other mental disorders, which are not controlled in our analysis. Longitudinal design needs to specify the direction of the relationships between childhood trauma and mental health or experimentally observe childhood trauma to explore the resultant changes in mental health in the following research.

CONCLUSION

This study found that childhood trauma was positively associated with COVID-19 related psychological impact (avoidance, intrusion, and hyperarousal), anxiety, depression, and stress symptoms. In addition, the results of the series mediation analysis indicated an underlying mechanism of the association between childhood trauma and mental health: severer childhood trauma was able to predict poorer mental health outcomes *via* COVID-19 pandemic related psychological impact and sleep quality. Early interventions should be implemented to raise public awareness of adverse consequences of childhood trauma, whether emotional or physical, and poor mental health *via* family and social strategies. Extra attention should be paid to individuals who are experiencing or have experienced trauma or bully in the past. In addition, psychiatrists should also take patients' history of childhood trauma into consideration when making treatment decisions/in clinical decision-making.

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 Sichuan University. Written informed consent for participation was not provided by the participants' legal guardians/next of kin because: Written informed consent is difficult to obtain because we collected data via Wechat online survey. Because the questionnaire was anonymous, we assumed that participants consented to participate in our study by returning the questionnaire.

AUTHOR CONTRIBUTIONS

MX, YT, and LZ contributed to the writing of this article and the statistical analysis. QW and TL led the whole study, including carrying out this study, and putting forward the study. MD, YW, YH, YL, and LX contributed to the data collection and statistical analysis. All authors contributed to editing the manuscript and have approved the final manuscript.

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Sleep Disturbances Are Associated With Depressive Symptoms in a Chinese Population: The Rugao Longevity and Aging Cohort

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Objective: To investigate the cross-sectional and longitudinal relationships between sleep disturbances and depressive symptoms in older Chinese adults.

Methods: This study included baseline and 3.5-year follow-up data of 1,631 Chinese men and women aged 70 years or older from the aging arm of the Rugao Longevity and Aging Study. Depressive symptoms were assessed by the 15-item Geriatric Depression Scale (GDS). Sleep disturbances were assessed by using the Pittsburgh Sleep Quality Index (PSQI). Logistic regression models were used to estimate the odds ratios (ORs) of the associations.

Results: In the cross-sectional analysis, individuals with greater total PSQI scores exhibited significantly higher risk of "depressive symptoms" (OR: 1.31, 95% CI: 1.21–1.41) and "some depressive symptoms" (OR: 1.22, 95% CI: 1.17–1.28). Specifically, higher scores on the sleep efficiency PSQI subscale were associated with greater odds for "depressive symptoms" (OR: 1.54, 95% CI: 1.30–1.84) and "some depressive symptoms" (OR: 1.42, 95% CI: 1.29–1.57). Our longitudinal analyses indicated an association between greater PSQI total scores at baseline and greater odds of having "some depressive symptoms" at follow-up (OR: 1.07, 95% CI: 1.00–1.14). Additionally, higher scores on the sleep efficiency PSQI subscale had an association with higher odds for "some depressive symptoms" (OR: 1.21, 95% CI: 1.04–1.41).

Conclusions: Poor self-reported global sleep quality and sleep efficiency PSQI subscale scores were associated with levels of depressive symptoms in an older Chinese population, indicating that global sleep quality and sleep efficiency may be risk factors for depression and can possibly predict the levels of depressive symptoms.

Keywords: sleep disturbance, depressive symptoms, Chinese older population, risk factor, sleep efficiency

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INTRODUCTION

Depression among the elderly population, with an estimated prevalence of 8–16%, is a major public health problem that has attracted worldwide attention (1, 2). Depression presents a heavy disease burden of long-term care on families and society as a whole (3, 4). Therefore, the prevention and treatment of depression have become urgent tasks in the field of public health. Depression has been

recognized as being associated with genetic (5), physical, behavioral, and socioeconomic factors (6). A potential effort to reduce depression levels has been targeting sleep disturbances.

Two previous longitudinal studies revealed that poor self-reported sleep quality was associated with an increased risk of depression. One analysis was conducted in the context of the Study of Osteoporotic Fractures (SOF), and the other was conducted within the prospective Osteoporotic Fractures in Men (MrOS) study. Both studies utilized the Geriatric Depression Scale (GDS) to measure depressive symptoms. Maglione et al. reported that baseline sleep disturbances were associated with a greater chance of worse depressive symptoms 5 years later (7). Paudel et al. revealed that among non-depressed older men, poor self-reported sleep quality was also associated with increased odds of depression 3.4 years later (8).

Before sleep disturbance can be established as a risk factor for depression, more evidence needs to be accumulated in different ethnic and age groups within older populations. In this study, we aimed to explore the relationship between sleep disturbances and depression symptoms at baseline in 1,631 Chinese adult participants aged 70 years or older. We also reassessed depressive symptoms after a 3.5-year follow up, further probing into the question of whether sleep disturbances or its subcomponents at baseline could potentially predict future depressive symptoms.

METHODS

Participants

The data came from the aging arm of the Rugao Longevity and Aging Study (RuLAS), a population-based, observational, two-arm cohort study conducted in Rugao, Jiangsu Province, China. Approximately 1960 older adults were recruited based on 5-year age and sex strata, equally among 31 villages, in 2014. Our first follow-up was conducted after 1.5 years in the summer of 2016, and the second follow-up was conducted in the winter of 2017 (3 years after baseline). The third follow-up was conducted in the winter of 2019 (5 years after baseline) (9, 10). The current study focused on participants in the second and fourth waves (∼1.5 and 5 years after the original assessment) of the RuLAS. In this study, the second wave was recognized as the baseline because data from the Pittsburgh Sleep Quality Index (PSQI) questionnaire were collected starting with the second wave. In the cross-sectional analysis, a total of 1,631 participants were included after excluding participants who appeared to suffer from major diseases (stroke, myocardial infarction, and cancer). Out of 1,631 individuals, 1,279 participants returned and completed both GDS and PSQI questionnaires at baseline. After excluding 459 participants who reported "some depressive symptoms" (GDS 3–5) or "depressive symptoms" (GDS ≥6), the remaining 820 participants had reported few depressive symptoms (GDS 0–2). Of these, including older adults with few depressive symptoms, 679 completed GDS questionnaires at the 3-year follow-up. Our longitudinal analyses were conducted on this subset of 679 participants. A schematic of the inclusion and exclusion of older Chinese adults in the longitudinal analysis is shown in **Figure 1**. The Human Ethics Committee of the School of Life Sciences of Fudan University, Shanghai, China, approved this study (No: BE1815). Written informed consent was obtained from all participants prior to the study.

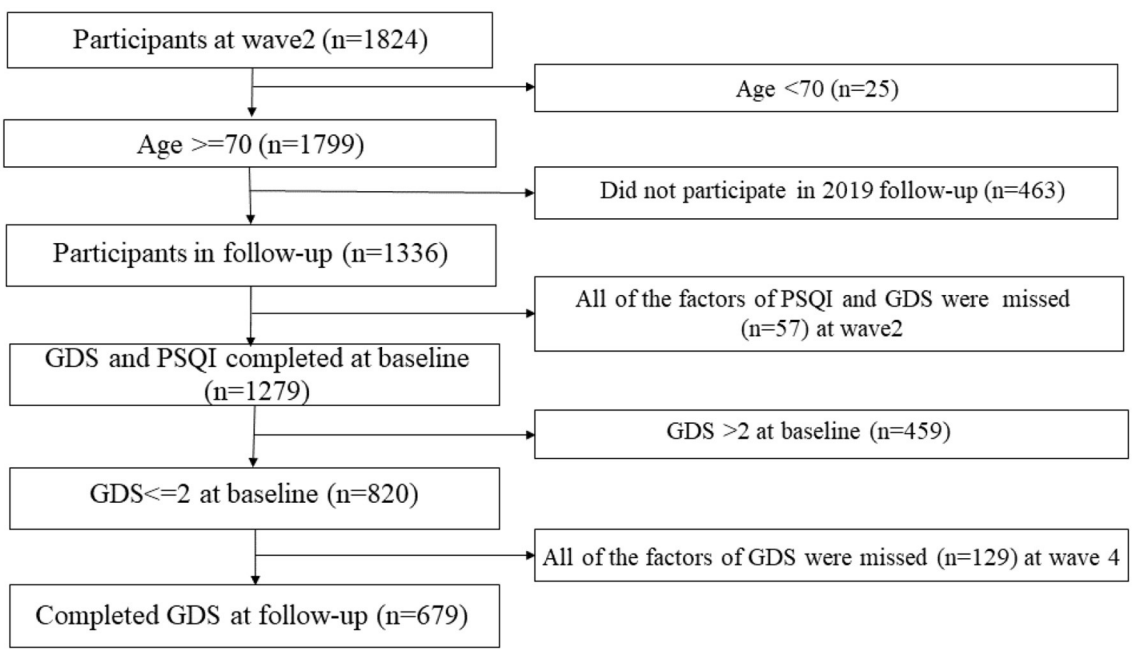

FIGURE 1 | Recruitment and inclusion of participants. Reasons for not including participants are given on the right. GDS, Geriatric Depression Scale; *n*, number; RuLAS, Rugao Longevity and Aging Study.

TABLE 1 | Characteristics of participants according to the level of depressive symptoms at baseline.

Characteristics	All (n = 1,631)	GDS ≥ 6 (n = 111)	3 ≤ GDS ≤ 5 (n = 489)	0 ≤ GDS ≤ 2 (n = 1,031)	*P*-value
Age group, *n* (%)					0.372
70–74	481 (29.49)	41 (36.94)	128 (26.18)	312 (30.03)	
75–79	687 (42.12)	41 (36.94)	200 (40.90)	446 (42.93)	
80–84	368 (22.56)	18 (16.22)	128 (26.18)	222 (21.37)	
85+	95 (5.82)	11 (9.91)	33(6.75)	51(4.91)	
Sex					0.093
Male	787 (48.25)	58 (52.25)	217 (44.38)	512 (49.28)	
Female	839 (51.44)	53 (47.75)	272 (55.62)	514 (49.47)	
Education					0.597
Illiterate	767 (47.03)	56 (50.45)	258 (52.76)	515 (49.57)	
Literate	829 (50.83)	55 (49.55)	221 (45.19)	491 (47.26)	
Marital status					0.396
Current marital	1,041 (63.83)	70 (63.06)	305 (62.37)	666 (64.10)	
Other	547 (33.54)	41 (36.94)	175 (35.79)	331 (31.86)	
Smoking					**<0.001**
None	1,425 (87.37)	76 (68.47)	422 (86.30)	902 (86.81)	
Smoker	132 (8.09)	32 (28.83)	46 (9.41)	79 (7.60)	
Drinking					**<0.001**
None	1,412 (86.57)	62 (55.86)	425 (86.91)	888 (85.47)	
Drinker	134 (8.22)	45 (40.54)	41 (8.38)	85 (8.18)	
BMI category					0.067
<24	907 (55.61)	62 (55.86)	259 (52.97)	586 (56.40)	
24–28	533 (32.68)	43 (38.74)	173 (35.38)	317 (30.51)	
≥28	175 (10.73)	5 (4.50)	53 (10.84)	117 (11.26)	
PSQI score					
≤5	952 (58.37)	43 (38.74)	194 (39.67)	715 (69.35)	
>5	679 (41.63)	68 (61.26)	295 (60.33)	316 (30.65)	

Others in marital status means windowed, divorced, and unmarried. GDS, Geriatric Depression Scale; PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation; BMI, body mass index; Bold means statistically significant.

Depressive Symptoms

Depressive symptoms were assessed using the Chinese version of the 15-item GDS (11). This form of the GDS consisted of 15 self-reported yes-or-no questions that were derived from the GDS-30. The GDS-15 scale has previously been validated for use in community-living older Asian adults (12). A previous review reported that the best performance for the GDS was with a cutoff of 5/6 for the GDS-15 (13). A standard cutoff of ≥ 6 on the GDS revealed 91% sensitivity and 65% specificity when evaluated against diagnostic criteria (14). In this study, we implemented the validated cutoff of 6 to capture no/some and high depressive symptoms. Depressive symptoms were categorized into three groups, based on clinical relevance [0–2 (normal), 3–5 (some depressive symptoms) and ≥ 6 (depressed)] (7). For simplicity and consistency, patients with particular levels of depressive symptoms at follow-up were divided into three groups [0–2 (normal), 3–5 (some depressive symptoms) and ≥ 6 (depressed)]. The changes in GDS score between baseline and follow-up were calculated for each study participant. The participants with an increased GDS score ≥ 2 points were considered to have "worsening depressive symptoms." This threshold was chosen based upon the distribution of changes in GDS scores in our samples because the GDS scores used in this study were able to distinguish older Chinese adults with the greatest increase in GDS score (highest quartile) between baseline and 3-year follow-up (7).

Sleep Measures

Global sleep quality was assessed using the PSQI (15). The PSQI is a validated 19-item self-reported measure of sleep disturbances. It has been validated and demonstrated to have good psychometric properties in an ethnically similar population (16). The Chinese version of the PSQI has good overall reliability (r = 0.82–0.83) and test-retest reliability (r = 0.77–0.85) in community of adults with primary insomnia (16, 17). The PSQI had internal consistency and a reliability coefficient (Cronbach's alpha) of 0.703 for its seven components. The PSQI was divided into seven subcomponent scores: sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, sleep medication use, and daytime dysfunction. Each subcomponent score ranges from 0 to 3, and global PSQI scores range from 0 to 21, with higher scores reflecting more severe symptoms. Total PSQI scores are

TABLE 2 | Associations between sleep disturbance and depressive symptom levels at baseline.

Sleep variables	Some depressive symptoms OR (95% CI)	*P*-value	Depressive symptoms OR (95% CI)	*P*-value
PSQI Total Score				
Base model	1.22 (1.17–1.27)	**<0.001**	1.30 (1.21–1.40)	**<0.001**
Multivariable adjusted	1.22 (1.17–1.28)	**<0.001**	1.31 (1.21–1.41)	**<0.001**
PSQI >5 PSQI ≤5				
Base model	3.44 (2.75–4.31)	**<0.001**	3.58 (2.40–5.40)	**<0.001**
Multivariable adjusted	3.56 (2.77–4.58)	**<0.001**	3.81 (2.45–6.02)	**<0.001**
Sleep quality factor				
Base model	1.37 (1.15–1.64)	**<0.001**	1.69 (1.23–2.33)	**0.001**
Multivariable adjusted	1.37 (1.10–1.70)	**0.004**	1.61 (1.10–2.34)	**0.013**
Sleep latency factor				
Base model	1.40 (1.24–1.59)	**<0.001**	1.69 (1.35–2.10)	**<0.001**
Multivariable adjusted	1.35 (1.18–1.54)	**<0.001**	1.67 (1.33–2.10)	**<0.001**
Sleep duration factor				
Base model	1.60 (1.35–1.89)	**<0.001**	1.91 (1.47–2.47)	**<0.001**
Multivariable adjusted	1.65 (1.38–1.97)	**<0.001**	1.96 (1.48–2.59)	**<0.001**
Sleep efficiency factor				
Base model	1.43 (1.31–1.57)	**<0.001**	1.55 (1.32–1.82)	**<0.001**
Multivariable adjusted	1.42 (1.29–1.57)	**<0.001**	1.54 (1.30–1.84)	**<0.001**
Sleep disturbances factor				
Base model	1.56 (1.24–1.97)	**<0.001**	1.76 (1.16–2.62)	**0.007**
Multivariable adjusted	1.46 (1.14–1.87)	**0.003**	1.61 (1.03–2.49)	**0.034**
Sleep medication use factor				
Base model	1.95 (1.16–3.65)	**0.018**	1.01 (0.07–3.24)	0.995
Multivariable adjusted	2.23 (1.16–5.19)	**0.029**	1.36 (0.09–6.45)	0.74
Daytime dysfunction factor				
Base model	1.35 (1.19–1.53)	**<0.001**	1.63 (1.33–2.00)	**<0.001**
Multivariable adjusted	1.33 (1.16–1.52)	**<0.001**	1.62 (1.31–2.01)	**<0.001**

Odds ratios and 95% confidence intervals for falling into the "some depressive symptoms" or "depressed" groups are given according to baseline subjective sleep measures. GDS, Geriatric Depression Scale; PSQI, Pittsburgh Sleep Quality Index; CI, confidence interval. The base model p-value adjusted nothing, and the multivariable adjusted p-value adjusted for age, sex, education, marriage, drinking, smoking, and self-reported health status. Bold means statistically significant.

expressed as a continuous variable and as a categorical variable: PSQI $>$ 5 vs. PSQI $\leq$ 5 (18). Questionnaires were administered by trained physicians. The trained physicians were present during the entire duration of the assessment to provide clarifications if participants had trouble understanding any of the items in the questionnaires. These measures were verbally administered by these physicians in cases where the participants were illiterate.

Covariables

Demographic information included age, sex (male or female), marital status (currently married, others), and education (illiterate, literate). Lifestyle included smoking status (non-smoker, smoker), drinking status (non-drinker, drinker), body mass index (BMI) [normal or underweight (<24.0), overweight (24.0–27.9), and obese (≥28.0)] and self-reported health status.

Statistical Analyses

Continuous variables are reported as the mean ± standard deviation (SD), and categorical variables are reported as percentages. The relationship between sleep disturbance and depressive symptoms were assessed using logistic regression models. The differences in the characteristics of the participants at baseline and at the 3.5-year follow-up based on the level of depressive symptoms were also assessed using logistic regression models. Covariates known to be associated with levels of depressive symptoms at follow-up or with sleep disturbances were included in multivariable models. Logistic regression models were first used to estimate the odds ratio (ORs) for falling into different depressive symptom level categories (i.e., "some depressive symptoms" (GDS 3–5) or "depressed" (GDS ≥ 6) at follow-up). Logistic regression models were then used to estimate the OR for having a two-point or greater increase in GDS score at follow-up. Models were adjusted for age, sex, education, marriage status, smoking status, drinking status and self-reported health status for multiple variables. *P*-values $<$ 0.05 were considered statistically significant. All analyses were conducted using R x64 4.0.2 ("https://www.r-project.org/,").

RESULTS

Characteristics of the Participants

Table 1 describes the baseline characteristics of the study population categorized into different depressive symptom

TABLE 3 | Associations between sleep disturbance at baseline and depressive symptom level at the 3-year follow-up.

Sleep variables	Some depressive symptoms OR (95% CI)	*P*-value	Depressed symptoms OR (95% CI)	*P*-value
PSQI total score				
Base model	1.09 (1.03–1.15)	**0.003**	1.09 (0.98–1.21)	0.115
Multivariable adjusted	1.07 (1.00–1.14)	**0.036**	1.03 (0.97–1.16)	0.669
PSQI >5 PSQI ≤5				
Base model	1.44 (1.03–2.02)	**0.032**	2.03 (1.09–3.82)	**0.026**
Multivariable adjusted	1.36 (0.94–1.96)	0.104	1.84 (0.94–3.66)	0.077
Sleep quality factor				
Base model	1.18 (0.88–1.56)	0.266	1.22 (0.71–2.09)	0.467
Multivariable adjusted	1.10 (0.76–1.59)	0.601	0.71 (0.35–1.40)	0.337
Sleep latency factor				
Base model	1.25 (1.03–1.51)	**0.022**	1.31 (0.91–1.85)	0.132
Multivariable adjusted	1.15 (0.94–1.41)	0.173	1.32 (0.89–1.94)	0.16
Sleep duration factor				
Base model	1.16 (0.91–1.46)	0.221	1.05 (0.65–1.62)	0.822
Multivariable adjusted	1.10 (0.86–1.40)	0.455	0.90 (0.52–1.48)	0.705
Sleep efficiency factor				
Base model	1.25 (1.09–1.44)	**0.002**	1.34 (1.04–1.72)	**0.024**
Multivariable adjusted	1.21 (1.04–1.41)	0.014	1.21 (0.91–1.61)	0.173
Sleep disturbances factor				
Base model	1.44 (1.00–2.07)	**0.0496**	1.03 (0.48–2.08)	0.939
Multivariable adjusted	1.29 (0.88–1.89)	0.186	0.76 (0.33–1.65)	0.5
Sleep medication use factor				
Base model	1.58 (0.69–4.35)	0.286	1.46 (0.12–5.52)	0.605
Multivariable adjusted	1.14 (0.43–3.21)	0.776	1.27 (0.11–5.16)	0.741
Daytime dysfunction factor				
Base model	1.08 (0.88–1.31)	0.471	0.98 (0.64–1.43)	0.931
Multivariable adjusted	1.06 (0.86–1.32)	0.575	0.85 (0.52–1.31)	0.497

GDS, Geriatric Depression Scale; PSQI, Pittsburgh Sleep Quality Index; CI, confidence interval. The base model was not adjusted, and the multivariable model was adjusted for age, sex, education, marriage, drinking, smoking, and self-reported health status. Bold means statistically significant.

groups. The mean age was 77.2 ± 4.12 years; 51.44% ($n = 839$) were females; 47.03% ($n = 767$) were illiterate; and 63.83% ($n = 1041$) were currently married. A total of 6.81% ($n = 111$) of the participants had depressive symptoms, and 16.19% ($n = 264$) had sleep disturbance at baseline. Smoking status and drinking status were associated with "some depressive symptoms" and "no or few depressive symptoms." There was no significant difference among the groups with "depressive symptoms," "some depressive symptoms," and "no or few depressive symptoms" in age, sex, marital status, literacy, or BMI. Of the participants without evidence of depression at baseline, 31.66% exhibited "some depressive symptoms" and 6.48% revealed "depressive symptoms" at the 3.5-year follow-up examination.

Associations Between Sleep Disturbances and Depressive Symptoms at Baseline

Table 2 indicates that poor global sleep quality (PSQI > 5) was significantly associated with the follow up "some depressive symptoms" (OR: 3.44, 95% CI: 2.75–4.31) and "depressive symptoms" (OR: 3.58, 95% CI: 2.40–5.40) after adjusting for confounding factors. PSQI subcomponents, including sleep quality (OR: 1.61, 95% CI: 1.10–2.34), sleep latency (OR: 1.67, 95% CI: 1.33–2.10), sleep duration (OR: 1.96, 95% CI: 1.48–2.59), sleep efficiency (OR: 1.54, 95% CI: 1.30–1.84), sleep disturbance (OR: 1.61, 95% CI: 1.03–2.49), and daytime dysfunction (OR: 1.62, 95% CI: 1.31–2.01), were also associated with "depressive symptoms" after adjusting for confounding factors.

Associations Between Baseline Sleep Disturbances and Depressive Symptoms at Follow-Up

Table 3 indicates that global sleep quality was associated with "some depressive symptoms" (OR: 1.09, 95% CI: 1.03–1.15) at follow-up, and this association remained significant after adjusting for confounding factors. Poor global sleep quality (PSQI > 5) was associated with "some depressive symptoms" (OR: 1.44, 95% CI: 1.00–2.02), and no significant association was detected after adjusting for confounding factors. Interestingly, the PSQI subcomponents sleep latency (OR: 1.25, 95% CI: 1.03–1.51), sleep efficiency (OR: 1.25, 95% CI: 1.09–1.44), and sleep disturbance (OR: 1.25, 95% CI: 1.00–2.07) were associated with "some depressive symptoms." After adjustment, only sleep efficiency retained an association with "some depressive

TABLE 4 | Associations between baseline sleep disturbance and odds of increased depressive symptoms at the 3-year follow-up.

Sleep factors	≥2 Point increase in GDS OR (95% CI)	*P*-value
PSQI Total Score		
Base model	1.05 (0.99–1.10)	0.086
Multivariable adjusted	1.03 (0.97–1.08)	0.359
PSQI >5 PSQI ≤5		
Base model	1.30 (0.95–1.79)	0.102
Multivariable adjusted	1.14 (0.82–1.59)	0.344
Sleep quality factor		
Base model	1.14 (0.88–1.49)	0.313
Multivariable adjusted	1.12 (0.81–1.57)	0.487
Sleep latency factor		
Base model	0.96 (0.80–1.15)	0.683
Multivariable adjusted	0.95 (0.78–1.14)	0.563
Sleep duration factor		
Base model	1.09 (0.87–1.36)	0.445
Multivariable adjusted	1.03 (0.82–1.31)	0.774
Sleep efficiency factor		
Base model	1.09 (0.95–1.24)	0.216
Multivariable adjusted	1.09 (0.94–1.25)	0.254
Sleep disturbances factor		
Base model	0.98 (0.69–1.39)	0.927
Multivariable adjusted	0.97 (0.67–1.39)	0.857
Sleep medication use factor		
Base model	1.33 (0.58–3.32)	0.482
Multivariable adjusted	1.13 (0.41–2.84)	0.788
Daytime dysfunction factor		
Base model	1.12 (0.93–1.35)	0.234
Multivariable adjusted	1.10 (0.90–1.35)	0.358

Odds ratios and 95% confidence intervals for worsening depressive symptoms (≥2-point increase in GDS score) are given for older adults with sleep disturbances at baseline compared to those without sleep disturbances. Base models were crude models without adjusting any variables. Multivariable models were adjusted for age, sex, education, marriage status, smoking status, drinking status and self-reported health status. CI, confidence interval; GDS, Geriatric Depression Scale; PSQI, Pittsburgh Sleep Quality Index.

symptoms" (OR: 1.21, 95% CI: 1.04–1.41). The category defined by PSQI score > 5 was associated with "depressive symptoms" (OR: 2.03, 95% CI: 1.09–3.82), while no association was revealed after adjusting cofounding factors. The PSQI subcomponent sleep efficiency had an association with "depressive symptoms" (OR: 1.34, 95% CI: 1.04–1.72). Interestingly, there was a lack of association between sleep efficiency and depressive symptoms after adjusting for confounding factors (OR: 1.21, 95% CI: 0.91–1.61). The PSQI subcomponents sleep quality, sleep duration, sleep medication use, and daytime dysfunction had no association with "some depressive symptoms" and "depressive symptoms."

Associations Between Sleep Disturbances and Worsening of Depressive Symptoms at Follow-Up

Table 4 shows that ∼38.7% ($n = 263$) of older Chinese adults showed a ≥ 2-point increase in depressive symptoms. However, we observed no significant association between baseline PSQI total score or PSQI subcomponent scores and worsening of depressive symptoms at follow-up.

DISCUSSION

In this longitudinal analysis of Chinese community-dwelling older people with few or no depressive symptoms at baseline, poorer global sleep quality, and sleep efficiency there appeared to be risk factors for "some depressive symptoms" but not increased risk of worsening of depressive symptoms at follow-up (∼3.5 years later). In the cross-sectional analysis, we observed that the level of depressive symptoms was associated with sleep disturbances (self-reported poor global sleep quality and sleep efficiency). Overall, the cross-sectional association between sleep disturbances and depressive symptoms were attenuated in our longitudinal analysis. To our knowledge, we are the first to investigate whether baseline sleep disturbances could increase the risk of worsening depressive symptoms at follow-up in an older Chinese population. More importantly, we found for the first time that those with more reported sleep disturbance at baseline had greater odds of developing "some depressive symptoms."

One cross-sectional study reported that sleep quality was a risk factor for depression, and the ORs of "depressive symptoms" and "some depressive symptoms" were 3.7- and 2.1-fold, respectively, for those with sleep disturbances at baseline (19). Another study also found that women with "some depressive symptoms" and "depressive symptoms" had greater odds of reporting poor sleep (20). In our cross-sectional analysis, we observed that the ORs for "depressive symptoms" and "some depressive symptoms" were 3.56- and 3.81-fold, respectively, for those with sleep disturbances at baseline which were consistent with the above two studies. A longitudinal study in a large cohort of older men revealed associations between worse sleep quality at baseline and more depressive symptoms at follow-up ∼3.4-years later (8). A previous longitudinal study in a large cohort reported that older women with few or no depressive symptoms at baseline who were reported to have sleep disturbances had a greater risk of worse depressive symptoms 5 years later (7). Interestingly, our longitudinal analysis indicated that among non-depressed older adults at baseline, poor self-reported global sleep quality was associated with "some depressive symptoms" but not the risk of worsening depressive symptoms. This discrepancy could have been due to the shorter follow-up period (∼3.5 years) in the current study. Another possible reason is that the SOF included only female participants and the MrOS included only male participants. Hence, these findings require verification in more cohorts.

In our cross-sectional analysis, we observed that sleep efficiency and daytime sleep PSQI subcomponents were associated with depressive symptoms regardless of adjustment for confounding factors. In the longitudinal analysis, the sleep efficiency PSQI subcomponent at baseline was associated with "some depressive symptoms" at the 3.5-year follow-up after adjusting for confounding factors. This interesting observation indicated that in older adults without depression, poor sleep

efficiency may increase the risk of "some depressive symptoms." On the other hand, poor sleep efficiency had no association with "depressive symptoms" at the 3.5-year follow-up after adjusting for confounding factors. The studies mentioned above (7, 8) did not find any relationship between sleep efficiency and depression. This discrepancy could be due to the differences in age, as the latter study consisted of women only, most of whom were older than 80 years, whereas the current study included men and women who were mostly younger than 80 years. A previous study reported that older adults show decreased sleep efficiency over time, with an 18.6% decline observed between 40 and 100 years of age (21). In addition, we found that the daytime sleep PSQI subcomponents were associated with depressive symptoms. This observation was consistent with previous population-based studies, which have examined the association between daytime sleep and depressive symptoms (22). We detected no significant association between PSQI scores at baseline and the odds of worsening depressive symptoms ($\geq$2 point increase in GDS). The main difference could be due to the differences in population and sample size.

Marta Jackowska et al. reported that compared to an optimal duration, short ($\leq$5 h) but not long ($\geq$8 h) sleep hours were linked to elevated depressive symptoms (23). Sun et al. indicated that short sleep duration (<5 h, 5–6 h) significantly impacted depressive symptoms, while long sleep duration (>9 h) had no association with depressive symptoms (24). Lai et al. found that long sleep duration ($\geq$ 9 h) was a risk factor for depression (22). Our study did not establish a relationship between sleep duration and the worsening of depressive symptoms. This discrepancy may be because the English Longitudinal Study of Aging (ELSA) included an English cohort, while the China Health and Retirement Longitudinal Study (CHARLS), Yilan Study in Taiwan (YILAN) and RuLAS included Chinese cohorts. Alternatively, the differences may have been influenced by time cutoffs, as Marta Jackowska took 7–8 h as a reference, Sun et al. took 7–8 h as a reference, and Lai et al. took 6–7 h as a reference. In addition, various studies have used different sleep and depression scales. The ELSA used the 8-item Centre for Epidemiological Studies Depression scale (CES-D), the CHARLS used the 10-item version of the Centre for Epidemiological Studies Depression scale (CESD-10), and the YILAN cohort used the Hospital Anxiety and Depression Scale (HADS). Hence, further investigation requires verification in other cohorts.

In summary, the current study assessed global sleep quality among older adults using the PSQI and validated the relationship between baseline sleep disturbances and follow-up depressive symptoms. However, there are several limitations of this analysis. First, our analysis was designed to make use of data that were collected as part of a large study. Hence, it was not designed to address our hypothesis, and the outcome measures were not predefined. Second, depressive symptoms were assessed by questionnaire rather than standard criteria for depression such as those from the International Classification of Diseases (ICD) or Diagnostic and Statistical Manual of Mental Disorder (DSM). Therefore, conclusions about psychiatric diagnosis cannot be made with certainty. Third, factors such as personal medical issues, antidepressant use, and family stress that may impact both sleep and mental health outcomes were not accounted for in this study. Finally, the generalizability of the study was limited, and more studies are needed to validate these findings in other cohorts.

In conclusion, findings of the present study contribute to the current literature in terms of the relationship between sleep disturbance and depressive symptoms in an older Chinese population. Together with the observations in the aforementioned studies, poor global sleep quality and sleep efficiency may be risk factors for depression and can predict levels of depressive symptoms.

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 Human Ethics Committee of the School of Life Sciences of Fudan University, Shanghai, China, approved this research (No: BE1815). Written consent was obtained from all participants prior to participation.

AUTHOR CONTRIBUTIONS

CQ: conceptualization, data analysis, and writing-original draft preparation. YY and XiaW: conceptualization and writing-reviewing and editing. HZ, QS, and XiW: data collection and data cleaning. All authors contributed to the article and approved the submitted version.

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Analysis of Serum Vitamin D Level and Related Factors in Patients With Restless Legs Syndrome

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Objective: This study aimed to detect serum vitamin D (VitD) levels in patients with primary restless legs syndrome (RLS). The further objective was to analyze the relationship of VitD levels with the severity of RLS symptoms, sleep, anxiety, and depression.

Methods: The serum 25-hydroxyvitamin D [25(OH)D] levels of 57 patients with primary RLS and the healthy physical examinees in our hospital during the same period were detected. The International Restless Legs Syndrome Study Group (IRLSSG) rating scale for measuring RLS severity and Pittsburgh Sleep Quality Index (PSQI) Scale, 24-item Hamilton Depression Rating Scale ($HAMD_{24}$), and 14-item Hamilton Anxiety Scale ($HAMA_{14}$) were used to assess the severity of symptoms, sleep, and emotional state of patients with RLS. Based on VitD level and IRLSSG score, they were grouped for analysis.

Results: The serum 25(OH)D level was significantly lower in patients with RLS than in healthy controls, and the incidence of insufficient serum VitD levels was significantly higher in patients with RLS than in healthy people (both $P < 0.05$). The serum VitD level was significantly lower in (extremely) severe patients with RLS than in mild to moderate patients with RLS ($P < 0.05$). The IRLSSG scale score and $HAMD_{24}$ score were significantly higher in patients with RLS with insufficient serum VitD levels than those with normal serum VitD levels (both $P < 0.05$). Correlation analysis of IRLSSG scale score with serum VitD level and each scale score in patients with RLS showed that IRLSSG scale score was negatively correlated with VitD level, but positively correlated with PSQI, $HAMA_{14}$, and $HAMD_{24}$ scores. The results of correlation analysis between serum VitD levels and each scale score in patients with RLS indicated that serum VitD levels were negatively correlated with IRLSSG scale scores, PSQI scores, and $HAMD_{24}$ scores.

Conclusion: The serum VitD level is generally lower in patients with RLS than in healthy people, and lower serum VitD level is associated with more severe symptoms of RLS, worse quality of sleep, and worse depression.

Keywords: restless legs syndrome, vitamin D, severity of symptoms, sleep quality, depression

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INTRODUCTION

Restless legs syndrome (RLS) is one of the most common sleep-related sensorimotor disorders of the central nervous system, which is mainly manifested as indescribable limb discomfort, such as "prickly or stinging sensation," "creeping sensation," and "burning sensation" in the resting state, especially before going to bed or during quiet rest. It can occur on one side or both sides of the limbs, specifically in the lower limbs. The above limb discomfort symptoms are usually unbearable, forcing patients to move or massage their limbs to relieve the discomfort symptoms (1). The prevalence of RLS is approximately 0.1–15% (2–4). Secondary RLS can be secondary to chronic kidney disease, iron deficiency anemia, diabetes, pregnancy, Parkinson's disease, and multiple sclerosis, etc.

At present, relevant studies mainly focus on brain iron deficiency, neurotransmitter regulation disorders including dopaminergic system, and genetic factors. Brain iron deficiency is considered to be the key pathogenesis, which is jointly affected by environmental factors and genetic inheritance (5). Vitamin D (VitD) is involved in regulating the activity of the amygdala to improve patients' depression and anxiety.

Recent studies have reported (6–8) the presence of generally insufficient serum VitD levels in patients with primary RLS. This clinical retrospective study aimed to explore the correlation of the serum VitD level with the severity of RLS symptoms, sleep quality, anxiety, and depression in patients with primary RLS, so as to provide a basis for the prevention and treatment of RLS.

MATERIALS AND METHODS

Research Subjects

A total of 57 primary patients with RLS that were treated in the Department of Neurology, the First Hospital of Hebei Medical University from October 2019 to October 2020 were enrolled in this study. Another 57 age- and gender-matched healthy people who underwent physical examinations during the same period were selected as the control group.

Inclusion Criteria

Patients that conformed to the diagnostic criteria of RLS. The consensus by the International Restless Legs Syndrome Study Group (IRLSSG) in 2014 proposed new diagnostic criteria of RLS/Willis-Ekbom disease (WES) (9).

Exclusion Criteria

(1) RLS secondary to chronic kidney disease, renal failure, iron deficiency anemia, pregnancy, peripheral neuropathy, Parkinson's disease, and Parkinson's syndrome, drug-induced factors, including taking anti-depressants or sedatives and sleeping pills, familial and genetic factors; (2) other sleep disorders such as rapid eye movement sleep behavior disorder, sleep apnea syndrome, etc.; (3) metabolic syndrome, osteoporosis, cerebrovascular disease, respiratory diseases, malignant tumors, thyroid diseases, various mental diseases, liver and kidney diseases, and other diseases that affected serum VitD levels; (4) patients taking calcium, calcidiol capsules, and other drugs that affected serum VitD levels or drugs that alleviated RLS; (5) pregnant and lactating women. This study was approved by the Ethics Committee of First Hospital of Hebei Medical University, and written informed consent was obtained from the enrolled patients.

Research Methods

Collecting General Information

The information such as the name, gender, age, chief complaint, present medical history, and previous underlying diseases of the patients and healthy controls was collected.

Evaluation of Symptoms, Sleep Quality, and Mood of the Patients

Professional physicians inquired about RLS symptoms, severity, sleep quality, anxiety, and depression of patients with RLS, and conducted corresponding scale assessments, including the IRLSSG rating scale for measuring RLS severity, Pittsburgh Sleep Quality Index (PSQI) scale, 24-item Hamilton Depression Rating Scale ($HAMD_{24}$), and 14-item Hamilton Anxiety Scale ($HAMA_{14}$).

Detection of Serum VitD Level

Early morning fasting venous blood was collected from patients with RLS and healthy controls, and magnetic particle chemiluminescence immunoassay was used to detect serum 25-hydroxyvitamin D [25(OH)D] levels.

Grouping

According to the serum 25(OH)D level of patients with primary RLS, they were divided into normal VitD level [25(OH)D $\geq$ 20 ng/ml] group and insufficient VitD level [25(OH)D $<$ 20 ng/ml] group. According to the severity of limb discomfort (10, 11), patients with RLS were divided into mild to moderate RLS group (IRLSSG: 1–20 points) and (extremely) severe RLS group (IRLSSG: 21–40 points).

Statistical Analysis

The statistical software SPSS 25 (IBM, Chicago) was used for statistical analysis. The measurement data conformed to normal distribution were expressed as the mean $\pm$ *SD*, and the independent sample *t*-test was used for the comparison between groups. The measurement data of non-normal distribution were expressed as the median and interquartile range, and the Mann-Whitney U-test was used for comparison between groups. The measurement data were expressed by the number of cases (percentage) method, and the comparison between groups was performed by χ^2-tests. Pearson correlation analysis was used for analysis between serum VitD level and IRLSSG scale score. $P < 0.05$ indicated that the difference was statistically significant.

RESULTS

Baseline Information

A total of 57 patients with RLS were enrolled in this study, including 19 men (33.33%) and 38 women (66.67%). The ratio of men to women patients with RLS was 1:2. The age ranged from 15 to 78 years, with a mean age of (57.56 $\pm$ 13) years. A total of

TABLE 1 | Comparison of gender, age, and VitD level between RLS group and healthy control group.

	Primary RLS group ($n = 57$)	Healthy control group ($n = 57$)	F/χ^2	P
Gender (female/male)	38/19	40/17	0.162	0.687
Age ($\bar{\chi} \pm S$, years)	57.56 ± 13.00	57.68 ± 12.90	0.049	0.960
VitD level ($\bar{\chi} \pm S$, ng/ml)	16.07 ± 5.43	27.00 ± 5.00	0.224	0.000*
Incidence of insufficient VitD level (n, %)	46 (80.70%)	1 (1.57%)	73.309	0.000*

*$P < 0.05$.

TABLE 2 | Comparison of clinical data between mild to moderate RLS patient group and (extremely) severe RLS patient group.

	Mild to moderate RLS group	(Extremely) severe RLS group	F	P
No. of cases (n, %)	36 (63.16%)	21 (36.84%)		
VitD level ($\bar{\chi} \pm S$, ng/ml)	17.26 ± 5.44	14.04 ± 4.88	0.121	0.029*
PSQI ($\bar{\chi} \pm S$, 分)	15.92 ± 3.73	16.19 ± 2.07	6.404	0.758
$HAMA_{14}$ ($\bar{\chi} \pm S$, 分)	15.19 ± 5.12	16.71 ± 5.08	0.744	0.283
$HAMD_{24}$ ($\bar{\chi} \pm S$, 分)	16.22 ± 6.14	17.71 ± 6.91	0.075	0.402

*$P < 0.05$.

57 cases were enrolled in the healthy control group, including 17 men (29.82%) and 40 women (70.18%), aged 18–79 years, with a mean age of (57.68 ± 12.9) years. No significant difference was found in age and gender between the two groups ($P > 0.05$). The serum VitD level was lower in patients with RLS than in the healthy controls, and the incidence of insufficient serum VitD level was significantly higher in primary patients with RLS than in healthy people (both $P < 0.05$) (see **Table 1**).

Comparison of Clinical Data of Patients With Mild to Moderate RLS and Those With (Extremely) Severe RLS

Among 57 patients with RLS, 36 patients (63.16%) had mild to moderate RLS, including 12 men and 24 women aged 31–74 years, with a mean age of (56.81 ± 12.33) years. There were 21 (36.84%) (extremely) severe patients with RLS, including 7 men and 14 women aged 15–78 years, with a mean age of (58.86 ± 14.28) years. No significant difference was found in gender and age between the two groups ($P > 0.05$). The serum VitD level of (extremely) was significantly lower in severe patients with RLS than in mild to moderate patients with RLS ($P < 0.05$) (see **Table 2**).

Comparison of RLS Severity, Sleep Quality, and Anxiety and Depression in Normal Serum VitD Level Group and Insufficient VitD Level Group

Among 57 patients with RLS, 11 patients (19.3%) were in the normal VitD level group, including 5 men and 6 women aged 38–69 years, with a mean age of (59.36 ± 9.1) years; 46 patients (80.7%) were in the VitD level group, including 14 men and 32 women aged 15–78 years, with a mean age of (57.13 ± 13.81) years. There was no statistical difference in gender and age between the two groups ($P > 0.05$). The IRLSSG scale score and $HAMD_{24}$ score of patients with RLS were significantly higher in the insufficient serum VitD level group than in the normal serum VitD level group (both $P < 0.05$) (see **Table 3**).

Correlation Analysis of IRLSSG Score With Serum VitD Level and Various Scale Scores in Patients With RLS

Pearson correlation analysis showed that IRLSSG score was negatively correlated with serum VitD level ($r = -0.395$, $P = 0.002$), but positively correlated with PSQI score, $HAMA_{14}$ score, and $HAMD_{24}$ score ($r = 0.374$, $P = 0.004$, $r = 0.348$, $P = 0.008$, $r = 0.347$, $P = 0.008$) (see **Table 4**).

Correlation Analysis Between Serum VitD Level and Various Scale Scores in Patients With RLS

Pearson correlation analysis indicated that serum VitD level was negatively correlated with IRLSSG score, PSQI score, and $HAMD_{24}$ score ($r = -0.395$, $P = 0.002$, $r = -0.304$, $P = 0.022$, $r = -0.295$, $P = 0.027$) (see **Table 5**).

DISCUSSION

Vitamin D participates in the synthesis and release of neurotransmitters, and plays an anti-inflammatory, anti-oxidant, and neuroprotective role, exerting an important effect on regulating the occurrence and development of sleep, anxiety, and depression (12, 13). Vitamin D deficiency can lead to reduced levels of dopamine and its metabolites in the brain, and the decreased release of dopamine in the substantia nigra of the midbrain and dopaminergic transmission disorders are common pathogenesis of RLS. Multiple studies have found that VitD deficiency is common in patients with RLS. A cross-sectional study of 102 patients with RLS by Cakir et al. (5) found that

TABLE 3 | Comparison of clinical data between the normal VitD level group and the insufficient VitD level group.

	Normal VitD level group	Insufficient VitD level group	*Z/F*	*P*
No. of cases (*n*, %)	11 (19.3%)	46 (80.7%)		
IRLSSG [$M(P_{25}, P_{75})$, points]	14 (11, 18)	19 (15.75, 23)	−2.147	0.032*
PSQI ($\bar{\chi} \pm S$, points)	14.91 ± 4.46	16.28 ± 2.82	3.352	0.204
$HAMA_{14}$ ($\bar{\chi} \pm S$, points)	15.09 ± 6.36	15.91 ± 4.83	2.619	0.636
$HAMD_{24}$ ($\bar{\chi} \pm S$, points)	12.82 ± 5.47	17.72 ± 6.31	0.240	0.021*

*$P < 0.05$.

TABLE 4 | Pearson correlation analysis of IRLSSG score with serum VitD level and various scale scores.

	r	*P*
VitD level	−0.395	0.002*
PSQI	0.374	0.004*
$HAMA_{14}$	0.348	0.008*
$HAMD_{24}$	0.347	0.008*

*$P < 0.05$.

TABLE 5 | Pearson correlation analysis between the VitD level of patients with RLS and various scale scores.

	r	*P*
IRLSSG	−0.395	0.002*
PSQI	−0.304	0.022*
$HAMD_{24}$	−0.294	0.027*

*$P < 0.05$.

the incidence of VitD deficiency was higher in patients with RLS (52.63 vs. 37.78%), and the PSQI scores of patients with VitD deficiency were higher ($P < 0.05$); patients with RLS with VitD deficiency had more frequent symptoms of limb discomfort. Almeneessier et al. (14) studied 1,136 non-pregnant women with RLS in Saudi Arabia and found that VitD deficiency was an independent risk factor for RLS [odds ratio (OR): 2.147 (1.612–2.86), $P < 0.001$]. A meta-analysis of 9,590 patients with RLS showed (15) that there was a significant correlation between serum VitD levels and RLS (95% Cl: −5.96 to −0.81, $P = 0.01$, $I^2 = 86.2\%$). This study also found that patients with primary RLS had low serum VitD levels, and the incidence was higher in patients with insufficient VitD levels than in healthy people.

Restless leg syndrome occurs at any age, but the prevalence of RLS is higher in women than in men; and the incidence of RLS in women is approximately twice that of the general population (16, 17), which may be related to low serum iron and ferritin levels during pregnancy, high estrogen levels, VitD deficiency and calcium metabolism disorders (18, 19). A prospective case-control study by Balaban et al. (20) showed that the average serum VitD level was lower in female patients with RLS than in patients who are men and that there was a significant negative correlation between female VitD levels and the severity of RLS disease ($r = -0.47$, $P = 0.01$). In this study, the ratio of men to women patients with RLS was 1:2. However, there was no difference in VitD levels between male and female patients, which might be related to the small sample size in this study.

Serum VitD levels were lower in patients with (extremely) severe RLS than in those with mild to moderate RLS, which were negatively correlated with IRLSSG scores. The results of this study suggested that more severe symptoms of limb discomfort in patients with RLS were associated with lower serum VitD levels. Therefore, it is controversial whether correcting insufficient serum VitD levels can improve the symptoms of limb discomfort in patients with RLS. Wali et al. (21) recommended VitD supplement treatment to patients with primary RLS and insufficient VitD levels. When the VitD level was adjusted to >50 nmol/L, the severity of RLS was evaluated and compared with the score before taking the supplement. It was found that the IRLSSG score was significantly decreased ($P = 0.002$). This preliminary study revealed that drug supplementation with VitD could ameliorate the severity of RLS symptoms. Tutuncu et al. (7) conducted a prospective self-controlled case study to treat 21 patients with RLS with insufficient VitD levels by taking 50,000 units of VitD supplements per week for 2 months. After 2 months, the patients had normal VitD levels, and some of the IRLSSG scores were also improved, including the severity of symptoms ($P < 0.001$), the impact on sleep ($P < 0.001$), the assessment of symptoms ($P = 0.002$), and the assessment of the impact of disease on life ($P < 0.001$). There was a trend of improvement in the two sub-items of seizure frequency ($P = 0.11$) and mood ($P = 0.051$). Nonetheless, several opposite conclusions were also drawn from this study. Wali et al. (22) conducted a 12-week randomized placebo-controlled trial and found that compared with the placebo group, 35 subjects who received oral 50,000 IU VitD capsules experienced no significant changes in the severity of RLS symptoms. The results showed that VitD supplementation failed to alleviate the symptoms of RLS. It is inconclusive whether drugs supplemented with VitD are effective in the treatment of RLS. Long-term, large-sample prospective cohort studies, and clinical trials are still needed to support this relationship and evaluate the efficacy of VitD for the treatment of RLS. However, for patients with RLS with insufficient VitD levels, regular exposure to sunlight, outdoor exercise, and dietary supplementation with VitD are all recommended.

Patients with RLS often experience various discomforts such as limb pain, swelling, burning, creeping sensation, which can lead to difficulty falling asleep and sleep interruption. Patients with RLS may suffer daytime sleepiness, fatigue, inattention, and decreased interest, depression, irritability, and other anxiety and depression emotions, affecting the quality of sleep and quality of life of patients (2, 23–25). Vitamin D regulates the production of melatonin in the body and plays an important role in regulating the circadian rhythm of sleep. In addition, VitD is associated with increased levels of γ-aminobutyric acid, glutamine, and glutamate in the hippocampus, prefrontal cortex, and anterior cingulate gyrus, which may help regulate depressive mood and anti-anxiety effects (26, 27). A retrospective study by Atalar et al. (28) showed that compared with patients with RLS with normal VitD levels, patients with RLS with VitD deficiency had worse sleep quality ($P < 0.05$). Turk et al. (29) reported that 91.9% of patients with RLS had prolonged sleep latency, poor sleep quality, short sleep duration, and daytime dysfunction. Patients with moderate to severe RLS had a higher incidence of night sleep disturbance, daytime fatigue, and depression (16). Yilmaz et al. (30) found that the RLS severity score was positively correlated with the anxiety and depression scale scores ($P < 0.05$). The probability of depression in patients with RLS was 2.5–5 times higher than that in patients without RLS, and the probability of depression and the severity of insomnia both increased with the worsened severity of RLS symptoms (31). This study found that the worse symptoms of patients with RLS led to the worse sleep quality, and the more severe anxiety and depression accompanied. In addition, the lower serum VitD level of patients with RLS was associated with the more severe RLS symptoms, the worse quality of sleep, and the worse depression.

In conclusion, VitD deficiency is more common in patients with RLS. The lower the serum VitD level in patients with RLS, the more severe the symptoms of limb discomfort in patients with RLS, the worse the quality of sleep, and the worse the depression. Clinicians should pay attention to the detection of serum VitD levels and the evaluation of anxiety and depression during the diagnosis and treatment of RLS. However, whether VitD deficiency will cause the occurrence of RLS and the aggravation of symptoms as well as their causal relationship remains to be further studied. Conventional drug supplemented with VitD as an intervention for RLS is still controversial, and a large number of long-term prospective cohort studies and clinical trials are needed to confirm the findings. However, dietary supplementation with VitD, regular exposure to sunlight, and outdoor exercise is recommended for patients with RLS. Given that this is a clinical retrospective study with a small sample size, multi-center, large-sample clinical studies are needed in the future to further improve placebo-controlled study and explore the changes in RLS symptoms, mood, and sleep quality before and after supplementation with VitD. In our next study, we will aim to analyze the correlation between vitD level and RLS symptoms by age.

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 First Hospital of Hebei Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

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

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Excessive Daytime Sleepiness Is Associated With Non-motor Symptoms of Multiple System Atrophy: A Cross-Sectional Study in China

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Objectives: Excessive daytime sleepiness (EDS) in multiple system atrophy (MSA) has received scant attention in the literature, thus the present cross-sectional study aimed to investigate the prevalence of EDS and its potential risk factors among Chinese patients with MSA.

Methods: A total of 66 patients with MSA (60.6% males) were consecutively recruited. Eighteen patients (27.3%, 13 men) with Epworth Sleepiness Scale score >10 were defined as having EDS. Demographic, motor [Unified Multiple-System Atrophy (UMSARS)] and non-motor symptoms [Non-Motor Symptoms Scale (NMSS)], and sleep parameters [polysomnography (PSG)] were compared between patients with MSA with and without EDS. A logistic regression analysis was used to calculate the risk factors of EDS in patients with MSA.

Results: There were no significant differences in age, sex, MSA onset age, disease duration, MSA sub-type, and motor symptom severity between MSA patients with and without EDS. However, compared with the MSA patients without EDS, their counterparts with EDS had higher scores of NMSS (65.3 ± 23.1 vs. 43.4 ± 25.3, $P = .0002$), Hamilton Anxiety (HAMA) [15.3 (10.3–20.0) vs. 9.5 (3.0–15.0), $P = 0.006$], Hamilton Depression (HAMD) [13.7 (12.5–17.8) vs. 9.0 (4.0–13.0), $P = 0.015$], and Fatigue Severity Scale (FSS) [29.8 (17.3–47.8) vs. 18.7 (10.3–21.8), $P = 0.040$]. Conversely, the patients with EDS had lower score of Mini-Mental State Examination (MMSE) [23.3 (20.3–27.0) vs. 25.7 (22.0–29.0), $P = 0.023$]. Similarly, there was a significantly lower percentage of N3 sleep (%) [0.3 (0–0) vs. 2.0 (0–0), $P = 0.007$] and a higher apnea-hypopnea index (AHI/h) [30.5 (14.5–47.8) vs. 19.3 (5.0–28.7), $P = 0.034$] in patients with EDS. After adjusting for age, sex, disease duration, MSA sub-type, and UMSARS score, the odds ratio (OR) (95% CI) of EDS was higher while increasing scores in FSS [1.06 (1.02–1.11)], HAMA [1.16 (1.04–1.28)], HAMD [1.13 (1.02–1.25)], NMSS [1.04 (1.01–1.07)], and AHI [1.03 (1.00–1.10)]. The OR of EDS was lower while the MMSE score was increasing [0.85 (0.72–1.00)].

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Conclusions: The presence and severity of EDS may be significantly associated with the non-motor dysfunction, including fatigue, anxiety, depression, cognitive dysfunction, and sleep-related breathing disorder, but not with the motor dysfunction in MSA.

Keywords: excessive daytime sleepiness, motor symptoms, non-motor symptoms, sleep parameters, multiple system atrophy

INTRODUCTION

Multiple system atrophy (MSA) is defined as an episodic and rapidly progressing neurodegenerative disease characterized by Parkinsonism, autonomic dysfunction, and/or ataxia. According to its clinical manifestations, MSA is classified into MSA-P in the event that the patient presents with Parkinsonism symptoms and MSA-C if the patient develops cerebellar dysfunction (1). Currently, non-motor symptoms are well-known to have a significant impact on the quality of life as well as the motor symptoms among patients with MSA (2). Excessive daytime sleepiness (EDS) is a common non-motor symptom in patients with MSA. The previously reported prevalence of EDS in patients with MSA was 24–28% (2, 3), which was significantly higher than the prevalence of 2% in the healthy control group (2). EDS was considered as the result of inadequate sleep or sleep-related breathing disorder (SRBD) in MSA (2–4), but the most relevant cause might be the neural systems pathophysiological impairment, including cholinergic neurons in the mesopontine tegmentum, hypocretin/orexin neurons of the lateral hypothalamus, serotonergic neurons of the rostral raphe, and dopaminergic neurons in the ventral periaquapular gray matter (5–7).

A series of studies has found that EDS might be a preclinical marker of Parkinson's disease (PD) (8–10). In particular, a longitudinal study revealed that EDS increases with disease progression in PD (8, 9), which was considered as the degeneration of the lower brain stem involved in sleep-wake regulation. Although MSA is also classified into synucleinopathies as well as PD, there were only two studies concerned with the association between EDS and MSA until now. In previous studies, EDS was found to be weakly correlated with the severity of motor symptoms in patients with MSA (2, 4). However, there is no literature about differences in clinical features, such as the motor and non-motor symptoms between MSA patients with and without EDS. Thus, the present study investigates the prevalence of EDS among Chinese patients with MSA and compares the motor and non-motor symptoms between MSA patients with and without EDS. Furthermore, we explored the potential influencing factors on EDS among patients with MSA.

METHODS

Participants

The present cross-sectional study enrolled 66 consecutive patients with "probable MSA" from the Department of Neurology of West China Hospital between 2017 and 2020. The diagnosis of MSA was based on the standard criteria of the Second consensus statement (2008) by neurologists (11). Patients were included if they (1) met the diagnostic criteria for probable MSA, (2) completed the assessments of subjective questionnaire scales and polysomnography (PSG), (3) and showed no signs of intracranial lesion on brain magnetic resonance imaging. Patients were excluded if they (1) had signs or symptoms of other neurologic diseases; (2) used medications or substances that might affect their sleep cycle, such as hypnotic drugs, antidepressants, selective serotonin reuptake inhibitors, and antipsychotic agents; or (3) were critically ill or presented unstable vital signs. The study was approved by the West China Hospital Clinic Research Ethics Committee, and all patients and their guardians provided written informed consent.

Questionnaires

All patients were evaluated using several questionnaires validated in Chinese, and all the questionnaires were rated by clinicians. Epworth Sleepiness Scale (ESS) was used to assess subjective daytime sleepiness. EDS was defined as an ESS score > 10 (12). Sleep quality was assessed by the Pittsburgh Sleep Quality Index (PSQI). The Rapid Eye Movement (REM) Sleep Behavior Disorder Questionnaire (RBDSQ) was used to diagnose REM-sleep behavior disorder (RBD) (13). The Non-Motor Symptoms Scale (NMSS) (nine domains) was used to evaluate the severity of the non-motor symptoms. The symptoms of depression and anxiety were assessed using the Hamilton Depression Rating Scale (17 items) and Hamilton Anxiety Rating Scale (HAMA), respectively. Patients were evaluated for fatigue using the Fatigue Severity Scale (FSS). The Mini-Mental State Examination (MMSE) was used to evaluate cognitive function. The severity of motor symptoms was assessed using the Unified Multiple System Atrophy Rating Scale (UMSARS).

PSG

All recruited patients underwent an overnight video-PSG assessment in the Sleep Medicine Center of West China Hospital. The continuous recordings included electroencephalography (F4–M1, C4–M1, O2–M1, F3–M2, C3–M2, O1–M2), electrooculography (ROC–M1, LOC–M2), submental electromyography, right and left anterior tibialis surface electromyography, and electrocardiography. Other measurements included oxygen saturation, nasal-oral flow, thoracic and abdominal respiratory efforts, and body position. The PSG results were scored by sleep technicians and interpreted by sleep specialists. Sleep stages and associated events were manually scored in 30-s epochs, according to the guidelines for scoring sleep and related events published by the American Academy of Sleep Medicine (14). The diagnosis of sleep-related

breathing disorder (SRBD) was based on PSG measurement with the Apnea-Hypopnea Index (AHI) >5/h (15).

Statistical Analysis

Data were analyzed using SPSS 19.0 (IBM, Chicago, IL, USA). Continuous data showing normal distribution were expressed as the mean ± SD, while continuous skewed data were reported as the median (interquartile range). Group differences were calculated using Student's *t*-test or the Mann-Whitney *U*-test for continuous variables. Differences in categorical data were calculated by the Chi-square test. Logistic regression analysis was used to estimate the odds ratio (OR) and 95% CI after adjusting for potential confounding factors, including quantitative variables (age, disease duration, UMSARS score) and categorical variables (sex, MSA sub-type). Values of $p < 0.05$ were considered to indicate statistical significance.

RESULTS

This study included 66 patients with probable MSA (40 men), and 27.3% of patients ($n = 18$) were diagnosed with EDS based on ESS score >10 (12). The mean ESS score of the patients with MSA wasere 6.0 (2.8–11.0). Among the patients with MSA, there were 47 MSA-P (14 with EDS) and 19 MSA-C (4 with EDS) subtypes. There was no significant difference in the prevalence of EDS between patients with MSA-C and MSA-P ($P = 0.643$). In addition, the prevalence of SRBD in MSA patients was 78.8% (52/66) and no significant difference was found in the rates of SRBD between patients with MSA-C (89.5%) and MSA-P (74.5%).

Demographic and Clinical Characteristics

The comparisons of demographic and clinical characteristics between patients with and without EDS are presented in **Table 1**. There were no significant differences in age, MSA onset age, disease duration, UMSARS, RBDSQ, and PSQI scores between the two groups. However, compared with the MSA patients without EDS, their counterparts with EDS had higher scores of FSS, NMSS, HAMA, and HAMD. Conversely, the patients with EDS had lower MMSE scores ($P < 0.05$).

The comparisons of the subitems of the NMSS scale between MSA patients with and without EDS are shown in **Table 2**. Patients with EDS had higher scores for sleep/fatigue, mood disorder, perceptual problems, attention/memory dysfunction, gastrointestinal dysfunction, unexplained pain, and weight changes.

Sleep Parameters

The comparisons of PSG parameters between MSA patients with and without EDS are shown in **Table 3**. No significant differences were found between MSA patients with and without EDS in terms of total sleep time (TST), sleep efficiency (SE), sleep latency (SL), the percentages of N1, N2, and REM sleep stage, minimum SaO_2, and periodic leg movement index. However, there were significant differences in sleep-breathing-related variables between the two groups. Compared with the MSA without EDS group, the MSA with EDS group had significantly higher AHI, central apnea index (CAI), and hypopnea index (HI). Similarly, there was a slightly higher obstructive apnea index (OAI) in patients with EDS. In addition, the MSA with EDS group had a lower percentage of N3 sleep.

Risk Factors of EDS

Figure 1 shows the risk factors of EDS in patients with MSA. After adjusting for age, sex, disease duration, MSA subtype, and UMSARS score, the risk of EDS in patients with MSA were significantly higher while increasing scores in FSS [1.06 (1.02–1.11)], HAMA [1.16 (1.04–1.28)], HAMD [1.13 (1.02–1.25)], NMSS [1.04 (1.01–1.07)], and AHI [1.03 (1.00–1.10)]. Conversely, the risk of EDS in patients with MSA was significantly lower while the MMSE score was increased [0.85 (0.72–1.00)]. **Supplementary Table 1** presents the process of logistic regression analysis. Therefore, the risk of EDS in patients with MSA is associated with more severe symptoms of fatigue, anxiety, depression, cognitive dysfunction, and SRBD.

DISCUSSION

As far as we know, there is little literature investigating the differences of motor and non-motor symptoms between MSA patients with and without EDS. The present study found that the prevalence of EDS was 27.3% among patients with MSA, which is rather similar to those previously reported in Japan (24%) and in Europe (28%) (2, 4). Notably, a previous study showed that the incidence of EDS in MSA was similar to that of patients with PD (28 and 29%, respectively).Thus, these findings indicated that EDS is relatively common in patients with MSA as well as other synucleinopathies like PD.

REM-sleep behavior disorder (RBD) is characterized by the loss of muscular atonia and prominent motor behavior during REM sleep, which is a common symptom in patients with MSA (16). The prevalence of RBD is up to 69–100% in patients with MSA (17–19). Therefore, RBD is considered as a "red flag" which is associated with the faster progression and greater severity of synucleinopathies including PD and MSA (20). This study investigates the association between EDS and clinical symptoms including motor and non-motor symptoms and addressed the question of whether EDS—like RBD—aggravates the progression of MSA (20). Finally, we found there were no differences in age, disease duration, MSA sub-type, and UMSARS scores between the groups with and without EDS. Similarly, a previous study reported that there was no correlation between EDS and the severity of motor symptoms in patients with MSA (2). Even so, a larger study is necessary to determine the relationship between EDS and motor dysfunction in MSA.

In the current study, a significantly higher score of NMSS was found in MSA patients with EDS, especially in sleep/fatigue, mood/apathy, perceptual problems, attention/memory, gastrointestinal, pain, and weight dimensions. Moreover, MSA patients with EDS had higher scores of HAMA and HAMD than those without EDS. Previous studies showed that the risk of EDS was increased by the level of depression (21, 22). This indicated that the symptoms of depression and anxiety might increase the

TABLE 1 | Demographic and clinical characteristics of multiple system atrophy (MSA) patients with and without excessive daytime sleepiness (EDS).

	Total ($n = 66$)	MSA with EDS ($n = 18$)	MSA without EDS ($n = 48$)	*P*
Age, y	63.1 (54.8–68.3)	64.8 (59.8–72.5)	62.4 (54.0–66.8)	0.334
Male/female	40/26	13/5	27/21	0.237
Age at onset, y	60.2 ± 10.3	62.0 ± 9.6	59.4 ± 10.6	0.369
Disease duration, y	2.8 (1.0–3.0)	2.5 (1.0–3.1)	2.9 (1.1–3.0)	0.959
MSA sub-type (P/C)	47/19	14/4	33/14	0.643
ESS	6.0 (2.8–11.0)	14 (12.0–17.3)	3.0 (2.0–6.0)	**0.000**
PSQI	6.6 (3.0–9.5)	7.8 (3.8–10.0)	6.2 (3.0–8.0)	0.099
RBDSQ	4.7 (1.5.0–7.5.0)	5.7 (2.0–9.0)	4.3 (1.0–6.0)	0.110
FSS	21.7 (11.0–30.0)	29.8 (17.3–47.8)	18.7 (10.3–21.8)	**0.040**
NMSS	49.4 ± 26.4	65.3 ± 23.1	43.4 ± 25.3	**0.002**
MMSE	25.0 (22.0–29.0)	23.3 (20.3–27.0)	25.7 (22.8–29.0)	**0.023**
HAMA	11.1 (4.0–17.5)	15.3 (10.3–20.0)	9.5 (3.0–15.0)	**0.006**
HAMD	10.3 (4.0–15.0)	13.7 (12.5–17.8)	9.0 (4.0–13.0)	**0.015**
UMSARS I	13.23 ± 5.8	14.8 ± 5.7	12.7 ± 5.7	0.182
UMSARS II	16.5 (12.0–20.3)	18.61 (15.0–21.5)	15.8 (12.0–20.0)	0.083
UMSARS IV	1.7 (1.0–2.0)	1.9 (1.0–3.0)	1.7 (1.0–2.0)	0.257

ESS, Epworth Sleepiness Scales; FSS, Fatigue Severity Scale; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; MSA, Multiple system atrophy; MMSE, Mini-mental State Examination; MSA sub-type (P/C), MSA sub-type (Parkinsonism/cerebellar ataxia); NMSS, Non-Motor Symptoms Scale; PSQI, Pittsburgh Sleep Quality Index; RBDSQ, Sleep Behavior Disorder Questionnaire; UMSARS, Unified Multiple-System Atrophy Rating Scale. Values are n (%), mean ± SD or median (interquartile range). The bold value of P value are $P < 0.05$.

TABLE 2 | Non-motor symptoms scale (NMSS) of MSA with and without EDS.

	Total ($n = 66$)	MSA with EDS ($n = 18$)	MSA without EDS ($n = 48$)	*P*
Cardiovascular	1.9 (0–3.3)	3.0 (0–4.5)	1.5 (0–1)	0.335
Sleep/fatigue	7.0 (2.0–12.0)	11.8 (8.0–16.0)	5.2 (1.0–8.8)	**0.000**
Mood/apathy	8.1 (0.8–12.0)	12.3 (5.0–15.3)	6.5 (0–11.8)	**0.007**
Perceptual problems	1.5 (0–1.3)	2.5 (0–4.3)	1.1 (0–0.8)	**0.036**
Attention/memory	3.7 (0–7.0)	5.9 (2.8–8.0)	2.9 (0–5.0)	**0.005**
Gastrointestinal	4.5 (0–8.0)	6.4 (2.0–9.5)	3.7 (0–6.0)	**0.041**
Urinary	9.7 (4–15.3)	8.6 (0.8–12.3)	10.4 (4.0–16.8)	0.750
Sexual dysfunction	8.4 (0–15.0)	8.6 (2.8–18.0)	8.3 (0–14.3)	0.484
Miscellaneous	4.6 (0–7.3)	6.3 (3–9.3)	3.9 (0–6.0)	**0.036**
Pain	1.0 (0–0)	2.0 (0–4.0)	0.63 (0–0)	**0.028**
dysgeusia/ dysosmia	1.8 (0–2.0)	2.1 (0–4.5)	1.8 (0–1.5)	0.582
weight	0.23 (0–0)	0.7 (0–1.3)	0.04 (0–0)	**0.004**
desudation	1.48 (0–3.0)	1.5 (0–3.3)	1.5 (0–2.3)	0.454

NMSS, Non-Motor Symptoms Scale. Values are median (interquartile range). The bold value of P value are $P < 0.05$.

incidence and severity of EDS in patients with MSA, meanwhile, EDS also might deteriorate the symptoms of depression and anxiety in patients with MSA. Our findings suggested that more attention should be paid to MSA patients with EDS and timely intervention on mood disorders might alleviate patients' daytime sleepiness.

Our findings suggested that the severity of fatigue may increase the risk of EDS and lead to more severe EDS. A previous study found that EDS and fatigue are common in patients with MSA and there was a significant correlation between fatigue and EDS (23). Therefore, the interaction between fatigue and EDS indicated that EDS may deteriorate the symptom of fatigue, on the other hand, fatigue may increase the risk of EDS. EDS was reported to be common in the patients of dementia with Lewy bodies (DLB) and PD with dementia (24), other studies also found that EDS could influence cognitive function and increase the risk of dementia (25, 26). Similarly, in the present study, we found more severe cognitive impairment might increase the risk of EDS in patients with MSA. Future studies with larger sample size and follow-up observation are needed to elucidate

TABLE 3 | Comparisons of sleep parameters between MSA patients with and without EDS.

	Total (n = 66)	MSA with EDS (n = 18)	MSA without EDS (n = 48)	*P*
TST, min	337.0 ± 90.2	350.8 ± 80.4	331.8 ± 93.9	0.449
SE, %	66.0 ± 17.3	68.0 ± 16.0	65.2 ± 17.9	0.277
SL, min	22.9 (5–28)	16.2 (5.4–23.1)	25.4 (5.0–29.0)	0.708
N1, %	32.2 (30.6–42.35)	35.4 (20.9–48.7)	30.9 (17.5–40.2)	0.163
N2, %	48.1 ± 14.6	45.2 ± 14.0	49.2 ± 14.8	0.333
N3, %	1.5 (0–0.32)	0.3 (0–0)	2.0 (0–0)	**0.007**
REM, %	18.3 ± 3.8	19.1 ± 6.9	18.0 ± 8.1	0.614
WASO, min	151.1 ± 83.9	150.3 ± 85.3	151.4 ± 84.2	0.962
Arousal index/h	19.7 (13.6–23.6)	18.6 (10.6–22.4)	20.1 (11.5–24.8)	0.746
AHI/h	22.3 (6.1–32.7)	30.5 (14.5–47.8)	19.3 (5.0–28.7)	**0.034**
OAI/h	7.4 (0–9.0)	12.8 (0–34.8)	5.8 (0–5.5)	0.080
CAI/h	0.4 (0–0.4)	1.8 (0–0.3)	1.0 (0–1.2)	**0.016**
HI/h	11.7 (3.4–17.3)	17.3 (8.6–20.6)	9.8 (2.6–15.2)	**0.018**
Minimum SaO_2, %	85.4 (83–90)	84.2 (79.8–90.0)	85.9 (84.3–90.0)	0.323
PLMI/h	25.2 (4.3–43.5)	21.9 (4.3–36.60)	26.3 (4.1–44.6)	0.619

AHI, apnea–hypopnea index; CAI, Central apnea index; EDS, excessive daytime sleepiness; HI, hypopnea index; MSA, Multiple system atrophy; OAI, obstructive apnea index; REM, rapid eye movement; SaO_2, oxygen saturation; SE, sleep efficiency; SL, sleep latency; TST, total sleep time. Values are n (%), mean ± SD or median (interquartile range). The bold value of P value are P < 0.05.

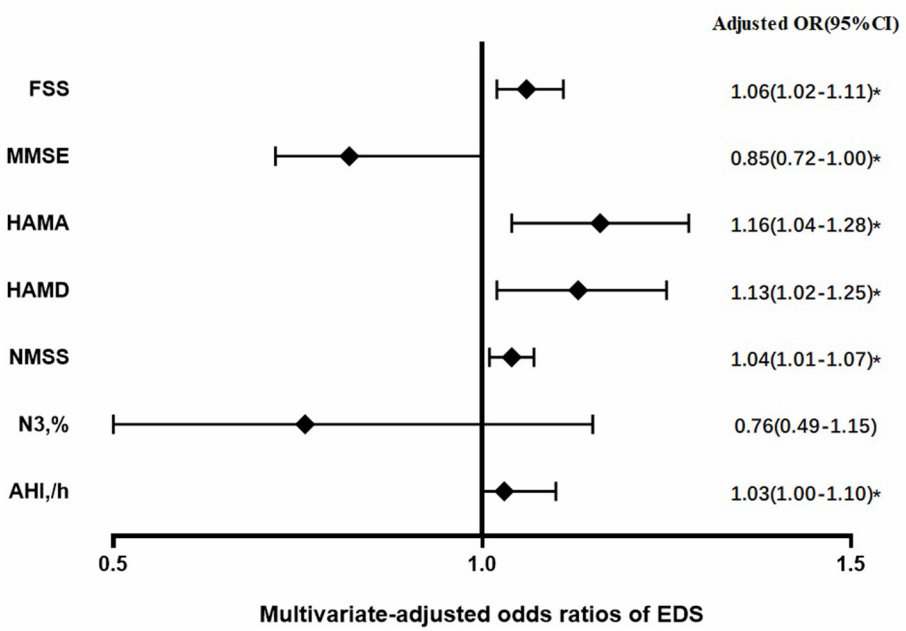

FIGURE 1 | Risk factors of excessive daytime sleepiness (EDS) in patients with multiple system atrophy (MSA) after adjustment for age, sex, disease duration, MSA sub-type, and UMSARS score; OR, odds ratio; CI, confidence interval; *P < 0.05.

the relationship between EDS and cognitive function in patients with MSA.

Our study found that MSA patients with EDS had a worse gastrointestinal function and weight loss. Gastrointestinal dysfunction is one of the common autonomic dysfunctions (AUD) in synucleinopathies including MSA, PD, DLB, and pure autonomic failure (27). Patients with MSA manifested severe autonomic dysfunction due to severe impairment in the central and peripheral autonomic networks (28). Our findings suggested that MSA patients with EDS could have more widespread impairment in the central and peripheral autonomic networks than those without EDS. In addition, the effect of gastrointestinal dysfunction can partially underlie the worsened weight loss in patients with MSA with EDS.

Sleep-related breathing disorder, including central sleep apnea, obstructive sleep apnea, and hypopnea, is common sleep disorder in patients with PD or MSA (29). Previous studies have shown that ∼15–70% of patients with MSA develop sleep-related breathing disorders (6, 7, 30). Our results showed that MSA patients with EDS had a higher prevalence of central sleep apnea and hypopnea compared to those without EDS. Furthermore, the results of logistic regression analysis indicated that more severe sleep-breathing disorders might result in a higher risk of EDS in MSA. This finding is consistent with the consensus that EDS may be stronger associated with SRBD (31). In addition, we found the percentage of N3 sleep was significantly lower in MSA patients with EDS than that without EDS. The reduction of the N3 stage might be due to the more severe SRBD in MSA patients with EDS.

The strengths of the present study included the considerable sample size and the comprehensive clinical and PSG variables. However, several limitations should be noted in this study. First, the diagnosis of MSA was based on clinical assessment and no autopsy confirmed the diagnosis, but we strictly followed the standard diagnostic criteria to ensure accuracy and consistency. Second, all patients that we included were required to have met the diagnostic criteria of probable MSA, which may have contributed to a selection bias toward more severe cases. Third, patients who took medicines such as hypnotic drugs antidepressants were excluded, which may potentially mean that patients with severe non-motor symptoms were excluded. Fourth, the EDS diagnosis was based on a questionnaire but no objective assessments of sleepiness, such as the multiple sleep latency test (MSLT). Finally, this is a cross-sectional study, and the present results should be verified and extended by larger, multicenter longitudinal studies of MSA in the future.

CONCLUSION

Our study found that 27.3% of patients with MSA had EDS, and the non-motor dysfunction including fatigue, anxiety, depression, cognitive dysfunction, and sleep-related breathing disorders were associated with an increased risk of EDS. These results may suggest that the difference of involved brain area between patients with and without EDS. Further study on the anatomic pathologic mechanism underlying EDS in MSA is needed.

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 West China Hospital Clinic Research Ethics Committee. Written informed consent to participate in this study was provided by the patient/participants or patient/participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

HW collected data, conducted statistical analysis, interpreted the data, and writing the manuscript. XT conducted statistical analysis and interpreted the data. JZ and YX collected data, conducted statistical analysis, and revised the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.798771/full#supplementary-material

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Poor Sleep Quality Associated With Enlarged Perivascular Spaces in Patients With Lacunar Stroke

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Background and Objective: Enlarged perivascular spaces (EPVSs) are considered as an MRI marker of cerebral small vessel diseases and were reported to be associated with brain waste clearance dysfunction. A previous study found that interstitial fluid clearance in the mouse brain occurred mainly during sleep. However, the relationship between sleep quality and EPVS in humans has not been well-understood. Thus, we aimed to investigate the relationship between sleep and EPVS in humans.

Methods: This retrospective study was conducted in patients with lacunar stroke in the Neurology Department of Beijing Chaoyang Hospital. Patients with EPVS >10 on one side of the basal ganglia (BG) and white matter slice containing the maximum amount were defined as the BG-EPVS group and the white matter (WM)-EPVS group, respectively. Patients with EPVS <10 in the slice containing the maximum amount were defined as the control group. Sleep quality was evaluated by the Pittsburgh Sleep Quality Index (PSQI) including seven components, where a score of 6 or higher indicated poor sleep quality. Spearman's correlation analysis and the binary logistic regression analysis were performed to analyze the relationship between poor sleep quality and BG-EPVS and WM-EPVS, respectively.

Results: A total of 398 patients were enrolled in this study, including 114 patients in the BG-EPVS group and 85 patients in the WM-EPVS group. The proportion of poor sleep quality in the BG-EPVS group was higher than that in the control group (58.8 vs. 32.5%, $p < 0.001$). The score of PSQI, subjective sleep quality, sleep latency, sleep duration, and sleep efficiency were higher in the BG-EPVS group than that in the control group ($p < 0.05$). The proportion of poor sleep quality was also higher in the WM-EPVS group than that in the control group (50.6 vs. 35.3%, $p = 0.031$). The score of sleep duration and sleep disturbances was higher in the WM-EPVS group than that in the control group. Spearman's correlation analysis showed that poor sleep quality was positively associated with BG-EPVS ($\rho = 0.264$, $p < 0.001$) and WM-EPVS ($\rho = 0.154$, $p = 0.044$). The binary logistic regression analysis showed that poor sleep quality, longer sleep latency, and less

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sleep duration were independently related to BG-EPVS and poor sleep quality, less sleep duration, and more serious sleep disturbances were independently related to WM-EPVS after adjusting for confounders ($P < 0.05$).

Conclusion: Poor sleep quality was independently associated with EPVS in BG and WM.

Keywords: enlarged perivascular spaces, Virchow-Robin spaces, cerebral small vessel diseases, Pittsburgh Sleep Quality Index, sleep quality

INTRODUCTION

Perivascular spaces, or Virchow–Robin spaces, are perivascular compartments surrounding the small cerebral penetrating vessels, serving as a protolymphatic system and playing an important role in interstitial fluid and solute clearance in the brain. They will dilate with the accumulation of interstitial fluids (1). Enlarged perivascular spaces (EPVSs), visible on MRI, appear as punctate or linear signal intensities similar to cerebrospinal fluid (CSF) on all the MRI sequences in white matter (WM-EPVS), basal ganglia (BG-EPVS), hippocampus, and brainstem (2, 3). There are some differences in the anatomical structure, mechanisms, and risk factors of BG-EPVS and WM-EPVS (4). Now, EPVS are considered as an MRI marker of cerebral small vessel diseases and are associated with age, hypertension, white matter hyperintensities (WMH), brain atrophy, and lacunes (2, 5). Some studies found that EPVSs were associated with impaired cognitive function (6), incident dementia (7), and Parkinsonism syndrome (8, 9). Therefore, it is very important to understand the pathogenesis and risk factors for EPVS.

Xie et al. (10) found that interstitial fluid clearance in the mouse brain occurred mainly during sleep, which suggested a homeostatic function of sleep through removing waste generated from neuronal metabolism. It is reasonable that poor sleep quality in humans may disrupt the removal of neurotoxins, interrupt the drainage of interstitial fluid, and possibly result in dilation of the perivascular spaces. In addition, some studies have demonstrated that poor sleep quality was associated with brain atrophy and WMH which share some risk factors with EPVS (11, 12). However, the relationship between EPVS and sleep in humans is scarcely explored. In this study, we aimed to explore whether sleep quality is associated with BG-EPVS and WM-EPVS.

MATERIALS AND METHODS

Figure 1 was the research flowchart and presented the research process.

Study Subjects

This retrospective study was conducted as a case-control study in patients with lacunar stroke. We identified all patients with acute lacunar stroke admitted to the Neurology Department of Beijing Chaoyang Hospital affiliated to Capital Medical University from April 2015 to May 2017. Lacunar stroke was confirmed by MRI and defined as a lesion of increased signal on axial diffusion-weighted imaging (DWI) $\leq$20 mm in the distribution of a small penetrating artery. Patients with lacunar stroke were excluded if: (1) they had a history of severe ischemic or hemorrhagic stroke (the largest diameter of infarct size >20 mm) on DWI and fluid-attenuated inversion recovery (FLAIR), traumatic or toxic or infectious brain injury, and brain tumor because of affecting assessments on EPVS; (2) they had possible cardioembolic sources or large-vessel cerebrovascular diseases defined as internal carotid, middle cerebral, or basilar intracranial artery stenosis >50%; (3) they had other systemic diseases including recent myocardial infarction or angina pectoris disorders, heart failure, infections, nephrosis, pulmonary diseases, liver diseases, or tumor which might affect the sleep quality.

The BG-EPVS group, the WM-EPVS group, and the control group were selected from the leaving patients with lacunar stroke according to the following inclusion criteria. Inclusion criteria of the BG-EPVS group: (1) Patients with BG-EPVS >10 on one side of the basal ganglia slice containing the maximum amount (**Figure 2A**); (2) agreed to participate in this study; (3) finished the sleep assessments. Inclusion criteria of the WM-EPVS group: (1) Patients with WM-EPVS >10 on one side of the white matter slice containing the maximum amount (**Figure 2C**). The other inclusion criteria were the same as that of the BG-EPVS group. Inclusion criteria of the control group: (1) Patients with EPVS <10 on one side of the slice containing the maximum amount (**Figures 2B,D**). The other inclusion criteria were the same as that of the BG-EPVS group. A subset of controls was, respectively, matched to the BG-EPVS group and the WM-EPVS group by age (±2 years) and sex, with one control for each case. This was due to the fact that age and sex have been found to be associated with EPVS. The cutoff >10 EPVS was used as a high grade in our previous studies and showed an excellent intrarater Cohen *k* score (13, 14).

Ethical Standard Statement

This study was approved by the Ethics Committee of Beijing Chaoyang Hospital Affiliated to Capital Medical University and was conducted in accordance with the Declaration of Helsinki. All the participants provided written informed consent.

General Clinical Characteristics Assessments

Age, sex, body mass index (BMI), past medical history including history of hypertension, diabetes mellitus, current smoking, and current alcohol consumption were collected. All blood

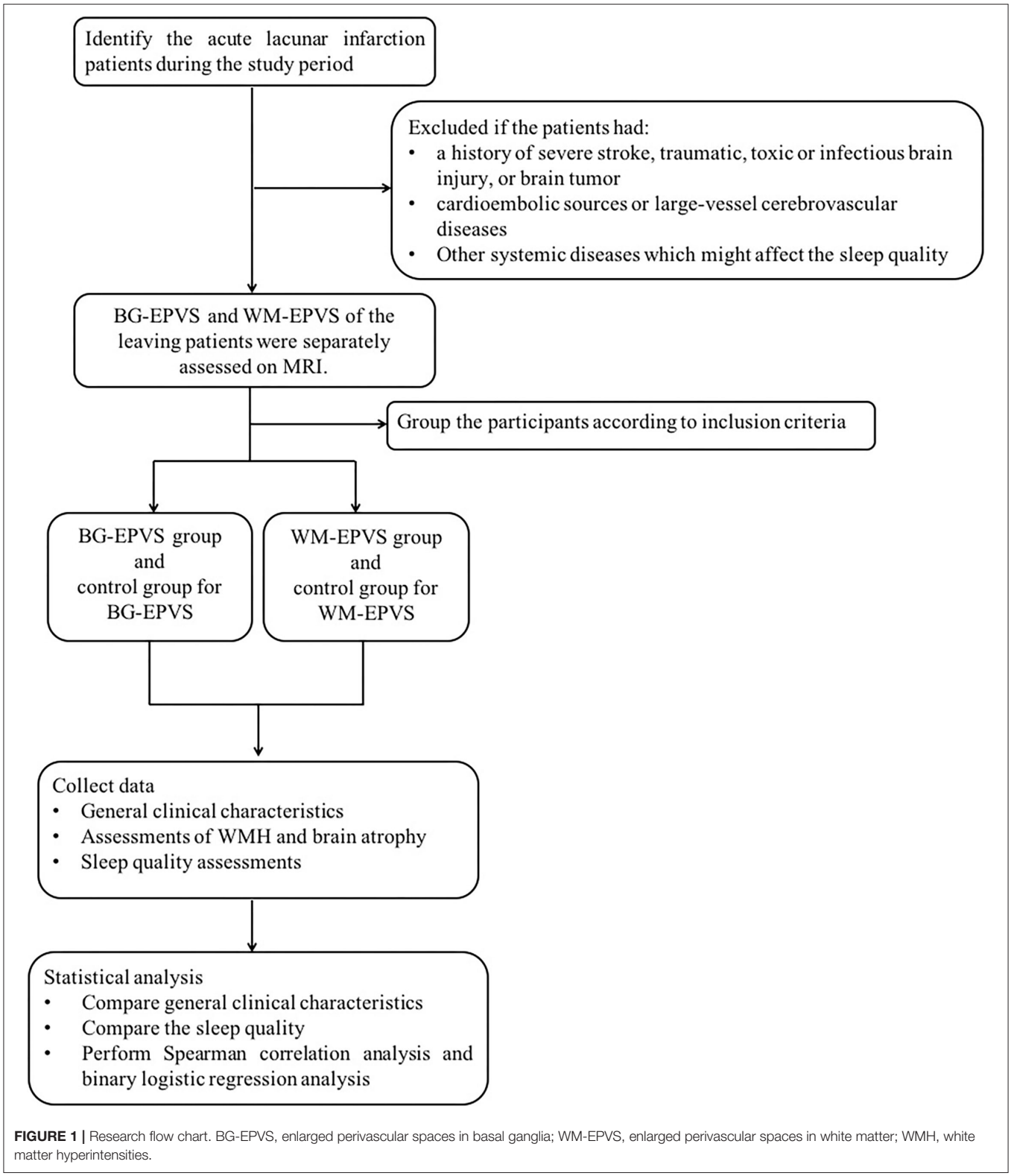

FIGURE 1 | Research flow chart. BG-EPVS, enlarged perivascular spaces in basal ganglia; WM-EPVS, enlarged perivascular spaces in white matter; WMH, white matter hyperintensities.

samples were collected in the morning after an overnight and sent to the clinical laboratory of our hospital for the measurement of serum indices. Laboratory tests included total cholesterol (TC), triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), hemoglobin A1c (HbA1c), blood urea nitrogen (BUN), and creatinine.

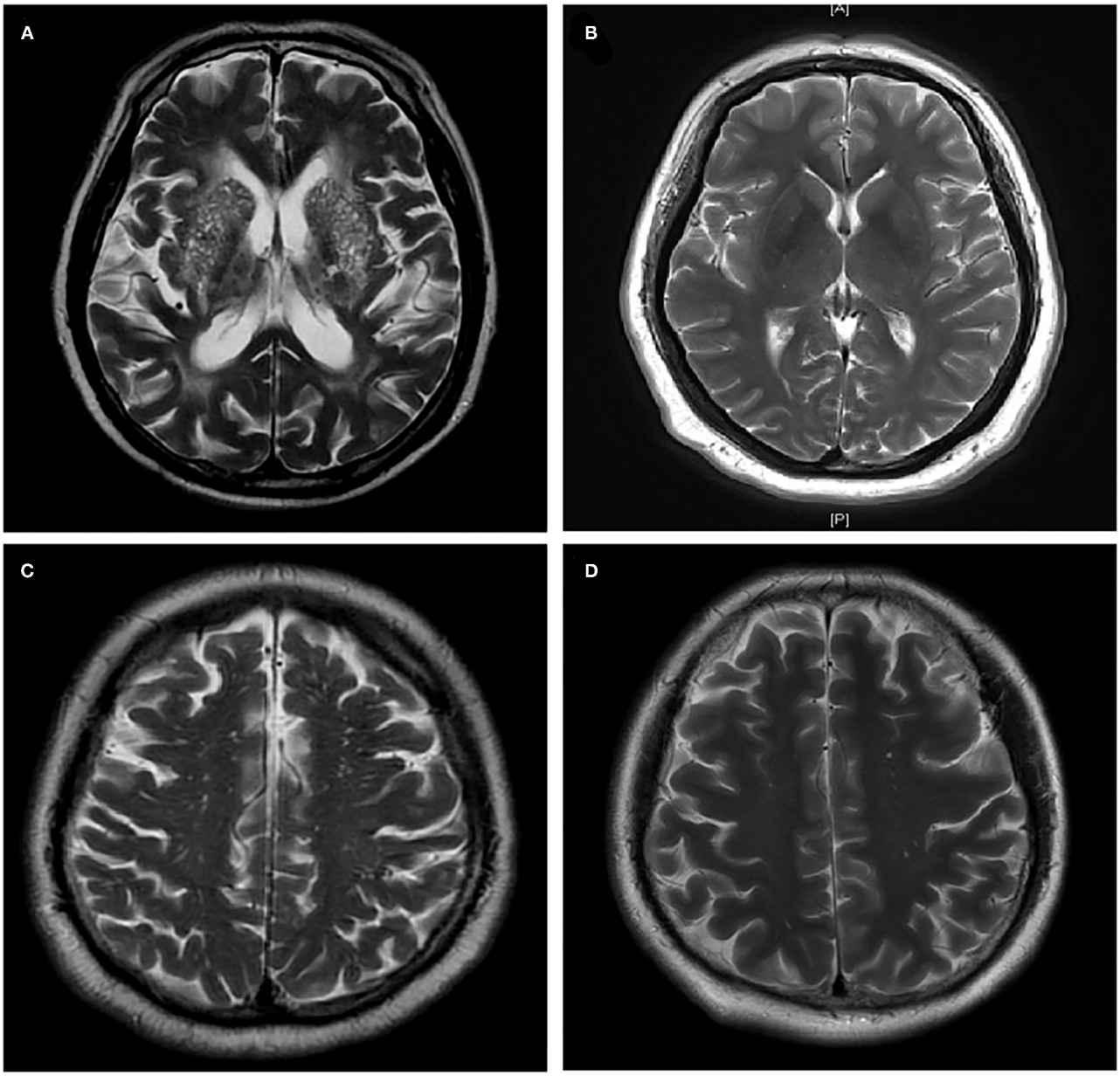

FIGURE 2 | Enlarged perivascular spaces group and control group. **(A)** Enlarged perivascular spaces in basal ganglia (BG-EPVS) group (Patients with EPVS >10 on one side of the basal ganglia slice containing the maximum amount); **(B)** control group for BG-EPVS (Patients with EPVS <10 on one side of the basal ganglia slice containing the maximum amount); **(C)** enlarged perivascular spaces in white matter (WM-EPVS) group (Patients with EPVS >10 on one side of the white matter slice containing the maximum amount); **(D)** control group for WM-EPVS (Patients with EPVS <10 on one side of the white matter slice containing the maximum amount).

MRI Examinations and Assessments of EPVS, WMH, and Brain Atrophy

The neurological image examinations were performed in the Radiology Department of our hospital. MR imagines were acquired on a 3.0 T MR scanner (Siemens, Erlangen, Germany). MRI sequences included axial T1-weighted, axial T2-weighted, axial DWI, and coronal FLAIR.

Enlarged perivascular spaces were defined as CSF-like signal intensity lesions of round, ovoid, or linear shape of <3 mm and located in areas supplied by perforating arteries. We distinguished lacune from EPVS by their larger size (>3 mm), spheroid shape, and surrounding hyperintensities on FLAIR (2). BG-EPVS and WM-EPVS were separately assessed according to the number in the slice containing the maximum amount.

White matter hyperintensities were scored by the Fazekas scale. A detailed description of the assessment has been previously published (15). Periventricular and deep WMH were evaluated separately and totaled together as Fazekas scores. Brain

atrophy was evaluated according to the visual rating scale of global cortical atrophy (GCA) (16). In mild brain atrophy (point 1) there is sulcal opening peripherally, moderate brain atrophy (point 2) is characterized by widening along the length of the sulci, and severe brain atrophy (point 3) is present when there is gyral thinning.

The intrarater agreement for the rating of EPVS, WMH, and brain atrophy was assessed on a random sample of 50 individuals with a month interval between the first and second readings. Assessments of EPVS, WMH, and brain atrophy were performed by two experienced neurologists blinded to clinical information to avoid bias. Random scans of 50 individuals were independently examined by the two experienced neurologists blinded to each other's readings. The *k* statistics of intrarater and interrater agreement was 0.80 or above, indicating good reliability. The disagreement was resolved by discussing it with other co-authors.

Sleep Quality Assessment

Sleep quality was assessed by the Pittsburgh Sleep Quality Index (PSQI) (17), which is a self-rated questionnaire. It assesses sleep quality and disturbances in the previous month and consists of 19 individual items generate seven components scores: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction due to sleepiness (maximum score is 21 points). The cutoff value for poor sleep quality is $\geq$6 points (18). The PSQI questionnaire was conducted seven days after the onset of lacunar stroke.

Statistical Analysis

Continuous variables were summarized as mean values $\pm$ SD or median (interquartile range) according to whether their distribution conformed to a normal distribution. Categorical variables were presented as absolute numbers and percentages. Continuous variables with both normal distribution and homogeneity of variance were compared with Student's *t*-test, whereas were compared with the Wilcoxon rank-sum test. The chi-squared test was used for the comparison of categorical variables. Spearman correlation analysis was performed to observe the correlation between poor sleep quality and EPVS. Grouping was considered as the dependent variable and binary logistic regression analysis was performed to explore if poor sleep quality was independently related to BG-EPVS and WM-EPVS after adjusting for confounding factors. Analysis was performed with Statistical Package for Social Sciences (SPSS) (version 21.0), and statistical significance was accepted at $p < 0.05$.

RESULTS

General Clinical Characteristics of Participants

During the study period, 482 patients with acute lacunar infarction were identified. However, 20 patients were excluded because of the history of severe ischemic or hemorrhagic stroke, 35 patients were excluded because of large-vessel cerebrovascular diseases, 5 were excluded because of a history of tumor, and 7 were excluded because of atrial fibrillation. Of the leaving 415 patients with lacunar infarction, 114 patients were enrolled into the BG-EPVS group and 85 patients were enrolled into the WM-EPVS group. The same number of age and sex-matched controls were also recruited in the same population. Finally, 398 patients were enrolled in the study. The mean age of the cohort was 68 $\pm$ 9.8 years and 221 (55.5%) of them were men. In total, 142 subjects were current smokers and 78 were current alcohol users. In total, 300 subjects had a history of hypertension, and 171 had diabetes. The general clinical characteristics of the BG-EPVS group, the WM-EPVS group, and the control group are given in **Table 1**.

There were no statistical significances in BMI, the proportion of current alcohol, hypertension, and diabetes between the BG-EPVS group and the control group. The proportion of current smoking in the BG-EPVS group was lower than that in the control group. The BG-EPVS group had higher level of blood urea nitrogen (median: 5.53 vs. 4.85 mmol/l, $p = 0.003$) and lower level of HbA1c (median: 6.0 vs. 6.8%, $p = 0.001$). Considering the imaging characteristics, the BG-EPVS group had more serious WMH [Fazekas scale: 5 (4–6) vs. 2 (2–4), $p < 0.001$] and brain atrophy [GCA scale: 1 (1–2) vs. 1 (0–1), $p < 0.001$].

The comparative results of general clinical characteristics between the WM-EPVS group and the control group were different from those between the BG-EPVS group and the control group. The proportion of current smoking in the WM-EPVS group was higher than that in the control group (43.5 vs. 24.7%, $p = 0.010$). There were no statistical significances in the proportion of current alcohol, hypertension, and diabetes, the levels of laboratory tests, and imaging characteristics between the WM-EPVS group and the control group.

Association Between Sleep Quality and BG-EPVS

The PSQI score, proportion of poor sleep quality, and scores of sleep components including subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction due to sleepiness are given in **Table 2**.

The BG-EPVS group had the higher PSQI score and a higher proportion of poor sleep quality (PSQI score $\geq$6 points) than the control group [PSQI score: 6 (4–10) vs. 4 (3–7), $p < 0.001$, poor sleep quality: 58.8 vs. 32.5%, $p < 0.001$]. Spearman's correlation analysis showed that the PSQI score and poor sleep quality were positively associated with BG-EPVS (PSQI score: $\rho = 0.248$, $p < 0.001$, poor sleep quality: $\rho = 0.264$, $p < 0.001$). The results of the binary logistic regression analysis showed that poor sleep quality was independently related to BG-EPVS after adjusting for current smoking, level of HbA1c, blood urea nitrogen, WMH, and brain atrophy. The detailed analysis results are shown in **Table 3**.

Furthermore, we analyze the relation between sleep components and BG-EPVS. The score of subjective sleep quality [1 (1–2) vs. 1 (0–1), $p = 0.001$], sleep latency [1 (0–3) vs. 1 (0–1), $p = 0.004$], sleep duration [1 (0–2) vs. 1 (0–1), $p = 0.003$], and sleep efficiency [1 (0–2) vs. 0 (0–1), $p = 0.021$] were higher in the BG-EPVS group than that in the control group, which mean that the BG-EPVS group had longer sleep latency, less sleep duration, and lower sleep efficiency. There was no

TABLE 1 | General clinical characteristics of participants.

Characteristics	BG-EPVS group	control group for BG-EPVS	*P*	WM-EPVS group	control group for WM-EPVS	*P*
n	114	114	–	85	85	–
Age[a], years	71 ± 8.5	69 ± 9.4	0.174	68 ± 9.8	70 ± 9.3	0.295
Sex, male (%)	69 (60.5)	45 (39.5)	0.410	58 (68.2)	49 (57.6)	0.204
BMI[a], kg/m^2	24.9 ± 2.8	25.4 ± 3.0	0.168	25.4 ± 2.8	25.2 ± 3.2	0.759
Current smoking (%)	31 (26.3)	53 (46.5)	0.003	37 (43.5)	21 (24.7)	0.010
Current alcohol (%)	23 (20.2)	26 (22.8)	0.603	17 (20.0)	12 (14.1)	0.308
Hypertension (%)	90 (78.9)	79 (69.3)	0.096	70 (82.4)	61 (71.8)	0.101
Diabetes (%)	45 (39.5)	54 (47.4)	0.229	36 (42.4)	36 (42.4)	1.000
TC[a,b], mmol/L	4.3 ± 1.04	4.5 ± 1.22	0.116	4.35 (3.64–5.11)	4.22 (3.58–5.08)	0.589
Triglyceride[b], mmol/L	1.32 (1.01–1.86)	1.40 (1.05–2.06)	0.331	1.35 (1.03–2.05)	1.32 (0.95–1.84)	0.476
HDL[b], mmol/L	1.13 (0.93–1.30)	1.10 (0.90–1.30)	0.604	1.10 (0.90–1.30)	1.20 (1.00–1.40)	0.136
LDL[a], mmol/L	2.60 ± 0.83	2.70 ± 0.93	0.711	2.77 ± 0.86	2.56 ± 0.83	0.100
HbA1[b], %	6.0 (5.6–6.8)	6.8 (5.8–8.0)	0.001	6.2 (5.6–7.6)	6.1 (5.7–7.2)	0.875
BUN[a,b], mmol/L	5.53 (4.50–6.85)	4.85 (3.84–6.24)	0.003	5.63 ± 1.98	5.72 ± 1.70	0.307
Creatinine[b], umol/L	68.4 (56.8–81.7)	64.6 (54.5–79.7)	0.294	68.5 (56.2–84.4)	66.3 (54.7–77.9)	0.362
WMH[b], point	5 (4–6)	2 (2–4)	<0.001	3 (2–6)	4 (2–6)	0.196
Brain atrophy[b], point	1 (1–2)	1(0–1)	<0.001	1 (0–1)	1 (0–2)	0.186

BMI, body mass index; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HbA1c, hemoglobin A1c; BUN, blood urea nitrogen; WMH, white matter hyperintensities.

[a]Continuous variables with normal distribution were expressed as mean values ± standard deviation and were compared with Student's t-test.

[b]Continuous variables with non-normally distribution were expressed as median (interquartile range) and compared with Wilcoxon rank-sum test.

TABLE 2 | Sleep variables by Pittsburg Sleep Quality Index of the enlarged perivascular space (EPVS) group and the control group.

Sleep variables	BG-EPVS group	control group for BG-EPVS	*P*	WM-EPVS group	control group for BG-EPVS	*P*
Pittsburgh Sleep Quality Index, point	6 (4–10)	4 (3–7)	<0.001	6(3–8.5)	5(3–7.5)	0.165
Poor sleep quality (%)	58.8	32.5	<0.001	50.6	35.3	0.031
Subjective sleep quality, point	1 (1–2)	1 (0–1)	0.001	1(1–2)	1(1–2)	0.281
Sleep latency, point	1 (0–3)	1 (0–1)	0.004	1(0–2)	1(0–2)	0.935
Sleep duration, point	1 (0–2)	1 (0–1)	0.003	1(0–2)	1(0–1.5)	0.025
Sleep efficiency, point	1 (0–2)	0 (0–1)	0.021	1(0–2)	1(0–1)	0.211
Sleep disturbances, point	0 (0–1)	0 (0–1)	0.545	1(0–1)	0(0–1)	0.006
Use of sleeping medication, point	0 (0–0)	0 (0–0)	0.054	0(0–0)	0(0–0)	1.000
Daytime dysfunction, point	1 (1–2)	1 (0–2)	0.124	1(0–2)	1(0–2)	0.655

The above non-normal distributed continuous variables were expressed as median (interquartile range) and compared with the Wilcoxon rank-sum test.

TABLE 3 | Results of the binary logistic regression analysis between sleep quality and enlarged perivascular spaces in basal ganglia (BG-EPVS).

Sleep variables	B	*P*	Odds ratio	95% Confidence intervals
Poor sleep quality (%)	0.754	0.022	2.125	1.113–4.058
Sleep latency	0.293	0.048	1.340	1.003–1.791
Sleep duration	0.360	0.024	1.434	1.050–1.958
Sleep efficiency	0.244	0.120	1.276	0.938–1.735

Binary logistic regression analysis was performed adjusting for current smoking use, level of hemoglobin A1c and blood urea nitrogen, WMH, and brain atrophy.

statistical significance in the score of sleep disturbances, use of sleeping medication, and daytime dysfunction between the BG-EPVS group and the control group. The results of the binary logistic regression analysis showed that longer sleep latency and less sleep duration were independently related to BG-EPVS after adjusting for current smoking, level of HbA1c, blood urea nitrogen, WMH, and brain atrophy. The detailed analysis results are shown in **Table 3**.

Association Between Sleep Quality and WM-EPVS

The PSQI score, proportion of poor sleep quality, and sleep components score of the WM-EPVS group and the control group for WM-EPVS are shown in **Table 2**.

Although there was no statistical difference in PSQI score between the WM-EPVS group and the control group, the proportion of poor sleep quality (PSQI score ≥6 points) was higher in the WM-EPVS group than that in the control group (50.6 vs. 35.3%, $p = 0.031$). Spearman's correlation analysis

TABLE 4 | Results of the binary logistic regression analysis between sleep quality and enlarged perivascular spaces in white matter (WM-EPVS).

Sleep variables	B	*P*	Odds ratio	95% Confidence intervals
Poor sleep quality (%)	0.632	0.048	1.882	1.005–3.527
Sleep duration	0.408	0.016	1.504	1.080–2.094
Sleep disturbance	0.814	0.010	2.257	1.220–4.175

The binary logistic regression analysis was performed adjusting for current smoking use.

showed that poor sleep quality was positively correlated to WM-EPVS ($\rho = 0.154$, $p = 0.044$). The binary logistic regression analysis indicated that poor sleep quality was independently related to WM-EPVS (**Table 4**).

About the relation between sleep components and WM-EPVS, the score of sleep duration [1 (0–2) vs. 1 (0–1.5), $p = 0.025$] and sleep disturbances [1 (0–1) vs. 0 (0–1), $p = 0.006$] were higher in the WM-EPVS group than that in the control group. The results of the binary logistic regression analysis indicated that less sleep duration and sleep disturbance were independent risk factors for WM-EPVS (**Table 4**).

DISCUSSION

In this study, we explored the relationship between sleep quality and BG-EPVS and WM-EPVS, respectively, in a lacunar infarction population. We found that poor sleep quality was positively related to BG-EPVS and WM-EPVS. The binary logistic regression analysis showed that poor sleep quality was independently associated with BG-EPVS and WM-EPVS after adjusting for confounders. In addition, we found patients with BG-EPVS had longer sleep latency, less sleep duration, and lower sleep efficiency. Patients with severe WM-EPVS had less sleep duration and more serious sleep disturbances. Binary logistic regression analysis showed that longer sleep latency and less sleep duration were independently related to BG-EPVS, and less sleep duration and more serious sleep disturbances were independently related to WM-EPVS.

Perivascular spaces are thought to serve as a protolymphatic system and play an important role in maintaining neural homeostasis (1). The sulcal CSF is either cleared through the arachnoid granulations or enters the parenchyma via the perivascular spaces, where it combines with interstitial fluid prior to exiting the brain. This perivascular drainage system also allows for the clearance of toxic metabolites within the parenchyma and possibly plays a role in the immunological response of the brain (19–21). EPVSs are thought to be the result of a perivascular blockage, which can be exacerbated by beta-amyloid deposition around cerebral vessels, arteriosclerosis, and decreased arterial pulsatility. In addition, venular amyloid and collagenosis may also contribute to the development of EPVS (22, 23). Although a few EPVS visible on MRI can be normal, the presence of many is not normal and they are associated with some age-related disorders, including cognitive dysfunction, Parkinson's syndrome, WMH, and lacunar infarction (1, 3). It is very important to explore the risk factors for the large amount of EPVS. In this study, EPVS > 10 on one side of the slice containing the maximum amount was defined as the EPVS group. The cutoff >10 EPVS has been used as a high grade in previous studies and showed an excellent intra-rater Cohen k score.

Previously, several studies investigated the relationship between sleep and other MRI markers of cerebral small vessel diseases, such as WMH, lacunar infarction, and deep microbleeds (12, 18). However, to the best of our knowledge, the clinical studies specifically addressing the association between EPVS and sleep quality were scarce. Courtney Berezuk et al. (24) explored the relationship between EPVS in basal ganglia and white matter and sleep by polysomnography among 26 patients with stroke or vascular risk factors. Findings from the study suggested that sleep efficiency was negatively correlated with total EPVS and BG-EPVS, and wake after sleep onset was positively correlated with BG-EPVS. Oscar H. Del Brutto et al. (25) assessed the association between sleep parameters with the PSQI and enlarged BG-PVS in older adults. They found that poor sleep efficiency was independently associated with enlarged BG-PVS, suggesting that sleep may influence structural changes in these fluid-filled cavities. In this study, we analyzed the relationship between sleep quality and BG-EPVS and WM-EPVS, respectively. We found that poor sleep quality was not only independently related to BG-EPVS, but also WM-EPVS. In addition, our results showed that the relation between sleep variables and BG-EPVS was not exactly the same as the relation between sleep variables and WM-EPVS. This might be related to the different pathogenesis of EPVS at the different brain regions. WM-EPVS might reflect cerebral amyloid angiopathy (26), whereas BG-EPVS mainly indicate hypertensive arteriopathy (2), which might be related to the different anatomical structures of EPVS in basal ganglia and white matter. The arteries in the basal ganglia are surrounded by two distinct coats of leptomeninges separated by a perivascular space which is continuous with the perivascular space around arteries in the subarachnoid space, whereas there is only a single periarterial layer of leptomeninges surrounding the arteries in the cerebral cortex and they penetrate into the white matter (27). It was speculated that the anatomical variability may account for differences in clearance efficiency along these drainage pathways. In addition, the influence of age and hypertension on BG-EPVS seems to be stronger than that on WM-EPVS (28). The association between BG-EPVS and WMH also appears to be stronger than that between WM-EPVS and WMH. The exact reason and mechanisms should be further explored in the future.

The potential pathophysiological mechanisms underlying the association between sleep and EPVS are complex and still not completely understood. In an experimental mice model, Xie et al. examined the clearance rates of exogenous and endogenous (beta-amyloid) tracers during awake, sleep, and anesthetized condition (10). They found that the rate of clearance in mice was greatest during sleep. When mice were awake, the tracer influx into the perivascular space decreased compared to natural and anesthesia-induced sleep. The clearance rate of beta-amyloid in the sleeping mice was two times as quick as that in awake mice. These results were explained by a 60% increase in interstitial space volume fraction during sleep, indicating decreased tissue resistance, allowing for greater fluid influx/efflux. This sleep-deprived increase in interstitial space volume may be modulated

by changes in sleep-related neurotransmitters, simultaneously modulating sleep onset and metabolite clearance. Therefore, it is reasonable that poor sleep quality contributes to the development of EPVS by influencing the clearance rates of exogenous and endogenous tracers in the brain. This study suggested that poor sleep quality and less sleep duration were independently related to EPVS in both basal ganglia and white matter, which supported the hypothesis. Of course, this should be further demonstrated in the future.

There were some limitations in this study. First, this study was based on patients with lacunar infarction in a small single center, and the cohort may not represent the general population. Second, this was not a prospective cohort study, and the causal relationship between poor sleep quality and EPVS could not be established. Third, sleep quality was assessed by the PSQI. The self-reported sleep variables are less accurate than overnight polysomnography recordings. Despite these limitations, this study investigated the relationship between sleep quality and EPVS in a larger sample compared to the previous study in humans. The PSQI questionnaires have the advantage of being easy to use in clinical practice and reflect the subjective feelings, discomfort, and dissatisfaction with their sleep. We found poor sleep quality was independently associated with EPVS, which would provide some information about the risk factors and pathogenesis for EPVS.

In summary, we found that poor sleep quality was independently related to BG-EPVS and WM-EPVS in patients with lacunar stroke. In addition, we found longer sleep latency and less sleep duration were independently related to BG-EPVS, and less sleep duration and more serious sleep disturbances were independently related to WM-EPVS. The relationship should be further assessed by longitudinal studies in the future.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

WH and SY conceived and designed the experiments. JY and SY participated in the data collection. WQ and LY assessed the imagings. JY participated in the analysis of the data. SY drafted the manuscript. WH and JY revised the manuscript. All authors read and approved the final manuscript to be published.

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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.2021.809217/full#supplementary-material

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Cerebrospinal Fluid TNF-α and Orexin in Patients With Parkinson's Disease and Rapid Eye Movement Sleep Behavior Disorder

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Background: Parkinson's disease (PD) pathological changes begin before motor symptoms appear. Rapid eye movement sleep behavior disorder (RBD) has the highest specificity and predictive value of any marker of prodromal PD. Tumor necrosis factor α (TNF-α) plays a part in the pathology of PD and disease conversion in isolated RBD (iRBD). TNF can also directly impair the hypocretin system in mice *in vivo*. As a result, we intend to investigate the effect of TNF-α on orexin levels in PD patients with RBD.

Method: Participants were recruited from the Department of Neurology of Xuanwu Hospital, Capital Medical University to engage in assessments on motor symptoms, sleep, cognition, etc. Then we collected blood and cerebrospinal fluid of all patients and 10 controls' cerebrospinal fluid. The levels of TNF-α in the serum and cerebrospinal fluid, as well as the level of orexin in the cerebrospinal fluid, were measured in the patients.

Results: The difference in TNF- levels in cerebrospinal fluid and serum between the three groups were not statistically significant. The levels of orexin in the three groups were not significantly lower than in the control group. UPDRS-III scores were significantly higher in the PD+RBD and PD-RBD groups than in the iRBD group. There was no statistically significant difference in H-Y stages, PSQI, or ESS scores between the PD+RBD and PD-RBD groups.

Conclusion: Our findings suggest that TNF-α may not have a significant effect on the orexinergic system in patients with Parkinson's disease and iRBD. As a result, it is necessary to investigate the changes in TNF-α and orexin levels in different disease stages and to enlarge the sample size to determine whether TNF-α affects the function of the orexin system, which may be related to the occurrence of RBD and disease progression in Parkinson's disease.

Keywords: rapid eye movement sleep behavior disorder, Parkinson's disease, cerebrospinal fluid, TNF-α, orexin

INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative disease characterized clinically by resting tremor, bradykinesia, rigidity, and postural balance disorder. The presence of fibrillar aggregates, known as Lewy bodies (LBs), in which α-synuclein is a major constituent, is a histopathological hallmark of Parkinson's disease (1). With the in-depth study of the disease, non-motor symptoms (NMS) have received increasing attention and have become a new research hotspot in Parkinson's disease. Hyposmia, autonomic dysfunction, anxiety and depression, cognitive impairment, and sleep disturbances are a few examples.

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by loss of muscle atonia with abnormal dream-enacting behavior during REM sleep (2), which can result in injuries to these individuals and their bed partners. Idiopathic or isolated RBD (iRBD) is defined as RBD in the absence of any relevant neurological disorder or other precipitating factors (2). According to a longitudinal study, the majority of patients are eventually diagnosed with synucleinopathies such as Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA) (3). Multicenter prospective cohort studies have shown that over 60% of iRBD developed overt α-synucleinopathies in a decade or more and the phenoconversion rate was 6.25% per year (4). A meta-analysis confirmed a risk of more than 90% at 14 years (5). Furthermore, RBD confirmed by polysomnography (PSG) has by far the highest specificity and predictive value of any prodromal PD marker (6). According to Braak, α-synuclein deposition begins in the anterior olfactory nucleus, the dorsal motor nucleus of the vagus (7), implying that the pathological changes of PD begin before motor symptoms manifest. As a result, the clinical diagnosis for Parkinson's disease treatment may be delayed. For this reason, identifying reliable biomarkers is critical.

Orexins, also known as hypocretins, are neuropeptides produced by the hypothalamus and play a part in metabolism, feeding, reward, addiction, and sleep-wake control (8). According to the LU-SAPER model (9), orexin may indirectly participate in the innervation of spinal motor neurons by the sublaterodorsal tegmental nucleus (SLD) *via* fiber projections to the lateral pontine tegmentum (LPT), influencing REM atonia during sleep.

TNF-α, a potent pro-inflammatory cytokine, is recognized as an important mediator of neuroinflammation in the brain (10). TNF-α produced in large by activated microglia contributes to neuroinflammatory processes in a variety of neurological disorders (11). TNF-α has been shown to play a role in the pathology of Parkinson's disease (12) and disease conversion in iRBD (13). According to a study, TNF can impair the hypocretin system directly *in vivo* in mice. The research also suggests that repeated TNF challenge induces RBD-like behavior and sleep dysfunction in mice, as well as a decrease in learning, cognition, and memory (14).

As a result, we wonder if there are any links between the levels of TNF-α and orexin in cerebrospinal fluid (CSF) in patients with Parkinson's disease and rapid eye movement sleep behavior disorder. We recruited patients to investigate the above-mentioned correlations. TNF-α and orexin levels in cerebrospinal fluid and serum TNF-α were measured and compared.

METHOD

Participants

Patients with Parkinson's disease and iRBD were recruited for this study from the Department of Neurology of Xuanwu Hospital, Capital Medical University. To assess subjects on motor symptoms, sleep, cognition and emotion, we used Unified Parkinson's Disease Rating Scales part III (UPDRS-III), Hoehn-Yahr (H-Y) stage, Pittsburgh sleep quality index (PSQI), Epworth sleepiness scale (ESS), REM Sleep Behavior Disorder Questionnaire-Hong Kong (RBDQ-HK), Cognitive impairment uses Montreal Cognitive Assessment (MoCA), Hamilton rating scale for anxiety (HAMA) and Hamilton rating scale for depression (HAMD). Patients were classified in iRBD, PD with RBD (PD+RBD), PD without RBD (PD–RBD) groups. The following were the inclusion criteria for Parkinson's disease patients: (1) diagnosis refer to MDS clinical diagnostic criteria for Parkinson's disease (15), (2) age range of 40 to 80 years. The diagnosis of RBD refers to the International Classification of Sleep Disorders, Third Version (ICSD-3). Exclusion criteria were as follows: (1) those with parkinsonism from a cause other than Parkinson's disease, (2) those with a history of head injury, brain tumor, encephalitis, stroke; and abnormal electroencephalography (EEG) suggesting epilepsy, (3) those who take sleeping pills or antipsychotics, use sedative-hypnotic drugs or alcohol to help sleep and are unable to withdraw, (4) those who are unable to complete overnight PSG. The following criteria were used to select 10 age-matched control subjects: no neurodegenerative diseases, no sleep disorders, and no epilepsy. The overnight video-polysomnograph examination was performed and analyzed for 145 patients.

Clinical Assessment

Patients were subjected to a thorough neurological examination, which included the Unified Parkinson's Disease Rating Scale part III (UPDRS III) and the Hoehn-Yahr (H-Y) stage for motor symptoms. The REM Sleep Behavior Disorder Questionnaire-Hong Kong (RBDQ-HK) was used to assess RBD. Daytime sleepiness and sleep quality were assessed using the Epworth sleepiness scale (ESS) and the Pittsburgh sleep quality index (PSQI). Cognitive impairment was evaluated using the Montreal Cognitive Assessment (MoCA). To quantify anxiety and depressive symptom severity, the Hamilton rating scale for anxiety (HAMA) and Hamilton rating scale for depression (HAMD) were used.

Video-Polysomnograph

The Compumedics E-series polysomnography monitoring system, manufactured in Australia by Compumedics, was used to monitor patients' sleep throughout the night. The monitoring content includes EEG (electrodes installed in accordance with the international 10–20 system, respectively F3, F4, C3, C4, O1-A2, O2-A1), electrooculogram, chin, and both lower limbs EMG, mouth Nasal airflow (pressure sensing and thermal

sensing), chest and abdomen breathing, electrocardiogram, and blood oxygen saturation.

CSF and Serum Samples Collection and Analysis

CSF was collected from 20 patients *via* lumbar puncture standardized procedures and placed in siliconized polypropylene tubes. The samples were then centrifuged for 10 min at 4°C within 30 min of blood collection. After centrifugation, the extracted samples were stored at −80°C. The level of orexin was measured by radioimmunoassay. TNF-α level was measured by chemiluminescent immunoassay. TNF-α was evaluated using the IMMULITE/IMMULITE 1000 TNF-α kits (Siemens Healthcare Diagnostics, Llanberis, UK) according to manufacturer instructions. The average intra- and inter-assay coefficients of variation were 3.5% and 6.5%, respectively.

Statistical Analysis

We used mean, standard deviation, median, range, and quartile to present data. The SPSS version 25 software package was used to perform all statistical analyses. One-way ANOVA was used to analyze data with a normal distribution. We used the Kruskal Wallis H test for non-normal distribution data. The chi-square test was used to analyze data for categorical variables. Pearson correlation analysis was used to assess the statistical relationship between TNF-α and orexin levels. A p-value of <0.05 was considered statistically significant.

RESULTS

Demographics and Clinical Assessments

According to the inclusion criteria listed above, a total of 145 patients were studied, including 38 PD patients with RBD, 55 PD patients without RBD, and 52 iRBD patients. Clinical data were compared between the PD+RBD, PD-RBD, and iRBD groups (motor symptoms, non-motor symptoms: cognition, emotion, and sleep). There was no significant difference in age or gender ratio among the included patients. UPDRS-III scores were significantly higher in the PD+RBD and PD-RBD groups than in the iRBD group [22 (14.89, 34.50) vs. 17 (15.45, 26.50) vs. 1 (0, 2.25), $P < 0.001$]. There was no remarkable difference in H-Y stages, PSQI, ESS scores between PD+RBD and PD-RBD groups. However, RBDQ-HK scores in the iRBD group were significantly higher than those in the other groups with

TABLE 1 | Demographics and clinical tests including Unified Parkinson's Disease Rating Scale part III (UPDRS-III) and Hoehn-Yahr (H-Y) stage scores, Pittsburgh sleep quality index (PSQI), Epworth sleepiness scale (ESS), REM Sleep Behavior Disorder Questionnaire-Hong Kong (RBDQ-HK), Montreal Cognitive Assessment (MoCA), Hamilton rating scale for anxiety (HAMA), Hamilton rating scale for depression (HAMD) in Parkinson's disease (PD), isolated rapid eye movement sleep behavior disorder (iRBD) and PD with RBD subjects.

	PD+RBD		PD-RBD		iRBD		*P*-value
	N		*N*		*N*		
Age (mean ± SD), years	38	64.35 ± 9.83	55	59.94 ± 9.17	52	63.33 ± 8.88	0.053
Gender (Male number/%)	38	22.00/57.89%	55	29.00/52.73%	52	33.00/63.46%	0.532
UPDRS-III [M, (P25, P75)]	9	22.00 (14.89, 34.50)	5	17.00 (15.45, 26.50)	10	1.00 (0, 2.25)	<0.001[bc]
H-Y stage (mean, range)	36	2.06, 1–4	48	2.03, 1–3	-	-	-
PSQI [M, (P25, P75)]	9	5.00 (4.50, 7.86)	5	8.00 (5.86, 16.50)	10	6.00 (2.75, 6.72)	0.115
ESS (mean ± SD)	37	4.50 ± 3.55	43	5.00 ± 4.24	48	4.88 ± 4.29	0.854
RBDQ-HK (mean ± SD)	37	22.38 ± 18.74	43	15.66 ± 14.28	48	34.07 ± 19.16	<0.001[ac]
MoCA (mean ± SD)	21	21.01 ± 4.28	21	21.77 ± 4.38	20	23.87 ± 3.11	0.067
HAMA (mean ± SD)	12	18.17 ± 5.82	6	14.92 ± 6.76	19	12.24 ± 6.00	0.040[b]
HAMD (mean ± SD)	12	13.92 ± 3.98	6	14.08 ± 4.59	19	8.92 ± 8.87	0.106
TIB [M, (P25, P75)], min		500.50 (518.00, 578.50)		545.75 (521.35, 567.60)		546.50 (523.35, 578.35)	0.773
TST [M, (P25, P75)], min		365.00 (313.00, 457.00)		380.75 (305.00, 427.50)		385.50 (329.10, 443.25)	0.483
SE [M, (P25, P75)], %		69.90 (55.60, 81.70)		68.55 (56.15, 78.95)		71.80 (60.60, 82.55)	0.477
SL [M, (P25, P75)], min		13.50 (6.50, 32.50)		23.75 (12.00, 50.85)		23.25 (7.60, 42.00)	0.133
WASO [M, (P25, P75)], min		102.00 (57.00, 154.00)		101.00 (77.50, 154.60)		95.00 (50.85, 154.00)	0.559
N1 [M, (P25, P75)], %TST	38	9.00 (5.80, 14.80)	55	8.75 (5.10, 15.10)	52	9.50 (6.40, 13.80)	0.919
N2 [M, (P25, P75)], %TST		49.20 (37.10, 56.60)		50.60 (38.90, 60.60)		52.20 (45.00, 58.75)	0.612
N3 [M, (P25, P75)], %TST		21.90 (10.50, 34.60)		21.95 (15.30, 31.75)		18.20 (12.65, 27.20)	0.305
R [M, (P25, P75)], %TST		14.70 (12.70, 22.60)		13.40 (9.05, 19.00)		17.80 (14.25, 21.40)	0.011[c]
AHI [M, (P25, P75)], /hr		6.20 (2.30, 17.50)		2.50 (0.25, 8.50)		6.15 (1.75, 19.45)	0.054
PLMSI [M, (P25,P75)], /hr		0 (0, 49.30)		0 (0, 46.00)		0 (0, 59.10)	0.859

N, number; SD, standard deviation; M, median; P25, 25% percentile values; P75, 75% percentile values.

[a]*p-values significant differences were found between PD+RBD and PD-RBD groups.*

[b]*p-values significant differences were found between PD+RBD and iRBD groups.*

[c]*p-values Significant differences were found between PD-RBD and iRBD groups.*

statistical significance (22.38 ± 18.74 vs. 15.66 ± 14.28 vs. 34.07 ± 19.16, $P < 0.001$). Although there was no statistically significant difference, the MoCA score in the PD+RBD group was lower than the PD-RBD group (21.01 ± 4.28 vs. 21.77 ± 4.38). The PD+RBD group's HAMA score was significantly higher than the iRBD group's (18.17 ± 5.82 vs. 14.92 ± 6.76, $P = 0.004$). Nonetheless, there was no discernible difference in HAMD scores between the three groups. **Table 1** shows the demographics and clinical scores of study participants, as well as their comparison.

Biomarker Data

In this study, no significant difference was observed in the serum TNF-α levels among the three groups (5.73 ± 0.73 vs. 6.01 ± 1.31 vs. 4.51 ± 0.45 pg/ml, $P = 0.773$). Also, no significant difference was observed in the CSF TNF-α levels between the three groups (4.20 ± 0.37 vs. 4.47 ± 0.58 vs. 6.28 ± 2.20 pg/ml, $P = 0.368$). CSF orexin levels were abnormal (<200 pg/ml) in all PD+RBD, PD-RBD and iRBD patients (177.69 ± 46.04, 177.31 ± 29.40, 166.23 ± 40.62 pg/ml). Yet the orexin levels of the three groups were not significantly lower than the control group. Furthermore, there

TABLE 2 | Biomarkers including tumor necrosis factor-alpha (TNF-α) in serum and cerebrospinal fluid (CSF), orexin in cerebrospinal fluid in the three groups.

	PD+RBD ($n = 9$)	PD–RBD ($n = 4$)	iRBD ($n = 7$)	Control ($n = 10$)	*P*-value
Serum TNF-α (mean ± SD), pg/mL	5.73 ± 0.73	6.01 ± 1.31	4.51 ± 0.45	NA	0.773
CSF TNF-α (mean ± SD), pg/mL	4.20 ± 0.37	4.47 ± 0.58	6.28 ± 2.20	NA	0.368
CSF orexin (mean ± SD), pg/mL	177.69 ± 46.04	177.31 ± 29.40	166.23 ± 40.62	218.83 ± 43.36	0.224

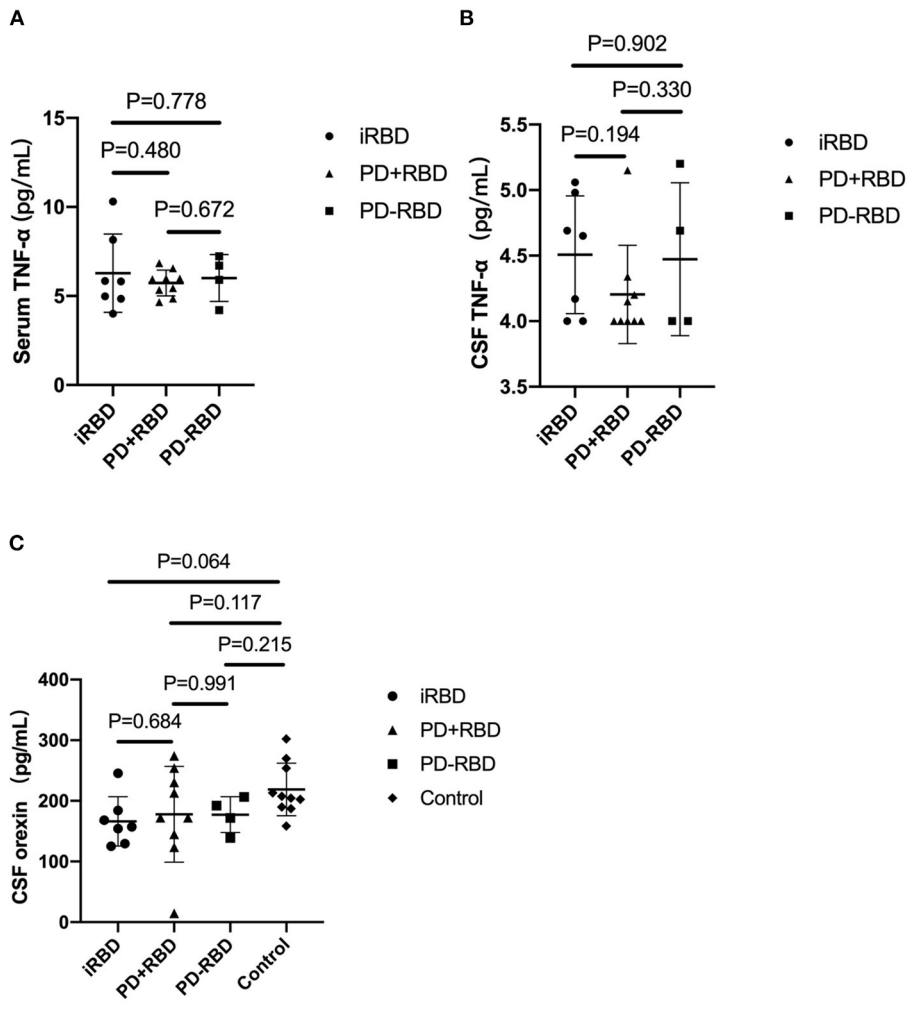

FIGURE 1 | The levels of TNF-α in serum and cerebrospinal fluid (CSF) in PD patients with RBD, PD patients without RBD, and isolated RBD patients **(A,B)**. The levels of orexin in CSF in the four groups **(C)**. Bars represent the mean values, and T bars indicate the standard deviations.

was no significant correlation between the levels of TNF-α and orexin ($P = 0.647$) (see **Table 2**, **Figure 1**).

DISCUSSION

This study explored biomarkers in serum and CSF in iRBD and Parkinson's disease patients. Also, we attempt to untangle the relationship between inflammatory marker TNF-α and the orexinergic system. We speculated that TNF-α may not induce the onset and progression of neurodegenerative diseases by acting on the orexin system.

Evidence suggests that CSF and blood biomarkers closely reflecting the pathophysiology of Parkinson's disease, such as major intermediary filament of astrocytes glial fibrillary acidic protein (GFAP) (16), a marker of astroglial activation YKL-40 (17) and proinflammatory cytokines tumor necrosis factor-alpha, IL-6, and IL-12 (12), may have diagnostic and prognostic value.

Inflammation, specifically glial activation, has been linked to the progressive degenerative process in Parkinson's disease. Increased level of TNF-α in CSF from PD patients has been observed in previous studies (18, 19). Furthermore, as with the prodromal phenotype of Parkinson's disease, the neurodegenerative process of iRBD is mediated by TNF-α similarly (13), suggesting that a-synuclein pathologies have already existed in iRBD and play a role in the activation of microglia. However, it is still unclear how it affects the onset and progression of the disease.

Interestingly, TNF-α was found to downregulate orexin levels and exhibit increased REM sleep electromyographic activity in a previously published animal study *via* a protein degradation mechanism (14). As we all know, orexin deficiency is a common feature of narcolepsy type one patients (20). It is unknown whether orexin has any effect on neurodegenerative disease. According to Luppi et al., orexin is indirectly involved in spinal motor neuron innervation in the lower part of the dorsolateral tegmental nucleus (SLD) *via* fiber projections to the pontine tegmental nucleus, and orexin deficiency can cause decreased neuronal excitability in SLD, resulting in muscle atonia in REM sleep (9). This study sheds light on clinical research. However, the results of current studies on the level of orexins in CSF from Parkinson's disease and iRBD patients vary. Several studies have found that the number of orexin neurons in the post-mortem hypothalamus and the level of orexin in ventricular CSF are significantly lower than in controls (21–23). Despite the fact that the differences were not statistically significant, our study found that orexin levels in the three groups decreased when compared to controls. Orexin plays a neuroprotective role in Parkinson's disease *via* a variety of mechanisms, including maintaining the firing of nigral dopamine neurons (24). We believe that the lower levels of orexin found in our study indicate that the orexinergic system dysfunction plays a role in the pathogenesis of Parkinson's disease. Furthermore, functional abnormalities may have occurred during the prodromal stage of Parkinson's disease. However, orexin levels may have no relation to disease progression or phenotype. Another study suggests that high levels of orexin in Parkinson's disease are linked to the loss of REM muscle atonia (25). According to the study, orexin enhances muscle activity *via* both direct effects on spinal motor neurons and indirect effects on locus coeruleus neurons. Furthermore, some studies show no significant reduction in orexin levels in CSF from Parkinson's disease and iRBD patients (26, 27). The difference in CSF orexin levels between their results and our study could be explained by the CSF collection method. Another possible explanation for these disparities is that the patients in the studies were sampled differently. TNF-α levels in serum and CSF of PD patients with RBD were not significantly different from those of other groups in this study, implying that TNF-α may not have a significant effect on the orexinergic system.

Although there was no statistically significant difference, the UPDRS-III score in the PD+RBD group was higher than the PD-RBD group, which is consistent with previous research that PD patients with RBD have more severe motor impairment (28). Except for the fact that the RBDQ-HK score of the PD+RBD and iRBD group was higher than that of the PD-RBD group, we found no significant difference among the three groups in sleep scale scores. Despite the lack of a significant difference, the mean value of MoCA in the PD+RBD group was lower than PD-RBD group. Many studies have found that PD patients with RBD have a higher risk of cognitive impairment (29). The link between RBD and cognitive dysfunction could be due to the brainstem nuclei involved in RBD mediating cognition (30). The study found no more depression in the PD+RBD group than in the other two groups, which is consistent with previous research (31). Furthermore, our study discovered that PD patients with RBD were more anxious than iRBD patients, which may result from comorbidity. Furthermore, a study indicates that dysfunctions in the raphe nucleus and the locus ceruleus cause anxiety in Parkinson's disease patients (32). It has also been reported that PD patients with RBD are more likely to experience anxiety and depression, and it is believed that the presence of RBD causes anxiety and depression in PD patients, which can further affect the sleep quality of patients (33). Sleep architecture did not differ significantly among the three groups, except for a higher proportion of REM sleep in iRBD patients compared to the PD-RBD group.

There are several limitations to this study. First, in patients who do not complain of abnormal behaviors in their sleep, the object of inquiry about the PSQI and RBDQ-HK should be the family members or caregivers of the patient rather than the patient himself. The resulting scale scores more accurately reflect the patients' actual RBD severity. Second, this study didn't further divided patients with or without therapeutic medication into subgroups. After the symptomatic improvement, the results of scales such as UPDRS, RBDQ-HK, HAMA may be different from those obtained prior to medication, and fail to reflect the actual situation, causing bias in the results. Third, PD patients with RBD were not further classified as to whether RBD appeared before or after motor symptoms of PD. We wonder if the time node at which RBD first appears may be related to the severity of neuroinflammatory reactions in the central and peripheral nervous system. Finally, the sample size of this study is small, and more patients should be recruited in the study in the future.

In conclusion, our study investigated biomarkers of phenoconversion in Parkinson's disease and iRBD, as well as the relationship between inflammatory factor TNF-α and orexinergic system in clinical aspect, which might be useful for risk stratification of disease conversion. In the future, the effects of TNF-α and orexin on Parkinson's disease should be studied and discussed in a larger sample size.

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 Xuanwu Hospital, Capital Medical University Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YY, YZ, YC, YH, ZH, JM, NL, and SZ: conceived and designed the experiments. YY, YZ, YC, YH, ZH, and JM: performed the experiments. YY, YZ, YC, and YH: analyzed the data. YY, YZ, YC, NL, and SZ: wrote the paper. All authors read and approved the content.

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Decreased Transition Rate From Situational Insomnia to Chronic Insomnia by One-Week Internet Cognitive Behavioral Treatments for Insomnia During the COVID-19 Pandemic

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Purpose: The purpose of the study was to determine the long-term effects of one-week self-guided internet cognitive behavioral treatments for insomnia (CBTI) on situational insomnia during the COVID-19 pandemic.

Patients and Methods: The participants with situational insomnia ($n = 194$) were recruited from March 2020 to April 2020 in Guangzhou, China. The insomnia severity index (ISI), pre-sleep arousal scale (PSAS), and hospital anxiety and depression scale (HADS) were evaluated at baseline and a one-week internet CBTI program was delivered to all individuals. The participants were divided into the complete treatment group (the participants completed all seven modules of the CBTI course, $n = 75$), and the incomplete treatment group (the participants completed 0–6 modules of the CBTI course, $n = 119$). A total of 135 participants completed the post-intervention assessments. At 3 months follow-up, a total of 117 participants (complete treatment group: $n = 51$; incomplete treatment group: $n = 66$) completed the assessments of the ISI, PSAS and HADS. The transition rate from situational insomnia to chronic insomnia (duration of insomnia $\geq$ 3 months and ISI $\geq$ 8) was calculated in the two groups. Linear mixed effect model was used to investigate the effect of group (between the two groups), time (baseline vs. follow-up), and interaction (group x time) on various questionnaire score.

Results: The transition rate from situational insomnia to chronic insomnia was significantly lower in the complete treatment group compared to the incomplete treatment group (27.5%, 14/51 vs. 48.5%, 32/66, $p = 0.023$). There were significant differences in group effect ($p = 0.032$), time effect ($p = 0.000$) and group $\times$ time effect ($p = 0.048$) between the two groups in the ISI total score. The ISI total scores decreased in both groups during follow-up compared to their baseline values, with a greater magnitude of decrease in the complete treatment group. There were no significant group x time effects

between the two groups in the PSAS-total score, PSAS-somatic, PSAS-cognitive score, HADS total score, HADS anxiety score or HADS depression score.

Conclusion: Our results suggested that one-week self-guided internet CBTI prevented the development of chronic insomnia from situational insomnia during the COVID-19 pandemic.

Keywords: CBTI, insomnia severity index (ISI), pre-sleep arousal scale (PSAS), hospital anxiety and depression scale (HADS), hyperarousal, COVID-19

INTRODUCTION

Situational insomnia, a form of primary insomnia according to Diagnostic and Statistical Manual of Mental Disorders (DSM-5), is a common health problem (1). Situational insomnia usually lasts no more than a month (e.g., a few days or a few weeks) and is often related to specific stressful circumstances, such as life events or rapid changes in sleep schedules or environment, or use of stimulants such as caffeine. Most people have experienced situational insomnia, especially in response to situational stress (2). Situational insomnia usually resolves when the initial stressful event or situation is settled. However, poor sleep in unusual circumstances may also depend upon individual sensitivity to the stress (3). For example, for individuals who are more vulnerable to sleep disturbances, insomnia may persist over time long after the resolution of the initial stressful event and become chronic.

The Corona Virus Disease 2019 (COVID-19) is by far the largest outbreak of atypical pneumonia since the severe acute respiratory syndrome (SARS) outbreak in 2003. Within weeks of the initial outbreak the total number of cases and deaths exceeded those of SARS (4), which created enormous stress for the public. The COVID-19 pandemic and its societal consequences of mass home confinement created a stressful situation for many people across the globe. Being forced to stay at home, work from home, do home-schooling with children, drastically minimize outings, and reduce social interaction, could have major impacts on sleep (5). It has been shown that there is a significant increase in the incidence of insomnia during the COVID-19 pandemic (6). Sleep plays a fundamental role in both mental and physical health. For instance, sleep is involved in emotion regulation (7) and immune functions (8). Chronic insomnia and prolonged sleep loss increase risks of long-term adverse consequences for mental, physical, and occupational health (9). Therefore, the individuals who experienced significant sleep disturbances during the COVID-19 pandemic may be at greater risk for the long-term adverse health outcomes. Thus, protecting sleep during this pandemic is particularly important to build resilience and cope more effectively with the social confinement, distress, and uncertainty.

Around the world, COVID-19 epidemic continues to spread, creating significant disturbances in people's sleep and potentially triggering more situational insomnia. The COVID-19 pandemic seems to be a precipitating factor for the development of situational insomnia in a stressful atmosphere (10). The occurrence and course of situational insomnia are associated with the risk of developing chronic insomnia (11). Ellis et al. reported that about 40% of the patients with situational insomnia eventually developed chronic insomnia (12, 13). Therefore, it is necessary to seek effective intervention methods to prevent the development of chronic insomnia from situational insomnia.

Cognitive behavioral treatment for insomnia (CBTI) is currently considered the preferred treatment for insomnia (14). It has been shown that the internet CBTI treatment significantly reduced sleep latency and improved insomnia symptoms. The improvement in sleep lasted as long as 1 year after treatment (15). Recent evidence shows that CBTI can be used to treat sudden-onset (acute) insomnia due to rapid stress-induced situation changes (16, 17). For example, CBTI has been shown to improve sleep in patients with post-traumatic stress disorder (PTSD) and the effects lasted for at least 6 months (18). We previously demonstrated that one-week internet CBTI resulted in an immediate improvement of situational insomnia and pre-sleep somatic hyperarousal in the adults recruited from the community during the COVID-19 pandemic (19). We hypothesized that one-week internet CBTI could prevent the development of chronic insomnia from situational insomnia. In this study we performed self-guided one-week internet CBTI to the adults with situational insomnia in the community during the COVID-19 pandemic. The long-term effects of CBTI on insomnia, pre-sleep arousal, anxious and depressive symptoms were determined at 3 months after the intervention.

MATERIALS AND METHODS

Participants and Procedures

The study protocol was approved by the Ethics Committee in Nanfang Hospital, Southern Medical University. Individuals with situational insomnia were recruited through a campaign named "The Prevention and Protection Handbook against Epidemic" sponsored by the local government of Guangzhou, China from March to April in 2020. The diagnosis of situational insomnia was based on the following criteria according to the DSM-5: (a) the individual had sleep-onset insomnia and/or sleep-maintenance insomnia for at least three nights a week (>30 min each time); (b) the duration of insomnia lasted no more than a month; (c) the sleep disturbance (or the associated daytime fatigue) caused significant distress or impairment in social, occupational or other areas of functioning; and (d) a, b and c occurred despite adequate opportunity for sleep. The inclusion criteria were as follows: (1) adults aged between 18 and 64 years, (2) individual was diagnosed as situational insomnia, and (3) individual had an insomnia

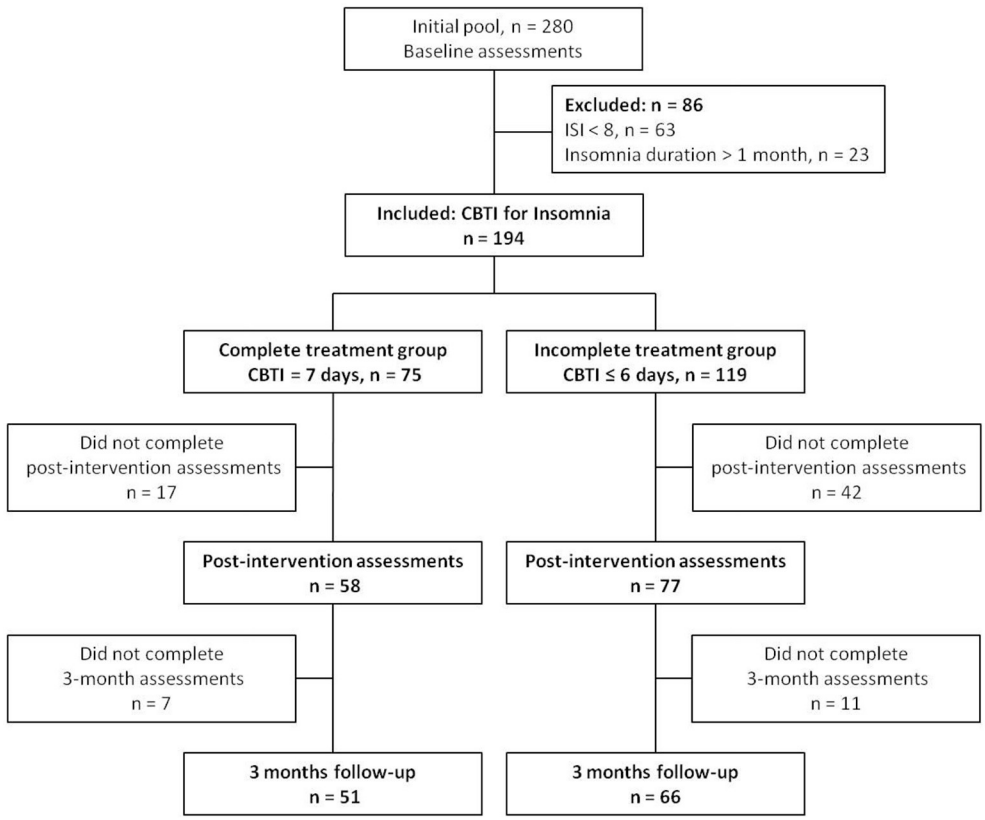

FIGURE 1 | Flow chart of the study.

severity index (ISI) score of 8 or more. The exclusion criteria were as follows: (1) individual who had insomnia for more than a month, and (2) the ISI score was <8. As shown in the flow chart (**Figure 1**), among the initial pool of participants ($n = 280$) recruited for the study, 63 participants were excluded because their ISI scores were <8, and 23 participants were excluded because they suffered from insomnia for more than a month.

The signed informed consent form was obtained from all participants prior to starting the study. The pre-test online questionnaire was collected when participants completed their registration, ISI, pre-sleep arousal scale (PSAS), hospital anxiety and depression scale (HADS) were assessed. A total of 194 participants completed baseline scale assessment. The 7-day internet CBTI course was delivered to all participants using a social media platform named Wechat. The CBTI course consisted seven modules (about 15 min each), including sleep hygiene education (day 1), sleep restriction (day 2), stimulation control (day 3), relaxation training (day 4), cognitive reconstruction (day 5), core thoughts about sleeping medicine (day 6), and summary and review (day 7) (19). After the first login, the system recorded the login history automatically. The participants were divided into complete treatment group (the participants completed all 7 modules of the CBTI course, $n = 75$), and incomplete treatment group (the participants completed 0–6 modules of the CBTI course, $n = 119$). Following 7 days of CBTI, the participants were asked to complete the second online questionnaire for the assessment of ISI, PSAS, and HADS within 1 week. A total of 135 completed the post-intervention online assessments, with 58 in the complete treatment group and 77 in the incomplete treatment group ($n = 6$, 10, 6, 9, 11, 21, and 14 for completion of 0, 1, 2, 3, 4, 5 and 6 modules of CBTI, respectively). At 3 months after the CBTI intervention, we sent out 3 reminders via Wechat within 1 week to remind all participants to submit the online assessments of ISI, PSAS and HADS. A total of 117 participants completed the 3 months follow-up assessments. The chronic insomnia was defined as (1) duration of insomnia symptoms $\geq$ 3 months, and (2) ISI $\geq$ 8. The frequency of insomnia symptoms was not considered in the definition of chronic insomnia. The transition rate from situational insomnia to chronic insomnia was calculated in the complete treatment and incomplete treatment groups.

Measures

Insomnia Severity Index (ISI)

The ISI was used to evaluate the severity of insomnia. ISI consists of seven items. Each item is rated on a 5-point Likert scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = extremely severe), with higher total scores indicating more severe insomnia. The score ranges for severity ratings for insomnia are: <8: no insomnia symptoms; 8–14: mild insomnia; 15–21: moderate

insomnia; and 22–28: severe insomnia. ISI has adequate internal consistency and is a reliable self-report measure to evaluate perceived sleep difficulties. It can be used as a screening tool clinically or an outcome measure in insomnia treatment research (20). The ISI measures the initial, middle and late insomnia, sleep satisfaction, interference of insomnia with daytime functioning, noticeability of sleep problems by others, and distress about sleep difficulties. The ISI has adequate psychometric properties and sensitivity to detect insomnia and evaluate treatment response. Thorndike et al. validated an online ISI version and showed that the online ISI version and paper-and-pencil ISI version were comparable (21).

Pre-sleep Arousal Scale (PSAS)

The PSAS was used to evaluate pre-sleep arousal. The PSAS is composed of two subscales: cognitive arousal and somatic arousal, each contains 8 items. Each item is rated on a 5-point Likert scale that ranges from 1 (not at all) to 5 (extremely). The cognitive subscale describes cognitive arousal such as worry about falling asleep, being mentally alert at bedtime, and inability to shut off thoughts). The somatic subscale addresses physical arousal such as racing heart, muscle tension, and rapid breathing. The PSAS cognitive or somatic scores range from 8 to 40. High scores on both subscales indicate hyper arousal (22). The PSAS has been widely used as an effective screening tool for identifying sleep disturbances.

Hospital Anxiety and Depression Scale (HADS)

The HADS was used to assess the anxiety and depression symptoms. The HADS is a self-assessment questionnaire that focuses on the psychic symptoms of mood disorders. The HADS has seven items each for anxiety (HADS-A) and depression (HADS-D) subscales. HADS-A items focus on symptoms related to generalized anxiety, while HADS-D items focus on anhedonia symptoms, a central aspect of depression. Each item is rated on a 0–3 scale (ranging from 0 = no not at all, to 3 = yes definitely) with the total subscale score ranges from 0 to 21. Score ranges for severity ratings for depression or anxiety subscale are: 0–7 (Minimal), 8–10 (Mild), 11–13 (Moderate) and 14–21(Severe) (19).

Statistical Analysis

All the analyses were performed using SPSS (version 22.0) and R (version 3.6.1) with package "lme4". Demographic data and sleep patterns are presented as mean ± SD, percentage and interquartile range (IQR) as appropriate. The comparison between any two groups was analyzed using the Chi-square test or independent-samples *t*-test. Linear mixed effect model was used to investigate the effect of group (complete treatment vs. incomplete treatment), time (baseline vs. follow-up), and interaction (group x time) on various questionnaire score. In the linear mixed effect model, we put "subject" in the random effect and "time", "group", and "time x group" in the fixed effect with a varying intercept. Statistical significance was considered at level of $p < 0.05$.

TABLE 1 | Demographic data.

	Complete treatment ($n = 58$)	Incomplete treatment ($n = 77$)	t or χ^2 value	*p* value
Age (years)	37.5 ± 11.8	36.7 ± 11.6	t = 0.377	0.707
BMI (kg/m^2)	21.9 ± 2.7	21.9 ± 3.3	t = −0.055	0.956
Gender			$\chi^2 = 0.263$	0.608
Male	15 (25.9)	23 (29.9)		
Female	43 (74.1)	54 (70.1)		
Highest education level			$\chi^2 = 3.775$	0.151
High school diploma or less	10 (17.3)	17 (22.1)		
Bachelor's degree	30 (51.7)	47 (61.0)		
Master's or doctoral degree	18 (31.0)	13 (16.9)		
Marital status			$\chi^2 = 0.472$	0.790
Single	20 (34.5)	31 (40.3)		
Married	34 (58.6)	41 (53.2)		
Divorced	4 (6.9)	5 (6.5)		
With whom the subject lives			$\chi^2 = 1.694$	0.638
Alone	12 (20.7)	22 (28.6)		
Parents	20 (34.5)	23 (29.8)		
Child	23 (39.7)	26 (33.8)		
Friends	3 (5.1)	6 (7.8)		
Employment status			$\chi^2 = 4.994$	0.289
Full time	45 (77.6)	54 (70.1)		
Part time	3 (5.2)	1 (1.3)		
Unemployed	4 (6.9)	5 (6.5)		
Retired	2 (3.4)	9 (11.7)		
Student	4 (6.9)	8 (10.4)		
Monthly income (¥)			$\chi^2 = 4.242$	0.236
<3,000	7 (12.1)	12 (15.6)		
3,000–5,000	13 (22.4)	28 (36.4)		
5,000–10,000	18 (31.0)	17 (22.0)		
>10,000	20 (34.5)	20 (26.0)		

Data are mean ± SD or N (%); BMI, body mass index; ¥, Chinese Yuan.

RESULTS

Demographic Characteristics and Sleep Patterns

The demographic data of the subjects of the complete treatment and incomplete treatment groups are presented in **Table 1**. The mean age was 37.5 years and 36.7 years for the complete treatment group and incomplete treatment group, respectively. The body mass index (BMI) was in the normal range (average 21.9 kg/m^2) in both groups. The gender composition was similar in the two groups; the percentage of females was above 70% in both groups. There were no statistically significant differences between the two groups in education level, marital status, with whom the subject lives, employment status and monthly income.

There were no statistically significant differences between the complete treatment and incomplete treatment groups in the frequency of using tea, coffee, alcohol, cigarette in the previous year (**Table 2**). Most of the participants (67–80%) in the two

TABLE 2 | Uses of tea, coffee, alcohol and cigarettes in the past year.

	Complete treatment ($n = 58$) N (%)	Incomplete treatment ($n = 77$) N (%)	χ^2 value	p value
Tea			1.182	0.554
Never	12 (20.7)	16 (20.8)		
Seldom (1–3 times/week)	27 (46.5)	42 (54.5)		
Often (>3 times/week)	19 (32.8)	19 (24.7)		
Coffee			1.245	0.537
Never	19 (32.7)	32 (41.5)		
Seldom (1–3 times/week)	28 (42.3)	34 (44.2)		
Often (>3 times/week)	11 (19.0)	11 (14.3)		
Alcohol			1.579	0.454
Never	20 (34.5)	30 (39.0)		
Seldom (1–3 times/week)	36 (62.1)	41 (53.2)		
Often (>3 times/week)	2 (3.4)	6 (7.8)		
Cigarettes			1.672	0.383
Never	47 (81.0)	63 (81.8)		
Seldom (1–3 times/week)	9 (15.5)	8 (10.4)		
Often (>3 times/week)	2 (3.5)	6 (7.8)		

TABLE 3 | Sleep pattern.

	Complete treatment ($n = 58$)	Incomplete treatment ($n = 77$)	t or χ^2 value	p value
Time to go to bed [median (IQR)]				
Weekdays	22:00 (00:56–23:05)	22:30 (01:52–23:30)	t = 0.436	0.664
Weekends	22:02 (01:00–23:29)	22:35 (02:00–23:30)	t = 0.216	0.830
Time to wake [median (IQR)]				
Weekdays	07:15 (06:37–09:15)	07:40 (07:00–08:52)	t = −1.001	0.316
Weekends	08:45 (07:30–10:00)	08:30 (07:30–10:15)	t = 0.973	0.331
Daytime nap (minutes, mean ± SD)	24.66 ± 29.70	24.48 ± 29.83	t = 0.034	0.973
Sleep latency [minutes, N (%)]			$\chi^2 = 8.401$	0.035*
<10	3 (5.2)	5 (6.5)		
11–30	17 (29.3)	23 (29.9)		
31–60	25 (43.1)	17 (22.1)		
>60	13 (22.4)	32 (41.5)		
Sleep duration (hours/day, mean ± SD)	6.52 ± 3.55	6.52 ± 2.78	t = 0.011	0.992

**Indicates significance between the complete treatment group and the incomplete treatment group ($p < 0.05$, t - test). IQR, interquartile range.*

groups never or seldom (1–3 times/week) drank tea or coffee, and over 90% of the participants in both groups did not or seldom drink alcohol in the past year. Only 3.4% and 7.8% of the participants in the complete treatment group and incomplete treatment group, respectively, smoked more than 3 times a week in the past year.

The sleep patterns of the complete treatment and incomplete treatment groups at baseline are presented in **Table 3**. The two groups had similar going to bed time and wake up time for weekdays and weekends. There were no statistically significant differences in daytime nap time between the two groups. Significant difference ($p = 0.035$) was observed between the two groups in the sleep latency. The sleep latency was >60 min in 22.4% and 41.5% of the participants in the complete treatment group and incomplete treatment group, respectively. The average sleep duration was 6.5 h in both groups during the COVID-19 outbreak. There were no statistically significant differences between the two groups in sleep duration.

Effect of CBTI on Insomnia

The transition rates from situational insomnia to chronic insomnia are presented in **Figure 2**. The transition rates were significantly lower ($p = 0.023$) in the complete treatment group (27.5%, 14/51) compared to the incomplete treatment group (48.5%, 32/66).

The time courses of ISI in the complete treatment and the incomplete treatment groups are presented in **Figure 3**. There were no significant differences between the two groups in ISI at baseline. There were significant time effect ($p = 0.000$), group effect ($p = 0.032$) and group × time effect ($p = 0.048$) between the two groups in ISI at 3 months follow-up. The ISI total scores decreased in both groups during follow up compared to their baseline values, with a greater magnitude of decrease in the complete treatment group (**Figure 3**).

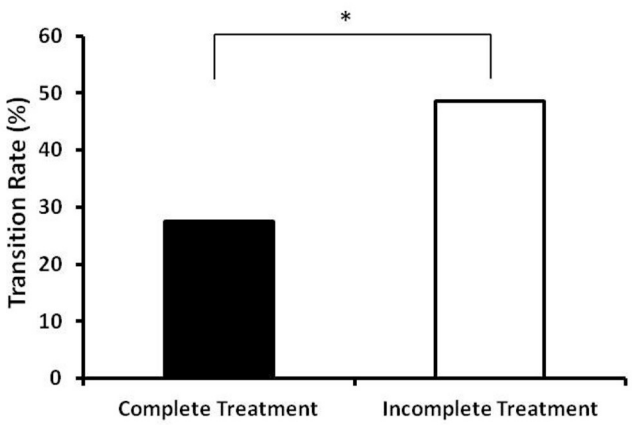

FIGURE 2 | Transition rates from situational insomnia to chronic insomia in the complete treatment group and incomplete treatment group. The complete treatment group had a significantly lower transition rate compare to the incomplete treatment group (27.5%, 14/51 vs. 48.5%, 32/66). *Indicates significant differences between the two groups ($p < 0.05$).

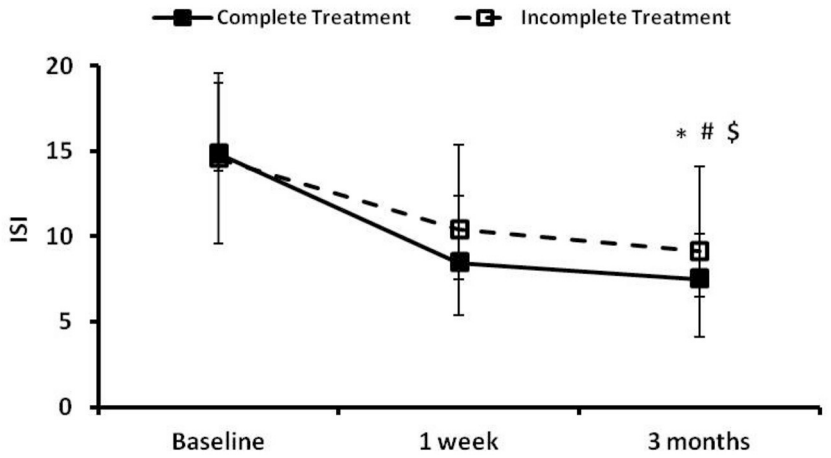

FIGURE 3 | The insomnia severity index (ISI) at the preintervention baseline, and 1 week and 3 months following cognitive behavioral treatments for insomnia (CBTI). *, #, and $ indicate significant differences ($p < 0.05$) for the time effect, group effect and group × time effect, respectively. Complete treatment group, $n = 58$; incomplete treatment group, $n = 77$.

Effect of CBTI on the PSAS

The time courses of PSAS in the complete treatment and the incomplete treatment groups are presented in **Figure 4**. There were no significant differences in PSAS-total score, PSAS-somatic score or PSAS-cognitive scores between the two groups at baseline. Significant time effects and group effects ($p < 0.05$) were found between the two groups in the PSAS-total score (**Figure 4A**), the PSAS-somatic score (**Figure 4B**) and cognitive score (**Figure 4C**). There were no significant group × time effects observed between the two groups in the PSAS-total score, PSAS-somatic score or PSAS-cognitive score.

Effect of CBTI on the HADS

The time courses of HADS in the complete treatment and the incomplete treatment groups are presented in **Figure 5**. There were no significant differences in the HADS-total, HADS-A or HADS-D scores at baseline between the two groups. Significant time effects ($p < 0.05$) between the two groups were found in the total score (**Figure 5A**), anxiety score (**Figure 5B**), and depression score (**Figure 5C**). There were no significant group effects and group × time effects observed between the two groups in the HADS-total score, HADS-anxiety score or HADS-depression score.

DISCUSSION

Our results showed that one-week internet CBTI program reduced insomnia at 1 week and 3 months follow-up. The CBTI also reduced the transition rate from situational insomnia to chronic insomnia at 3 months follow up. Our findings suggest that the one-week internet CBTI intervention result in both short-term and long-term improvement in sleep in individuals with situational insomnia during the COVID-19 pandemic. To our best knowledge, this is the first study to investigate the long-term effect of one-week internet CBTI on situational insomnia in the general population in the community during the COVID-19 pandemic.

CBTI is currently considered the preferred treatment to insomnia (14). Traditional CBTI requires face-to-face interviews. The treatment procedure is complex, time-consuming and costly. It typically requires patients to travel to the hospital/clinic for the face-to-face treatment, thus it may interfere with patients' routine work (23). The Internet CBTI has been paid more and more attention by experts and scholars these years, especially during the COVID-19 pandemic. Some professional committees recommend internet CBTI as the preferred method of intervention for insomnia (24).

The central principle of the CBTI is to target sleep-related dysfunctional thoughts, feelings, and behaviors and control the insomnia symptoms (25). Ellis and colleagues developed a "one-shot" CBTI intervention specifically to prevent the transition from acute insomnia to chronic insomnia (26). The "one-shot" CBTI includes a single 60- to 70-min session of CBTI, with an accompanying self-help pamphlet. The single session of CBTI has been shown to effectively reduce the transition rate from acute insomnia to chronic insomnia. It has been shown that there were no significant differences between the group treatment vs. the individualized treatment; both groups showed a remission rate of ∼70% at 1-month follow-up (16). Randall evaluated the effects of "one-shot" CBTI on acute insomnia among prison inmates and showed a satisfactory remission rate at 1-month follow-up (17). Consistent with previous study (16), with similar pre-intervention ISI scores in the participants, we also observed similar remission rate (∼73%) in the participants who completed the one-week CBTI at 3-month follow-up.

We have reported that one-week internet CBTI reduced pre-sleep somatic hyperarousal post-intervention (19). However, there were no statistically significant group × time effects observed between the complete treatment group and the incomplete treatment group in pre-sleep arousal at 3 months follow-up. People with hyperarousal trait were more likely

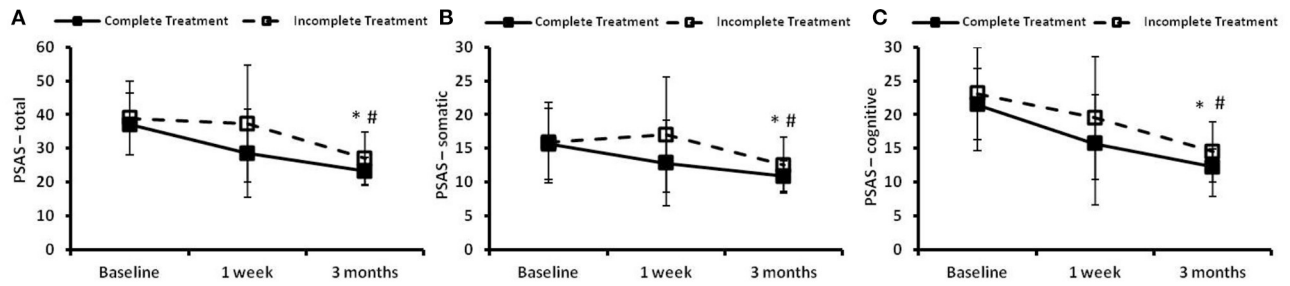

FIGURE 4 | The pre-sleep arousal scale (PSAS) at the preintervention baseline, and 1 week and 3 months following cognitive behavioral treatments for insomnia (CBTI). **(A)** PSAS-total; **(B)** PSAS-somatic; **(C)** PSAS-cognitive. * and # indicate significant differences ($p < 0.05$) for the time effect and group effect, respectively. Complete treatment group, $n = 58$; incomplete treatment group, $n = 77$.

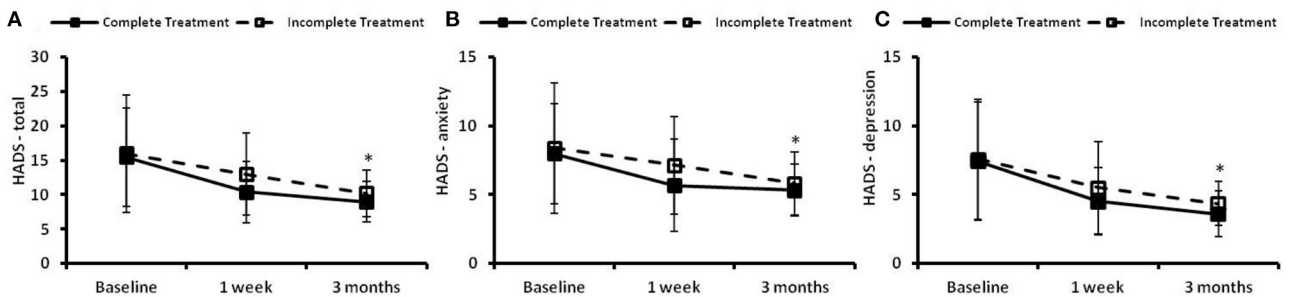

FIGURE 5 | The hospital anxiety and depression scale (HADS) at the preintervention baseline, and 1 week and 3 months following cognitive behavioral treatments for insomnia (CBTI). **(A)** HADS–total; **(B)** HADS–anxiety; **(C)** HADS–depression. *Indicates significant differences ($p < 0.05$) for the time effect. Complete treatment group, $n = 58$; incomplete treatment group, $n = 77$.

to develop poor sleep during the COVID-19 (27). Effective interventions that target on hyperarousal were important in the treatment of insomnia. Hyperarousal refers to a broad pattern of excessive, poorly modulated responsiveness to stimuli during wakefulness (28). The 3P model of situational insomnia (predisposing, precipitating, and perpetuating) was proposed by Spielman and colleges in the 1980s (29). Hyperarusal can serve as a marker of predisposition or vulnerability to insomnia (29, 30). Hyperarousal is a key component in most prevailing etiological models of insomnia (31–33). People with cognitive hyperarousal trait have more dysfunctional beliefs about sleep (e.g., catastrophizing negative fallout of a poor night's sleep). Somatic hyperarousal (e.g., muscle tension) in bed presages poor sleep and is tied to reduced sleep efficiency and quality. Kalmbach et al. compared the intervention effects of CBTI and sleep restriction therapy (SRT) on menopausal insomniacs, showing that CBTI was more effective in reducing pre-sleep somatic hyperarousal and dysfunctional beliefs about sleep compared to the SRT in postmenopausal women (34). In a randomized controlled trial of 5 weeks of computerized cognitive behavioral therapy (cCBT), Vincent et al. showed that improvements in hyperarousal and time awake in bed partially mediated the impact of cCBT on sleep, and hyperarousal was a more significant mediator in explaining change associated with cCBT for insomnia (35).

In our study, there were no statistically significant differences (group × time effects) between the complete treatment group and the incomplete treatment group in improving anxiety and depressive symptoms. It has been shown that CBTI is beneficial for patients with residual depression and insomnia (36, 37). CBTI has been considered as an effective insomnia treatment for people with insomnia comorbid with depressive symptomatology (38). A randomized controlled study involving 1,149 participants with insomnia showed significantly better improvement in depression and anxiety symptoms through a self-help cognitive behavioral therapy program for insomnia (SHUTI) (39). However, CBTI has been shown to be more effective in treating insomnia than depression (38, 40). The inconsistency between our study and previous studies may be explained by following reasons. Firstly, the relaxation training of one-week CBTI was relatively short compared to the online CBTI treatment of 6 weeks or more (39, 41). Secondly, the program in our study only contained four relaxation audio pieces. Individual preferences for audio may affect the effectiveness of the treatment (42–44). A systematic review showed that progressive muscle relaxation training, music intervention and yoga were the most effective interventions for depression (43). Thirdly, our one-week internet CBTI program only used text and audio as a delivery method; it was possible that some of the participants did not understood all the details and key points of training.

There were some limitations in this study. Firstly, this was not a randomized controlled trial. The two groups were allocated based on how many days of CBTI the participants completed. We were comparing the effect of the complete treatment (7 days of CBTI) and the incomplete treatment (0–6 days of CBTI) on insomnia. Since the two groups were not randomly assigned, there may be selection bias and other confounding variables affecting the results. Secondly, the sample size in this study was relatively small. Only 60% of the participants (117 out of 194) completed the assessments at 3 months follow-up. Thirdly, all the questionnaires used for the assessments of ISI, PSAS and HADS were self-reported. The data may be prone to social desirability bias. Fourthly, the only follow-up duration in this study was 3 months. Although the current follow-up duration (3 months) allowed for establishing the diagnosis of chronic insomnia based on DSM5 criteria, long-term follow-up (e.g., 6 or 12 months) is needed for future study to examine whether the treatment effects of CBTI sustain over time.

In conclusion, our results showed that one-week internet CBTI program improved insomnia symptoms and reduced the transition rate from situational insomnia to chronic insomnia at 3 months follow-up, suggesting that one-week self-guided internet CBTI prevented the development of chronic insomnia from situational insomnia during the COVID-19 pandemic.

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 Ethics Committee of Nanfang Hospital of Southern Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FF and BZ: conceptualization. SL, FF, CZ, and BZ: methodology. FF: writing–original draft. FF, CZ, HL, XL, LY, and GX: formal analysis. FF, HL, XL, YX, LZ, LL, LY, and GX: investigation and resources. CZ, SL, and BZ: writing–review and editing. GX, CZ, HL, LL, and LZ: data curation. XL, GX, and BZ: funding acquisition. BZ: supervision and project administration. All authors have approved the final manuscript.

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A Cross-Sectional Study on the Relationship Among Cytokines, 5-HT2A Receptor Polymorphisms, and Sleep Quality of Non-manual Workers in Xinjiang, China

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Background: Studies have shown that cytokine activity changes during the sleep-wake process, suggesting that inflammatory factors may be involved in a mechanism affecting sleep quality. Furthermore, the serotonergic system is also one of the essential components of airway relaxation during sleep, especially the serotonin 2A receptor (5-HTR2A) type that plays an important role in the sleep-wake process. Therefore, this research aimed to investigate the effects of cytokines and *5-HTR2A* polymorphisms on sleep quality in non-manual workers in Urumqi, Xinjiang in order to explore the relationship between the three.

Methods: This study used a cluster sampling method to randomly select non-manual workers who worked in Urumqi, Xinjiang for at least 1 year. From July 2016 and December 2017, this study recruited 1,500 non-manual workers for physical examination in the First Affiliated Hospital of Xinjiang Medical University. According to the inclusion and exclusion criteria, 1,329 non-manual workers were finally included in the questionnaire study. It used the Pittsburgh Sleep Quality Index questionnaire to assess sleep quality. Moreover, another 15% of respondents were randomly selected as the experimental study group. The polymerase chain reaction restriction fragment length polymorphism was used to detect *5-HTR2A* gene genotypes. Simultaneously, the cytokine (IL-1β, IL-2, IL-6, and TNF-α) content was evaluated using an enzyme-linked immunoassay.

Results: The results showed that among the 1,329 respondents, 870 had sleep quality problems, and the detection rate was 65.46%. The distribution of −1438G/A genotypes in the *5-HTR2A* gene was significantly different among different sleep quality groups ($p < 0.05$), with no statistical significance present when comparing to T102C ($p > 0.05$). Logistic regression analysis showed that the AG [odds ratio (OR) = 2.771, 95% confidence interval (CI): 1.054–7.287] and GG (OR = 4.037, 95% CI: 1.244–13.105) genotypes at −1438G/A loci were both associated with poor sleep quality and were thus considered the susceptibility genotypes for sleep problems. Furthermore, IL-1β was shown to be a protective factor for sleep quality (OR = 0.949, 95% CI: 0.925–0.974). The interaction results showed that AG×IL-1β (OR = 0.952, 95% CI: 0.918–0.987) was associated with a lower risk of sleep problems than AA×IL-1β.

Conclusion: Cytokines and *5-HTR2A* polymorphisms not only have independent effects on sleep but also may have cumulative effects. Therefore, it is necessary to further explore the related mechanisms affecting sleep quality to improve the sleep quality of non-manual workers.

Keywords: *5-HTR2A*, cytokines, sleep quality, non-manual workers, cross-sectional study

INTRODUCTION

Sleep is a complex physiological process that accounts for about one-third of human life (1, 2). Good quality sleep can regulate a variety of physical and psychological activities that are beneficial to human health. The term "sleep quality" is commonly used in sleep medicine, yet a standard definition of sleep quality has not been identified. "Sleep quality" is sometimes used to refer to a collection of sleep measures including total sleep time (TST), sleep onset latency (SOL), degree of fragmentation, total wake time, sleep efficiency, and sometimes sleep disruptive events such as spontaneous arousals or apnea (3). Poor sleep quality is a subjective experience in which the amount and/or quality of sleep is insufficient and interferes with daily functioning during the day. The occurrence of sleep problems may cause adverse reactions, such as lethargy and fatigue, increase susceptibility to psychological problems, including anxiety and depression, and elevate the risk of death and cardiovascular diseases like hypertension and coronary heart disease (4–8). Thus, sleep problems have gradually become a common phenomenon, placing a heavy burden on health services worldwide (9).

At present, the incidence of sleep problems varies among different occupational groups in different regions of the world. For example, the incidence rate of insomnia among Japanese workers is 23.2–39.2% (10) and 33.2% in Iranian bank staff (11). The research has shown that manual labor has fixed hours, while white-collar occupations have unlimited hours and often longer than expected (12). There are several studies reporting sleep disturbances in shift workers in manual or service occupations. However, only a few studies have investigated sleep problems in white-collar workers. White-collar workers are described as being associated primarily with higher education and specific skills, or with low-skilled jobs that are primarily social rather than physical (13). Studies have found that long working hours affected sleep quality among male workers and female non-manual workers (14, 15). With the rapid development of the social economy, the form of work gradually changed to mental labor. Non-manual workers, namely white-collar workers, may experience more stress and a fast-paced lifestyle and become prone to anxiety, depression, and other psychological problems, which may affect their sleep quality. Therefore, the sleep problems of non-manual workers cannot be ignored.

Sleep is affected by various aspects. In addition to the environmental factors, such as stress and demands associated with work (16), the impact of physiological and genetic factors on sleep has also been extensively studied. There is evidence of a link between sleep and immune function (17). IL-1β and TNF can accumulate after prolonged wakefulness and appear to promote sleep (18, 19). And cytokines are small-molecule soluble proteins that induce changes in local states by modulating neural activity affecting sleep processes (20). The studies have shown that the expression levels of pro-inflammatory cytokines such as IL-1β and IL-6 are altered with changes in sleep rhythms. Their rising or falling levels can affect nervous system activity, triggering depression and anxiety, which are often accompanied by sleep disorders (21, 22). Studies have found that inflammatory cytokines in the central system are involved in the sleep-wake process. TNF-α can act on established sleep regulation circuits, and its acute enhancement or inhibition can inhibit or promote sleep (23). Furthermore, sleep has long been considered to be regulated by the interplay of circadian and homeostatic mechanisms (24). The immune system modulates circadian rhythms by promoting the expression of immunomodulators that alter sleep rhythm processes mediated by the central nervous system (25, 26). Evidence for the role for IL-1β and TNF in the regulation of physiological sleep has been derived from electrophysiological, biochemical, and molecular genetic studies. IL-1β and TNF increase non-REM (NREM) sleep in several species (rat, mouse, monkey, cat, rabbit, and sheep) irrespective of the route of administration (27, 28).

Among the genetic factors, serotonin (5-HT) can regulate a variety of physiological functions, including appetite, thermoregulation, allodynia, and hormone secretion (29, 30). The observation by Brodie et al. (31) in 1955 that cerebral 5-HT depletion by reserpine induces sedation prompted investigation of the role of 5-HT in the regulation of sleep–wake behavior. The importance of the 5-HT system in sleep regulation is supported by both experimental data and clinical observations: pharmacological manipulations that affect the 5-HT system by altering neurotransmitter synthesis, release, binding, or re-uptake and metabolism result in profound alterations in sleep (18). Its transporter (5-HTT) is an important adjustment factor of the 5-HT activity, which is highly correlated with insomnia (32). The effect of 5-HT is mediated by seven receptor families, includes 5-HT1 to 5-HT7. A variety of studies have demonstrated that 5-HT2 receptors play a major role in the regulation of the sleep-waking cycle. Studies have found that the blockade of 5-HT2 receptors induced significant changes in the phases of sleep and wake in adult rats (33, 34). Ritanserin not only significantly enhanced deep SWS but also improved the index of sleep efficiency (number of intermittent awakenings after sleep onset) in the old rats (35). And ketanserin induced significant differences in the phases of sleep and wake of rats (36). Moreover, the association between the 5-HT2A receptor and sleep has also been found in molecular biology studies. As an important part of the serotonergic system, the expression

of the 5-HT2A receptor is controlled by genes. Thus, encoding the receptor polymorphism may affect the functional state of the receptor and thus the activity of 5-HT. Current studies have confirmed that *5-HTR2A* polymorphisms were associated with sleep disorders (37). In addition, the −1438G/A polymorphism of the *5-HTR2A* gene has been found to be associated with the risk of sleep problems in obstructive sleep apnea syndrome (38–42). A genetic association study on the *5-HTR2A* gene revealed a −1438G/A polymorphism, which is a new G-A base change at −1438G/A in the promoter region, which has a very strong linkage imbalance with the T102C polymorphism (43). Therefore, this study mainly evaluated the effects of T102C and −1438G/A in the *5-HTR2A* gene on sleep quality.

Although there have been reports on the effects of cytokines and *5-HTR2A* polymorphisms on sleep, few studies have explored the relationship between cytokines, *5-HTR2A* polymorphisms, and sleep for non-manual workers. Therefore, this study carried out a cross-sectional study in Urumqi, Xinjiang, taking non-manual workers as research objects to investigate and evaluate their sleep quality. The contents of cytokines (IL-1β, IL-2, IL-6, and TNF-α) and the 5-HTR2A polymorphisms were also detected, further examining the independent and interactive effects of cytokines and *5-HTR2A* polymorphisms on sleep quality from the molecular biological perspective. To explore the related mechanism and influencing factors of poor sleep quality, and provide a theoretical basis for improving the sleep status, physical, mental health, and quality of life of non-manual workers.

METHODS

Subjects

This study was carried out at the Physical Examination Center of the First Affiliated Hospital of Xinjiang Medical University, and the survey period was from July 2016 to December 2017. The questionnaire was conducted in conjunction with the physical examination of the non-manual workers. The study protocol was approved by the Ethics Committee of Xinjiang Medica University, and all participants voluntarily provided their written informed consent before the investigation. The study subjects were non-manual workers working in the Urumqi of Xinjiang Province, China. According to the Occupational Classification Code of the People's Republic of China, the occupational groups of the first and second categories (administrative state organizations, party and mass organizations, enterprises, institutions, professional, and technical personnel) were selected as the overall target. A total of 1,500 non-manual workers (teachers, civil servants, and doctors) were recruited using the cluster sampling method.

The inclusion criteria were as follows: individuals who worked for more than 1 year and were between 20 and 60 years old. The exclusion criteria included the following: history of cardiovascular disease, mental disease, thyroid disease, and other diseases that may cause sleep disorders; sleep apnea syndrome, narcolepsy, restless leg syndrome; and hospitalization or medication for sleep disorders taken within 3 months.

A total of 1,500 questionnaires were sent out, and 1,329 valid questionnaires were recovered after excluding unqualified participants and questionnaires with <80% of the contents. The effective recovery rate of the questionnaires was 88.6%. The sample size was calculated by the formula:

$$n = \frac{Z_\alpha{}^2 \pi (1 - \pi)}{\delta^2} \quad (1)$$

where n, sample size; Z, statistics for significance tests; $Z_\alpha = 1.96$ ($\alpha = 0.05$); π, the prevalence of population; δ, Tolerable error. According to the findings of the Chinese Sleep Association, the prevalence of sleep disorders in China was 38.2% (44). When the allowable error was <3%, the sample size was calculated to be 1,008. However, since cluster sampling was adopted in this study, it should be increased by 50%, and the sample content of this study was finally calculated to be 1,500.

In addition, 200 participants (15% of respondents) were randomly selected as the subjects of the experiment. A total of 166 subjects were tested after excluding individuals that did not meet the criteria for DNA extraction, as well as those with hemolysis and apparent sediment present during the test, which severely affected the cytokine determination results. Then, sex and age were used as matching factors to conduct 1:1 propensity score matching (PSM) on 166 subjects, and 68 pairs were successfully matched for a total number of 136 subjects included in the final analysis.

MEASURES

Sleep Quality

The Pittsburgh Sleep Quality Index (PSQI) (45) was used to evaluate the sleep status of non-manual workers because it was easy to use, has high reliability and validity, and is highly correlated with polyhypnotic electroencephalogram test results. It has become a commonly used scale for clinical evaluation in psychiatric departments abroad. According to the Chinese version of the reliability and validity study as well as the study carried out by Tsai et al. (46), the Chinese version of the PSQI (CPSQI) has shown good internal consistency and reliability (Cronbach's α = 0.82–0.83). And the retest reliability of 14–21 days was 0.85 (all subjects) and 0.779 (primary insomnia) (47). The table was composed of 19 self-rated and five other items (not included in scoring). The scoring items were subjective sleep quality, sleep time, sleep efficiency, sleep disorder, use of hypnotic drugs, and daytime dysfunction. Each component was scored on a scale from 0 to 3, and the total score of each component was the total PSQI score ranging from 0 to 21. The higher the score, the worse the sleep quality. Sleep quality problems were defined using a threshold of 5, with scores ≥5 considered to indicate poor sleep quality (37).

Blood Sample Collection and Preservation

Venous blood samples were obtained as part of a health examination. High-fat diet and alcohol consumption were avoided for 3 days prior to blood collection. Blood samples were collected between 9 and 11 a.m. by medical staff at the medical

center, where 4 mL of elbow venous blood were drawn on an empty stomach, collected in an ethylenediaminetetraacetic acid anticoagulant tube (namely an anticoagulant containing ions) placed in an icebox at −4°C, transported back to the laboratory, and cryopreserved at −20°C until use.

Cytokine Assay

The IL-1β, IL-2, IL-6, and TNF-α content was assayed using an enzyme-linked immunoassay strictly according to the manufacturer's instructions (Xinze Baoxin Biotech, Urumqi, China) and measured with an automatic microplate analyzer (Model 680; Bio-Rad, Hercules, CA, USA).

Genotyping

Genomic DNA was extracted using the Whole Blood Genome Extraction kit (Tiangen Biotech, Beijing, China). The polymerase chain reaction-restriction fragment length polymorphism technique was used to analyze polymorphisms. The total volume of each reaction mixture was 20 μL, and gDNA was amplified using PCR instruments (My Cycler; Bio-Rad). A total of 10 μL of PCR product were used in each enzyme-digested mixture, with the final volume totaling 30 μL. The fragments were analyzed using electrophoresis on a 2.5% agarose gel and visualized with ultraviolet light. The primers and genotypes for T102C and −1438G/A are listed in **Tables 1**, **2**.

Quality Control

Investigators with similar training informed the subjects of the purpose and content of the research, so that they could fully understand the significance of the research and to ensure their active cooperation. Two research team members were utilized for data entry and data verification. All laboratory instruments were calibrated to ensure standard operation before experimental work. During the experiment, the contaminated and clean areas were strictly separated. All samples and reagents were properly stored to prevent cross-contamination.

TABLE 1 | PCR primer sequences.

Genetic loci	Primer direction	Sequence	Amplified fragment length
T102C	F	5′-TCTGCTACAAGTTCTGGCTT-3′	342 bp
	R	5′-CTGCAGCTTTTTCTCTAGGG-3′	
−1438G/A	F	5′-AGCCAGTTCAATGGTGAT-3′	404 bp
	R	5′-ATGTCATAAGCTGCAAGG-3′	

TABLE 2 | Genotype information for T102C and −1438G/A.

Genetic loci	Enzyme-digested fragment length	Genotype
T102C	342 bp	CC
	216, 126 bp	TT
	342, 216, 126 bp	CT
−1438G/A	404 bp	AA
	153, 251 bp	GG
	404, 153, 251 bp	AG

Statistical Analysis

Epidata 3.0 (The Epidata Association, Odense, Denmark) was used to establish a database for data entry. SAS 9.4 statistical software (SAS Institute Inc., Cary, NC, USA) was used for data analysis. Comparison of sleep quality problem detection rate, Hardy-Weinberg genetic balance of *5-HTR2A* gene, and genotypes among different sleep quality groups was performed using a chi-square test. Cytokine levels (IL-1β, IL-2, IL-6, and TNF-α) were not consistent with a normal distribution and were represented using M(Q25, Q75). Cytokine level comparisons among different sleep quality groups and *5-HTR2A* genotypes were performed using non-parametric tests. Multiple regression analysis was used to investigate the effect between cytokines and *5-HTR2A* polymorphisms on sleep quality. The PSM method was used for data matching, where

TABLE 3 | Sleep quality distribution among different demographic characteristics.

Characteristics	Number	Poor sleep quality (%)	χ^2	*p*-value
Sex				
Male	516	347 (67.25%)	1.189	0.276
Female	813	523 (64.33%)		
Age (years old)				
≤35	589	375 (63.67%)	2.508	0.285
35∼50	607	411 (67.71%)		
≥50	133	84 (63.16%)		
Education				
Technical secondary school and below	149	82 (55.03%)	8.073	0.004*
Bachelor degree or above	1,180	788 (66.78%)		
Marriage				
Unmarried	226	150 (66.37%)	0.100	0.752
Married	1,103	720 (65.28%)		
Job				
Teacher	811	544 (67.08%)	2.493	0.287
Civil servants	204	130 (63.73%)		
Doctor	314	196 (62.42%)		
Length of service (years)				
<15	503	319 (63.42%)	11.171	0.004*
15∼30	454	324 (71.37%)		
>30	372	227 (61.02%)		
Professional title				
Elementary	338	211 (62.43%)	2.568	0.277
Intermediate	639	431 (67.45%)		
Advanced	352	228 (64.77%)		
Monthly income (yuan)				
≤3,000	849	533 (62.78%)	7.484	0.006*
>3,000	480	337 (70.21%)		

*$p < 0.05$.

the matching error was 0.03. The significance level was set at 0.05 (bilateral).

RESULTS

Demographics and Sleep Quality Distribution

Among 1,329 subjects, 870 had sleep quality problems (65.46% detection rate; **Table 3**). Associations between poor sleep quality and education level, length of service, and monthly income were statistically significant ($p < 0.05$). No significant relationship was identified between poor sleep quality and other variables ($p > 0.05$). Subjects with a bachelor's degree or greater (66.78%) were more likely to have sleep problems than those with a technical secondary school education and lower (55.03%). Subjects whose length of service was 15–30 years (71.37%) were more susceptible to having poor-quality sleep than those with service length of <15 years (63.42%) and >30 years (61.02%). Compared to individuals with a monthly income of ≤3,000 yuan (62.78%), those earning >3,000 yuan (70.21%) had a higher probability of experiencing poor sleep.

Relationship Between Cytokines and Sleep Quality

The IL-1β content in different sleep quality groups was different ($p < 0.05$), suggesting that cytokines may be involved in sleep regulation (**Table 4**). However, there was no statistical significance between sleep quality and other cytokines ($p > 0.05$).

Hardy-Weinberg Genetic Equilibrium Test

Hardy-Weinberg genetic balance test was used to analyze the distribution of T102C and −1438G/A genotypes in the *5-HTR2A* gene. The results showed that the actual values of each genotype were in good agreement with the expected values, and these differences were not statistically significant ($p > 0.05$), which was in agreement with the law of genetic balance (**Table 5**).

Relationship Between *5-HTR2A* Gene and Sleep Quality

Chi-square test was used to analyze the distribution of T102C and −1438G/A genotypes across different sleep quality groups (**Table 6**). The results showed that −1438G/A genotypes were different in different sleep quality groups ($p < 0.05$), while T102C genotypes were not statistically significantly different ($p > 0.05$).

TABLE 4 | Cytokine comparison between different sleep quality groups.

Sleep quality	*n*	IL-1β	IL-2	IL-6	TNF-α	Total
Non-poor sleep quality	68	29.38 (16.56, 45.94)	40.10 (33.63, 49.20)	64.67 (62.00, 68.35)	51.50 (27.50, 72.75)	136
Poor sleep quality	68	16.88 (10.00, 32.19)	44.10 (33.23, 52.38)	64.00 (60.75, 67.83)	50.25 (28.75, 72.00)	
Z		−3.916	−0.494	−1.097	−0.194	
p-value		<0.001*	0.621	0.273	0.846	

*$p < 0.05$.

TABLE 5 | Hardy-Weinberg genetic equilibrium test.

Genetic loci	Genotype	Actual value	Expected value	*N*	χ^2	*p*-value
T102C	CC	26	33	136	5.767	0.056
	CT	82	68			
	TT	28	35			
−1438G/A	AA	31	35	136	1.451	0.484
	AG	75	68			
	GG	30	33			

TABLE 6 | Distribution of T102C and −1438G/A genotypes across different sleep quality groups.

Genetic loci	Genotype	Number	Poor sleep quality	Non-poor sleep quality	Total	χ^2	*P*
T102C	CC	26	10	16	136	2.670	0.263
	CT	82	41	41			
	TT	28	17	11			
−1438G/A	AA	31	9	22	136	7.305	0.026*
	AG	75	41	34			
	GG	30	18	12			

*$p < 0.05$.

TABLE 7 | Distribution of T102C and −1438G/A genotypes across different sleep quality groups.

Genotype		Number	IL-1β	IL-2	IL-6	TNF-α	Total
T102C	CC	26	21.88 (10.00, 35.31)	44.10 (34.38, 47.83)	64.00 (61.33, 68.67)	49.00 (23.95, 70.00)	136
	CT	82	23.75 (12.50, 35.50)	42.60 (33.60, 51.93)	64.83 (61.92, 68.09)	57.50 (28.25, 77.63)	
	TT	28	23.12 (11.25, 35.94)	40.65 (31.30, 51.73)	63.67 (61.50, 65.92)	44.50 (28.25, 69.00)	
	H		0.679	0.575	0.507	1.555	
	p-value		0.712	0.750	0.776	0.459	
−1438G/A	AA	31	26.25 (15.00, 35.00)	40.20 (33.70, 47.20)	64.33 (61.67, 68.33)	54.50 (24.50, 62.50)	136
	AG	75	22.50 (12.50, 35.25)	44.10 (34.10, 51.70)	64.33 (61.33, 68.00)	53.50 (27.50, 78.00)	
	GG	30	23.75 (11.25, 36.56)	40.15 (31.50, 52.75)	64.00 (62.50, 66.41)	47.00 (29.75, 73.00)	
	H		0.886	1.920	0.001	0.751	
	p-value		0.642	0.383	1.000	0.687	

TABLE 8 | Logistic regression analysis of cytokines, *5-HTR2A* polymorphisms, and sleep quality.

Variables	β	SE	χ^2	*P*	OR (95% CI)
A1438G					
AA					Ref
AG	1.019	0.493	4.267	0.039*	2.771 (1.054–7.287)
GG	1.396	0.601	5.396	0.020*	4.037 (1.244–13.105)
IL-1β	−0.052	0.013	15.605	<0.001*	0.949 (0.925–0.974)

*$p < 0.05$.

TABLE 9 | Interaction effect between cytokines and *5-HTR2A* polymorphisms on sleep quality.

Comparison group	Reference group	OR (95% CI)	AOR (95% CI)
−1438G/A×IL-1β	AA×IL-1β		
AG×IL-1β		0.979 (0.960–0.999)*	0.952 (0.918–0.987)*
GG×IL-1β		0.991 (0.964–1.019)	0.964 (0.913–1.017)

*OR, odds ratio; CI, confidence interval; *p < 0.05.*

Relationship Between Cytokines and *5-HTR2A* Gene

There were no statistically significant differences in cytokine comparisons in different T102C and −1438G/A genotypes ($p > 0.05$; **Table 7**).

Correlation Analysis of Cytokines, *5-HTR2A* Polymorphisms, and Sleep Quality in Non-manual Workers

Sleep quality status served as the dependent variable, while T102C and −1438G/A genotypes and cytokines (IL-1β, IL-2, IL-6, and TNF-α) were considered to be independent variables. Multivariate logistic regression analysis was performed. The results showed that −1438G/A was a risk factor for sleep quality after adjusting for confounding factors, such as length of service, education, and monthly income. Compared to AA, both AG [odds ratio (OR) = 2.771, 95% confidence interval (CI): 1.054–7.287] and GG (OR = 4.037, 95% CI: 1.244–13.105) increased the risk of developing sleep problems. However, T102C genotypes were not associated with an increased risk of sleep problems. In addition, IL-1β was a protective factor of sleep quality (OR = 0.958, 95% CI: 0.933–0.983) (**Table 8**).

Interaction Effect Between Cytokines and *5-HTR2A* Polymorphisms on Sleep Quality in Non-manual Workers

To further explore the potential interaction between cytokines and *5-HTR2A* gene in predicting the risk of sleep quality problems, interaction items between cytokines and −1438G/A genotypes were introduced into the logistic regression model. The results showed that there was an interaction between cytokines and −1438G/A, which was still present after adjusting for confounding factors, such as length of service, education, and monthly income (**Table 9**). Compared to AA×IL-1β, AG×IL-1β (OR = 0.952, 95% CI: 0.918–0.987) was associated with a lower risk of sleep problems ($p < 0.05$).

DISCUSSION

The aim of this study was to investigate and evaluate the sleep quality of non-manual workers in Urumqi, Xinjiang, and to analyze the effects of cytokines and *5-HTR2A* polymorphisms on sleep quality to explore the relationship among the three. The results showed that of the 1,329 study subjects, 870 had sleep problems, and the detection rate was 65.46%. The distribution of sleep problems was different among non-manual workers with different education levels, lengths of service, and monthly incomes. For professionals, sleep disorders do not only affect health, but may also influence work quality and productivity. Therefore, it is crucial to promote sleep quality and develop targeted prevention and intervention measures.

Inflammatory cytokines are active signaling molecules secreted by immune cells. In addition to participating in the immune response, Il-6 and TNF-α can also affect neurotransmitter metabolism, neuroplasticity, and neuroendocrine function. They are also related to depression,

sleep disorders, and cognitive development (48–53). Previous study has found that the sleep-wake cycle is related to the immune system (22). The results of this study showed that in the analysis of the relationship between sleep quality and cytokines, the IL-1β content was statistically significantly different among different sleep quality groups, suggesting that cytokines may be involved in the sleep-wake process, which is similar to the study by Ren et al. (21). The psychoneurologic-immune model suggested that psychological factors could affect health through immune downregulation. When occupational stress was high, it may regulate the sleep process through immune activation. Cytokines are known to induce other adaptive changes in the central nervous system function, such as activation of the thalamic-pituitary-adrenal (HPA axis) system and, in particular, IL-1β and TNF-α both increase non-rapid eye movement sleep (NREMS). Animal studies have also shown that IL-1β and TNF-α were important mediators of the increase in NREMS volume and intensity (53). Sleep influences two primary effector systems, the HPA axis, and sympathetic nervous system, which together shift the basal gene expression profile toward increased pro-inflammatory type (54, 55). Activation of β-adrenergic signaling induces increase in NF-κB, inflammatory gene expression, production of pro-inflammatory cytokines and markers of systemic inflammatory markers (56). Because sleep is associated with a drop in sympathetic outflow (57), sympathetic effector pathway activation is one such biologically plausible mechanism to explain the associations between sleep quality, short sleep duration, and increases in inflammation markers.

Modern medicine describes the occurrence of insomnia using three major factors: susceptible, inducing, and persistent factors (58). Genetic influence on sleep was first reported in the 1930s, demonstrating greater consistency in sleep parameters between identical and fraternal twins. Genome-wide association studies have shown that some genes and their polymorphisms are associated with sleep problems (59–61). Serotonin (5-HT) is a monoamine neurotransmitter that plays an important role in regulating physiological functions, such as pain and cognition in sleep-eating sexual behavior and temperature (62). Previous studies have shown that of all 5-HT receptor subtypes, 5-HT2A and 5-HT1A receptors are primarily involved in the quantitative and qualitative aspects of wakefulness, NREMS, and REMS (62, 63). This study analyzed the influence of the 5-HT2A receptor gene on sleep, showing that the −1438G/A of *5-HTR2A* gene was associated with sleep quality in non-manual workers and that both AG and GG genotypes could increase the risk of sleep quality problems, which was consistent with the research results by Gao et al. (61). However, the T102C was not associated with sleep quality. A meta-analysis evaluating the association between *5-HTR2A* polymorphism and obstructive sleep apnea (OSA) syndrome found that T102/C of *5-HTR2A* was not a factor in OSA (64). Multivariate logistic regression analysis showed that −1438G/A and IL-1β were both factors affecting sleep quality.

To further explore the relationship among these three factors, the effect of the *5-HTR2A* gene and cytokine interaction on sleep was analyzed. The results showed that the interaction between −1438G/A polymorphism and IL-1β had an effect on sleep quality and served as a protective factor for it, indicating that genetic and physiological factors have a cumulative effect on sleep quality. Simultaneously, this study also suggests that the interaction between *5-HTR2A* gene and cytokines may affect the sleep quality of non-manual workers. Evidence from animal studies has also shown that interactions between immune signaling molecules (such as the cytokine IL-1β) and brain neurochemical systems (such as the serotonin system) are amplified during infection, indicating that these interactions might underlie the changes in sleep that occur during infection (18). IL-1β and 5-HT systems engage in reciprocal interactions that contribute to the regulation of NREM sleep (18).

The present research adopted a cross-sectional study method to explore the relationship among cytokines, *5-HTR2A* polymorphisms, and sleep quality. Both cytokines and *5-HTR2A* polymorphisms were found to affect sleep quality of non-manual workers. A potential interaction between the two factors in the occurrence of sleep quality problems was also identified. That is, the cumulative effect between 5-HTR2A and cytokines was greater than the independent effect. These results may suggest that the 5-HTR2A gene polymorphism may increase the risk of poor sleep quality, but this effect may not be the same in individuals with different IL-1β concentrations.

However, there are still some deficiencies in the present research, and further improvement is needed in future studies. First, the evaluation of sleep quality was based completely on PSQI, a subjective questionnaire survey lacking objective sleep quality evaluation tools and resulting in lower study accuracy. Ideally, laboratory-based polysomnography recordings could be obtained from subjects to confirm the current findings; however, this requires a amount of labor and time, and is also expensive. Second, some confounding factors related to sleep quality, such as shift work, shift frequency, occupational stress and other work-related factors, were not considered in this study. Third, the present study examined the *5-HTR2A* gene polymorphism, but the results would have been more reliable if we had quantified the 5-HT levels of the study participants and examined the relationship between cytokines, 5-HT, *5-HTR2A* gene polymorphisms and sleep quality.

CONCLUSION

Both cytokines and *5-HTR2A* polymorphisms are associated with sleep quality, and both can be used as predictors of sleep quality problems. In addition, there may be an interaction between cytokines and *5-HTR2A* polymorphisms when considering sleep quality. Specifically, effective detection of IL-1β can influence the independent effect of *5-HTR2A* polymorphisms on sleep quality. Future research will require a larger sample size and a cohort study to verify the association among these factors and provide a stronger theoretical basis for improving sleep quality in non-manual workers.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

JW, XG, PG, and JL designed the study, contributed to the acquisition, analysis, interpretation of data, involved in drafting the manuscript, and revising it for important intellectual content. All authors contributed substantially to the work presented in this paper, reviewed, and approved the final manuscript.

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Sleep Misperception and Associated Factors in Patients With Anxiety-Related Disorders and Complaint of Insomnia: A Retrospective Study

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Purpose: Data on sleep parameters by polysomnography (PSG) in patients with anxiety-related disorders are limited. Although the disturbance and risk factors of sleep misperception have been implicated in psychopathology, its role in anxiety-related disorders remains unclear. This retrospective study aimed to explore the characteristics and sleep parameters in patients with anxiety-related disorders and different sleep perception types, and to explore the associated factors for sleep misperception.

Methods: Patients with anxiety-related disorders who had complaint of insomnia for more than 3 months were collected at Wuhan Mental Health Center between December 2019 and July 2021. Patients underwent a two-night PSG monitoring and completed a self-reported sleep questionnaire. Behaviors were assessed using 30-item Nurses' Observation Scale for Inpatient Evaluation (NOSIE-30). Patients were divided into normal sleep perception (NSP), positive sleep perception abnormality [PSPA; overestimation of total sleep time (TST) >60 min], and negative sleep perception abnormality (NSPA; underestimation of TST >60 min) groups. PSG indicators and NOSIE-30 scores were compared among groups using the one-way analysis of variance and the Kruskal-Wallis test. Multiple linear regression analysis was performed to determine the associated factors for misperception index.

Results: The subjective and objective TST were 5.5 ± 1.9 h and 6.4 ± 1.7 h in 305 patients, respectively. Sixty-nine (22.6%) had PSPA, 80 (26.2%) had NSP, and 156 (51.1%) had NSPA. Subjective TST and objective sleep parameters were significantly different among groups. No statistical differences in NOSIE-30 subscale and total scores were observed among groups. Sex, rapid eye movement (REM)/TST (%), sleep efficiency, number of awakenings, Non-rapid eye movement of stage 2 sleep (NREM)/TST (%), REM spontaneous arousal times, sleep latency, diagnosis, social competence, and manifest psychosis were associated with sleep misperception.

Conclusion: Sleep misperception is common in patients with anxiety-related disorders. Various sleep perception types have different PSG profiles, but similar personal and social behaviors. These data may be helpful to conduct personalized treatment.

Keywords: misperception index, sleep misperception, anxiety-related disorders, polysomnography, total sleep time

INTRODUCTION

Sleep is an important psychophysiological process for mental health (1). Sleep disturbance in mental disorders can negatively affect cognitive, emotional, and social functions (2). Anxiety-related disorders, as a branch of mental disorders, are characterized by abnormal maladaptive forms of emotional response to potential threat. The common types of anxiety-related disorders according to the fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-V) include generalized anxiety disorder, obsessive-compulsive disorder, social anxiety disorder, separation anxiety disorder, panic disorder, agoraphobia, and specific phobia (3). Increasing evidence demonstrates sleep disturbance in patients with anxiety-related disorders (4, 5), with a potentially bidirectional relationship. However, current findings in sleep profiles are mostly focused on individual anxiety-related disorders, and sleep assessment modality was inconsistent among studies (5). A comprehensive evaluation of sleep disturbance in this whole branch of mental disorders is needed.

Objective measures have been increasingly used for the analysis of sleep problems. However, an interesting phenomenon, discrepancy between subjective and objective sleep parameters, often appears. This sleep misperception is directly reflected in the divergence of subjective and objective total sleep time (TST), including underestimation and overestimation of TST. Patients will frequently go to the hospital due to dissatisfaction with sleep quality, seeking for solution. Sleep misperception has been implicated in many kinds of insomnia. The prevalence of sleep misperception in the sleep disorder population varied widely, ranging from 9.2 to 55.5% (6 7 9), due to different definitions of sleep misperception used. Polysomnography (PSG) is arguably the objective standard to assess sleep parameters. Although the diagnosis of insomnia is usually not based on objective parameters, it is necessary to use both objective and subjective methods for capturing the sleep experience and its characteristics. However, most of the current studies on sleep misperception excluded patients with mental disorders. Currently, only a small number of studies analyzed sleep misperception, with scarce data on subjective and objective sleep parameters in psychiatric patients. A study by Wenigmann et al. assessed psychiatric patients with sleep disorders, and sleep misperception was observed in 52% of the 249 examined patients (6). Bian et al. reported a sleep misperception rate of 43.2% in 148 patients with schizophrenia (7). Interestingly, 38.5% of patients with schizophrenia showed overestimation of their TST (7). However, sleep misperception with quantitative analysis of sleep parameters is limited in patients with anxiety-related disorders. Although a previous study preliminarily provided some evidence on sleep disturbance in anxiety-related disorders by collectively using meta-analysis and combining subjective and objective measures together, differences between subjective and objective data among patients with different sleep perception were not characterized. In addition, further studies are needed to identify the associated factors for sleep misperception.

This study aimed to explore the characteristics and sleep parameters in patients with anxiety-related disorders and different sleep perception types, and to explore the associated factors for sleep misperception. We hope to provide some reliable evidence for sleep assessment, clinical classification, and appropriate treatment of patients with anxiety-related disorders.

METHODS

Patients

This was a retrospective study conducted in the Wuhan Mental Health Center between December 2019 and July 2021. The inclusion criteria were as follows: (1) age $\geq$18 years; (2) diagnosis of anxiety-related disorders according to DSM-V criteria (3); (3) stable disorder; (4) complaint of insomnia for more than 3 months; and (5) ability to understand the study objective and willingness to complete the assessments. The exclusion criteria were as follows: (1) severe anxiety, as indicated by Self-rating Anxiety Scale score $\geq$70 (8); (2) other DSM-V axis I disorders; (3) prior electroconvulsive therapy within 1 month; (4) cognitive impairment, as indicated by Mini-Mental State Examination (MMSE) score $\leq$27 (9); (5) abuse of drugs or other substances; (6) other significant sleep disorders according to the third edition of International Classification of Sleep Disorder (ICSD-3) (10), including obstructive sleep apnea hypopnea syndrome (OSAHS), rapid eye movement (REM) or non-REM (NREM) parasomnia, circadian rhythm sleep-wake disorders, and movement disorders (such as restless leg syndrome and periodic leg movement disorder); (7) have used any medicine or health care products to regulate sleep in the past 5 days; and/or (8) incomplete data. The study was approved by the Ethics Committee of Wuhan Mental Health Center (No.KY201908.28). Written informed consent was obtained from each patient before examinations.

Data Collection

Demographics, diagnosis of anxiety-related disorders, and medication history (in the last 6 months) were collected during the interview with a psychiatrist, two board-certified neurologists, and an expert in sleep medicine. After interview,

patients underwent PSG monitoring and completed a self-reported sleep questionnaire. Blood pressure was measured before and after PSG monitoring.

Polysomnography Monitoring

Patients received two-night standard PSG monitoring using a Compumedics-Greal PSG monitor (Australia Compumedics Limited). To exclude other sleep disorders and first night effect, data during the second night were collected for analysis. All patients entered the monitoring room at 21:30 and were asked to schedule their sleep and wake-up time according to daily routine. The monitoring room was quiet and comfortable, with proper room temperature, humidity, and light. Psychoactive substances, such as alcohol, tea, and coffee, were not allowed. The monitoring started from 22:00 to 7:00 the next morning. Complete records of electroencephalogram, electrooculogram, electromyogram, electrocardiogram, thermal airflow sensor, nasal pressure transducer, chest and abdomen respiratory movement, limb movement, body position, blood oxygen saturation, and snore sensor indicators for 6 h or longer were deemed as a successful monitoring. Patients with unsuccessful monitoring needed to be monitored again at next night. Items were recorded and analyzed according to American Academy of Sleep Medicine (AASM) criteria, version 2.6 (11), including TST, sleep latency, sleep efficiency (TST/time in bed$\times$100%), the percentage of NREM sleep (N1, N2, and N3 period) and REM sleep to TST, wake after sleep onset (WASO), number of awakenings, arousal index, and spontaneous arousal times. Arousal from sleep was deemed present when there were limb movements or respiratory events with oxygen desaturation for $\geq$10 s. Spontaneous arousal was defined as that which was not caused by respiratory events, oxygen desaturation, or limb movement. All Participants were asked to stop taking any sleep-affecting medication at least 5 days prior to testing as judged by our sleep specialist.

Self-Reported Sleep Questionnaire

After successful PSG monitoring, patients were instructed to fill a questionnaire with four questions: (1) What time did you go to bed last night? (2) How long did it take you to fall asleep last night? (3) What time did you wake up this morning? (4) How long did you sleep last night?

Sleep Perception

There are no recognized diagnostic criteria for sleep perception. According to previous studies (12–14), sleep perception abnormality is defined as a more than 60 min difference between self-reported subjective TST and PSG-measured objective TST. Positive sleep perception abnormality (PSPA) is defined as subjective overestimation of TST (subjective TST—objective TST >60 min). Negative sleep perception abnormality (NSPA) is defined as subjective underestimation of TST (objective TST—subjective TST >60 min). Normal sleep perception (NSP) is defined as $\leq$60 min discrepancy between subjective TST and objective TST. Sleep perception is calculated as subjective TST/objective TST (15). Lastly, sleep perception is calculated as (objective TST—subjective TST) (17).

Nurses' Observation Scale for Inpatient Evaluation

The 30-item Nurses' Observation Scale for Inpatient Evaluation (NOSIE-30) is a highly sensitive scale to assess the behavioral changes in patients with psychiatric disorders (16–19). A Chinese version of NOSIE-30 was used in this study (20), which comprises 7 subscales: social competence, social interest, personal neatness, irritability, manifest psychosis, retardation, and depression. The first three subscales indicate positive behaviors, while the last four reflect negative behaviors. Each item is scored using a 5-Likert scale ranging from 0 (never) to 4 (always). Higher score indicates a higher frequency of each particular behavior.

Statistical Analysis

Statistical analysis was performed using SPSS 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were tested for normal distribution using Shapiro-Wilk test. Continuous variables, in accordance with normal distribution, were expressed as mean $\pm$ standard deviation and were compared among groups using one-way analysis of variance with *post-hoc* Bonferroni correction. Continuous variables with skewed distribution were expressed as median [interquartile range IQR)], and were compared among groups using the Kruskal-Wallis test with *post-hoc* Bonferroni correction. Categorical variables were expressed as frequency (percentage) and were compared among groups using chi-square test or Fisher exact test, where appropriate. Multiple linear regression analysis was performed to determine the associated factors for misperception index, and stepwise method was used for the selection of independent variables. $p < 0.05$ was considered statistically significant.

RESULTS

General Information and Sleep Parameters in the Total Patients With Anxiety-Related Disorders

Between December 2019 and July 2021, a total of 305 patients who met the eligibility criteria with complete data were included in the analysis (**Figure 1**). The mean age was 44.0 $\pm$ 16.6 years, and 182 (59.7%) were females. Of 305 patients, 150 (49.2%) had generalized anxiety disorder, 81 (26.6%) had obsessive-compulsive disorder, 20 (6.6%) had mixed anxiety disorder, 15 (4.9%) had somatic symptom-related anxiety disorder, 14 (4.6%) had social anxiety disorder, 12 (3.9%) had separation anxiety disorder, five (1.6%) had hypochondriac anxiety disorder, four (1.3%) had panic disorder, and four (1.3%) had specific phobia. Sixty-nine (22.6%) had PSPA, 80 (26.2%) had NSP, and 156 (51.1%) had NSPA (**Table 1**). Regarding the sleep parameters in all the 305 patients, the subjective and objective TST were 5.5 $\pm$ 1.9 h and 6.4 $\pm$ 1.7 h, respectively. The sleep latency was 44.4 $\pm$ 38.5 min, and the sleep efficiency was 73.2 $\pm$ 18.6%. The misperception index was 0.1 $\pm$ 0.5 (**Table 2**).

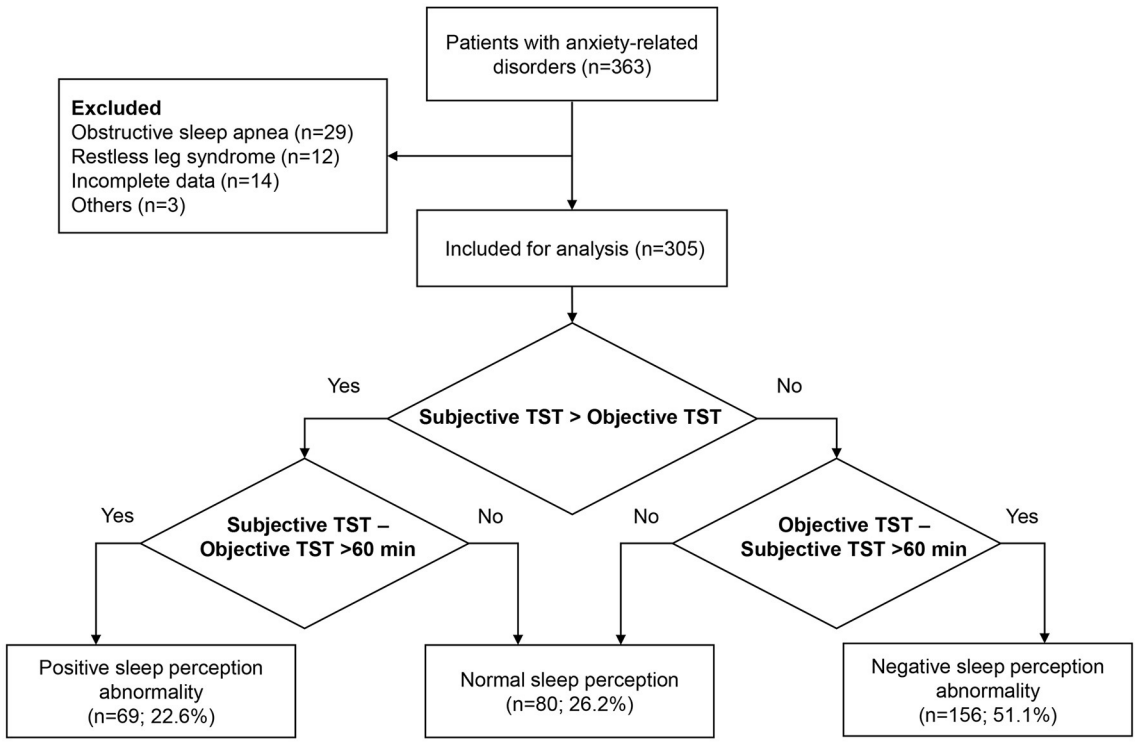

FIGURE 1 | Study flowchart.

Comparisons of General Information, Sleep Parameters, and NOSIE-30 Scores Among Patients With Anxiety-Related Disorders and Different Sleep Perception Types

More females presented with PSPA or NSPA ($p < 0.01$) (**Table 1**). The lowest subjective TST and the highest objective TST were observed in the NSPA group [4 h (IQR, 4–6) and 8 h (IQR, 7–8)], followed by the NSP group [6 h (IQR, 5–6.3) and 6 h (IQR, 5–6)] and PSPA group [8 h (IQR, 7–8) and 4 h (IQR, 4–6)], with significant differences between each two groups after *post-hoc* Bonferroni correction ($p < 0.01$). Number of awakenings, total spontaneous arousal times, NREM spontaneous arousal times, sleep latency, sleep perception, and misperception index were also significantly different between each two groups ($p < 0.01$). Arousal index showed no statistical difference between the NSPA and NSP groups, but both were significantly higher than the PSPA group ($p < 0.01$). REM spontaneous arousal times and the percentage of REM sleep to TST showed no statistical differences between the NSPA and NSP groups, but all were significantly lower than the PSPA group ($p < 0.01$). The percentage of N1 period and N2 period to TST only showed significant differences between the NSP and PSPA groups ($p < 0.01$). The percentage of N3 period to TST only showed significant difference between the NSPA and PSPA groups ($p < 0.01$). Sleep efficiency and WASO showed no statistical differences between the NSP and PSPA groups, but all showed significant difference when compared with the NSPA group ($p < 0.01$) (**Table 2**). As shown in **Table 3**, there were no significant differences in subscale scores or total scores of NOSIE-30 among the three groups ($p > 0.05$).

Multiple Linear Regression Analysis of Associated Factors for Sleep Perception

The explanatory variable was defined as the "sleep perception = objective TST–subjective TST." Before performing multiple regressions, the first task was to conduct a variable screening. Using a forward stepwise regression method to select variables (age, sex, BMI, all variables shown in **Tables 2**, **3**), the selection criteria was that significance-level p-value was <0.05. If the p-value is >0.05, the variable will be eliminated. The final retained variables were sex, REM/TST, sleep efficiency, number of awakenings, Non-rapid eye movement of stage 2 sleep (NREM)/TST (%), REM spontaneous arousal times, sleep latency, diagnosis, social competence, and manifest psychosis. If multiple collinearity tests (VIF, Variance Inflating Factor) are >5, it indicates a collinearity problem among variables. Otherwise, there is no collinearity problem among variables. **Table 4** shows the regression results. Moreover, from the analysis of **Table 4**, we found that the VIF statistic of each explanatory variable was <5, indicating that there was no multiple collinearity problem among the variables, which was in line with the assumption of multiple linear regression. Then, Durbin-Watson (DW)test statistics was used to test whether the regression residue is self-phase when the DW statistic approached 2, indicating that the residue is not autocorrelated. The regression results showed that

TABLE 1 | Patient characteristics.

Characteristic	Total ($n = 305$)	PSPA ($n = 69$)	NSP ($n = 80$)	NSPA ($n = 156$)	*P*
Age (years)	44.0 ± 16.6	46 (24, 57)	48 (34, 59)	46 (29, 56)	0.159
Sex					<0.01
Male	123 (40.3)	26 (37.7)	44 (55.0)	53 (34.0)	
Female	182 (59.7)	43 (62.3)	36 (45.0)	103 (66.0)	
BMI (kg/m^2)	22.6 ± 3.6	23 (20, 24)	23 (21, 25)	22 (20, 25)	0.098
SBP before PSG (mmHg)	120.3 ± 14.9	119.5 ± 14.2	121.2 ± 13.1	120.2 ± 16.0	0.783
DBP before PSG (mmHg)	76.5 ± 11.2	75 (68, 81)	78 (71, 84)	75.5 (70, 82)	0.140
SBP after PSG (mmHg)	117.2 ± 14.5	114 (105, 121)	118.5 (112, 126)	117 (106, 125)	0.077
DBP after PSG (mmHg)	75.2 ± 9.6	72 (66, 80)	78 (72, 84)	75 (70, 79)	0.019
Medication history					
Sedative hypnotic drugs	198 (73.8)	36 (52.2)	57 (71.3)	105 (67.3)	0.035
Antidepressants	148 (48.5)	27 (39.1)	39 (48.8)	82 (52.6)	0.177
Mood stabilizers	42 (13.8)	10 (14.5)	8 (10.0)	24 (15.4)	0.514
Antipsychotic drugs	22 (7.2)	7 (10.1)	5 (6.3)	10 (6.4)	0.563
Antianxiety drugs	16 (5.2)	1 (1.4)	7 (8.8)	8 (5.1)	0.135
Diagnosis					<0.01
Generalized anxiety disorder	150 (49.2)	27 (39.1)	36 (45.0)	87 (55.8)	
Obsessive-compulsive disorder	81 (26.6)	9 (13.0)	23 (28.8)	49 (31.4)	
Mixed anxiety disorder	20 (6.6)	5 (7.2)	11 (13.8)	4 (2.6)	
Somatic symptom-related anxiety disorder	15 (4.9)	9 (13.0)	5 (6.3)	1 (0.6)	
Social anxiety disorder	14 (4.6)	11 (15.9)	2 (2.5)	1 (0.6)	
Separation anxiety disorder	12 (3.9)	5 (7.2)	0	7 (4.5)	
Hypochondriac anxiety disorder	5 (1.6)	1 (1.4)	1 (1.3)	3 (1.9)	
Panic disorder	4 (1.3)	2 (2.9)	0	2 (1.3)	
Specific phobia	4 (1.3)	0	2 (2.5)	2 (1.3)	

Data are mean ± standard deviation, median (interquartile range), or n (%). BMI, body mass index; SBP, systolic blood pressure; PSG, polysomnography; DBP, diastolic blood pressure; PSPA, positive sleep perception abnormality; NSP, normal sleep perception; NSPA, negative sleep perception abnormality.

the DW was 1.920, close to 2, indicating that the residue has no autocorrelation.

The adjusted goodness-of-fit R^2 was 0.663, indicating that each explanatory variable can explain 66.3% of the information volume of the explained variable, and more than half of the information can be explained, indicating a good fitting effect. The model gameplay test F statistic was 60.855, and the significance-level p-value was <0.05, suggesting that the established multiple linear regression was valid.

Finally, multiple linear regression analysis showed that the sleep perception was associated with sex, REM/TST, sleep efficiency, number of awakenings, N2/TST, REM spontaneous arousal times, sleep latency, diagnosis, social competence, and manifest psychosis (**Table 4**).

DISCUSSION

This study compared clinical characteristics, sleep parameters, misperception index, and behaviors among patients with different sleep perception types (PSPA, NSP, and NSPA). Subjective TST and all the objective sleep parameters were significantly different among the three groups. Interestingly, although there were differences in the diagnoses of anxiety-related disorders among groups, similar personal and social behaviors were observed by NOSIE-30. Regarding results of the linear regression, younger age, more REM spontaneous arousal times, higher sleep latency, lower percentage of N3 period to TST, higher sleep efficiency, and higher WASO were associated with the increase in misperception index.

In our study, all the 305 patients were diagnosed with anxiety-related disorders, with the overall subjective TST of 5.5 ± 1.9 h and objective TST of 6.4 ± 1.7 h. This is consistent with previous studies that claimed that there is a universal difference between subjective and objective sleep time for all insomnia patients (21–23). Subjective sleep disturbance, decreased TST, and sleep continuity are robust in patients with anxiety-related disorders, with minor evidence for diminished sleep depth (5). However, studies that directly examined the distribution of different sleep perception types among patients with anxiety-related disorders are scarce. Underestimation of TST is prevalent among general insomniacs with normal objective TST (14, 21). In addition, some insomniacs can accurately estimate sleep time, while some may overestimate their TST (14). This phenomenon is also observed in our study of patients with anxiety-related disorders, of whom 51.1% underestimated their sleep time, 22.6% accurately estimate sleep time, and 26.2% overestimated their sleep time. The proportion of patients with normal sleep perception in our study was largely lower than general insomniacs and other psychiatric patients with sleep disorders (6, 7, 21). This indicates that patients with anxiety-related disorders who complain of insomnia may have worse sleep misperception. Pre-sleep cognitive activity is

TABLE 2 | Polysomnography indicators, sleep perception, and misperception index.

Item	Total ($n = 305$)	PSPA ($n = 69$)	NSP ($n = 80$)	NSPA ($n = 156$)	*P*
Subjective TST (h)	5.5 ± 1.9	8 (7, 8)	6 (5, 6.3)[a]	4 (4, 6)[ab]	<0.01
Objective TST (h)	6.4 ± 1.7	4 (4, 6)	6 (5, 6)[a]	8 (7, 8)[ab]	<0.01
Number of awakenings (n)	64.1 ± 58.4	2 (1, 6)	57.5 (16, 96)[a]	76 (53, 111)[ab]	<0.01
Arousal index (per hour)	12.7 ± 14.5	4 (0, 10)	11.5 (6, 19)[a]	11 (8, 16)[a]	<0.01
Spontaneous arousal times (min)					
Total	40.8 ± 35.6	6 (3, 11)	37 (9, 60)[a]	52 (32, 72)[ab]	<0.01
NREM	38.7 ± 31.2	12 (9, 18)	32.5 (15, 54)[a]	47 (28, 64)[ab]	<0.01
REM	7.9 ± 9.4	11 (2, 21)	2 (1, 7)[a]	4 (1, 10)[a]	<0.01
Sleep latency (min)	44.4 ± 38.5	86 (78, 92)	50 (22, 81)[a]	13.5 (6, 32)[ab]	<0.01
N1/TST (%)	17.5 ± 15.3	10 (8, 18)	16 (13, 23)[a]	14 (9, 22)	<0.01
N2/TST (%)	77.0 ± 57.3	54 (28, 92)	70 (58, 91)[a]	64 (54, 73)	<0.01
N3/TST (%)	12.2 ± 10.9	14 (10, 19)	12 (3, 18)	8 (0, 17)[a]	<0.01
REM/TST (%)	29.3 ± 26.4	58 (47, 69)	14 (7, 49)[a]	15 (8, 20)[a]	<0.01
Sleep efficiency (%)	73.2 ± 18.6	60 (46, 76)	69.5 (58, 80)	85 (76, 91)[ab]	<0.01
WASO (min)	86.3 ± 68.7	72 (55, 129)	111.5 (66, 147)	54 (24, 79)[ab]	<0.01

Data are mean ± standard deviation or median (interquartile range). Number of awakenings: the sum number of awake when falling asleep during the full night; Arousal index: the sum number of arousals ×60/TST (per hour); Spontaneous arousal times: the sum minutes of spontaneous arousal after falling sleep; TST, total sleep time; NREM, non-rapid eye movement; REM, rapid eye movement; WASO, wake after sleep onset; PSPA, positive sleep perception abnormality; NSP, normal sleep perception; NSPA, negative sleep perception abnormality.
[a] $p < 0.0167$ vs. PSPA by post-hoc Bonferroni correction.
[b] $p < 0.0167$ vs. NSP by post-hoc Bonferroni correction.

TABLE 3 | Results of the nurses' observation scale for in-patient evaluation (NOSIE-30).

Item	Total ($n = 305$)	PSPA ($n = 69$)	NSP ($n = 80$)	NSPA ($n = 156$)	*P*
Social competence	35.6 ± 4.1	36 (34, 38)	36 (34, 38)	36 (34, 38)	0.424
Social interest	16.5 ± 8.2	16 (12, 20)	16 (10, 20)	18 (10, 20)	0.996
Personal neatness	27.4 ± 3.8	28 (24, 28)	28 (24, 32)	28 (24, 32)	0.757
Irritability	8.5 ± 7.5	6 (0, 10)	8 (2, 12)	8 (4, 12)	0.135
Manifest psychosis	0.4 ± 1.6	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.164
Retardation	3.9 ± 4.2	2 (0, 6)	4 (2, 6)	2 (0, 6)	0.111
Depression	2.9 ± 3.9	2 (0, 4)	2 (0, 6)	1 (0, 4)	0.687
Positive behaviors[a]	79.4 ± 11.8	80 (74, 86)	80 (70, 86)	80 (72, 86)	0.971
Negative behaviors[b]	15.7 ± 12.1	12 (6, 18)	16 (6, 24)	14 (6, 22.5)	0.136
Total score	191.9 ± 17.8	196 (186, 204)	192 (180, 204)	194 (182, 202)	0.532

Data are mean ± standard deviation or median (interquartile range). PSPA, positive sleep perception abnormality; NSP, normal sleep perception; NSPA, negative sleep perception abnormality.
[a] Positive behaviors include the subscales of social competence, social interest, and personal neatness.
[b] Negative behaviors include the subscales of irritability, manifest psychosis, retardation, and depression.

common in patients with anxiety-related disorders which are associated with underestimation of sleep time (5). These patients might also have paranoid ideation. Despite that 67.3% of patients in the NSPA group had used sedative hypnotic drugs, they still underestimated the sleep time. However, the high use rate of sedative hypnotic drugs seems not entirely useless. There were a certain number of patients with NSP or overestimation of TST in our study, which might be attributed to the effect of sedative hypnotic drugs. It was also possible that patients who overestimated their sleep time had potential cognitive impairment. A similar situation was observed in a study by Bian et al. (7), which showed that 43.2% of patients with stable schizophrenia presented sleep misperception, including 38.5% with overestimation of TST and 4.7% with underestimation of TST (7). Patients with schizophrenia tend to exaggerate their sleep quality, even for those with stable disease after effective antipsychotics treatment (24). Brain structure abnormality and alterations in neurotransmitters related to time perception may exist in patients with schizophrenia. In addition, COMT and ANKK1 genes are considered to be the possible reasons that lead to time misperception in these patients (25). Further research is needed to confirm whether neurophysiological mechanisms also exist in patients with anxiety-related disorders which contribute to sleep misperception.

In this study, we found that the sleep structure was completely different among groups. Patients with underestimation of TST

TABLE 4 | Multiple linear regression analysis of associated factors for sleep perception.

Variable	Beta [95%CI]	*p*	VIF
C	−0.392 [−2.582, 1.799]	0.725	–
REM/TST (%)	−0.039 [−0.048, −0.031]	<0.01	1.709
sex	0.465 [0.097, 0.833]	0.013	1.041
Sleep efficiency (%)	0.051 [0.04, 0.062]	<0.01	1.377
Number of awakenings (n)	0.007 [0.003, 0.011]	<0.01	1.519
N2/TST (%)	0.006 [0.003, 0.01]	0.001	1.257
Spontaneous arousal times of NREM (min)	−0.034 [−0.054, −0.013]	0.001	1.147
Sleep latency (min)	−0.01 [−0.017, −0.004]	0.002	1.913
Diagnosis	−0.063 [−0.122, −0.003]	0.039	1.098
Social Competence	−0.057 [−0.103, −0.01]	0.017	1.125
Manifest psychosis	−0.135 [−0.251, −0.018]	0.024	1.064
Adj-R^2		0.663	
F		60.855 ($p < 0.01$)	
DW		1.920	

TST, total sleep time; REM, rapid eye movement; WASO, wake after sleep onset; NREM, non-rapid eye movement.

showed lower sleep latency and WASO, but more NREM spontaneous arousal times and higher sleep efficiency than those with overestimation of TST or NSP. A study by Liu et al. grouped patients with OSAHA using the same method and showed similar results with our study in sleep structure among groups (12). Although patients in the NSPA group entered the sleep cycle faster, they had more spontaneous arousal times during the NREM period. They had difficulty in entering the REM period and would wake rapidly, with lower percentage of REM period to TST and WASO. Thus, they might believe that they get insufficient sleep, owing to decreased sleep depth and poor sleep continuity. Frequent periodic electroencephalogram changes during NREM period might be the reasons for sleep misperception (26, 27), but this needs further research. Despite the different sleep structure among groups, no differences were observed in personal and social behaviors. Some previous studies also analyzed the impact of sleep misperception on psychiatric symptoms, but the results are controversial (7, 14, 22, 28). The association of sleep misperception with psychiatric symptoms needs further investigation.

Identifying associated factors can help us carry out personalized treatment in risk population, which is also one of the objectives of our study. Sex, REM/TST (%), sleep efficiency, number of awakenings, N2/TST (%), REM spontaneous arousal times, sleep latency, diagnosis, social competence, and manifest psychosis were associated with sleep misperception. This was expected and consistent with the interplay of sleep structural parameters and was supported by previous studies (5, 12).

Although patients with insomnia often show a discrepancy between self-reported and objective sleep parameters, none of the standard treatment has been identified for insomnia have specifically targeted misperception of sleep. In our study, 73.8% of patients used sedative hypnotic drugs with high frequency prescription for insomnia in the last 6 months. Unnecessary use of sedative hypnotic drugs may bring side effects or lead to drug addiction syndrome and disrupt the integrity of sleep. Hence, treatment for self-reported sleep disorders should be reconsidered. Sleep misperception can be improved after psychotherapy (such as cognitive-behavioral therapy) for patients with insomnia (29). This might also be feasible in patients with anxiety-related disorders without any side effects, which deserves further investigations.

To our knowledge, this is the first study that explored the discrepancy between objective measures and subjective experience among patients with anxiety-related disorders in a large-scale study in China. However, there are still some limitations. First, potential bias was inevitable due to the retrospective nature and single-center design. Second, no data of imaging and pathological examinations were available in this study. Finally, only a two-night PSG was performed. Sleep time and misperception data obtained during multiple nights (such as seven nights) or by averaging might provide more valuable information with little variability.

In conclusion, this study indicates that sleep misperception is prevalent in patients with anxiety-related disorders. Objective sleep parameters differed in patients with various sleep perception types, with similar personal and social behaviors. Our results provide quantitative evidence for further study of sleep misperception in patients with anxiety-related disorders.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Wuhan Mental Health Center. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CZ and GL were involved in study conception and design. YL, XZ, BL, LH, FT, XL, CH, and HL were involved in the acquisition of data. YL and XZ were involved in the analysis and interpretation of data and were involved in drafting the manuscript. All authors were involved in revising the manuscript. All authors have also read and approved the final manuscript.

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SYSTEMATIC REVIEW
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The Role of Acupuncture in the Management of Insomnia as a Major or Residual Symptom Among Patients With Active or Previous Depression: A Systematic Review and Meta-Analysis

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Background: Due to concerns about risks associated with antidepressants and/or hypnotics, complementary therapies such as acupuncture have been sought by patients with active or previous depression to manage insomnia. This systematic review aimed to clarify if acupuncture is effective and safe enough to be recommended as an alternative or adjuvant therapy to standard care in ameliorating concomitant or residual insomnia, two types of insomnia associated with depression.

Methods: Randomized controlled trials (RCTs) of depression-related insomnia (DI) treatment *via* acupuncture *vs.* waitlist-control or placebo-/sham-acupuncture and RCTs of DI treatment *via* acupuncture alone or combined with standard care [Western pharmacotherapy and/or cognitive-behavioral therapy (CBT)] *vs.* standard care alone were searched for from seven databases from inception to December 2021. Cochrane criteria were followed.

Results: Twenty-one studies involving 1,571 participants were analyzed. For insomnia as a major symptom of active depression, meta-analyses suggested that acupuncture significantly reduced the global scores of both the Pittsburg Sleep Quality Index (PSQI) [MD = −3.12, 95% CI (−5.16, −1.08), $p < 0.01$] and Hamilton Depression Scale (HAMD) [SMD = −2.67, 95% CI (−3.51, −1.84), $p < 0.01$], in comparison with placebo-acupuncture. When compared with conventional pharmacotherapy (antidepressants and/or hypnotics), the results favored acupuncture in decreasing PSQI [MD = −1.17, 95% CI (−2.26, −0.08), $p = 0.03$] and HAMD [SMD = −0.47, 95% CI (−0.91, −0.02), $p = 0.04$]. Acupuncture was comparable to conventional pharmacotherapy in reducing scores of each domain of PSQI. For insomnia as a residual symptom of previous or partially remitted depression, acupuncture conferred a very limited, non-significant

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therapeutic advantage against sham-/placebo-acupuncture. Whether acupuncture has an add-on effect to conventional pharmacotherapy in this type of insomnia has not been investigated. Also, no study was available to address the efficacy differences between acupuncture and CBT or the synergistic effect of these two therapies.

Conclusions: There is a low to moderate level of evidence supporting acupuncture as a safe and effective remedy alternative to or adjuvant to conventional pharmacotherapy (antidepressant and/or hypnotic) in improving insomnia and other depression symptoms among patients with active depression. Furthermore, the patients' complaint of disrupted sleep continuity is most likely to benefit from acupuncture. The benefit of acupuncture on residual insomnia associated with previous or partially remitted depression is limited. Future acupuncture studies need to consider applying optimal dosage and addressing deficiencies in trial quality.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021269880, PROSPERO, identifier: CRD42021269880.

Keywords: acupuncture, depression, insomnia, systematic review, meta-analysis, RCT

BACKGROUND

Depression is an increasing global burden and a common mental illness that affects both the psychological and physiological health (1), which in turn can severely limit social and cognitive functioning and diminish quality of life (2, 3). More than 300 million individuals throughout the world are estimated to suffer from depression, which is ranked by World Health Organization as the single largest contributor to global disability (1, 4). Disturbed sleep is the most prominent symptom among patients with depression (5). Up to 67–84% adults and 57% children and adolescents experience insomnia during depressive episodes (6). The polysomnography (PSG) data of depressed patients also reveal that they generally have extended sleep-onset latency (SOL), decreased sleep efficiency (SE), frequent nocturnal awakenings, early morning awakening, and reduced slow-wave sleep (SWS) (7, 8). Worst of all, sleep disturbances are usually underestimated or overlooked and are seldom a treatment target, given the common assumption that sleep problems are a concomitant symptom of depression and will diminish as depression subsides (5). This is despite evidence that depressive symptoms in some patients will not improve until sleep issues are resolved (9). Notably, insomnia is not only linked to more severe depressive symptoms, including suicidality, but is also associated with a poorer response to treatments for depression (6, 8), a longer duration of treatment (5), a slower recovery from their illness (2), and a lower rate of remission (5). In addition, persistent insomnia is usually a residual symptom of depression (10), occurring in approximately 95% of patients with incomplete remission of depression and 72% patients who have full remission following antidepressant treatment (6). These findings indicate that isolated antidepressive therapy may not provide an adequate remedy for patients with sleep problems (6). Consequently, resolving insomnia as a major or residual symptom in patients with active or previous depression, respectively, is crucial and has significant clinical relevance, because the former can interact with depression and thereupon then exacerbates and maintains each condition (11) and the latter constitutes a pivotal risk factor for a future depressive episode (relapse into depression) (6, 12) and contributes to undesirable clinical outcomes (5).

Cognitive-behavioral therapy for insomnia (CBT-i) is recommended as the most efficacious non-pharmacological therapy for insomnia and has also shown a therapeutic effect for DI (5, 13). Unfortunately, access to CBT-i treatment is restricted due to cost and a dearth of trained CBT-i providers, particularly in community-based sleep clinics and rural areas (14). Poor adherence is another challenge in delivering CBT-i in patients with DI, as insomniacs with elevated depressive symptom are more likely to terminate and drop out from CBT-i treatment early (15). The preferred class of drugs for DI is sedating antidepressant agents, including trazodone and mirtazapine (7, 8) or agomelatine (a melatonergic agonist and a 5-HT_{2c} antagonist) (16). Despite satisfactory curative effects, dependence and complaints such as dry mouth, nausea, dizziness, increased appetite and weight gain, and/or constipation (16, 17) reported during the course of treatment can result in treatment termination in some patients (18).

Complementary and alternative medicine (CAM) is becoming popular in the management of the insomnia–depression–anxiety symptom cluster (19); some evidence-based clinical practice guidelines (CPGs) in the Euro-American and Asian-Pacific regions include CAM therapies to inform clinicians' practice decisions on various types of insomnia (20). Acupuncture, an integral component of CAM, is a non-pharmaceutical therapy of traditional Chinese medicine (TCM) that stems from ancient clinical practice and has been widely practiced in China for over 4,000 years (21, 22). It involves the insertion of thin, sterile needles into the skin at defined sites (called "acupoints") for therapeutic purposes (21, 23, 24). After insertion, the needles are usually twisted back and forth manually (manual acupuncture, MA) or connected to an electric microcurrent device delivering

either high- or low-frequency impulses (electroacupuncture, EA), or a combination of both techniques is used (22, 24).

Acupuncture has been extensively utilized in clinical practice for the management of DI, and many randomized Controlled trials (RCTs) have been published (25). Nevertheless, the inconsistent findings (26, 27) and vast differences between research designs (25) disallow definitive conclusions with respect to the recommendation of acupuncture for DI. In light of the challenges in the current management of DI, we conducted this systematic review, aiming to address the following research questions: (1) could acupuncture be used as an isolated remedy for DI; (2) how effective and safe was acupuncture in the treatment of DI in comparison with standard care; and (3) when acupuncture was applied as an adjunctive remedy of standard care, could it further enhance the efficacy or minimize the side effects of Western pharmacotherapy? The current systematic review was carried out in accordance with the Cochrane Handbook for Systematic Reviews (28) and was reported following the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement* guidelines (29).

MATERIALS AND METHODS

Study Registration

The protocol for this systematic review was registered in the Prospective Register of Systematic Reviews (PROSPERO): no. CRD42021269880.

Eligibility Criteria

Studies included were formally published RCTs with parallel designs. Regardless of gender, race, and age, patients with a clinical diagnosis of depression as per standard diagnostic criteria and with insomnia as the major or residual symptom were included. Any trial without a standard diagnostic guideline for depression [e.g., *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV); *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-V); *International Classification of Diseases*, 10th edition (ICD-10); *International Classification of Diseases and Related Health Problems*, 11th edition (ICD-11); and *Chinese Classification of Mental Disorders*, third edition, (CCMD-3)] was excluded. Distinguished from general depression, depression associated with specific physiological stages in women (e.g., antenatal depression, postpartum depression, and perimenopausal depression) possesses a unique etiology and pathogenesis. Studies examining insomnia related to these specific depressions were not included in this review. Patients were excluded if poor sleep was caused by a sleep disorder(s) other than insomnia, or they had other sleep disorder(s) in addition to insomnia. Studies involving patients with comorbid DI and cardiovascular disease, cancer, cerebrovascular disease, endocrine diseases, other psychiatric and mental disorders (e.g., anxiety and schizophrenia), or other severe disorders were also excluded. There was no restriction based on the severity of either depression or insomnia. Interventions were restricted to the traditional needle acupuncture (TNA) including MA and EA or TNA combined with standard care for DI (antidepressants and/or hypnotics and sedatives and/or CBT-i). Comparator interventions were restricted to waitlist-control, placebo-/sham-acupuncture, or standard care. It should be explained that sham-acupuncture refers to a needle superficially placed in a region close to but not an acupoint (30); placebo-acupuncture such as Streitberger needles (31) or other blunt needle/device refers to a needle placed on the skin surface (not penetrating the skin) at the same acupoint as that of verum acupuncture or at a region beside an acupoint (30). The primary outcome was self-reported, validated sleep scales/questionnaires [e.g., Pittsburg Sleep Quality Index (PSQI), Insomnia Severity Index (ISI), and Athens Insomnia Scale (AIS)] and/or objective sleep parameters measured by sleep monitoring devices. Secondary outcomes included total clinical effectiveness rate, adverse events, and/or depression scales/questionnaires [e.g., Hamilton Depression Scale (HAMD) and Self-rating Depression Scale (SDS)]. There are several versions of HAMD, such as HAMD-6, HAMD-17, HAMD-21, HAMD-23, HAMD-24, and HAMD-27 (32). We did not include a restriction on the HAMD version for searching and including studies. Papers were excluded if they did not report the global scores of any validated sleep scale/questionnaire, even though they reported the clinical effectiveness rates based on the scale or reported partial items/domains of the scale/questionnaire.

Search Strategy and Data Extraction

Together with a professional medical librarian with a TCM background, we used filters to reliably identify studies and undertook a comprehensive search of three English electronic databases and four Chinese databases—MEDLINE (*via* PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), and EMBASE and Chongqing VIP database (CQVIP), China Biomedical Literature Service System (SinoMed), Wanfang Database, and China National Knowledge Infrastructure (CNKI)—from their inception date until December 2021, without language restriction. The search was carried out by combining search terms from four categories: (1) acupuncture, (2) depression, (3) insomnia, and (4) RCT. Searches were supplemented by retrieval of other sources, including the online trial registries such as the US ClinicalTrials.gov, WHO International clinical trials registry platform search portal, and any additional articles meeting eligibility criteria that were cited in reference lists of the included papers and existing systematic reviews, to avoid potential omission (see **Appendix 1** for detailed search terms and search strategies).

After screening the titles and abstracts, full texts were acquired and cross-checked for eligibility by two researchers (W-JZ and F-YZ). A predetermined data form was employed to extract the following information (demographic and clinical characteristics) from each study: identification information, publication year, types of DI (insomnia as a major symptom or a residual symptom of depression), grouping methods as well as number and gender of participants in each group, duration of DI, diagnostic criteria employed, TCM syndrome pattern of DI included, intervention protocols including acupuncture frequency, session and duration as well as acupoint selection, prescription in

comparator (frequency, session, and duration in placebo-/sham-acupuncture; or type, dosage, and oral frequency of Western medication; or regimen of CBT-i), outcome measures, results, follow-up duration and results, and adverse events (AEs). We also tried to contact the corresponding author of the original RCT to access missing data or to clarify other unclear or uncertain information.

Study Quality and Risk-of-Bias Assessment

Two evaluators (Q-QF and F-YZ) carried out standalone appraisal (including determining risk of bias and assessing the internal validity) of all the included studies using the Cochrane Collaboration's risk-of-bias tool (28). They also independently graded the methodological quality of each RCT on the basis of the modified Jadad scale ranging from 0 to 5 points [the scoring criteria and approach of the modified Jadad system refer to this review (33)]. The details of acupuncture procedure including completeness and reporting quality in each trial were described and appraised *via* the revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) checklist (Version 2010) (34). If consensus could not be reached, a third assessor (ZZ) was consulted in resolving any discrepancies.

DATA ANALYSIS AND EVIDENCE QUALITY ASSESSMENT

Data Analysis

Available data were merged for quantitative meta-analysis *via* the Cochrane Collaboration Review Manager Software (RevMan Version 5.4.1). The inverse-variance approach in RevMan was applied to assign weight to each included trial. Given that the primary outcome measure, global scores of sleep scales/questionnaires or objective sleep parameters, was a continuous variable, mean differences (MD) with 95% confidence intervals (CI) between the intervention and control group were calculated. When sufficient data were available (number of RCTs ≥ 3), all domains of PSQI except for "Use of sleeping medication" were included for data synthesis. This item was not analyzed because in most RCTs included, drugs were not allowed in treatment groups adopting acupuncture. For individual RCTs with continuous outcomes measured by a variety of scales or different versions of the same scale (e.g., 6-item HAMD, 17-item HAMD, and 24-item HAMD), standardized mean differences (SMD) were adopted as recommended by Cochrane. Risk ratios (RRs) with 95% CIs were adopted for dichotomous data, such as the total clinical effectiveness rate. The level of heterogeneity across studies was tested using the Q-test and I^2-test. Statistical significance was set at a two-tailed probability (p) < 0.05. We employed a fixed-effects model to pool data when the $p > 0.10$ in the Q-test and the $I^2 \leq 50\%$, which was considered to be an acceptable level of heterogeneity. Otherwise, a random-effects model was adopted to provide a more conservative estimate of effect. For significant clinical heterogeneity, subgroup analyses were performed based on different acupuncture stimulations (MA or EA), principle of acupuncture prescription (fixed, semi-standardized, and individualized), treatment frequency [<5 sessions per week or ≥5 sessions per week; note that when the treatment frequency varied over the course of treatment, the frequency was calculated with reference to a previous high-quality systematic review (35)], needle retention time (<30 or ≥30 min), different therapeutic schedules of standard care (pharmacotherapy or CBT-i), different medication in the controls (antidepressant, hypnotic, or antidepressant + hypnotic), and different versions of HAMD used. With STATA software (Version 17.0), sensitivity analysis and meta-regression analysis were employed to explore sources of heterogeneity as well and check robustness of the conclusions. We also investigated publication bias where at least 10 trials were included in the meta-analysis by implementing Egger's test and Begg's test with STATA software (Version 17.0).

Evidence Quality Assessment

The evidence quality, referring to the strength or reliability of study findings, was assessed by two independent raters (Q-QF and F-YZ), adhering to the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) framework, which classifies the certainty of evidence into four levels (36). The starting point for certainty in given effect estimates for RCTs is "High" but could be rated down as "Moderate," "Low," or "Very low" due to any restrictions with respect to risk of bias (that is, a risk of bias in the original RCTs), imprecision, inconsistency, indirectness, and publication bias (36).

RESULT ANALYSIS

In total, 776 potentially relevant articles were identified based on our search strategy in the initial search. After the duplicates were removed and a careful full-text screening was done, 21 studies (involving 1,571 participants) met the predefined criteria (**Figure 1**). All included studies were qualitatively analyzed, and 19 of them underwent quantitative synthesis (meta-analysis). The discarded studies with detailed reasons of irrelevance are summarized in **Appendix 2**.

Description of Studies

Of the 21 trials, two trials (26, 37) investigated the efficacy of acupuncture for depression-associated residual insomnia using a three-arm design with both placebo-acupuncture and sham-acupuncture as controls. The remaining 19 trials investigated the efficacy of acupuncture for active depression accompanying or comorbid with insomnia. Among them, three studies (27, 38, 39) employed placebo-acupuncture as control [study (27) was a three-arm RCT with both sham- and placebo-acupuncture as controls], 10 studies (40–49) employed standard care (antidepressant and/or hypnotics) as control, and the remaining six studies (50–55) compared the standard care (antidepressant and/or hypnotics) alone with acupuncture in addition to standard care. None of the 21 RCTs included CBT-i or waitlist-control. In the trials with pharmacotherapy as control, one trial used a hypnotic (clonazepam) (46) only, two trials used combined antidepressant and hypnotic

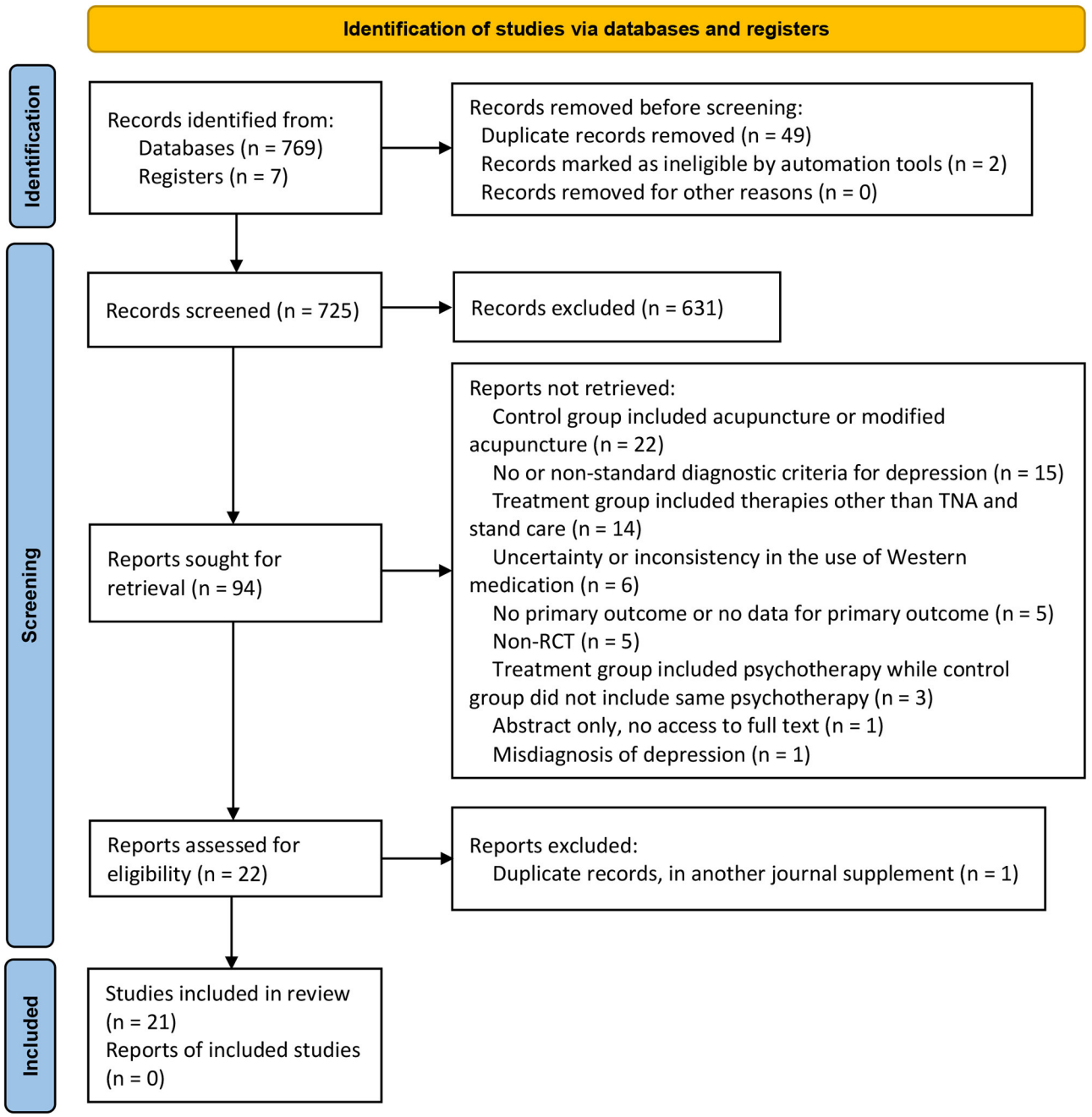

FIGURE 1 | Flow diagram of the study selection process.

[paroxetine + estazolam (40) and fluoxetine + eszopiclone (45)], and the rest used antidepressants only. The frequency of use of antidepressive or hypnotic agents from high to low were paroxetine (5/18), mirtazapine (4/18), venlafaxine (2/18), citalopram (1/18), escitalopram (1/18), sertraline (1/18), fluoxetine (1/18), clonazepam (1/18), estazolam (1/18), and eszopiclone (1/18). Eight out of the 21 trials (26, 27, 37, 40, 41, 44, 52, 54) appraised the clinical efficacy of EA, while the remaining 13 trials studied MA (**Table 1**).

Acupuncture treatment was delivered daily to approximately twice (1.75 times) per week for 3 to 24 weeks. The duration of each treatment session (needle retention time) ranged from 20 to 30 min. Sixteen RCT trials adopted a standardized treatment protocol, with a fixed selection of acupoints administered for each patient assigned to the same group at each acupuncture session. The remaining five trials (40, 49, 50, 54, 55) adopted a semi-standardized treatment protocol consisting of semi-fixed acupoints, including a predefined set of core/major acupoints

TABLE 1 | Study characteristics of 21 included studies.

References	Group/size (M, male; F, female)	Age (year)	Depression duration (m, month; y, year)	Diagnostic system	TCM syndrome type	Acupuncture interventions	Acupoints selection		Prescription in control group (placebo or Western medication)	Outcome measure tool	Acupuncture/ Acupuncture + Western medication compared with control (waitlist, placebo-/sham-acupuncture, Western medication)	Follow-up	Adverse events (AEs)
							Variation in acupoints	Acupoints					
Yin et al. (27)▲	EA/*n* = 30 (11 M, 19 F) Sham-EA/*n* = 30 (10 M, 20 F) Placebo-EA/*n* = 30 (11 M, 19 F)	EA/47.30 ± 14.89 Sham-EA/49.80 ± 15.13 Placebo-EA/46.77 ± 15.57	EA/5.67 ± 5.70 y Sham-EA/7.48 ± 6.23 y Placebo-EA/5.89 ± 5.64 y	DSM-IV	NR	30 min/session, 3 sessions/week (once every other day) for 8 weeks (continuous wave, 30 Hz, 0.1–1mA)	Fixed	EX, EX-HN3, GV20, GV24, HT7, PC6, SP6	Sham-EA (superficial acupuncture) or Placebo-EA (Streitberger acupuncture) on non-acupoins, 30 min/session, 3 sessions/week (once every other day) for 8 weeks	(i) PSQI (ii) $HAMD_{17}$ (iii) SDS (iv) HAMA (v) Actigraphy (SE, TST, ATs)	(i–i) compared with sham-EA $p < 0.01$ (i–ii) compared with placebo-EA $p < 0.05$ (ii–i) compared with sham-EA $p < 0.01$ (ii–ii) compared with placebo-EA $p < 0.01$ (iii–i) compared with sham-EA $p < 0.01$ (iii–ii) compared with placebo-EA $p < 0.01$ (iv–i) compared with sham-EA $p < 0.01$ (iv–ii) compared with placebo-EA $p < 0.01$ (v–i) TST, compared with sham-EA $p < 0.05$; SE, compared with sham–EA $p < 0.05$; ATs, compared with sham-EA $p > 0.05$ (v–ii) TST, compared with placebo-EA $p < 0.01$; SE, compared with placebo-EA $p < 0.01$; ATs, compared with placebo-EA $p > 0.05$	(i–iv) lower PSQI, HAMD, SDS, HAMA in EA at 4-week follow-up (v–i) no significant difference in TST, SE and ATs at 4-week follow-up between EA and sham-EA (v–ii) longer TST, higher SE in EA than in placebo-EA at 4-week follow-up; no significant difference in ATs at 4-week follow-up between EA and placebo-EA	EA/*n* = 3 [hand numbness and pain at acupoints] Sham-EA/*n* = 2 [hematoma (1), dizziness (1)] Placebo-EA/*n* = 1 [dizziness]
Qin et al. (38)▲	MA/*n* = 60 (23 M, 37 F) Placebo-MA/*n* = 60 (26 M, 34 F)	MA/39 ± 14 Placebo-MA/40 ± 14	NR	DSM-V	NR	30 min/session, 3 - 4 sessions/week (once every other day) for 4 weeks (Fluoxetine + Deanxit as basic treatment)	Fixed	BL18, EX, EX-HN1, EX-HN3, HT7, GV20, KI6, SP6	Placebo-MA (Streitberger acupuncture) 30 min/session, 3-4 sessions/week (once every other day) for 4 weeks at same acupoints (Fluoxetine + Deanxit as basic treatment)	(i) PSQI (ii) $HAMD_{24}$ (iii) total clinical effectiveness rate	(i) Compared with placebo-MA $p < 0.05$ (ii) Compared with placebo-MA $p < 0.05$ (iii) Compared with placebo-MA $p < 0.05$	No follow-up	NR
Zhao et al. (39)▲	MA/*n* = 34 (11 M, 23 F) Placebo-MA/*n* = 33 (13 M, 20 F)	MA/43.87 ± 10.51 Placebo-MA/45.16 ± 11.39	MA/4.66 ± 1.35 m placebo-MA/4.01 ± 1.50 m	DSM-V, ICD-10	NR	30 min/session, 3 sessions/week for 8 weeks	Fixed	EX-HN1, GB13, GV11, GV24, HT7	Placebo-MA (Streitberger acupuncture) 30 min/session, 3 sessions/week for 8 weeks at same acupoints	(i) PSQI (ii) $HAMD_{17}$ (iii) PSG (TST, SE, WASO, SOL, ATs, REM-SOL, TIB) (iv) serum Neuropeptide Y (v) serum substance P	(i) Compared with placebo-MA $p < 0.05$ (ii) Compared with placebo-MA $p < 0.05$ (iii–i) Compared with placebo-MA $p < 0.05$ (SOL, WASO, TST, SE) (iii–ii) Compared with placebo-MA $p > 0.05$ (TIB, ATs, REM-SOL) (iv) Compared with placebo-MA $p < 0.05$ (v) Compared with placebo-MA $p < 0.05$	No follow-up	No AEs
Chen et al. (40)▲	EA/*n* = 35 (11 M, 24 F) Paroxetine + Estazolam/*n* = 35 (9 M, 26 F)	NR	NR	DSM-V	NR	25 min/session, 5 sessions/week for 6 weeks (sparse wave, 2Hz)	Semi-standardized	EX-HN1, GB20, Gongxue (1.5 *Cun* below GB20), GV20, cluster needling on frontal region	Paroxetine 20 mg + Estazolam 1 mg/day for 6 weeks	(i) PSQI (ii) $HAMD_{17}$ (iii) PHQ-15 (iv) total clinical effectiveness rate	(i) Compared with Paroxetine + Estazolam $p < 0.01$ (ii) Compared with Paroxetine + Estazolam $p > 0.05$ (iii) Compared with Paroxetine + Estazolam $p < 0.01$ (iv) Compared with Paroxetine + Estazolam $p < 0.05$	No follow-up	NR

(Continued)

TABLE 1 | Continued

References	Group/size (M, male; F, female)	Age (year)	Depression duration (m, month; y, year)	Diagnostic system	TCM syndrome type	Acupuncture interventions	Acupoints selection		Prescription in control group (placebo or Western medication)	Outcome measure tool	Acupuncture/ Acupuncture + Western medication compared with control (waitlist, placebo-/sham-acupuncture, Western medication)	Follow-up	Adverse events (AEs)
							Variation in acupoints	Acupoints					
Chen (41)▲	EA/*n* = 34 (14M, 20F) Sertraline/*n* = 33 (14M, 19F)	EA/36.52 ± 10.22 Sertraline/40.45 ± 11.39	EA/5.55 ± 1.59 m Sertraline/4.78 ± 1.59 m	ICD-10, DSM-V, CDTE-TCM	NR	30 min/session, 7 sessions/week for 4 weeks (continuous wave, 2 Hz, 0.6mA)	Fixed	EX-HN3, GV20, BL13, BL15, BL18, BL20, BL23	Sertraline 50 mg/day for 4 weeks	(i) PSQI (ii) $HAMD_{17}$ (iii) total clinical effectiveness rate	(i) Compared with Sertraline $p > 0.05$ (ii) Compared with Sertraline $p > 0.05$ (iii) Compared with Sertraline $p > 0.05$	No follow-up	EA/*n* = 3 [hematoma] Sertraline/*n* = 15 [poor appetite (10), constipation (2), diarrhea (3)]
He (42)▲	MA/*n* = 32 (16 M, 16 F) Paroxetine/*n* = 32 (15 M, 17 F)	MA/45.38 ± 12.22 Paroxetine/42.25 ± 12.44	NR	ICD-10	NR	30 min/session, 7 sessions/week for 6 weeks	Fixed	GV20, HT7, PC6, Zhenjing, Shangen	Paroxetine 20 mg/day for 6 weeks	(i) PSQI (ii) SDS (iii) Total clinical effectiveness rate	(i) Compared with Paroxetine $p > 0.05$ (ii) Compared with Paroxetine $p < 0.05$ (iii) Compared with Paroxetine $p > 0.05$	(i) Lower PSQI in MA at 4-week follow-up (ii) Higher SDS in MA at 4-week follow-up (ii) Higher total clinical effectiveness rate in MA at 4-week follow-up	No AEs
Lin and Wang (43)▲	MA/*n* = 30 (14 M, 16 F) Escitalopram/*n* = 30 (16 M, 14 F)	MA/38.1 ± 10.3 Escitalopram/40.2 ± 9.1	MA/22.5 ± 12.9 m Escitalopram/20.5 ± 13.8 m	ICD-10	NR	30 min/session, 5 sessions/week for 4 weeks	Fixed	EX-HN1, EX-HN3, GV20, HT7, LR3, PC6, PC7	Escitalopram 10 mg/day for 4 weeks	(i) PSQI (ii) $HAMD_{17}$ (iii) total clinical effectiveness rate	(i) Compared with Escitalopram $p > 0.05$ (ii) Compared with Escitalopram $p > 0.05$ (iii) Compared with Escitalopram $p < 0.05$	No follow-up	MA/*n* = 2 [fainting] Escitalopram/*n* = 9 [constipation (5), nausea (4)]
Lin (44)▲	EA/*n* = 24 (7 M, 17 F) Citalopram/*n* = 24 (5 M, 19 F)	EA/48.42 ± 13.42 Citalopram/47.58 ± 11.06	EA/9.38 ± 9.30 m Citalopram/15.88 ± 21.24	ICD-10	NR	20 min/session, 3 sessions/week for 6 weeks + 2 sessions/week for 6 weeks + 1 session/week for 12 weeks (intermittent wave, 40 Hz)	Fixed	EX-HN1, EX-HN3, GV20, HT7, PC6, SP6	Citalopram 30 mg/day for 24 weeks	(i) PSQI (ii) PSG (TST, ATs) (iii) SDS (iv) MADRS (v) SAS	(i) Compared with Citalopram $p > 0.05$ (ii) Compared with Citalopram $p < 0.05$ (TST, ATs) (iii) Compared with Citalopram $p < 0.05$ (iv) Compared with Citalopram $p < 0.05$ (v) Compared with Citalopram $p < 0.01$	No follow-up	No AEs
Liu (45)▲	MA/*n* = 30 (4 M, 26 F) Fluoxetine + Eszopiclone/*n* = 30 (3 M, 27 F)	MA/53.16 ± 8.32 Fluoxetine + Eszopiclone/54.43 ± 10.21	MA/2.87 ± 1.00 y Fluoxetine + Eszopiclone/3.06 ± 0.85 y	CCMD-3, CDTE-TCM	NR	30 min/session, 4 sessions/week for 7.5 weeks	Fixed	CV6, CV10, CV12, CV13, EX-HN3, GV20, GV24, PC6, ST25, ST36	(Fluoxetine 20 mg/day + Eszopiclone 2 mg/day) for 7.5 weeks	(i) PSQI (ii) $HAMD_{17}$ (iii) Total clinical effectiveness rate (iv) Peripheral blood T-lymphocyte subsets (CD3, CD8, CD4/CD8, Ig M, Ig G)	(i) Compared with Fluoxetine + Eszopiclone $p < 0.05$ (ii) Compared with Fluoxetine + Eszopiclone $p < 0.05$ (iii) Compared with Fluoxetine + Eszopiclone $p > 0.05$ (iv) Compared with Fluoxetine + Eszopiclone $p > 0.05$	No follow-up	NR
Liu (46)▲	MA/*n* = 30 (16 M, 14 F) Clonazepam/*n* = 30 (18 M, 12 F)	MA/33.20 ± 9.85 Clonazepam/32.57 ± 10.17	MA/2.94 ± 5.60 m Clonazepam/2.88 ± 5.34 m	CCMD-3	Six TCM patterns (①②③④⑤⑥)	30 min/session, 6 sessions/week for 3 weeks	Fixed	0.5 *Cun* next to EX-HN1, 0.5 *Cun* up to EX-HN3, 0.5 *Cun* up to GB14, BL62, KI6, PC6, SP6	Clonazepam 1 mg/day, 2–4 days/week for 3 weeks	(i) PSQI (ii) SDS (iii) ChQoL (iv) total clinical effectiveness rate (v) SERS	(i) Compared with Clonazepam $p < 0.01$ (ii) Compared with Clonazepam $p < 0.05$ (iii) Compared with Clonazepam $p < 0.01$ (iv) Compared with Clonazepam $p < 0.05$ (v) Compared with Clonazepam $p < 0.01$	No significant difference in recurrence rate between two groups at 4- and 12-week follow-ups	MA/*n* = 2 [fainting] Clonazepam/*n* = 8 [dizziness (2), dry mouth (2), constipation (2), nausea and poor appetite (2)]

(Continued)

TABLE 1 | Continued

References	Group/size (M, male; F, female)	Age (year)	Depression duration (m, month; y, year)	Diagnostic system	TCM syndrome type	Acupuncture interventions	Acupoints selection		Prescription in control group (placebo or Western medication)	Outcome measure tool	Acupuncture/ Acupuncture + Western medication compared with control (waitlist, placebo-/sham-acupuncture, Western medication)	Follow-up	Adverse events (AEs)
							Variation in acupoints	Acupoints					
Wang and Liu (47)▲	MA/n = 45 (11 M, 34 F) Mirtazapine/n = 45 (13 M, 32 F)	MA/41.5 ± 4.6 Mirtazapine/39.1 ± 5.2	MA/4.9 ± 2.3 y Mirtazapine/5.1 ± 2.1 y	CCMD-3	NR	30 min/session, 3–4 sessions/week (once every other day) for 12 weeks	Fixed	EX-HN3, GV20, HT7, LR3, SP6, ST36	Mirtazapine 20 mg/day for 12 weeks	(i) PSQI (ii) $HAMD_{17}$ (iii) Total clinical effectiveness rate (iv) AEs rate	(i) Compared with Mirtazapine $p > 0.05$ (ii) Compared with Mirtazapine $p > 0.05$ (iii) Compared with Mirtazapine $p > 0.05$ (iv) Compared with Mirtazapine $p < 0.05$	No follow-up	MA/n = 0 Mirtazapine/n = 13 [EDS (5), dry mouth (3), dizziness (3), fatigue (2)]
Wang et al. (48)▲	MA/n = 35 (17 M, 18 F) Mirtazapine/n = 37 (18 M, 19 F)	MA/45.8 ± 6.8 Mirtazapine/44.7 ± 5.1	MA/3.3 ± 0.8y Mirtazapine/3.3 ± 1.1y	DSM-IV, CDTE-TCM	②	30 min/session, 6 sessions/week for 4 weeks	Fixed	EX-HN3, GV20, HT7, LI4, LR3	Mirtazapine 30 mg/day for 4 weeks	(i) PSQI (ii) $HAMD_{24}$ (iii) Serum 5-HT level (iv) Total clinical effectiveness rate (v) SERS	(i) Compared with Mirtazapine $p < 0.05$ (ii) Compared with Mirtazapine $p > 0.05$ (iii) Compared with Mirtazapine $p > 0.05$ (iv) Compared with Mirtazapine $p > 0.05$ (v) Compared with Mirtazapine $p < 0.05$	No follow-up	MA/n = 0 Mirtazapine/n = 5 [abnormal liver function (1), leukocytopenia (2), abnormal metabolism of blood fat (2)]
Ye and Yan (49)▲	MA/n = 40 (9 M, 31 F) Mirtazapine/n = 40 (12 M, 28 F)	NR	NR	CCMD-3	⑤⑦	30 min/session, 3-4 sessions/week (once every other day) for 12 weeks	Semi-standardized	EX-HN3, HT7, SP6	Mirtazapine 20 mg/day for 12 weeks	(i) PSQI (ii) $HAMD_{17}$ (iii) Total clinical effectiveness rate	(i) Compared with Mirtazapine $p > 0.05$ (ii) Compared with Mirtazapine $p > 0.05$ (iii) Compared with Mirtazapine $p > 0.05$	No follow-up	MA/n = 0 Mirtazapine/n = 6 [EDS (1), dry mouth (1), weight gain (1), increased appetite (1), dizziness (1), fatigue (1)]
Liu and Li (50)▲	MA + Venlafaxine/n = 30 (9 M, 21 F) Venlafaxine/n = 31 (8 M, 23 F)	MA + Venlafaxine/43.2 ± 9.0 Venlafaxine/40.2 ±9.3	NR	ICD-10	②⑤⑦	5 sessions/week for 12 weeks	Semi-standardized	GV20, GV26, HT7, LR3, PC6, SP6	Venlafaxine 75 mg/day for 12 weeks	(i) PSQI (ii) HAMD (iii) HAMA	(i) Compared with Venlafaxine $p < 0.05$ (ii) Compared with Venlafaxine $p < 0.05$ (iii) Compared with Venlafaxine $p < 0.05$	No follow-up	NR
Liu et al. (51)▲	MA + Mirtazapine/n = 30 (14 M, 16 F) Mirtazapine/n = 30 (20 M, 10 F)	MA + Mirtazapine/41.33 ± 8.89 Mirtazapine/40.27 ± 9.72	MA + Mirtazapine/18.00 ± 9.49 m Mirtazapine/15.77 ± 7.93 m	CCMD-3	NR	30 min/session, 7 sessions/week for 4 weeks	Fixed	BL62, EX-HN1, GV20, HT7, KI6, LR3, PC6	Mirtazapine 30 mg/day for 4 weeks	(i) PSQI (ii) HAMD (iii) Total clinical effectiveness rate (iv) SERS	(i) Compared with Mirtazapine $p < 0.05$ (ii) Compared with Mirtazapine $p < 0.05$ (iii) Compared with Mirtazapine $p < 0.05$ (iv) Compared with Mirtazapine $p < 0.05$	No follow-up	Reflected by SERS scores
Sun et al. (52)▲	EA + Venlafaxine/n = 20 (13 M, 7 F) Venlafaxine/n = 20 (12 M, 8 F)	EA + Venlafaxine/32.5 ± 10.3 Venlafaxine/31.5 ± 11.4	EA + Venlafaxine/14.9 ± 3.6 m Venlafaxine/15.1 ± 6.35 m	CCMD-3	NR	30 min/session, 5 sessions/week for 2 weeks	Fixed	EX-HN3, GV20, PC6, ST36	Venlafaxine 150mg/d for 2 weeks	(i) PSG (TST, NREM%, REM%) (ii) HAMD (iii) Total clinical effectiveness rate	(i) TST, compared with Venlafaxine $p < 0.05$; NREM%, compared with Venlafaxine $p < 0.05$; REM%, compared with Venlafaxine $p > 0.05$ (ii) Compared with Venlafaxine $p > 0.05$ (iii) Compared with Venlafaxine $p > 0.05$	No follow-up	EA + Venlafaxine/n = 5 [fatigure and EDS (2), poor appetite (1), elevated blood pressure (2)] Venlafaxine/n = 6 [EDS (2), nausea (2), poor appetite (1), elevated blood pressure (1)]
Tan et al. (53)▲	MA + Paroxetine/n = 50 (23 M, 27 F) Paroxetine/n = 50 (21 M, 29 F)	MA + Paroxetine/40.42 ± 5.65 Paroxetine/40.63 ± 5.29	MA + Paroxetine/2.39 ± 0.65 y Paroxetine/2.51 ± 0.70 y	ICD-10	NR	30 min/session, 3–4 sessions/week (once every other day) for 6 weeks	Fixed	EX-HN1, HT7, LR3, SP6	Paroxetine 20 mg/day for 6 weeks	(i) PSQI (ii) $HAMD_{17}$ (iii) Total clinical effectiveness rate (iv) SERS	(i) Compared with Paroxetine $p < 0.05$ (ii) Compared with Paroxetine $p < 0.05$ (iii) Compared with Paroxetine $p < 0.05$ (iv) Compared with Paroxetine $p < 0.05$	No follow-up	Reflected by SERS scores

(Continued)

TABLE 1 | Continued

References	Group/size (M, male; F, female)	Age (year)	Depression duration (m, month; y, year)	Diagnostic system	TCM syndrome type	Acupuncture interventions	Acupoints selection		Prescription in control group (placebo or Western medication)	Outcome measure tool	Acupuncture/ Acupuncture + Western medication compared with control (waitlist, placebo-/sham-acupuncture, Western medication)	Follow-up	Adverse events (AEs)
							Variation in acupoints	Acupoints					
Wang and Ai (54)▲	EA + Paroxetine/*n* = 45 (26 M, 19 F) Paroxetine/*n* = 35 (20 M, 15 F)	EA + Paroxetine/62.03 ± 4.11 Paroxetine/64.01 ± 4.41	EA + Paroxetine/2.59 ± 0.35 y Paroxetine/2.79 ± 0.26 y	CCMD-3	⑤⑧⑨	30 min/session, 7 sessions/week for 4 weeks (continuous wave)	Semi-standardized	EX-HN3, GV20, HT7, PC6, SP6, ST36	Paroxetine 20 mg/day for 4 weeks	(i) PSQI (ii) $HAMD_{17}$ (iii) Total clinical effectiveness rate	(i) Compared with Paroxetine $p < 0.05$ (ii) Compared with Paroxetine $p < 0.05$ (iii) Compared with Paroxetine $p < 0.01$	No follow-up	NR
Min and Zhu (55)▲	MA + Paroxetine/*n* = 30 (12 M, 18 F) Paroxetine/*n* = 30 (14 M, 16 F)	MA + Paroxetine/36.1 ± 9.5 Paroxetine/35.4 ± 9.4	MA + Paroxetine/9.0 ± 1.2 m Paroxetine/8.8 ± 1.1 m	ICD-10	NR	3 sessions/week for 6 weeks	Semi-standardized	EX-HN3, GB20, GV14, GV16, GV20, PC6, SP6	Paroxetine 30 mg/day for 6 weeks	(i) PSQI (ii) $HAMD_{17}$ (iii) SDS (iv) Total clinical effectiveness rate	(i) Compared with Paroxetine $p < 0.05$ (ii) Compared with Paroxetine $p < 0.05$ (iii) Compared with Paroxetine $p < 0.05$ (iv) Compared with Paroxetine $p < 0.05$	No follow-up	MA + Paroxetine/*n* = 6 [EDS (1), poor appetite and nausea (3), dry mouth (1), sweating (1)] Paroxetine/*n* = 7 [dizziness (1), poor appetite and nausea (4), sweating (2)]
Chung et al. (26)▼	EA/*n* = 60 (14 M, 46 F) Sham-EA/*n* = 60 (14 M, 46 F) Placebo-EA/*n* = 30 (3 M, 27 F)	EA/48.8 ± 9.9 Sham-EA/50.9 ± 9.5 Placebo-EA/47.4 ± 9.5	EA/8.7 ± 7.1 y Sham-EA/12.0 ± 11.4 y Placebo-EA/9.2 ± 8.4 y	DSM-IV	NR	30 min/session, 3 sessions/week for 3 weeks (square wave, 4-Hz)	Fixed	EX, EX-HN1, EX-HN3, GV20, HT7, PC6, SP6, TF_4	Sham-EA (superficial acupuncture) or placebo-EA (Streitberger acupuncture) on non-acupoins, 30 min/session, 3 sessions/week for 3 weeks	(i) PSQI (ii) ISI (iii) $HAMD_{17}$ (iv) SDS (v) Actigraphy (SOL, TST, WASO, SE) (vi) Sleep diary (SOL, TST, WASO, SE, sleep quality) (vii) ESS (viii) HAMA (ix) MFI (x) CTRS	(i–i) Compared with sham-EA $p > 0.05$ (i–ii) Compared with placebo-EA $p > 0.05$ (ii–i) compared with sham-EA $p > 0.05$ (ii–ii) Compared with placebo-EA $p > 0.05$ (iii–i) Compared with sham-EA $p > 0.05$ (iii–ii) Compared with placebo-EA $p > 0.05$ (iv–i) Compared with sham-EA $p > 0.05$ (iv–ii) Compared with placebo-EA $p > 0.05$ (v–i) Compared with sham-EA $p > 0.05$ (v–ii) Compared with placebo-EA $p > 0.05$ (vi–i) Compared with sham-EA $p > 0.05$ (vi–ii) Compared with placebo-EA $p > 0.05$ (vii–i) Compared with sham-EA $p > 0.05$ (vii–ii) Compared with placebo-EA $p > 0.05$ (viii–i) Compared with sham-EA $p > 0.05$ (viii–ii) Compared with placebo-EA $p > 0.05$ (ix–i) Compared with sham-EA $p > 0.05$ (ix–ii) Compared with placebo-EA $p > 0.05$ (x–i) Compared with sham-EA $p > 0.05$ (x–ii) Compared with placebo-EA $p > 0.05$	The results at 5-week follow-up were largely consistent with the results at post-treatment	EA/*n* = 41 [pain at acupoints (19), headache (8), fatigue (8), dizziness (3), nausea (3)] Sham-EA/*n* = 18 [pain at acupoints (6), headache (7), fatigue (4), nausea (1)] Placebo-EA/*n* = 6 [pain at acupoints (1), headache (3), dizziness (1), nausea (1)]

(Continued)

TABLE 1 | Continued

References	Group/size (M, male; F, female)	Age (year)	Depression duration (m, month; y, year)	Diagnostic system	TCM syndrome type	Acupuncture interventions	Acupoints selection		Prescription in control group (placebo or Western medication)	Outcome measure tool	Acupuncture/ Acupuncture + Western medication compared with control (waitlist, placebo-/sham-acupuncture, Western medication)	Follow-up	Adverse events (AEs)
							Variation in acupoints	Acupoints					
Yeung et al. (37)▼	EA/$n = 26$ (6 M, 20 F) Sham-EA/$n = 26$ (7 M, 19 F) Placebo-EA/$n = 26$ (3 M, 23 F)	EA/47.5 ± 8.5 Sham-EA/46.7 ± 9.7 Placebo-EA/50.1 ± 9.1	EA/8.9 ± 10.1 y Sham-EA/11.5 ± 9.4 y Placebo-EA/12.6 ± 8.6 y	DSM-IV	NR	30 min/session, 3 sessions/week for 3 weeks (square wave, 4 Hz)	Fixed	EX, EX-HN1, EX-HN3, GV20, TF_4	Sham-EA (superficial acupuncture) on non-acupoints or placebo-EA (Streitberger acupuncture) on the same acupoints as those in the EA group, 30 min/session, 3 sessions/week for 3 weeks	(i) PSQI (ii) ISI (iii) $HAMD_{17}$ (iv) SDS (v) Actigraphy (SOL, TST, WASO, SE) (vi) sleep diary (SOL, TST, WASO, SE, sleep quality) (vii) CTRS	(i–i) Compared with sham-EA $p > 0.05$ (i–ii) Compared with placebo-EA $p < 0.05$ (ii–i) Compared with sham-EA $p > 0.05$ (ii–ii) Compared with placebo-EA $p < 0.05$ (iii–i) Compared with sham-EA $p > 0.05$ (iii–ii) Compared with placebo-EA $p > 0.05$ (iv–i) Compared with sham-EA $p > 0.05$ (iv–ii) Compared with placebo-EA $p > 0.05$ (v–i) Compared with sham-EA $p > 0.05$; (v–ii) compared with placebo-EA $p > 0.05$; (vi–i) Compared with sham-EA $p > 0.05$; (vi–ii) SE, compared with placebo-EA $p < 0.05$; other parameters compared with placebo-EA $p > 0.05$; (vii–i) Compared with sham-EA $p > 0.05$; (vii–ii) Compared with placebo-EA $p > 0.05$	The results at 4-week follow-up were largely consistent with the results at post-treatment	EA/$n = 3$ [headache (2), dizziness (1)] Sham-EA/$n = 6$ [worsening of insomnia (1), hand numbness (2), hematoma (1), palpitation (1), pain at acupoints (1)] Placebo-EA/$n = 5$ [headache (2), dizziness (2), hand numbness (1)]

TCM patterns [① hyperactivity of the fire of the Heart, ② fire derived from stagnation of Liver-Qi, ③ interior disturbance of phlegm-heat, ④ hyperactivity of fire due to Yin deficiency, ⑤ deficiency of both Heart and Spleen, ⑥ deficiency of Heart-Qi and Gallbladder-Qi, ⑦ depression of Liver-Qi; ⑧ Liver depression and Spleen deficiency; ⑨ Spleen-Kidney Yang deficiency]; type of insomnia [insomnia as a major symptom of active depression (▲); insomnia as a residual symptom of previous or partial-remission depression (▼)]. For semi-standardized acupuncture prescriptions, only major/core acupoints are listed.

NR, no report; MA, manual acupuncture; EA, electroacupuncture; ICD-10, International Classification of Diseases (10th edition); CCMD-3, Chinese Classification of Mental Disorders (third edition); DSM-IV, Diagnostic and Statistical Manual of Mental Disorders (fourth edition); DSM-V, Diagnostic and Statistical Manual of Mental Disorders (fifth edition); CDTE-TCM, Criteria of Diagnosis and Therapeutic Effect of Diseases and Syndromes in TCM; PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index; ESS, Epworth Sleepiness Scale; HAMD, Hamilton Depression Scale; SDS, Self-rating Depression Scale; SAS, Self-rating Anxiety Scale; MADRS, Montgomery-Asberg Depression Rating Scale; HAMA, Hamilton Anxiety Scale; PHQ-15, Patient Health Questionnaire-15; MFI, Multidimensional Fatigue Inventory; ChQoL, Chinese quality-of-life instrument; SERS, Asberg Side Effects Rating Scale; CTRS, Credibility of Treatment Rating Scale; PSG, polysomnography; TIB, time in bed; SOL, sleep-onset latency; WASO, wake after sleep onset; ATs, awakening times; TST, total sleep time; SE, sleep efficiency; REM, rapid eye movement sleep; NREM, non-rapid eye movement sleep; REM-SOL, REM sleep-onset latency; 5-HT, 5-hydroxytryptamine; AEs, adverse events; EDS, excessive daytime sleepiness; BL13, Feishu; BL15, Xinshu; BL18, Ganshu; BL20, Pishu; BL23, Shenshu; BL62, Shenmai; CV6, Qihai, CV10, Xiawan; CV12, Zhongwan; CV13, Shangwan; EX, Anmian; EX-HN1, Sishencong; EX-HN3, Yintang; GB13, Benshen; GB14, Yangbai; GB20, Fengchi; GV11, Shendao; GV14, Dazhui; GV16, Fengfu; GV20, Baihui; GV24, Shenting; GV26, Shuigou; HT7, Shenmen; KI6, Zhaohai; LI4, Hegu; LR3, Taichong; PC6, Neiguan; PC7, Daling; SP6, Sanyingjiao; ST25, Tianshu; ST36, Zusanli; TF_4, Ear Shenmen.

utilized in combination with acupoints selected on the basis of each patient's symptoms or TCM pattern to which he/she presents. Individualized treatment protocol was not adopted in any RCT. The selection of acupoints varied and included acupoints located on the head, extremities, and abdomen. Among them, the five most frequently utilized acupoints were Baihui (GV20), Yintang (EX-HN3), Shenmen (HT7), Neiguan (PC6), and Sanyinjiao (SP6). In the five trials that included sham-/placebo-acupuncture (26, 27, 37–39), the sham-acupuncture was performed by superficially piercing a region close to but not an acupoint with a needle, and the placebo-acupuncture was performed by placing a Streitberger needle on the skin surface (not penetrating the skin) at the same acupoint as that of real acupuncture or at a region beside an acupoint (**Table 1**).

The major outcome measures and the time points at which they were evaluated are summarized in **Table 2**. All except one RCT (52) adopted PSQI global scores as the primary outcome measurement tool in assessing sleep quality and quantity. Six RCTs recorded changes in objective sleep parameters [e.g., total sleep time (TST), SE, SOL, wake after sleep onset (WASO), awakening times (ATs), and percentage of rapid eye movement sleep (REM) and non-REM] among patients at pre- and post-treatment, by either PSG (39, 44, 52) or actigraphy (26, 27, 37). In the assessment of depressed mood, 14 RCTs used the HAMD only (38–41, 43, 45, 47–54); three RCTs used the SDS only (42, 44, 46); and the remaining four RCTs included both scales (26, 27, 37, 55). HAMD-17 was used in 13 RCTs (26, 27, 37, 39–41, 43, 45, 47, 49, 53–55) and HAMD-24 in two (38, 48). The remaining three trials (50–52) did not depict which version of HAMD was utilized. Five studies (26, 27, 37, 42, 46) reported follow-up data from 1 to 12 weeks after the end of treatment (**Table 1**).

Sixteen studies (26, 27, 37, 39, 41–44, 46–49, 51–53, 55) reported detailed information of AEs. The most frequently reported AEs among participants receiving both acupuncture treatment and placebo-/sham-acupuncture treatment were hand numbness and/or pain at acupoints [(22/116) in acupuncture; (11/142) in placebo-/sham-acupuncture], fatigue [(8/60) in acupuncture; (4/90) in placebo-/sham-acupuncture], and headache [(10/86) in acupuncture; (12/142) in placebo-/sham-acupuncture]. The most relevant AEs associated with antidepressant and/or hypnotics were gastrointestinal symptoms, such as poor appetite, diarrhea, and constipation (38/183); abnormal blood or biochemical indicators such as abnormal liver function, leukocytopenia, or abnormal metabolism of blood fat (5/37); and excessive daytime sleepiness (8/105) (**Appendix 3**).

Study Quality Evaluation

Seventeen out of 21 trials provided an adequate description of the process and method of randomization (26, 27, 37–40, 42–46, 48, 51–55), while four trials (41, 47, 49, 50) only mentioned that an RCT design was fulfilled in the trial but did not adequately describe the randomization approach and procedure. All except for seven trials (26, 27, 37, 39, 40, 44, 46) were judged as unclear risk of bias for allocation concealment. Valid allocation concealment was achieved in those seven studies by the method of "opaque envelopes." Less than one-fifth of RCTs (26, 27, 37, 48) reported that the outcome evaluator was blinded. Incomplete outcome data were judged as low risk of bias in 20 studies. Among them, 12 studies (38–40, 46–52, 54, 55) reported no withdrawal of participants; three studies (26, 27, 37) addressed the dropout case and missing data with sound statistical methods such as intention-to-treat analysis; five studies (41–43, 45, 53) directly excluded data from those dropout cases, while reporting that the number of dropout cases was <10% of the initial samples, which is within the controllable range. Only one study (44) was evaluated as being a high risk of bias in this domain because the number of dropout cases reached 20% and no statistical treatment was assigned to those cases. For the item of selective outcome reporting, three trials (26, 27, 37) were appraised as being a low risk of bias due to accessible pre-registration information of the trial. The remaining studies were rated as being an unclear risk of bias because of unavailable protocols or because there was insufficient evidence and information to permit a clear judgment. "Blinding of personnel (acupuncturist)" in all studies was rated as a high risk of bias due to the nature of acupuncture. Acupuncture techniques require manipulation by a qualified professional to implement; blinding for acupuncturists hence is not feasible. It is reassuring that either placebo-acupuncture (Streitberger needles) or sham-acupuncture (superficial acupuncture at non-acupoints) was introduced as reasonable placebo in all five RCTs (26, 27, 37–39), where non-pharmaceuticals were used as control, to blind patients and improve the results reliability. "Blinding of participants (patients)" might be challenging in the remaining RCTs as they addressed the comparison between acupuncture/acupuncture + pharmacotherapy and pharmacotherapy alone. All studies addressed baseline balance adequately (**Figure 2, Appendices 4, 5**). In compliance with the modified Jadad system, six studies (26, 27, 37–39, 48) had high methodological quality as indicated by a score over 3 points; five studies (41, 44, 47, 49, 50) had low methodological quality as indicated by a score below 3 points; and the remaining studies with a score of 3 points were judged as being of moderate methodological quality. The average modified Jadad score of all 21 studies was 3.2 (**Appendix 4**).

Appendix 6 summarizes the details about acupuncture per STRICTA guidelines. Traditional Chinese acupuncture was used in all 21 trials, and treatment was provided in accordance with the TCM theory. As the core part of acupuncture therapy, the needling details were not clearly described in some RCTs. For instance, the exact depth of insertion was presented in detail in only nine trials (26, 27, 39, 41, 43–46, 48), and five studies (43, 45, 50, 52, 55) did not manifest the needle type used. All except two RCTs (50, 55) reported needle retention time which ranged from 20 to 30 min. Setting of treatment was described in only three trials (26, 27, 37). Similarly, only these three trials clearly presented the acupuncturist's background.

Analysis of Outcome Measures

The qualitative and quantitative analyses for outcome measures in the 21 included studies were classified into two categories according to the types of DI. In the first category (the therapeutic effect of acupuncture on insomnia as a major symptom of active

TABLE 2 | Trends of major outcomes for insomnia and depression in acupuncture (OR acupuncture + antidepressant and/or hypnotic) and comparison with controls in each study.

References	Type of insomnia	Comparison		Outcome measures for insomnia						Outcome measures for depression
				Subjective outcome	Objective outcome (data from PSG or actigraphy)					HAMD or SDS
				PSQI or ISI	TST	SOL	SE	WASO	ATs	
Yin et al. (27)	Major	*Vs.* the same group at different time points	4-week treatment *vs.* pre-treatment	↓	↑	Ø	↑	Ø	↓	↓
			Post-treatment *vs.* pre-treatment	↓	↑	Ø	↑	Ø	↓	↓
			4-week follow-up *vs.* pre-treatment	↓	↑	Ø	↑	Ø	↓	↓
		Acup *vs.* sham-/placebo-Acup at the same time point	4-week treatment	<	*Vs.* sham (–), *Vs.* placebo, >	Ø	*Vs.* sham (–), *Vs.* placebo, >	Ø	(–)	<
			Post-treatment	<	>	Ø	>	Ø	(–)	<
			4-week follow-up	<	*Vs.* sham (–), *Vs.* placebo, >	Ø	*Vs.* sham (–), *Vs.* placebo, >	Ø	(–)	<
Qin et al. (38)	Major	*Vs.* the same group at different time points	Post-treatment *vs.* pre-treatment	↓	Ø	Ø	Ø	Ø	Ø	↓
		Acup *vs.* placebo-Acup at the same time point	Post-treatment	<	Ø	Ø	Ø	Ø	Ø	<
Zhao et al. (39)	Major	*Vs.* the same group at different time points	Post-treatment *vs.* pre-treatment	↓	↑	↓	↑	↓	(–)	↓
		Acup *vs.* placebo-Acup at the same time point	Post-treatment	<	>	<	>	<	(–)	<
Chen et al. (40)	Major	*Vs.* the same group at different time points	Post-treatment *vs.* pre-treatment	↓	Ø	Ø	Ø	Ø	Ø	↓
		Acup *vs.* antidepressant + hypnotic at the same time point	Post-treatment	<	Ø	Ø	Ø	Ø	Ø	(–)
Chen (41)	Major	*Vs.* the same group at different time points	2-week treatment *vs.* pre-treatment	↓	Ø	Ø	Ø	Ø	Ø	↓
			Post-treatment *vs.* pre-treatment	↓	Ø	Ø	Ø	Ø	Ø	↓
			Post-treatment *vs.* 2-week treatment	↓	Ø	Ø	Ø	Ø	Ø	↓
		Acup *vs.* antidepressant at the same time point	2-week treatment	>	Ø	Ø	Ø	Ø	Ø	>
			Post-treatment	(–)	Ø	Ø	Ø	Ø	Ø	(–)
He (42)	Major	*Vs.* the same group at different time points	Post-treatment *vs.* pre-treatment	↓	Ø	Ø	Ø	Ø	Ø	↓
			4-week follow-up *vs.* post-treatment	(–)	Ø	Ø	Ø	Ø	Ø	(–)
		Acup *vs.* antidepressant at the same time point	Post-treatment	(–)	Ø	Ø	Ø	Ø	Ø	>
			4-week follow-up	<	Ø	Ø	Ø	Ø	Ø	<
Lin and Wang (43)	Major	*Vs.* the same group at different time points	Post-treatment *vs.* pre-treatment	↓	Ø	Ø	Ø	Ø	Ø	↓
		Acup vs. antidepressant at the same time point	Post-treatment	(–)	Ø	Ø	Ø	Ø	Ø	(–)
Lin (44)	Major	*Vs.* the same group at different time points	12-week treatment *vs.* pre-treatment	↓	↑	(–)	(–)	(–)	(–)	↓

(Continued)

TABLE 2 | Continued

References	Type of insomnia	Comparison		Outcome measures for insomnia						Outcome measures for depression
				Subjective outcome	Objective outcome (data from PSG or actigraphy)					HAMD or SDS
				PSQI or ISI	TST	SOL	SE	WASO	ATs	
			Post-treatment *vs.* pre-treatment	↓	↑	(–)	(–)	(–)	↓	↓
		Acup *vs.* antidepressant at the same time point	12-week treatment	(–)	(–)	Ø	Ø	Ø	<	>
			Post-treatment	(–)	(–)	Ø	Ø	Ø	<	>
Liu (45)	Major	*Vs.* the same group at different time points	Post-treatment *vs.* pre-treatment	↓	Ø	Ø	Ø	Ø	Ø	↓
		Acup *vs.* antidepressant + hypnotic at the same time point	Post-treatment	<	Ø	Ø	Ø	Ø	Ø	<
Liu (46)	Major	*Vs.* the same group at different time points	Post-treatment *vs.* pre-treatment	↓	Ø	Ø	Ø	Ø	Ø	↓
		Acup *vs.* hypnotic at the same time point	Post-treatment	<	Ø	Ø	Ø	Ø	Ø	<
Wang and Liu (47)	Major	*Vs.* the same group at different time points	Post-treatment *vs.* pre-treatment	↓	Ø	Ø	Ø	Ø	Ø	↓
		Acup *vs.* antidepressant at the same time point	Post-treatment	(–)	Ø	Ø	Ø	Ø	Ø	(–)
Wang et al. (48)	Major	*Vs.* the same group at different time points	Post-treatment *vs.* pre-treatment	↓	Ø	Ø	Ø	Ø	Ø	↓
		Acup *vs.* antidepressant at the same time point	Post-treatment	<	Ø	Ø	Ø	Ø	Ø	(–)
Ye and Yan (49)	Major	*Vs.* the same group at different time points	4-week treatment *vs.* pre-treatment	↓	Ø	Ø	Ø	Ø	Ø	↓
			8-week treatment *vs.* pre-treatment	↓	Ø	Ø	Ø	Ø	Ø	↓
			Post-treatment *vs.* pre-treatment	↓	Ø	Ø	Ø	Ø	Ø	↓
		Acup *vs.* antidepressant at the same time point	4-week treatment	(–)	Ø	Ø	Ø	Ø	Ø	(–)
			8-week treatment	(–)	Ø	Ø	Ø	Ø	Ø	(–)
			Post-treatment	(–)	Ø	Ø	Ø	Ø	Ø	(–)
Liu and Li (50)	Major	*Vs.* the same group at different time points	Post-treatment *vs.* pre-treatment	↓	Ø	Ø	Ø	Ø	Ø	↓
		Acup + antidepressant *vs.* antidepressant at same time point	Post-treatment	<	Ø	Ø	Ø	Ø	Ø	<
Liu et al. (51)	Major	*Vs.* the same group at different time points	Post-treatment *vs.* pre-treatment	↓	Ø	Ø	Ø	Ø	Ø	↓
		Acup + antidepressant *vs.* antidepressant at the same time point	Post-treatment	<	Ø	Ø	Ø	Ø	Ø	<
Sun et al. (52)	Major	*Vs.* the same group at different time points	1-week treatment *vs.* pre-treatment	Ø	Ø	Ø	Ø	Ø	Ø	↓
			Post-treatment *vs.* pre-treatment	Ø	↑	Ø	Ø	Ø	Ø	↓
		Acup + antidepressant *vs.* antidepressant at the same time point	1-week treatment	Ø	Ø	Ø	Ø	Ø	Ø	>

(Continued)

TABLE 2 | Continued

References	Type of insomnia	Comparison		Outcome measures for insomnia						Outcome measures for depression
				Subjective outcome	Objective outcome (data from PSG or actigraphy)					HAMD or SDS
				PSQI or ISI	TST	SOL	SE	WASO	ATs	
			post-treatment	Ø	>	Ø	Ø	Ø	Ø	(–)
Tan et al. (53)	Major	*Vs.* the same group at different time points	Post-treatment *vs.* pre-treatment	↓	Ø	Ø	Ø	Ø	Ø	↓
		Acup + antidepressant *vs.* antidepressant at the same time point	Post-treatment	<	Ø	Ø	Ø	Ø	Ø	<
Wang and Ai (54)	Major	*Vs.* the same group at different time points	1-week treatment *vs.* pre-treatment	↓	Ø	Ø	Ø	Ø	Ø	↓
			2-week treatment *vs.* pre-treatment	↓	Ø	Ø	Ø	Ø	Ø	↓
			3-week treatment *vs.* pre-treatment	↓	Ø	Ø	Ø	Ø	Ø	↓
			Post-treatment *vs.* pre-treatment	↓	Ø	Ø	Ø	Ø	Ø	↓
		Acup + antidepressant *vs.* antidepressant at same time-point	1-week treatment	<	Ø	Ø	Ø	Ø	Ø	<
			2-week treatment	<	Ø	Ø	Ø	Ø	Ø	<
			3-week treatment	<	Ø	Ø	Ø	Ø	Ø	<
			Post-treatment	<	Ø	Ø	Ø	Ø	Ø	<
Min and Zhu (55)	Major	*Vs.* the same group at different time points	Post-treatment *vs*. pre-treatment	↓	Ø	Ø	Ø	Ø	Ø	↓
		Acup + antidepressant *vs.* antidepressant at the same time point	Post-treatment	<	Ø	Ø	Ø	Ø	Ø	<
Chung et al. (26)	Residual	*Vs.* the same group at different time points	1-week post-treatment *vs*. pre-treatment	(–)	(–)	(–)	(–)	(–)	Ø	(–)
			5-week follow-up *vs*. pre-treatment	(–)	(–)	(–)	(–)	(–)	Ø	(–)
		Acup *vs.* sham-/placebo-Acup at the same time point	1-week post-treatment	(–)	(–)	(–)	(–)	(–)	Ø	(–)
			5-week follow-up	(–)	(–)	(–)	(–)	(–)	Ø	(–)
Yeung et al. (37)	Residual	*Vs.* the same group at different time points	1-week post-treatment *vs.* pre-treatment	↓	(–)	(–)	(–)	(–)	Ø	(–)
			4-week follow-up *vs.* pre-treatment	↓	(–)	(–)	(–)	(–)	Ø	(–)
		Acup *vs.* sham-/placebo-Acup at the same time point	1-week post-treatment	*Vs*. sham (–), *vs*. placebo, <	(–)	(–)	(–)	(–)	Ø	(–)
			4-week follow-up	*Vs*. sham (–), *vs*. placebo, <	(–)	(–)	(–)	(–)	Ø	(–)

↑, statistically increase; ↓, statistically decrease; >, statistically higher/longer/more; <, statistically lower/shorter/less; (–), no statistical changes/no statistical difference; Ø, N/A or no data; Type of insomnia (major, insomnia as a major symptom of active depression; residual, insomnia as a residual symptom of previous or partial-remission depression).

Acup, acupuncture; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index; HAMD, Hamilton Depression Scale; SDS, Self-rating Depression Scale; SOL, sleep-onset latency; WASO, wake after sleep onset; ATs, awakening times; TST, total sleep time; SE, sleep efficiency.

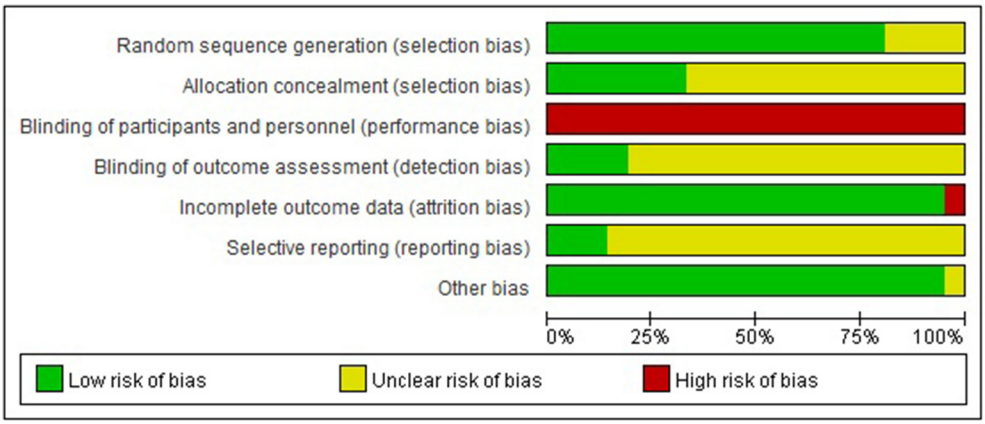

FIGURE 2 | Risk-of-bias graph. Other biases are assessed based on baseline balance.

depression), we further split the analyses into three sections: (1) acupuncture *vs*. placebo-/sham-acupuncture ($n = 3$ RCTs); (2) acupuncture *vs*. Western medication (antidepressant and/or hypnotic) ($n = 10$ RCTs); and (3) acupuncture combined with Western medication *vs*. Western medication ($n = 6$ RCTs). In the second category (the therapeutic effect of acupuncture on insomnia as a residual symptom of previous or partially remitted depression), we only qualitatively described the results because there were not enough RCTs ($n < 3$) to conduct meta-analysis (**Appendix 7**).

Effect of Acupuncture on Insomnia as a Major Symptom of Active Depression

Acupuncture vs. Placebo-/Sham-Acupuncture

Three RCTs (27, 38, 39) ($n = 277$) were under this category and addressed the comparison between verum- and placebo-acupuncture (by using Streitberger needles). They all included PSQI as the primary outcome measure. Due to the high heterogeneity ($p < 0.01$, $I^2 = 84\%$), a random-effects model was used. The results favored acupuncture in reducing PSQI global scores [MD = −3.12, 95%CI (−5.16, −1.08), $p < 0.01$]. These three RCTs also adopted HAMD (17- or 24-item version) to explore the regulating effect of verum- or placebo-acupuncture on depressed mood. The results favored acupuncture in reducing HAMD global scores as well [SMD = −2.67, 95%CI (−3.51, −1.84), $p < 0.01$; **Figure 3**]. One of the three RCTs also included sham-acupuncture (superficial acupuncture at non-acupoints) as another parallel control and came to the same conclusion (27).

In addition to subjective sleep quality and quantity, objective sleep parameters were shown to be improved with acupuncture but not placebo-/sham-acupuncture in two of the three trials (27, 39). In accordance with the records of actigraphy or PSG, acupuncture significantly shortened sleep-onset latency (SOL), prolonged the total sleep time (TST), elevated sleep efficiency (SE), and reduced wake after sleep onset (WASO) in comparison with placebo-/sham-acupuncture. Neither acupuncture nor placebo-/sham-acupuncture reduced the number of ATs (**Table 2**).

Only one RCT included follow-up (27). At the 4-week follow-up, the advantage of acupuncture over placebo-/sham-acupuncture in reducing PSQI and HAMD scores as well as in increasing TST and SE remained significant (**Table 2**).

Acupuncture vs. Western Medication

Ten RCTs ($n = 668$) were included in this comparison. Meta-analyses were carried out for four indices, namely, PSQI (global scores and six dimensions of PSQI), HAMD, SDS, and total clinical effectiveness rate. Subgroup analysis, sensitivity analysis, and meta-regression analysis were adopted to investigate the sources of heterogeneity where necessary. We did not perform meta-analysis for other outcome measures because there were fewer than three studies for each of them (**Appendix 7**).

Data Synthesis

PSQI Global Scores. All 10 trials employed PSQI as the primary outcome measure. Due to the high heterogeneity ($p < 0.01$, $I^2 = 91\%$), a random-effects model was used. The results favored acupuncture in reducing PSQI global scores [MD = −1.17, 95% CI (−2.26, −0.08), $p = 0.03$; **Figure 4**].

Six Dimensions of PSQI. Three of the 10 trials (n = 179) (41, 42, 44) reported the scores for each domain of PSQI in detail. No significant differences were identified between acupuncture and antidepressant (paroxetine, sertraline, or citalopram) in improving subjective sleep quality [MD = −0.01, 95% CI (−0.23, 0.21), $p = 0.94$], shortening sleep latency [MD = 0.05, 95% CI (−0.15, 0.25), $p = 0.64$], increasing sleep duration [MD = 0.01, 95% CI (−0.24, 0.25), $p = 0.95$] and habitual sleep efficiency [MD = −0.14, 95% CI (−0.42, 0.13), $p = 0.31$], and ameliorating sleep disturbances [MD = 0.03, 95% CI (−0.16, 0.22), $p = 0.72$] and daytime dysfunction [MD = 0.13, 95% CI (−0.11, 0.38), $p = 0.29$; **Figure 4**].

HAMD Global Scores. Seven trials (n = 496) (40, 41, 43, 45, 47–49) employed either 17-item or 24-item HAMD to quantify the participants' depression symptoms. A random-effects model was used because of the high heterogeneity ($p < 0.01$, $I^2 = 83\%$). The

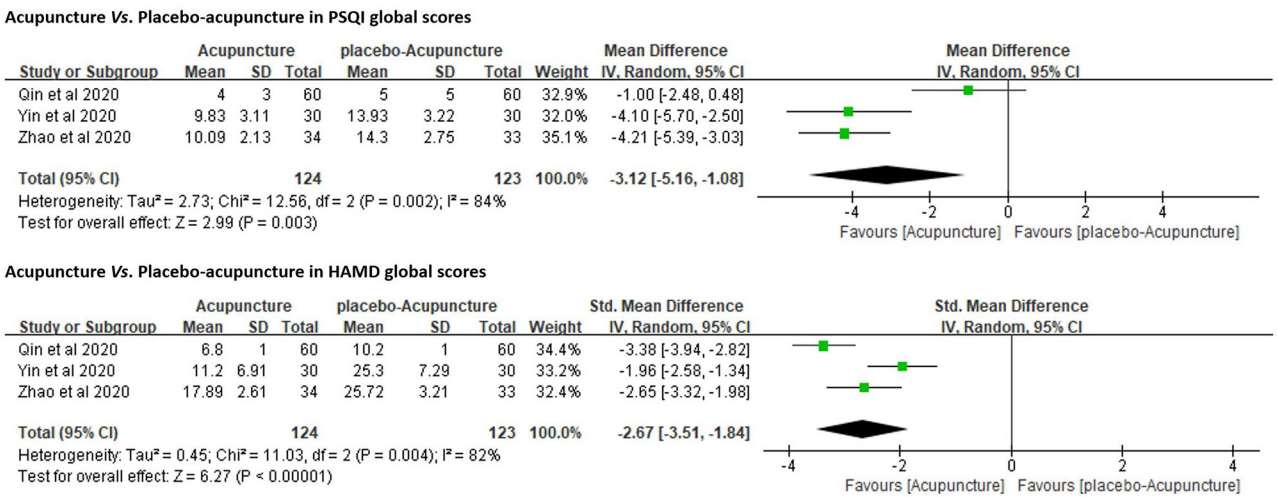

FIGURE 3 | Forest plots of acupuncture *vs.* placebo-acupuncture in PSQI and HAMD.

results favored acupuncture in reducing HAMD global scores [SMD = −0.47, 95% CI (−0.91, −0.02), $p = 0.04$; **Figure 4**].

SDS Global Scores. Three trials (n = 172) (42, 44, 46) employed SDS to assess the participants' depression levels. The resulting assessment was inconsistent with our analysis for HAMD. No significant differences were identified between acupuncture and antidepressant or hypnotic in reducing SDS global scores [MD = 2.10, 95% CI (−4.20, 8.39), $p = 0.51$; **Figure 4**].

Total Clinical Effectiveness Rate. All (n = 620) except one trial (44) compared the clinical effectiveness rates between acupuncture and pharmacotherapy for DI (**Appendix 8**). Pooled analysis results favored acupuncture in increasing the total effectiveness rate for DI [RR = 1.09, 95% CI (1.02, 1.17), $p = 0.01$; **Figure 4**].

Subgroup Analysis

On the basis of different acupuncture methods (MA or EA), principles of acupuncture prescription (fixed or semi-standardized), acupuncture treatment frequency [high (≥5 sessions per week) or low (<5 sessions per week)], and needle retention time (≥30 or <30 min), different medication in control groups (antidepressant alone, hypnotic alone, or antidepressant + hypnotic), and different versions of HAMD (17-item or 24-item), we conducted subgroup analyses under PSQI and HAMD. The significant interaction effect was identified between different acupuncture treatment frequencies under PSQI (χ^2 statistic 4.15, df = 1, $p = 0.04$). Acupuncture with high-frequency treatment sessions more significantly reduced PSQI scores in comparison with pharmacotherapy [MD = −1.76, 95% CI (−3.40, −0.13), $p = 0.03$]. In contrast, there was no significant difference between acupuncture with low-frequency treatment sessions and pharmacotherapy in reducing PSQI scores [MD = 0.07, 95% CI (−0.59, 0.73), $p = 0.84$]. Notably, no significant interaction effect was found between different acupuncture treatment frequencies under HAMD (χ^2 statistic 0.82, df = 1, $p = 0.36$). We also identified the significant interaction effect between different drugs in controls under PSQI (χ^2 statistic 33.66, df = 2, $p < 0.01$), while only one trial was included in the hypnotic subgroup and only two trials were included in the antidepressant + hypnotic subgroup. No interaction was identified in any other subgroups, which means the heterogeneity still could not be fully explained (**Appendix 9**).

There was also an interesting discovery about PSQI. When all 10 trials were pooled for effect size, acupuncture showed better effects than psychotropic drugs (antidepressant and/or hypnotic) in reducing PSQI global scores [MD = −1.17, 95% CI (−2.26, −0.08), $p = 0.03$]. However, in subgroup analysis, regardless of MA [MD = −1.12, 95% CI (−2.40, 0.16), $p = 0.09$] or EA [MD = −1.40, 95% CI (−3.24, 0.45), $p = 0.14$], acupuncture was only as effective as Western medicine in reducing PSQI global scores. Furthermore, there was no interaction effect between MA and EA (χ^2 statistic 0.06, df = 1, $p = 0.81$). Similar results were also identified in the subgroup analyses based on either principle of acupuncture prescription or needle retention time under PSQI (**Appendix 9**).

Sensitivity Analysis

With the purpose of addressing the high heterogeneity and checking the robustness of the pooled effect size, sensitivity analysis was carried out based on the outcome of PSQI global scores to ensure the results were not due to one or two studies. We chose influence analysis, by removing one study at a time and then recalculating the combined estimate on the remaining studies to evaluate the stability of the results. We did not execute sensitivity analysis for the other outcome measures due to the small number of studies included (<10). The results implied that each single study had little impact on the pooled estimate effects of PSQI, and the overall robustness and reliability of our study results were relatively high (**Appendix 10**).

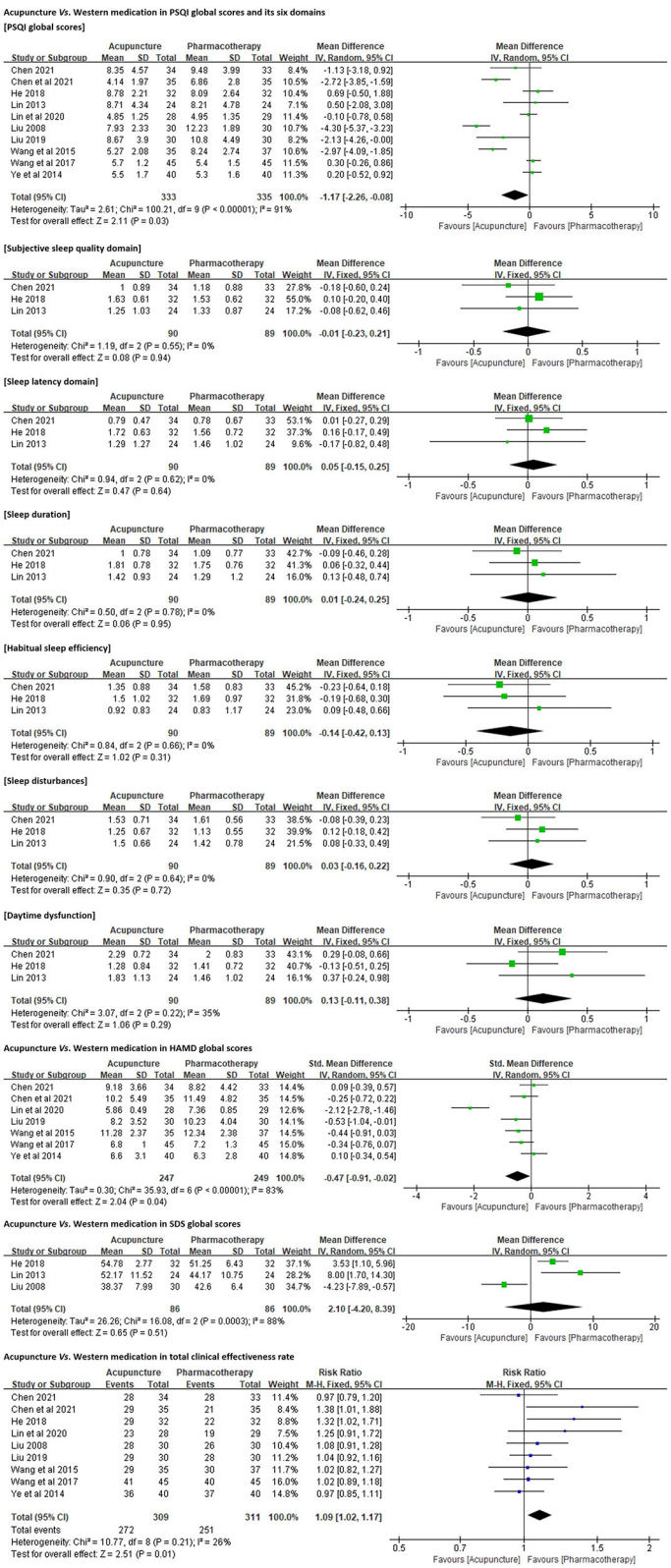

FIGURE 4 | Forest plots of acupuncture *vs.* Western medication in PSQI, HAMD, SDS, and total clinical effectiveness rate.

Meta-Regression Analysis

Similar to the sensitivity analysis, meta-regression analysis was only carried out based on the outcome of PSQI global scores as well. We performed univariate meta-regressions to investigate the sources of heterogeneity by treating publication year, study sample size, and acupuncture stimulation (MA or EA) as covariates. Multifactor meta-regressions were performed to find the sources of heterogeneity by taking medication used in controls (antidepressant alone, hypnotic alone, or antidepressant + hypnotic) and diagnostic criteria (ICD-10, DSM-IV, DSM-V, or CCMD-3) as covariates. However, the heterogeneity across the 10 included studies could not be substantially explained by publication year ($I^2 = 90.43\%$, $\tau^2 = 2.75$, $p = 0.36$), study sample size ($I^2 = 90.73\%$, $\tau^2 = 3.07$, $p = 0.66$), acupuncture stimulation ($I^2 = 91.25\%$, $\tau^2 = 3.16$, $p = 0.91$), medication used in controls ($I^2 = 92.78\%$, $\tau^2 = 3.13$, $p = 0.65$), or diagnostic criteria ($I^2 = 90.69\%$, $\tau^2 = 2.66$, $p = 0.39$; **Appendix 11**).

Acupuncture Combined With Western Medication vs. Western Medication

Under this category, six studies ($n = 398$) were included. All Western medications used in these six trials were antidepressants. Meta-analysis was carried out only for PSQI, HAMD, and total clinical effectiveness rate, but not for other indicators because there were fewer than three included trials for each of them. Similarly, subgroup analysis was performed where necessary.

Data Synthesis

PSQI Global Scores. PSQI was adopted as an outcome in five trials (n = 358) (50, 51, 53–55). A random-effects model was used to pool data ($p < 0.01$, $I^2 = 91\%$). The results favored acupuncture combined with Western medication in reducing PSQI global scores [MD = −2.99, 95% CI (−4.22, −1.76), $p < 0.01$; **Figure 5**].

HAMD Global Scores. All six trials (n = 398) used HAMD as an outcome. The results favored acupuncture in reducing HAMD global scores [SMD = −0.80, 95% CI (−1.17, −0.44), $p < 0.01$; **Figure 5**].

Total Clinical Effectiveness Rate. Five trials (n = 337) (51–55) compared the total clinical effectiveness rates between acupuncture combined with pharmacotherapy and pharmacotherapy alone for DI (**Appendix 8**), while no significant differences were identified between both groups [RR = 1.11, 95% CI (0.93, 1.33), $p = 0.24$; **Figure 5**].

Subgroup Analysis

For PSQI and HAMD, there was no significant interaction effect between subgroup analysis that was prespecified: MA *vs.* EA (χ^2 statistic 0.03, df = 1, $p = 0.87$ in PSQI; and χ^2 statistic 0.80, df = 1, $p = 0.37$ in HAMD), fixed acupuncture prescription *vs.* semi-standardized acupuncture prescription (χ^2 statistic 2.13, df = 1, $p = 0.14$ in PSQI; and χ^2 statistic 0.13, df = 1, $p = 0.72$ in HAMD), and high-frequency acupuncture treatment sessions *vs.* low-frequency acupuncture treatment sessions (χ^2 statistic 0.82, df = 1, $p = 0.37$ in PSQI; and χ^2 statistic 1.95, df = 1, $p = 0.16$ in HAMD) (**Appendix 12**). We did not perform subgroup analyses based on the HAMD version or different medication in the controls because not all six studies provided version information and all medications used in the control group were antidepressants.

A meaningful discovery about total clinical effectiveness rate was identified. When all five trials were pooled for effect size, there were no significant differences between acupuncture combined with antidepressants and antidepressants alone. Yet, in subgroup analysis, the results favored MA [RR = 1.23, 95% CI (1.05, 1.43), $p < 0.01$]. There remained no differences between EA combined with antidepressants and antidepressants alone [RR = 0.94, 95% CI (0.77, 1.13), $p = 0.51$]. Furthermore, there was a significant interaction effect between MA and EA (χ^2 statistic 4.69, df = 2, $p = 0.03$). We did not identify a significant interaction effect between different principles of acupuncture prescription (χ^2 statistic 0.07, df = 1, $p = 0.80$) or between different acupuncture treatment frequencies (χ^2 statistic 0.57, df = 1, $p = 0.45$) under total clinical effectiveness rate (**Appendix 12**).

In addition, each included trial addressed this comparison (acupuncture + Western medication *vs.* Western medication) had a 30-min needle retention time, and no subgroup analysis was required.

Acupuncture vs. Waitlist Control

No studies were identified under this comparison.

Acupuncture vs. CBT-i

No studies addressed this comparison.

Effect of Acupuncture on Insomnia as a Residual Symptom of Previous or Partially Remitted Depression

Two RCTs (26, 37) ($n = 228$) with a three-arm parallel design (EA *vs.* placebo-EA *vs.* sham-EA) from the same research team (Hong Kong, China) investigated the efficacy and safety of acupuncture on residual insomnia after remission or partial response of a major depressive disorder. Both RCTs presented that EA was well-tolerated but had very limited positive effects that were considered to be only non-specific effects. In the first study (published in 2011) (37), researchers found a slight advantage of EA and sham-EA over non-invasive placebo-EA in reducing PSQI and ISI scores at both 1- and 4-week post-treatment, while no significant difference was identified between EA and sham-EA at both time points. In addition, there was no significant between-group difference in actigraphy-derived objective sleep parameters (TST, SOL, SE, and WASO) as well as in HAMD and SDS scores among three acupuncture therapies. As an extension and optimization of the first study, the second study (published in 2015) (26) expanded the sample size, enriched the sample sources, and included more empirical acupoints used for insomnia in the intervention regimen. In this trial, there was a higher proportion of participants having sleep-diary-derived SOL <30 min in EA and placebo-EA groups at 1-week post-treatment, in comparison with the proportion of those in the sham-EA group, while no significant difference was identified between EA and placebo-EA. However, the researchers found no significant between-group difference among three acupuncture therapies in most of the other outcomes, including PSQI scores,

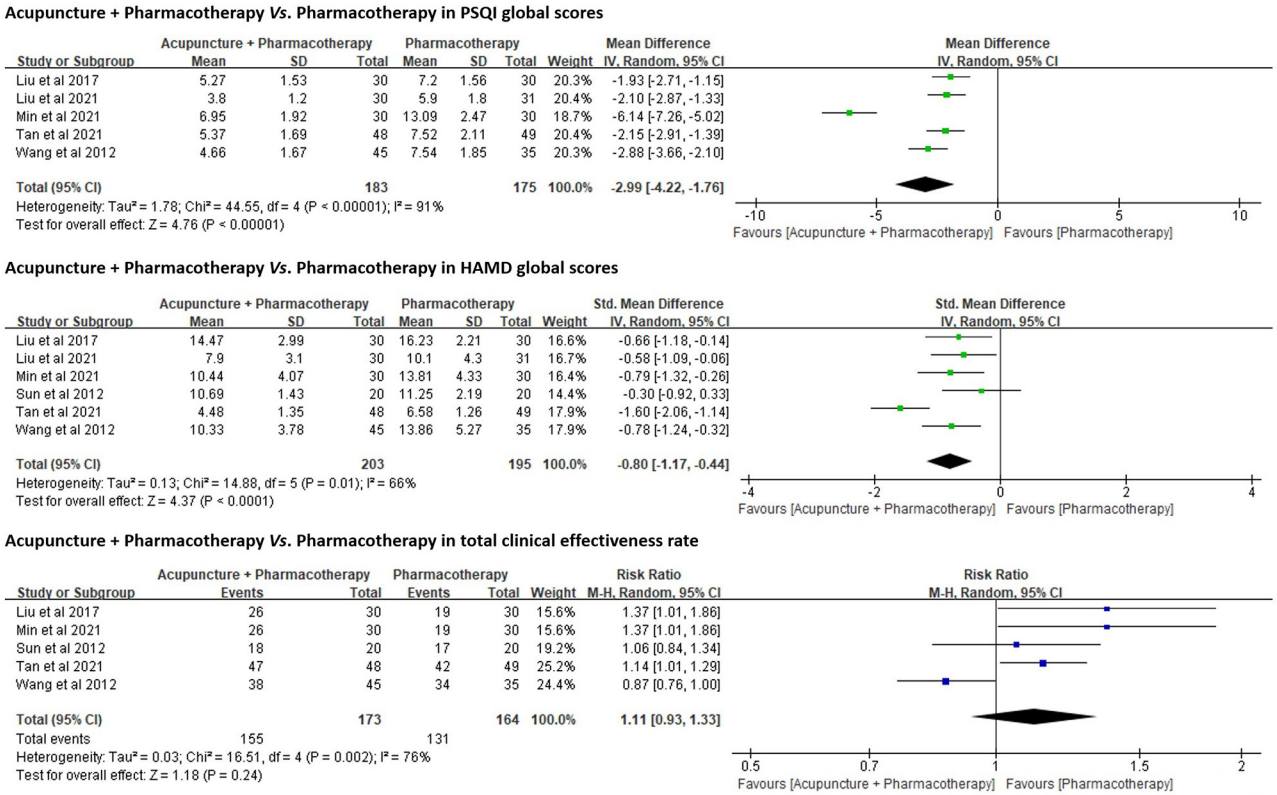

FIGURE 5 | Forest plots of acupuncture + Western medication *vs.* Western medication in PSQI, HAMD, and total clinical effectiveness rate.

actigraphy-derived sleep parameters (TST, SOL, SE, and WASO), and HAMD and SDS scores (**Table 2**).

Publication Bias Test

We adopted a linear regression analysis (Egger's test) to detect the publication bias based on PSQI in 20 included studies and based on HAMD in 18 included studies and found no statistically significant effect ($p = 0.154$ for PSQI and $p = 0.799$ for HAMD) (**Figure 6**). Publication bias tests were not carried out for the other outcome measures due to the small number of studies (<10).

Certainty and Quality of Evidence

The certainty and quality of evidence derived from meta-analyses of 15 major outcomes are illustrated in **Appendix 13**. In pursuance of the GRADE system, the quality of evidence ranged between very low and moderate (four were rated as "Very low;" 10 were rated as "Low;" and only one was rated as "Moderate"). The most common degradation factor was the risk of bias within the included RCTs, which involved 86.7% of outcomes.

DISCUSSION

Summary of Findings

Among patients with insomnia as a major symptom in active depression (that is, depression accompanying/comorbid with insomnia), acupuncture appeared to be superior to either placebo-acupuncture or antidepressants and/or hypnotics in improving both poor sleep and depressive symptoms. Acupuncture combined with these psychotropic substances certainly showed better effects than psychotropic substances alone. The reduction of PSQI and HAMD global scores varied from 1.2 to 3.1 points and 0.5 to 2.7 points, respectively, with significant clinical relevance. Nevertheless, quality of evidence supporting these positive results was very low to moderate owing to a lack of blinding of patients and evaluators. In the treatment of patients with insomnia as a residual symptom in previous or partially remitted depression, acupuncture appeared to only possess marginally better efficacy than placebo-acupuncture and had no superior efficacy to sham-acupuncture, indicating that the observed differences between verum- and placebo-acupuncture might be due to non-specific effects of needling. This conclusion is largely reliable as the evidence was derived from two high-quality and stringently designed RCTs (26, 37). Because of inadequate data, it is premature to conclude the intermediate- and long-term benefits and risks of acupuncture for patients with DI. Also, there were no data available clarifying the efficacy differences between acupuncture and CBT-i, or whether acupuncture combined with CBT-i was superior to CBT-i alone. Acupuncture appeared to be well tolerated and safe as the AEs were only mild and far less than those reported for antidepressants and/or hypnotics. The most

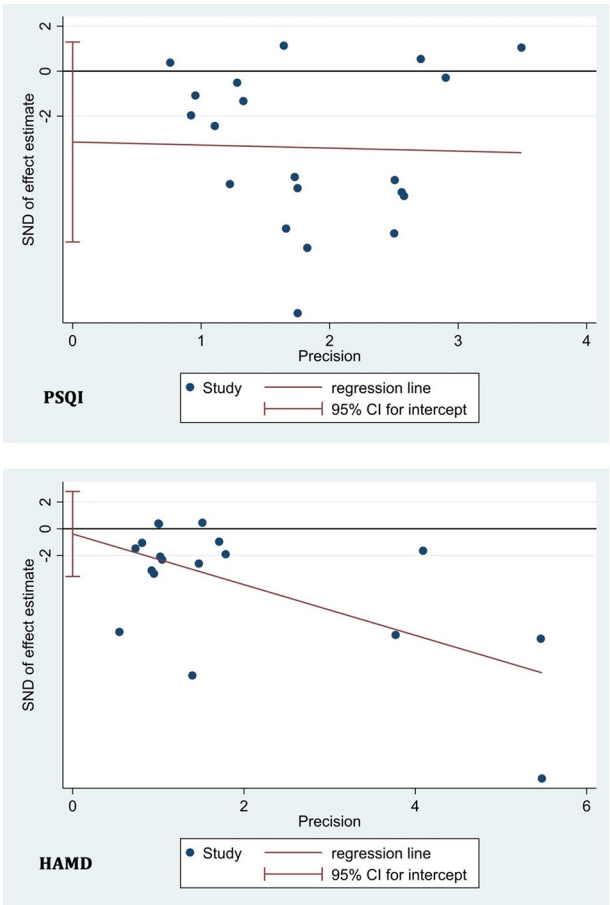

FIGURE 6 | Publication bias test based on PSQI and HAMD.

frequent AE of acupuncture was hand numbness and/or pain at acupoints, which usually resolved quickly after the needles were removed. Overall, acupuncture is safe in the management of DI, while its efficacy cannot be definitely concluded due to insufficient numbers and/or quality deficiencies of included RCTs.

Strengths, Limitations, and Comparison With Previous Systematic Reviews

To the best of our current knowledge, this is the first systematic review and meta-analysis comprehensively investigating the collective evidence regarding the efficacy of acupuncture as an alternative or adjuvant management to standard care in the management of insomnia as a major or residual symptom among patients with active or previous/partially remitted depression. For patients who have no access to CBT-i or patients whose symptoms are not well-controlled under the existing Western medication schedule or patients who are reluctant to immediately give up Western medication, our review in particular provides one more option and supports augmentation of hypnotic and antidepressive effects by combined application of acupuncture and conventional regimens (antidepressant and/or hypnotic). This is consistent with previous perceptions of the add-on effect of acupuncture (56). In the medical work *Schizophrenia, Sleep, and Acupuncture*, authors recommend that patients who are on psychotropic substances can consider receiving acupuncture as a supplementary therapy, because through restoring the harmony and balance in the body, acupuncture could enhance the effect of psychotropic agents (56).

We are conscious of five existing systematic reviews and meta-analyses (four in Chinese and one in English) on a similar theme (25, 57–60). However, four of them were carried out at least 5 years ago (25, 58–60). None of these five reviews discussed insomnia as a major or residual symptom of depression separately. All these reviews included many different forms of acupoint-based therapies, such as moxibustion (57, 58), auricular acupressure (57, 58, 60), intradermal needling (57, 58), fire acupuncture (57–59), and/or even Chinese herbal/patent medicine (25, 60) and ultraviolet blood irradiation therapy (25). Furthermore, some data derived from patients with DI due to stroke (25, 57) or malignant tumor (25) or patients with comorbid DI and anxiety disorder (25, 57–59) were also included for meta-synthesis. Four out of these five systematic reviews (25, 57–59) included at least one of three apparently ill-designed RCTs (61–63) in which diverse types of antidepressants were used as controls and the number of participants using each type of antidepressant was unclear. All such aforementioned practice introduces extra variability and makes it difficult to interpret the results. Here, we only focused on common forms of acupuncture (MA or EA) and ruled out RCTs in which patients were diagnosed as DI due to or comorbid with other physical and mental disorders, to reduce variability and subsequently to better reflect the real effect size. It is also noteworthy that incomplete retrieval was identified as a common issue in previous reviews. For instance, two RCTs (44, 52), published in 2012 and 2013, that were included in our review were not included in the four previous systematic reviews (25, 58–60), even though they met the inclusion criteria of those reviews. Those four systematic reviews performed literature search work no earlier than 2016. This thus can be seen as a case of incomplete search. Finally, all these five reviews did not consider or mention the different versions of HAMD employed in the included RCTs. In evidence synthesis, MD but not SMD thereby was inappropriately adopted for pooling the estimated effect size, which also undermined the reliability and accuracy of their results.

In addition to the stricter selection criteria and usage of widely accepted analysis tools as mentioned above, the merits of our current review also included the following: (1) considering the distinct clinical characteristics between two types of DI, the therapeutic effect of acupuncture on them was separately analyzed and different conclusions were drawn; (2) with limited data synthesis (derived from three RCTs), we were the first to report the significant efficacy differences between verum- and placebo-acupuncture on insomnia as a major symptom among patients with depression; (3) the STRICTA checklist and the GRADE system were introduced to appraise the reporting quality and evidence quality, respectively; and (4) we provided a complete list of excluded studies with justification for the exclusion of each, so as to present a transparent

and comprehensive screening process and enable readers to determine whether there is a risk of unjustified exclusion (64). The strengths of our study enable a more solid and reliable reference for clinicians when translating evidence into clinical practice for managing different types of DI.

The present review has a few limitations, the first of which was the number of studies available for assessment and the small sample sizes of each. Secondly, both the overall quality of the included trials and the quality of the synthesized evidence arising from the data of these trials was less than satisfactory. Thirdly, heterogeneity was high across the studies. We adopted sensitivity, subgroup, and meta-regression analyses but were unable to reasonably explain the potential source of the heterogeneity in specificity. Fourthly, acupuncture is a complex intervention, and the skills and experience of the operator are the linchpin. Some included studies did not clearly describe acupuncture parameters including depth of insertion and/or needle type used, and only three studies (26, 27, 37) explained the background of the acupuncturist. Those limitations impact the reproducibility and assessment of the real contribution. Fifthly, the medium- to long-term efficacy of acupuncture on DI remains elusive as only five studies (26, 27, 37, 42, 46) included follow-up. Sixthly, we excluded DI in or following stroke, cancer survivors, chronic pain, and feminine-specific physiological stage from the literature screening phase, although these conditions are quite common and the symptom cluster of sleep and emotional dysregulation in these special populations could be more severe (19). Caution thereby should be exercised in generalizing the positive benefits of the current review to DI in these special populations as mentioned. Finally, all RCTs were carried out in China. The sociocultural context may interact with biologic mechanisms and mediate the patient's experience of acupuncture (65). Due to cultural identity and confidence, Chinese individuals usually have high expectations of acupuncture (originating in China), which may inadvertently inflate and exaggerate the treatment outcomes (66). It is therefore unpredictable whether the results could be replicated in communities of other races and cultures. Further rigorous and well-designed trials with larger and more diverse clinical samples are required to build powerful and conclusive evidence. The improvement in reporting quality (completeness and clarity) of the acupuncture scheme is also required, which will be conducive to maximizing the transparency, reproducibility, and standardization of the treatment procedure as well as to facilitating the utilization of this therapy by clinical practitioners.

Interpretation of Findings

Since ancient times, acupuncture has been used to treat insomnia and/or depression (67, 68). In the past decade, at least 31 systematic reviews and at least 34 systematic reviews investigating the treatment of depression (67) and insomnia (68), respectively, with acupuncture, have been published, reflecting the continuous growth of attention and research interest in the management of psychological and sleep disorders by using acupuncture in the international medical community. Unfortunately, design deficiencies of included original RCTs or heterogeneities across individual studies hinder these reviews from yielding high-quality results and drawing firm conclusions (67, 68). Common shortcomings with potential solutions can be referred to in the findings outlined in these two overviews (67, 68), and our review has some additional reminders for clinical practitioners and researchers. In exploring the efficacy of acupuncture, four studies employed selective serotonin reuptake inhibitors (SSRIs), such as paroxetine (42), sertraline (41), escitalopram (43), and citalopram (44), alone as positive controls. The usage (particularly short-term usage) of this class of antidepressive agents however may deteriorate sleep quality, particularly increasing REM-SOL (5) and disrupting sleep continuity (5, 8). Reported by the US Food and Drug Administration, the average prevalence of treatment-emergent insomnia and daytime somnolence was 17% and 16%, respectively, among depressed patients treated with SSRIs (8, 69). In future studies with the same design (acupuncture *vs*. Western medicine), agomelatine, mirtazapine, or trazodone might be more appropriately chosen as valid controls, thus providing a truer picture of the efficacy of acupuncture and enhancing the trustworthiness of the results. Nearly three quarters of individuals suffering from depression will relapse at some point in their lives (5); insomnia not only affects a large proportion of the population on a recurrent and tenacious basis (70) but also can contribute to the depression relapses (5, 71). Hence, the long-term effect of any therapeutic strategy in the management of DI is of significant clinical importance. Insufficient data supported effect-size synthesis in this review and prevented us from judging how acupuncture treatment benefits were maintained at follow-ups. Future RCTs are recommended to include rational intermediate- and long-term follow-ups. Only three trials (26, 27, 37) included dropout/withdrawal cases in the final analysis. Other trials directly excluded data from these cases, which might partially skew the reliability of results. Such defects should also be addressed in future studies through sound statistical approaches (e.g., last observation carried forward and multiple imputation), so that an unbiased determination of the efficacy of acupuncture can be acquired.

In spite of these restrictions, the current review contributes many valuable new information and empirical insights.

A reduction of 3 points or more in PSQI global scores (72) and HAMD global scores (73) was chosen to indicate a minimal clinically significant difference in sleep and depression symptoms, respectively. A majority of the studies we retrieved concentrate on insomnia as a major symptom of active depression. Within this category of patients, our review found that acupuncture was better than either placebo-acupuncture or standard care (antidepressant and/or hypnotic) in reducing PSQI scores by 1.2–3.1, which is of clinical importance. Thus, acupuncture is significantly better than placebo and at least equivalent to standard care in improving poor sleep among patients with depression. Meanwhile, for the depressive symptoms in these patients, acupuncture was better than either placebo-acupuncture or standard care in reducing HAMD scores by 0.5–2.7. Although this score did not reach 3 points, which represented "minimal improvement," it suggests that acupuncture may have an antidepressive effect that

is at least no worse than that of antidepressants and/or hypnotics. In the further subgroup analysis, we identified that in comparison with standard pharmacotherapy, acupuncture with high-frequency treatment sessions (≥5 sessions per week) was more effective in improving patients' sleep quality and quantity but was not more effective in improving patients' depressive symptoms. Nevertheless, there was no significant difference between acupuncture with low-frequency treatment sessions (<5 sessions per week) and standard care in improving both insomnia and depression symptoms among patients. In addition, the stimulation of acupuncture (EA or MA), variation in treatment protocol (standardized treatment protocol with fixed acupoints or semi-standardized treatment protocol with predefined acupoints in combination with acupoints selected based on symptoms and/or TCM patterns), and needle retention time (20–30 or 30 min) did not appear to have a significant impact on the aforementioned results. On the basis of these findings, we here recommend that, when delivering acupuncture treatment for patients with active depression and concomitant insomnia, clinical practitioners may consider increasing the frequency of acupuncture treatment, such as providing five treatment sessions per week, to enhance the hypnotic effect of acupuncture. As a single non-drug therapy, acupuncture is at least as effective as psychotropic medications. Its effect in concurrently ameliorating both depression and insomnia and its safety are of significant value to patients with depression who also have concerns over their liver or kidney function, which could be compromised by pharmacotherapy. Despite the absence of correlational analysis, the trends in the change of PSQI and HAMD scores were largely positively correlated (**Table 2**), suggesting that as insomnia or depression ameliorated, other symptoms ameliorated as well. These findings are also consistent with the erstwhile knowledge of the complex interaction and bidirectionality between insomnia and depression (5, 74).

Insomnia is the most common residual symptom of depression (8, 75), which is not only linked to poorer quality of life (76) but also regarded as a critical factor in subsequent depression relapse (75, 76). Although the search was comprehensive, only two trials from the same research team concerning acupuncture for depression-associated residual insomnia were identified. One single-center trial ($n = 78$) (37) found a greater improvement in self-report sleep but not in objective sleep parameters or depressive symptoms, with EA being superior to non-invasive placebo-EA (Streitberger needle), but there was no difference between EA and sham-EA (superficial needling at non-acupoints). The team then ran a multicenter trial (26) ($n = 150$) and found similar results. The authors concluded that the limited hypnotic effect of acupuncture was largely due to its non-specific effects, such as general physiological effects of needling and electrostimulation (26, 37). These two RCTs are well-designed and graded as high-quality studies as assessed with the modified Jadad system and the Cochrane tool. We cannot deny the placebo effect of acupuncture; indeed, in the management of insomnia, positive beliefs, anticipation, and expectations concerning CAM may result in more favorable outcomes and higher satisfaction with CAM, i.e., the placebo effect (19, 77). The only concern of those two trials (26, 37) is if the acupuncture treatment was sufficient. The treatment was provided three times per week for 3 weeks with a total of nine sessions, which is substantially fewer in comparison to a total of 12–42 sessions over 4–24 weeks in trials included under the category addressing insomnia in active depression. This is consistent with our findings in a previous systematic review (22), which found that a minimum of 12 sessions of acupuncture treatment was needed for primary insomnia to produce a significant improvement on both TST and SE, and thus, it could be considered the "lowest threshold dosage" (22). Also, there may be a positive dose–response relationship between acupuncture's hypnotic effect and its dose (22). Dosage is a crucial factor for acupuncture's optimal clinical efficacy and has been found as one of the main reasons for the failure of many acupuncture trials to yield positive results (78). The robustness of the results of those two trials (26, 37) should be retested in future studies by further increasing the acupuncture dosage or after identifying the optimal acupuncture dosage (e.g., frequency of sessions, needle retention time, and/or length of treatment period). Despite satisfactory effects in attenuating residual insomnia of previous or partially remitted depression, conventional hypnotics, particularly with high doses, have been associated with antidepressant refractoriness and/or an elevated risk of developing a psychiatric disorder (76). Therefore, other potentially effective therapies (including combined application of acupuncture and hypnotic/antidepressant/CBT-i/repetitive transcranial magnetic stimulation) also need to be actively sought and determined; after all, the available evidence does not, in any case, support the use of acupuncture alone in managing residual insomnia associated with previous or partially remitted depression.

The third purpose of this systematic review was to determine whether acupuncture could amplify the therapeutic effect and/or attenuate the adverse reactions caused by psychotropic substances. Only limited evidence was attainable. Six RCTs (50–55) under this category showed that the combined therapy was more effective than antidepressants (venlafaxine, mirtazapine, or paroxetine) alone in ameliorating both poor sleep and depressed mood among patients with active depression accompanying or comorbid with insomnia. Moreover, subgroup analysis based on different acupuncture methods implied that MA might produce better efficacy than EA when combined with antidepressants. This superiority of MA over EA may be explained by the major demerit of EA, that is, the development of adaptation or tolerance that arises in fixed pulses with settled intensity and frequency (79). Two (52, 55) of the six RCTs reported that AEs in acupuncture combined with venlafaxine or paroxetine were slightly less than those in venlafaxine (5/20 *vs.* 6/20) or paroxetine (6/30 *vs.* 7/30) alone. Another two (51, 53) RCTs employed the Asberg Side Effects Rating Scale (SERS) and found that SERS scores were significantly lower in the combined therapy, indicating that AEs caused by mirtazapine or paroxetine were diminished when acupuncture was superimposed. Unfortunately, all these positive findings might be challenged because of the inadequate sample size and the less-than-rigorous design in original RCTs. Also in need of note here is that we tried but ultimately were not able to access

the SERS from either the reference lists or the corresponding authors of these two papers (51, 53). The reliability of SERS hence could not be judged. We recommend the inclusion of internationally endorsed and standard tools such as the Antidepressant Side-Effect Checklist (80), the UKU Side Effects Rating Scale (81), and/or the Frequency, Intensity, and Burden of Side Effects Rating Scale (82) in future studies to truly reflect the real impact of acupuncture on antidepressant-induced AEs. A previous systematic review revealed that acupuncture was helpful in reducing antidepressant-induced side reactions in the first 6 weeks of the treatment period among patients with depression (79). Most RCTs included in this review did not provide data on AEs, preventing evidence synthesis. Hence, whether acupuncture produces a similar benefit of attenuating side effects caused by antidepressants and/or hypnotics during the early onset of DI would be an attractive direction for future investigation.

Acupoint selection is one of the linchpins affecting the clinical effectiveness of acupuncture treatment (83). In the 19 trials focusing on insomnia as a concomitant symptom in active depression, the three most frequently utilized acupoints were GV20, EX-HN3, and HT7 (**Table 1**). Depending on "Indications of Acupuncture Points [GB/T 30233-2013]" (National Standard of the People's Republic of China, 2013 version) (84), these acupoints are all classic acupoints for the treatment of psychiatric and psychological disorders. The hypnotic and antidepressant effects possessed by these three acupoints can not only be explained through TCM meridian theory (84) but have also been confirmed by modern medicine approaches. In rodents with sleep deprivation, the instant sedative effect produced by acupuncture at GV20 is achieved by reducing the excitability of the cerebral cortex (85). This stimulation may also be associated with the regulation of 5-hydroxyindoleacetic acid and enhancement of acetylcholinesterase activity in the brain (85). In depressed rodents, acupuncture at GV20 and EX-HN3 showed significant antidepressive effects that were not inferior to those of fluoxetine, and this effect was associated with acupuncture-induced inhibition of the NLRP3 inflammasome signal pathway in the prefrontal cortex and reduction of cerebral inflammation (86). Similarly, acupuncture at HT7 was found to activate cerebral regions highly associated with cognition, sleep, and emotion (70). Coincidentally, in a previous systematic review summarizing herb/acupuncture prescriptions for insomnia, these three acupoints were also identified to be frequently used but were non-specific for TCM patterns (87). We thereby recommend that in the future treatment of active depression with insomnia as a concomitant symptom, practitioners can consider including these three acupoints as the core prescription and other acupoints that are appropriate to patients' different TCM syndromes, in order to comply with the individualized, syndrome differentiation principle of TCM. Since acupuncture has not been proven to be effective for residual insomnia associated with previous or partially remitted depression, we do not recommend any acupoints for this type of insomnia.

Six RCTs (26, 27, 37, 39, 44, 52) reported objective sleep parameters in participants, five of which also reported changes in PSQI. Trends between subjective and objective outcomes were largely consistent, albeit no correlation analysis was executed (**Table 2**). When patients spontaneously reported an improved sleep (reflected by decreased PSQI scores) following acupuncture treatment, researchers usually saw a shortened SOL (39), prolonged TST (27, 39, 44), increased SE (27, 39), and/or reduced WASO (39) in PSG/actigraphy data. The major difference between the subjective and objective indices was the number of awakenings. Two trials (27, 44) demonstrated that acupuncture significantly reduced ATs, while another trial (39) exhibited that acupuncture reduced only WASO but not ATs. No data synthesis was performed due to the heterogeneous study design. In any case, most of the findings are encouraging. Sleep in depression is characterized by disturbances of sleep continuity, including early morning awakening, prolonged SOL, decreased SE, and increased WASO and ATs (8, 88). The available findings at least confirm that the latter three types of disrupted sleep continuity may benefit from acupuncture treatment. Only two included RCTs (39, 52) investigated the effects of acupuncture on sleep structure/architecture through PSG and provided very limited evidence. One study revealed that acupuncture significantly shortened REM-SOL (39). But indeed, alteration of REM sleep (e.g., reduced REM-SOL, prolonged REM duration and first REM period, and increased REM density) itself is the most prominent feature of the sleep structure/architecture among depressed patients (8). It is hence indeterminate whether the observed change in REM-SOL was a manifestation of the development of depression over time or whether it was caused by acupuncture. Worse still, the relative excess of REM appears to come at the expense of stage N3 sleep (SWS) (89). Another study (52) illustrated that either acupuncture combined with venlafaxine or venlafaxine alone reduced REM%, increased NREM%, and prolonged TST, and the latter two effects caused by the combined therapy were more significant. These findings came as a surprise, because a reduction of SWS and disinhibition of REM sleep are typical characteristics of sleep in depressed patients (8), and this altered sleep structure/architecture appears to be normalized by acupuncture. Another electroencephalogram characteristic of depressed patients is a decreased delta ratio (the ratio of SWS between delta wave activity in the first and second sleep cycles) (8). The effect of acupuncture on this parameter, as well as the aforementioned REM sleep duration and density, should be further investigated in future studies.

The particular mechanism by which acupuncture affects DI is intriguing. Some evidence indicates that impaired metabolism of plasma neuropeptide Y (NPY) and the decreased plasma NPY may be involved in the pathogenesis or pathophysiological process of depression (90) and insomnia (91). Increased serum substance P (SP) has been observed in a proportion of patients with depression (92). Another study from China observed dysfunction in peripheral NPY- and SP-ergic neurons in patients with either primary insomnia or DI, with the latter group showing more severe SP-ergic neuronal dysfunction (93). One trial in the current review reported significant improvements in both insomnia and depressive symptoms among patients with DI after receiving acupuncture treatment, accompanied by increased serum NPY and decreased SP levels, and these positive changes were not identified in the placebo-acupuncture group (39). Another trial showed that abnormalities

in T-lymphocyte subsets and immunoglobulin due to DI were normalized by acupuncture intervention (45). Additionally, increased inflammatory cytokines levels (e.g., interleukin-6 and tumor necrosis factor) (5), dysregulation of neurotransmitters (e.g., serotonin and norepinephrine) (5), or gut microbiota alterations (94) may also explain the bidirectional relationship between depression and insomnia and/or may be involved in the pathogenesis and development of DI. Whether acupuncture's impact on DI is also associated with its modulation of these cellular events deserves further exploration and elucidation in future studies. Existing hypotheses also include that acupuncture exerts a hypnotic effect through the modulation of regional brain activity and functional connectivity, particularly in emotion-related areas (95). Shedding light on the mechanisms underlying acupuncture for DI *via* imaging techniques, e.g., functional magnetic resonance imaging, diffusion tensor imaging, and magnetic resonance spectroscopy, thereby would be another valuable and interesting direction.

CONCLUSIONS

This review has provided a low to moderate level of evidence supporting acupuncture as a safe and effective remedy alternative to or adjuvant to conventional pharmacotherapy (antidepressant and/or hypnotic) in improving insomnia as a major symptom among patients with active depression as well as their depressed mood. Furthermore, the complaint of disrupted sleep continuity in this category of patients is most likely to benefit from acupuncture. Future studies need to include appropriate patient–evaluator blinding methods in the trial design, to observe the intermediate- and long-term effects of acupuncture, to investigate whether there is a synergistic effect between acupuncture and CBT-i, and to introduce PSG as an outcome metric to elucidate the mechanisms underlying acupuncture on sleep architecture/structure, particularly REM-SOL, REM%, and NREM%. The effect of acupuncture on residual insomnia associated with previous or partially remitted depression requires further research employing optimal dosage of treatment. Searching for other potentially positive therapeutic strategies, including acupuncture combined with standard care (antidepressant and/or hypnotic, and/or CBT-i) in managing this type of insomnia, also remains warranted and urgent.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

ZZ, GK, and Q-QF designed this review. W-JZ, Q-QF, and F-YZ performed the database search, data extraction, and statistical analyses. F-YZ, QQ-F, and ZZ were involved in the quality assessment and bias risk analysis. F-YZ drafted the manuscript. SS, RC, and ZZ provided critical comments for revising the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.863134/full#supplementary-material

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Can Daytime Transcranial Direct Current Stimulation Treatment Change the Sleep Electroencephalogram Complexity of REM Sleep in Depressed Patients? A Double-Blinded, Randomized, Placebo-Controlled Trial

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Study Objectives: The purpose of this study was to determine the effects of daytime transcranial direct current stimulation (tDCS) on sleep electroencephalogram (EEG) in patients with depression.

Methods: The study was a double-blinded, randomized, controlled clinical trial. A total of 37 patients diagnosed with a major depression were recruited; 19 patients (13 females and 6 males mean age 44.79 ± 15.25 years) received tDCS active stimulation and 18 patients (9 females and 9 males; mean age 43.61 ± 11.89 years) received sham stimulation. Ten sessions of daytime tDCS were administered with the anode over F3 and the cathode over F4. Each session delivered a 2 mA current for 30 min per 10 working days. Hamilton-24 and Montgomery scales were used to assess the severity of depression, and polysomnography (PSG) was used to assess sleep structure and EEG complexity. Eight intrinsic mode functions (IMFs) were computed from each EEG signal in a channel. The sample entropy of the cumulative sum of the IMFs were computed to acquire high-dimensional multi-scale complexity information of EEG signals.

Results: The complexity of Rapid Eye Movement (REM) EEG signals significantly decreased intrinsic multi-scale entropy (iMSE) (1.732 ± 0.057 vs. 1.605 ± 0.046, $P = 0.0004$ in the case of the C4 channel, IMF 1:4 and scale 7) after tDCS active stimulation. The complexity of the REM EEG signals significantly increased iMSE (1.464 ± 0.101 vs. 1.611 ± 0.085, $P = 0.001$ for C4 channel, IMF 1:4 and scale 7) after tDCS sham stimulation. There was no significant difference in the Hamilton-24 ($P = 0.988$), Montgomery scale score ($P = 0.726$), and sleep structure (N1% $P = 0.383$; N2% $P = 0.716$; N3% $P = 0.772$) between the two groups after treatment.

Conclusion: Daytime tDCS changed the complexity of sleep in the REM stage, and presented as decreased intrinsic multi-scale entropy, while no changes in sleep structure occurred. This finding indicated that daytime tDCS may be an effective method to improve sleep quality in depressed patients. Trial registration This trial has been registered at the ClinicalTrials.gov (protocol ID: TCHIRB-10409114, in progress).

Keywords: depression, electroencephalogram, intrinsic multi-scale entropy, rapid eye movement, transcranial direct current stimulation, randomized, double-blinded, placebo-controlled trial

INTRODUCTION

Major depressive disorder (MDD) is a common mental disorder with high recurrence and disability rates. Specifically, the annual and lifetime prevalence rates are as high as 6.6 and 16.2% (1). Recurrences leave patients with a heavy economic burden, a lower quality of life, and could be incremental (2). Between 50 and 90% of patients with depression complain about sleep disturbances (3). The symptoms of depression are complex and changeable, among which sleep disturbance is prominent, and early awakening is the characteristic sleep change of depression (4). Common sleep subjective characteristics in patients with depression include insomnia, light sleep, more dreams, easy awakening at night and so on. Polysomnography (PSG) is widely used to detect objective sleep structure in patients with depression. PSG research started in the 1960s with studies showing that major depression is characterized by alterations in sleep continuity (5). Because other sleep disturbances are common among other mental disorders, rapid eye movement (REM) sleep disturbances are considered a characteristic manifestation of depression disorders (6). In 1966 Hartmann et al. (7) reported that the REM sleep latency of patients with a depression disorder shortened at the beginning of sleep, while the proportion of REM increased. Some studies have shown that REM sleep in depressed patients tends to normalize after treatment (3, 8). A shortened REM sleep latency that exists after remission of depressive symptoms indicates that patients have a higher risk of relapse (8).

In the past, MDD patients have been mainly treated with pharmaco- and psycho-therapy (9). The shortcomings of pharmacotherapy include the lack of early onset response to treatment and side effects, which frequently cause treatment non-compliance (10). Non-invasive brain stimulation (NIBS) is increasingly used as an additive treatment for depression. Two major types of NIBS techniques are currently in use for clinical and research [transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS)] (11). The latter technique, tDCS, delivers a weak current (1–2 mA) to the scalp for 10 min to regulate the membrane potential, which affects cortical activity and induces transient changes in brain function (12). Studies on tDCS and sleep have shown that using tDCS at night increases slow-wave sleep in healthy people (13). Studies have also shown that tDCS improves subjective sleep quality in college students (14). A subsequent analysis, however, revealed that tDCS treatment at night increases arousal in insomniacs (15). Existing studies have explored the efficacy of tDCS in the treatment of depression (16). tDCS is mostly treated in the daytime, with a frequency of five times a week, but few studies have explored the subjective and objective sleep quality at night (17–21).

An electroencephalogram (EEG) is a suitable option as a tool to investigate the brain. As a result, this method has been widely used for biomedical investigation (22, 23). The common methods of EEG signal analysis are linear and non-linear dynamic analyses. Studies have shown that non-linear EEG analysis can effectively explore the complexity of the human brain (24–26). Multi-scale entropy (MSE) is a typical non-linear approach, and the entropy of sleep EEG signals facilitates assessing the trajectory of brain maturation in newborns (27) and the characteristics of pathologic conditions, such as Parkinson's disease (28). There are two significant drawbacks to MSE. MSE does not reflect the presence of high frequencies in the signal. MSE is not adapted to non-stationary or non-linear signals (29), which are unluckily the characteristics of sleep EEG signals. To overcome these drawbacks, intrinsic MSE (iMSE) was applied in this study.

Current studies have shown that even a single tDCS treatment lasts for at least 24 h (30). As a treatment, it is more practical to implement therapy during the day in the clinic. Thus, we sought to determine if use of tDCS during the daytime improve Sleep EEG complexity at night in depressed patients?

MATERIALS AND METHODS

Study Design and Setting

Full details of the study design, rationale, and methods as reported in compliance with CONSORT guidelines have been previously published (31). The CONSORT checklist is shown in **Figure 1**. The current study was a parallel, randomized, double-blinded, sham-controlled design with participants in an initial 2-week RCT phase. All participants completed the treatment during the daytime (five times per week for 2 weeks). The trial was registered and approved by the Ethics Committee of Suzhou Guangji Hospital (ClinicalTrials.gov ID: TCHIRB-10409114). All patients signed the informed consent.

Participants

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) patients 20–65 years of age diagnosed with MDD according to DSM-5; (2) Hamilton Depression Rating scale-24 item (HDRS-24) score $\geq$20 with a

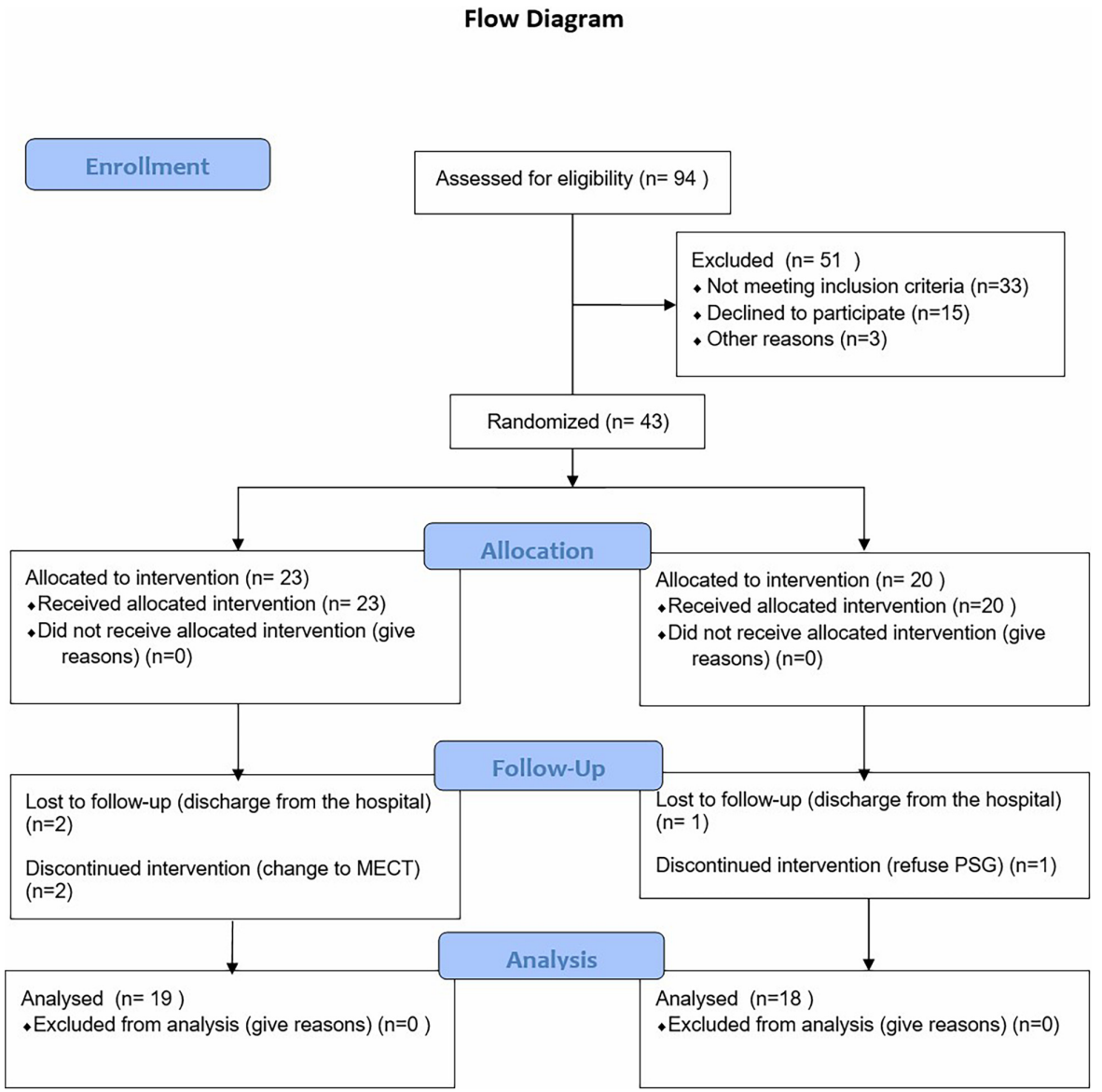

FIGURE 1 | Flow diagram of the progress through the phases of a parallel randomized trial of two groups.

third suicide factor score <3; (3) cognitive function sufficient to understand the research content and obtain informed consent; (4) escitalopram (20 mg/day) or duloxetine hydrochloride (60 mg/day) for 2 weeks; and (5) right-handed patients.

The exclusion criteria were as follows: (1) patients diagnosed with other psychiatric disorders, such as bipolar disorder or schizophrenia; (2) patients currently treated with modified electroconvulsive therapy (MECT) or rTMS within 6 months; (3) patients with severe medical and surgical diseases (epilepsy, dementia, craniocerebral injury, and severe liver dysfunction); and (4) recurrent headaches and skin allergies in the past.

Randomize and Interventions

Randomization

First, patients admitted to the ward diagnosed with depression were evaluated, screened out according to the admission criteria, and informed consent was signed. Patients completed PSG and scale assessments at baseline. Then, after 2 weeks of treatment with escitalopram (20 mg/day) or duloxetine (60 mg/day), the patients were divided into active group or sham group according to a random counting table by the operating technician. After 10 tDCS treatments over a 2-week period, the patients were reassessed with a scale and PSG.

Interventions

Treatment was performed in a quiet environment with minimal communication between the therapist and the subject; the patient was not permitted to fall asleep. The anodes and cathodes were connected to 35-cm^2 sponges soaked with 0.9% brine. According to the 10–20 system, F3 is the anode and F4 is the cathode.

The active tDCS group received 2-mA tDCS, and the current dose to the required parameter in 30 s. The stimulation lasted 20 min 5 times a week for a total of 10 stimulations. While the sham tDCS group had current for the first 10 s, and the current dropped to zero in 10–30 s, after which no current existed for the next 20 min. The sham button comes with the machine. The operator only needs to open the sham button.

Measures

Measurement of Depression Severity

The severity of depression was measured at baseline and after tDCS using the Hamilton Depression Rating Scale (HDRS-24) and Montgomery scales (MARDS).

Polysomnography

Polysomnography is defined as the continuous monitoring and simultaneous recording of physiologic activity during sleep (32). PSG was used to record sleep EEG signals. The subjects were recorded while lying in an electromagnetic shielding chamber. Standard scalp electrodes were placed by the International 10–20 System; C3, C4, F3, F4, O1, and O2 referred to mastoid electrodes. The EEG was recorded at a 128-Hz sample frequency. Impedances were <5,000 ohms. Monitoring was performed using the SOMNOmedics V6 PSG system (company, city, Germany), with electrodes and sensors placed in a sleep diagnostic montage, as follows: six brain leads (F4 – M1, F3 – M2, C4 – M1, C3 – M2, O2 – M1, and O1 – M2); two eye movement leads (E1 – M2 and E2 – M2); 2 mandible muscle leads (CHIN1 – chinZ and CHIN2 – chinZ); left and right tibia anterior muscle conductance; and cardiac conductance. Subjects also wore oral and nasal heat sensors, nasal pressure sensors, RIP chest and abdomen breath sensing plethysmography tape, microphone snores sensor, a Nonin finger pulse oxygen saturation probe, and a posture sensor. Sleep technicians manually analyzed sleep and related events according to the AASM Manual for the Scoring of Sleep and Associated Events rules [version 2.2 (33)], then a sleep physician issued a report.

Intrinsic Multi-Scale Entropy

The sleep EEG signals were assessed by the iMSE method, which is quite suitable for non-linear and non-stationary EEG signals.

For each sleep stage of each participant, iMSE was calculated on eight parts of continuous 1,000 EEG data points (7.8125s). Artifacts, such as eye movements, blinks, muscle activities, or other artifacts, were excluded by independent component analysis (ICA). The artifacts were also visually checked.

The iMSE consists of two major parts: to compute the intrinsic mode functions (IMFs) of the sleep EEG signal; and compute the MSE of the cumulative sums of each of the IMFs. The IMFs were extracted with the empirical mode decomposition (EMD), which expanded a given time series into a set of narrowband oscillatory modes that emerged naturally from the inherent oscillatory modes within the signal (34). Those modes were termed IMFs and are data-driven.

In this study iMSE was applied to analyze sleep EEG signals of depressed patients before and after active/sham tDCS stimulation.

The calculation of iMSE was divided into two major steps EMD [i] and MSE calculation.

Part 1 Empirical mode decomposition.

An input signal.

$$y_0(t),\ y_0 \in R,\ t \in Z\ and\ t = [1:n]$$

was decomposed into a series of IMFs with EMD in the following process:

First, the upper and lower envelopes were acquired by connecting the local maxima and minima of the signal, respectively, with cubic splines.

Second, the average of the two envelopes was then removed from the original signal.

The sifting process (envelopes-acquiring and average-removing) was then repeated several times (usually 10 times). The first set of the sifting process obtained the first IMF, which carried higher frequencies than the residual signal with the first IMF removed.

Then, the residual signal was deemed as the input for a new round of iterations. In each sifting process turn, IMFs with lower frequencies were derived from the newly obtained residue of the last turn.

Finally, the result of the EMD was a decomposition of the signal [$y_0(t)$] into the sum of the IMFs and a residue [r(t)]. That is,

$$y_0(t) = \sum_{m=1}^{n_m} c_m(t) + r(t)$$

where n_m is the number of IMFs (35).

Part 2 MSE calculation.

1. The "multi-scale" of MSE was reflected in the process of coarse-graining, which was carried out in the following ways:

$$y_j^{(\tau)} = \frac{1}{\tau} \sum_{i=(j-1)\tau+1}^{j\tau} x_i,\ 1 \le j \le N/\tau$$

   For scale $\tau = 1$, $y_j^{(1)}$ is the original signal and the length of the signal after coarse graining is N/τ .
2. Sample entropy was calculated for each coarse-grained time series. Sample entropy was calculated in the following way:

$$SampEn(m, r, N) = -\ln \frac{C^{m+1}(r)}{C^m(r)},$$

   where $C^m(r)$ represents the ratio of sequence pairs the distance of which is <r and the whole sequence pairs after the sequence $u(1), u(2), \ldots, u(N)$ is divided into $N - m+1$ sequences, the length of which is m (36).

TABLE 1 | Clinical characteristics of active and sham groups at baseline.

	Active group ($N = 19$)	Sham group ($N = 18$)	χ^2	P
Sex, N (%)			1.3	0.25
Male	6 (31.58%)	9 (50%)		
Female	13 (68.42%)	9 (50%)		
Age	44.79 ± 15.25	43.61 ± 11.89	24.32	0.612
BMI	22.07 ± 3.04	23.19 ± 2.99	35	0.373
Baseline HRSD-24	19.42 ± 7.33	25.11 ± 6.43	19.99	0.395
Baseline MADRS	19.16 ± 8.98	24.83 ± 7.73	23.66	0.423

There were no statistically significant demographic or clinical characteristics differences [mean ± S.D. (range)].

Outcome Measures

The primary outcome was change in the iMSE and sleep structure of PSG over the 2-week RCT phase. Secondary measures were HDRS-24 total and factor scores.

Numbers Analyzed

Due to the lack of previous work on iMSE-based clinical improvements before and after tDCS intervention in depression, the sample size calculation was not feasible. Instead, we surveyed similar work, and their sample sizes are 10 (37), 7 (38), 37 (39). Thus we planned to recruit at least 30 depressive patients for our study.

Blinding

Patients and scale evaluators were blinded to group assignment. The technician covers the instrument during treatment so that the patient cannot see the treatment parameters.

STATISTICAL ANALYSIS

The Chi-square test was performed to detect differences in primary physiological markers between the two groups. The mean ($\bar{x}$) and standard deviation (s) are expressed as $\bar{x} \pm s$ in tables.

A paired t-test or rank sum test were performed to detect differences in sleep structure and EEG complexity between pre- and post-treatment at every electrode site, every scale of MSE, and every IMF of EEG signals for active tDCS and sham tDCS groups. The alpha significance level was set at 0.05 and the 95% CI was also calculated.

The EEG complexity is acquired in multi-scale form, with different IMFs, scales of MSE, and electrode sites. Typically, the difference in EEG complexity before and after the stimulation is calculated in the case of channel C3, IMF 1:4, and MSE scale 7, the results of which are presented in the medians-quartiles form.

The sleep structure and HRDS-24 subscores were also analyzed using a two-sample t-test to detect early, middle, and late insomnia differences between active and sham groups.

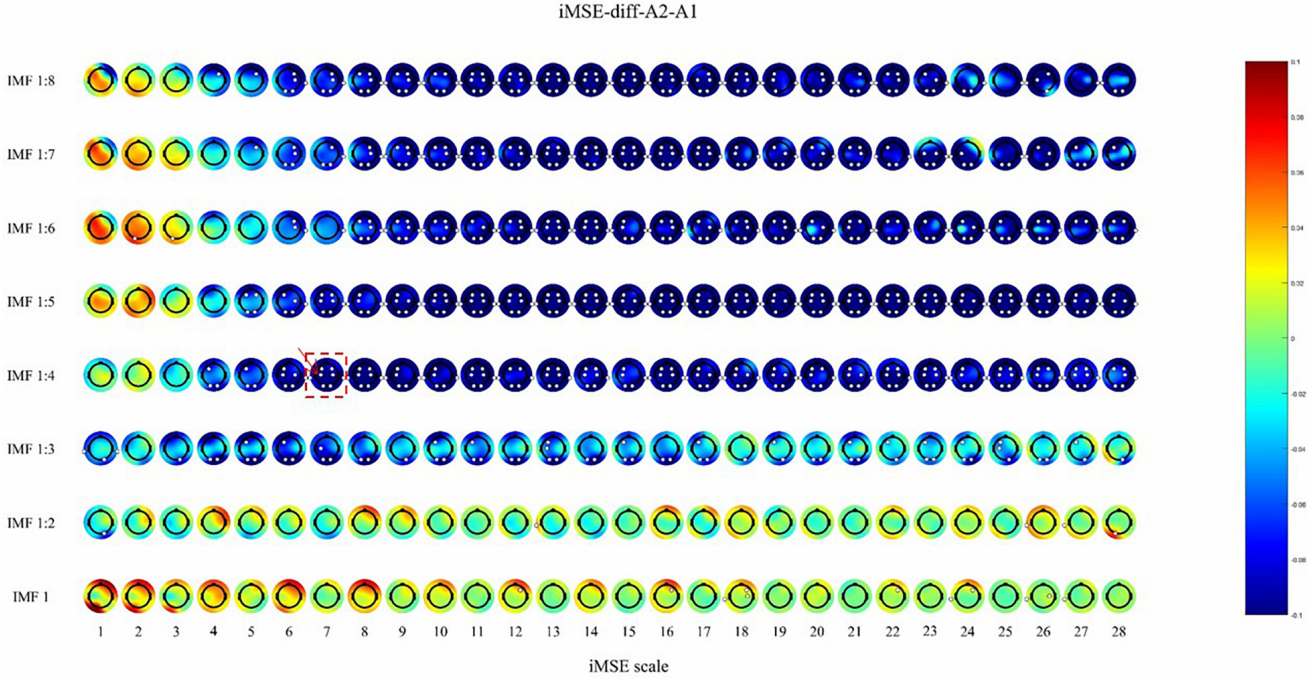

FIGURE 2 | The difference before and after active stimulation in iMSE for REM stage. Negative values indicate decreased iMSE after stimulation. The small white dots indicate significant differences ($p < 0.05$). the color reflects the difference in the sleep EEG complexity before and after the stimulation. For example, the position where the color is blue, corresponding to –0.08 on the color bar, indicates that the EEG complexity decreased by 0.08 after stimulation. The white dots indicate that there is a significant difference ($p < 0.05$) in EEG complexity.

RESULTS

Ninety-four patients admitted to the Sleep Department of Suzhou Guangji Hospital from October 2019 to December 2020 were evaluated. Among the patients, 33 did not meet inclusion criteria, 15 patients declined to participate, and 3 were discharged from the hospital without a cure after evaluation. Finally, 43 patients [active group (27) vs. sham group (24)] signed informed consent for the study, of whom 6 did not continue (**Figure 1**). In addition, patients were treated with monotherapy (escitalopram [20 mg/day] or duloxetine [60 mg/day]) 2 weeks after which the patients were randomly divided into active tDCS group ($n = 23$) and sham group ($n = 20$) using a random count table.

There were no statistically significant demographic or clinical characteristics differences (**Table 1**).

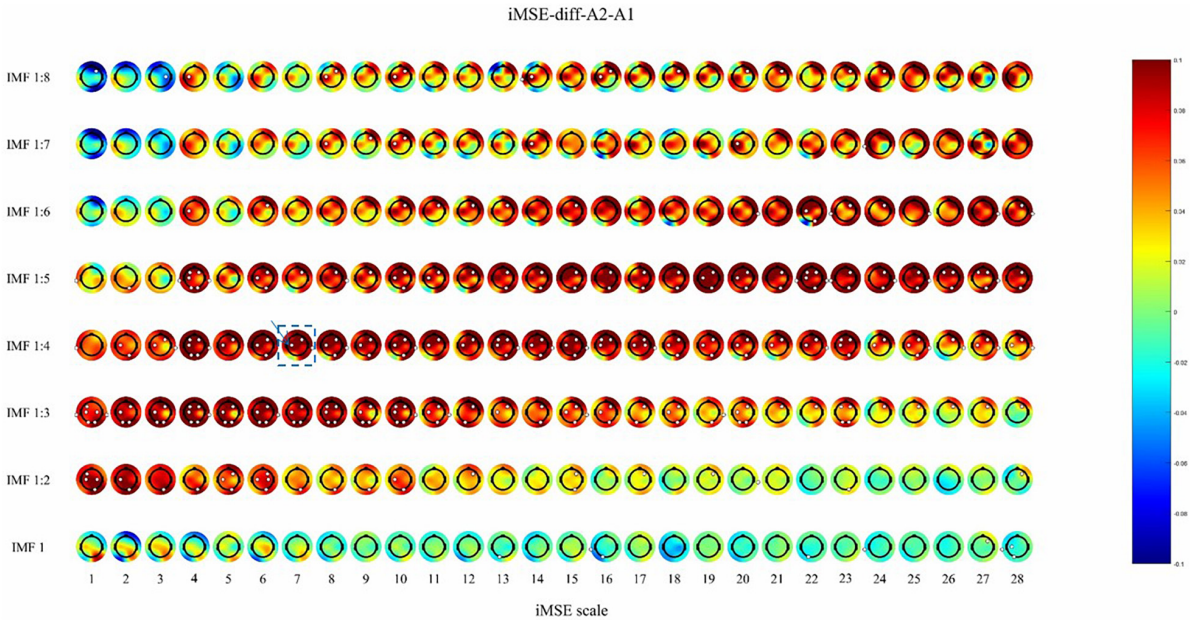

FIGURE 3 | The difference before and after sham stimulation in iMSE for REM stage. Positive values indicate increased iMSE after stimulation. The small white dots indicate significant differences ($p < 0.05$).

TABLE 2 | Polysomnography (PSG) sleep structure before and after treatment in tDCS and sham group.

	Before treatment	After treatment	*P*	95% CI
Active stimulation				
Sleep onset latency (SOL), min	27.03 ± 25.48	20.38 ± 21.12	0.387	[14.97, 45.76]
Total sleep time (TST),min	470.92 ± 56.44	483.22 ± 52.41	0.491	[428.94, 500.61]
Apnea hypopnea index (AHI)	6.36 ± 6.73	4.92 ± 5.22	0.465	[3.12, 11.05]
Stage 1 sleep ratio	15.67 ± 7.56	16.5 ± 9.71	0.770	[9.52, 20.97]
Stage 2 sleep ratio	66.8 ± 11.45	63.53 ± 11.03	0.376	[61.04, 75.84]
Stage 3 sleep ratio	4.48 ± 6.8	5.11 ± 7.24	0.785	[−0.45, 8.79]
REM sleep ratio	13.05 ± 9.94	14.86 ± 9.43	0.567	[5.77, 18.52]
REM latency, min	285.41 ± 131.09	244.5 ± 99.59	0.308	[226.03, 386.87]
Sham stimulation				
Sleep onset latency (SOL), min	47.89 ± 54.94	32.98 ± 32.67	0.343	[23.76, 86.92]
Total sleep time (TST), min	472.99 ± 71.04	484.41 ± 63.68	0.625	[420.14, 514.41]
Apnea hypopnea index (AHI)	9.04 ± 7.6	8.38 ± 10.4	0.836	[3, 15.73]
Stage 1 sleep ratio	15.12 ± 11.53	16.33 ± 10.17	0.748	[6.93, 22.12]
Stage 2 sleep ratio	67.16 ± 14.2	66.42 ± 9.45	0.860	[59.1, 75.95]
Stage 3 sleep ratio	3.38 ± 6.02	3.95 ± 5.5	0.775	[−0.94, 7.12]
REM sleep ratio	14.36 ± 7.92	13.29 ± 7.58	0.690	[9.48, 20.32]
REM latency, min	288.46 ± 100.37	283.94 ± 97.95	0.895	[221.43, 360]

There were no statistically significant differences before and after treatment in two group.

TABLE 3 | Changes in hamilton depression rating scale total score and each factor score from baseline to after treatment.

Parameter	Baseline					After 10-session tDCS				
	Active group	Sham group	*p*	95% CI	Test	Active group	Sham group	*p*	95% CI	Test
Depressed mood	2.05 ± 1.13	3.17 ± 0.79	**0.001***	[0.82, 2.13]	*t*-test	0.89 ± 0.81	0.83 ± 1.15	0.851	[0.26, 1.58]	*t*-test
Guilt	0.63 ± 0.83	1 ± 1.14	0.266	[−0.22, 1.1]	*t*-test	0.26 ± 0.45	0.22 ± 0.43	0.779	[−0.01, 0.58]	*t*-test
Suicide	0.63 ± 1.12	0.78 ± 1.26	0.711	[−0.24, 1.35]	*t*-test	0.21 ± 0.71	0.28 ± 0.75	0.782	[−0.32, 0.66]	*t*-test
Insomnia early	0.79 ± 0.85	1.06 ± 0.94	0.373	[0.06, 1.25]	*t*-test	0.26 ± 0.45	0.44 ± 0.78	0.392	[−0.26, 0.59]	*t*-test
Insomnia middle	0.79 ± 0.71	0.67 ± 0.59	0.574	[0.41, 1.29]	*t*-test	0.26 ± 0.45	0.28 ± 0.57	0.932	[−0.09, 0.6]	*t*-test
Insomnia late	0.63 ± 0.83	0.83 ± 0.86	0.472	[−0.04, 1.09]	*t*-test	0.16 ± 0.37	0.78 ± 0.94	**0.030***	–	Rank sum test
Work and activities	1.95 ± 1.39	2.78 ± 1	**0.046***	[0.71, 2.33]	*t*-test	0.79 ± 1.23	0.72 ± 1.07	0.861	[0.06, 1.6]	*t*-test
Retardation	0.37 ± 0.6	0.67 ± 0.77	0.217	–	Rank sum test	0.26 ± 0.45	0.5 ± 0.71	0.335	–	Rank sum test
Agitation	0.47 ± 0.7	0.67 ± 0.84	0.522	–	Rank sum test	0.21 ± 0.54	0.39 ± 0.78	0.420	[−0.32, 0.57]	*t*-test
Anxiety psychic	1.16 ± 0.9	1.83 ± 1.15	0.054	[0.13, 1.5]	*t*-test	0.68 ± 0.95	0.44 ± 0.78	0.408	[0.23, 1.39]	*t*-test
Anxiety somatic	1.89 ± 1.15	2.5 ± 1.15	0.119	[0.82, 2.35]	*t*-test	0.74 ± 0.87	0.94 ± 1	0.504	[0.01, 1.26]	*t*-test
Loss of appetite	0.32 ± 0.48	0.56 ± 0.62	0.193	[−0.18, 0.56]	*t*-test	0.21 ± 0.42	0.17 ± 0.51	0.777	[−0.08, 0.55]	*t*-test
Somatic symptoms	0.84 ± 0.83	1.28 ± 0.75	0.105	[0.08, 1.15]	*t*-test	0.21 ± 0.42	0.39 ± 0.5	0.250	–	Rank sum test
Sexual interest	0.11 ± 0.46	0.44 ± 0.92	0.162	[−0.55, 0.41]	*t*-test	0 ± 0	0.28 ± 0.83	0.152	[−0.52, 0.25]	*t*-test
Hypochondriasis	0.95 ± 1.03	0.78 ± 0.81	0.581	[0.41, 1.65]	*t*-test	0.16 ± 0.37	0.33 ± 0.59	0.287	[−0.27, 0.39]	*t*- test
Loss of weight	0.16 ± 0.5	0.28 ± 0.67	0.540	[−0.29, 0.49]	*t*-test	0.11 ± 0.46	0 ± 0	0.337	[−0.06, 0.37]	*t*-test
Insight	0.26 ± 0.45	0.39 ± 0.5	0.431	–	Rank sum test	0.21 ± 0.42	0.28 ± 0.46	0.645	[−0.12, 0.47]	*t*-test
Day–night change	1.16 ± 0.9	0.78 ± 0.88	0.202	[0.76, 1.94]	*t*-test	0.47 ± 0.7	0.33 ± 0.49	0.676	–	Rank sum test
Dispersonalization	0 ± 0	0 ± 0	–	–	–	0 ± 0	0 ± 0	–	–	–
Paranoid symptoms	0.11 ± 0.32	0.06 ± 0.24	0.592	[−0.06, 0.32]	*t*-test	0 ± 0	0 ± 0	–	–	–
Obsessive-compulsive	0.42 ± 0.77	0.33 ± 0.69	0.717	[−0.02, 0.95]	*t*-test	0.21 ± 0.54	0.11 ± 0.47	0.554	[−0.08, 0.6]	*t*-test
Helplessness	1.58 ± 0.61	1.56 ± 0.7	0.914	[1.16, 2.03]	*t*-test	0.68 ± 0.58	0.94 ± 0.94	0.315	[0.03, 1.07]	*t*-test
Hopelessness	0.84 ± 0.9	0.78 ± 0.65	0.805	[0.35, 1.4]	*t*-test	0.47 ± 0.51	0.61 ± 1.14	0.637	[−0.18, 0.99]	*t*-test
Self-abasement	1.21 ± 1.08	1.94 ± 1.35	0.076	[0.02, 1.65]	*t*-test	0.42 ± 0.77	0.61 ± 0.78	0.351	–	Rank sum test
Total	19.42 ± 7.33	25.11 ± 6.43	**0.017***	[11.89, 21.11]	*t*-test	11.37 ± 16.28	9.83 ± 9.53	0.730	[3.18, 21.13]	*t*-test

The t-test and rank-sum test were applied for statistical analysis for data with Gaussian and non-Gaussian distributions. Any significant change from baseline (p-value<0.05) is in bold and starred. "" means that significant change from baseline (p < 0.05).*

TABLE 4 | Changes in hamilton depression rating scale total score and each factor score before and after treatment in active-group and sham-group.

Parameter	Active-group				Sham-group			
	Baseline	After 10-session tDCS	*P*	95% CI	Baseline	After 10-session tDCS	*P*	95% CI
Depressed mood	2.05 ± 1.13	0.89 ± 0.81	**0.001***	[1.98, 3.27]	3.17 ± 0.79	0.83 ± 1.15	**0.000***	[3.67, 5]
Guilt	0.63 ± 0.83	0.26 ± 0.45	0.098	[0.38, 1.26]	1 ± 1.14	0.22 ± 0.43	**0.010***	[0.81, 1.97]
Suicide	0.63 ± 1.12	0.21 ± 0.71	0.174	[0.22, 1.46]	0.78 ± 1.26	0.28 ± 0.75	0.158	[0.33, 1.73]
Insomnia early	0.79 ± 0.85	0.26 ± 0.45	**0.023***	[0.61, 1.51]	1.06 ± 0.94	0.44 ± 0.78	**0.041***	[0.78, 1.95]
Insomnia middle	0.79 ± 0.71	0.26 ± 0.45	**0.010***	[0.66, 1.45]	0.67 ± 0.59	0.28 ± 0.57	0.054	[0.46, 1.25]
Insomnia late	0.63 ± 0.83	0.16 ± 0.37	**0.030***	[0.44, 1.29]	0.83 ± 0.86	0.78 ± 0.94	0.854	[0.26, 1.48]
Work and activities	1.95 ± 1.39	0.79 ± 1.23	**0.010***	[1.66, 3.39]	2.78 ± 1	0.72 ± 1.07	**0.000***	[3.1, 4.51]
Retardation	0.37 ± 0.6	0.26 ± 0.45	0.544	[0.08, 0.77]	0.67 ± 0.77	0.5 ± 0.71	0.502	[0.25, 1.25]
Agitation	0.47 ± 0.7	0.21 ± 0.54	0.200	[0.19, 1.01]	0.67 ± 0.84	0.39 ± 0.78	0.311	[0.26, 1.36]
Anxiety psychic	1.16 ± 0.9	0.68 ± 0.95	0.122	[0.79, 2]	1.83 ± 1.15	0.44 ± 0.78	**0.000***	[1.86, 3.2]
Anxiety somatic	1.89 ± 1.15	0.74 ± 0.87	**0.001***	[1.81, 3.15]	2.5 ± 1.15	0.94 ± 1	**0.000***	[2.55, 4.01]
Loss of appetite	0.32 ± 0.48	0.21 ± 0.42	0.475	[0.07, 0.66]	0.56 ± 0.62	0.17 ± 0.51	**0.047***	[0.36, 1.13]
Somatic symptoms	0.84 ± 0.83	0.21 ± 0.42	**0.006***	[0.73, 1.6]	1.28 ± 0.75	0.39 ± 0.5	**0.000***	[1.29, 2.15]
Sexual interest	0.11 ± 0.46	0 ± 0	0.324	[−0.06, 0.37]	0.44 ± 0.92	0.28 ± 0.83	0.572	[−0.07, 1.12]
Hypochondriasis	0.95 ± 1.03	0.16 ± 0.37	**0.003***	[0.83, 1.85]	0.78 ± 0.81	0.33 ± 0.59	0.069	[0.52, 1.49]
Loss of weight	0.16 ± 0.5	0.11 ± 0.46	0.738	[−0.13, 0.5]	0.28 ± 0.67	0 ± 0	0.087	[0.1, 0.74]
Insight	0.26 ± 0.45	0.21 ± 0.42	0.712	[0.01, 0.58]	0.39 ± 0.5	0.28 ± 0.46	0.494	[0.11, 0.77]
Day–night change	1.16 ± 0.9	0.47 ± 0.7	**0.013***	[0.98, 2.03]	0.78 ± 0.88	0.33 ± 0.49	0.069	[0.52, 1.49]
Dispersonalization	0 ± 0	0 ± 0	–	[0, 0]	0 ± 0	0 ± 0	–	[0, 0]
Paranoid symptoms	0.11 ± 0.32	0 ± 0	0.154	[0.01, 0.3]	0.06 ± 0.24	0 ± 0	0.324	[−0.03, 0.2]
Obsessive-compulsive	0.42 ± 0.77	0.21 ± 0.54	0.334	[0.09, 0.97]	0.33 ± 0.69	0.11 ± 0.47	0.265	[0.04, 0.84]
Helplessness	1.58 ± 0.61	0.68 ± 0.58	**0.000***	[1.63, 2.42]	1.56 ± 0.7	0.94 ± 0.94	**0.029***	Rank sum
Hopelessness	0.84 ± 0.9	0.47 ± 0.51	0.129	[0.55, 1.51]	0.78 ± 0.65	0.61 ± 1.14	0.594	[0.23, 1.49]
Self-abasement	1.21 ± 1.08	0.42 ± 0.77	**0.014***	[0.99, 2.23]	1.94 ± 1.35	0.61 ± 0.78	**0.001***	[1.87, 3.36]
Total	19.42 ± 7.33	11.37 ± 16.28	0.057	[15.13, 31.75]	25.11 ± 6.43	9.83 ± 9.53	**0.000***	[27.24, 38.26]

The t-test and rank-sum test were applied for statistical analysis for data with gaussian and non-gaussian distributions. Any significant change from baseline (p-value<0.05) is in bold and starred. "" means that significant change from baseline (p < 0.05).*

After active stimulation there was a significantly decreased iMSE compared with pre-treatment for the REM stage (**Figure 2**). In addition, after sham stimulation there was a significantly increased iMSE compared with pretreatment (**Figure 3**).

Recruitment

An interim analysis was performed because of slow accrual. We are still recruiting new subjects for later stratification analysis.

Sleep Structure and Measuring Scale Assessing

There was no difference in the sleep structure before and after stimulation, including sleep efficiency, REM latency, sleep latency, total sleep time, and REM/N1/N2/N3 percentage (**Table 2**) in the active and sham groups.

After the stimulation, there was a significant difference ($p < 0.05$) between the active and sham groups in the HRDS-24 early awakening scores. Active tDCS improves early awakening in depressed patients. In contrast, before the stimulation, there was no difference between the active and sham groups in the HRDS-24 early awakening scores (**Table 3**).

After the stimulation, there were significant difference ($P < 0.05$) before and after stimulation, including depressed mood, early, middle, and late insomnia, work and activities, somatic anxiety, somatic symptoms, hypochondriasis, day-night change, helplessness, and self-abasement in active groups (**Table 4**). There were significant differences ($P < 0.05$) before and after stimulation, including depressed mood, guilt, early insomnia, work and activities, somatic anxiety, somatic symptoms, helplessness, self-abasement, and total scores in the sham group (**Table 4**).

Complexity

After active stimulation there was a significantly decreased iMSE compared with pre-treatment for the REM stage (**Figure 2**). In addition, after sham stimulation there was a significantly increased iMSE compared with pretreatment (**Figure 3**). In **Figures 2**, **3**, the difference in EEG complexity is reflected by multiple dimensions with different channels, IMFs, and scales in the same figure. For a better demonstration of our findings, the typical result of a single channel, IMF, and scale is necessary, which have been marked in **Figures 2**, **3** with a red frame. Typically, the differences in variation trend are reflected in channel C3, IMF 1:4, and scale 7 (**Figure 4**).

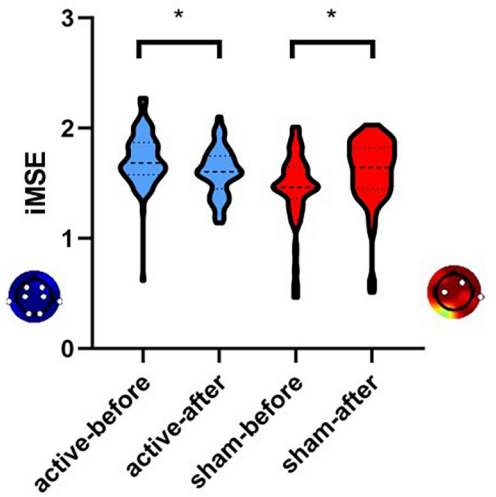

FIGURE 4 | The differences in variation trend of iMSE in the case of channel C3, IMF 1:4, and scale 7. There was a different variation trend in the iMSE between the active and sham groups. "*" means that significant change from baseline ($p < 0.05$). Red colors represent increased EEG complexity and blue colors represent decreased EEG complexity.

Harms

Due to the lack of an appropriate scale for evaluating adverse effects of tDCS, only an open-ended survey was conducted in this study. Two patients in the active group complained of headaches. There were no corresponding reports in the sham group.

DISCUSSION

In the current study iMSE was used for the first time to analyze the efficacy of tDCS in treating sleep EEG complexity in patients with depression. We showed that the complexity of REM EEG signals significantly decreased iMSE after tDCS active stimulation but the complexity of REM EEG signals significantly increased iMSE in tDCS sham group.

The typical sleep structure is divided into RME and NREM sleep; NREM sleep is divided into N1, N2, and N3 (40). The N3 sleep stage represents the deepest sleep, which is characterized on EEG by high amplitude slow delta waves, and therefore is frequently referred to delta sleep or slow wave sleep (SWS) (3). Several studies have shown that increased SWS during NREM improved sleep quality and enhances memory consolidation (41). SWS reduction is closely related to anxiety and depression (42).

Funk et al. showed that slow waves also occurred during REM (43). A study involving the EEG microstructure of REM sleep divided REM sleep into phasic and tonic REM (43, 44). Phasic REM is characterized by SWS, and EEG frequency is mainly in the delta-theta range between 2 and 8 Hz, while the EEG frequency of tonic REM sleep is mainly in gamma >32 Hz. Based on sleep EEG analysis, increased theta activity decreased EEG complexity (45). Studies on the sleep mechanism showed that increased theta activity contributed to enhancing emotional memory, which might be the sleep-related mechanism underlying tDCS in improving depression (46). In 2016 Mariani et al. (47) reported an inverse relationship between nighttime sleep quality and EEG complexity. Terzano et al. (48) found a negative correlation between sleep EEG complexity and deep sleep.

Entropy is a common non-linear feature of EEG that indicates the complexity of the EEG signal. Typically, the high complexity of sleep EEG reveals poor sleep quality. As one of the methods to measure EEG complexity, MSE has been used in relevant clinical studies. In 2010 Takahashi et al. (49) used MSE to measure cortical abnormalities and intervention effects in schizophrenia. In 2013 Okazaki et al. (50) used MSE to analyze EEG before and after electroconvulsive therapy for depression. The EEG complexity of all patients decreased after ECT treatment. In 2015, Kuo et al. (51). evaluated the sleep quality of 32 adults based on the sleep EEG MSE. Kuo et al. (51) reported that the average MSE values in the poor sleep efficiency group was higher than the good efficiency group. In our work, iMSE was applied, and we showed that REM sleep EEG complexity decreased during active tDCS stimulation, revealing that iMSE is a sensitive measure of sleep EEG complexity.

The iMSE was applied in this study fit for non-stationary and non-linear EEG signals. We found that EEG complexity decreased significantly during REM in patients with depression after active tDCS treatment, but increased in patients with sham tDCS treatment. The increase in EEG complexity during the REM period in the control group may have been related to antidepressant treatment. The common point of different antidepressant actions involved positive modulation of 5-HT and NE systems in the central nervous system. These neurotransmitters, mainly derived from the dorsal raphe and LC, respectively, inhibit cholinergic REM-on neurons in the LDT/PPT and lead to REM-off and arousal (52). This mechanism may account for the REM inhibitory effect of most antidepressants, which may cause sleep disorders and sleep fragmentation. For the sham-tDCS group, the reason for increased REM EEG complexity is likely related to antidepressants. At the same time, tDCS antagonizes the effect and improves sleep quality at night in patients with depression.

In the current study we showed that the HDRS-24 early awakening factor score in patients treated with active tDCS was significantly lower than the control group, suggesting that tDCS improved early awakening symptoms in patients with MDD. In both the treatment group and the control group, the scores of multiple factors of HAMD-24 decreased before and after treatment, which was considered to be related to the continued effect of the combined therapy. Meta-analyses suggest some efficacy of tDCS in the treatment of acute depression disorder with moderate effect size, and low efficacy in treatment-resistant depression (16). The subjects in this study were mainly inpatients with relatively severe depressive symptoms, and the addition of tDCS showed no significant effect on clinical manifestations of depression and the reduction of *HDRS-24* score.

Previous studies have shown that tDCS treatment improved sleep quality with tDCS treatment between 9:00 a.m. and 12:00 a.m. during the day or night (53–56). The tDCS studies in healthy populations and patients with insomnia produced inconsistent results. Marshall et al. reported that tDCS in sleep time improved slow-wave sleep in healthy subjects (13). In 2019 Frase et al. showed that tDCS in sleep time increased nighttime arousal in patients with insomnia, which had been associated with a decrease in arousal threshold in insomniacs (15). By treating tDCS during the daytime, we not only made it more practical in the clinic, but also avoided the arousal threshold problem.

Our results suggested that daytime tDCS improved nighttime REM sleep EEG complexity in patients with MDD and iMSE, an effective and sensitive measure of assessing sleep quality by changes the EEG complexity during night sleep.

There were three major limitations of our work. First, the REM period was not separated as first, second, and third REM for analysis, which will be studied in the future. Second, after 2 weeks of fixed drug treatment, the intervention of drugs in treatment has been reduced as much as possible, however, the use of a single antidepressant treatment is challenging. The sample size shall be expanded continually to analyze drug influence in separate groups. Third, beside items of insomnia symptoms in HRDS-24, there was no information regarding self-reported sleep quality in this study, We will add the sleep self-rating scale in corollary study.

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 the Ethics Committee of Suzhou Guangji Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZL mainly wrote this manuscript. XuZ and LF completed the evaluation of the experimental scale. YZ, WP, MY, YY, XF, and GL collected clinical data. YL and SG performed PSG analysis. NH was the originator of iMSE analysis methods and guided the explanation of the rationality of the methods. XiZ, XD, and RC helped in writing the manuscript. All authors have read and approved the final manuscript.

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Chronotypes, Sleep and Mental Distress Among Chinese College Students: A Cross-Sectional Study

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Objective: This study aimed to investigate the chronotypes and their relationship with sleep disturbances and mental distress among college students.

Methods: Students from a university in Guangzhou, China, were recruited through a cross-sectional online survey. Data were collected by self-reported questionnaires including socio-demographics, lifestyles and health conditions, sleep patterns on weekdays and weekends, as well as the reduced Morningness-Eveningness Questionnaire (rMEQ), the Insomnia Severity Index, the Epworth Sleepiness Scale, the Beck Depression Inventory-13, and the Zung Self-Rating Anxiety Scale. Multivariate analyses were performed to examine the associations of chronotypes with sleep compensation, sleep disturbances, and mental distress.

Results: A total of 1,607 questionnaires were received, among which 1,569 (97.6%) were valid for further analysis. Among these participants [mean age 19.86 ± 1.16 (15–27) years], morning types (M-types), intermediate types (I-types), and evening types (E-types) accounted for 14.9, 71.5, and 13.6%, respectively. The regression analysis revealed that E-types were positively associated with long sleep compensation on weekends (adjusted OR 2.443, 95%CI 1.740-3.429) compared with I-types, while M-types were the opposite (adjusted OR 0.623, 95%CI 0.392–0.990). E-types were also positively correlated with insomnia symptoms (adjusted OR 2.000, 95%CI 1.428–2.801), depressive symptoms (adjusted OR 2.068, 95%CI 1.496–2.858), and anxiety symptoms (adjusted OR 2.188, 95%CI 1.387–3.451). However, no significant association was found between chronotypes and excessive daytime sleepiness.

Conclusion: Our study found that E-types were associated with long sleep compensation on weekends and insomnia, depression, and anxiety symptoms. Our findings emphasized the importance of early recognition and intervention of E-types and their accompanied sleep problems and mental distress.

Keywords: chronotype, sleep compensation, insomnia, depression, anxiety

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INTRODUCTION

Chronotype refers to an individual's endogenous circadian rhythms and how it embeds into the 24-h day, which received increasing attention in the last decades (1, 2). There are three different categories of chronotypes: the morning type (M-type), the evening type (E-type), and the intermediate type (I-type) (3). Evidence demonstrated that chronotype widely affects physiology, cognition, and behavior (4). M-type individuals get up early and reach their peak of cognitive and physical performance in the morning compared with E-types who prefer later bed and wake times. Besides, M-type people find it difficult to stay awake at late-night hours, while E-type people plan their daily activities for the afternoon or evening and reach their peak performance later. Although the distinction of chronotypes is quite easy, most people are I-types rather than at the ends of this continuum (5). The individual differences in chronotypes seem to be influenced by age (6), gender (7), inherited (8), perinatal (9), and environmental factors to some extent (10).

Previous studies found that in addition to differences in sleep timing between different chronotypes, E-types had a shorter time in bed during the weekdays and slept longer on weekends than M-types (11). E-types were also associated with a greater likelihood of sleep disturbances, including insomnia (12, 13). Although previous research suggested that E-types were associated with poor sleep and daytime sleepiness (14), few studies investigated the chronotype with sleep disturbance and the sleep pattern of different chronotypes on weekdays and weekends among Chinese college students. A previous study in China indicated that E-type college students were associated with more sleep difficulties (15). Several studies showed that E-types were associated with increased risk for a constellation of negative health outcomes, including mental and physical health problems (16, 17). For instance, a meta-analysis (18) found a positive association between E-types and depressive symptoms in longitudinal and cross-sectional studies. However, the relationship between chronotypes and anxiety symptoms was inconsistent. Some research found that E-types are related to elevation in anxiety symptoms (19, 20), whereas another did not find a relationship between E-types and anxiety (13). Thus, the association between chronotype and mental distress remains unclear and warrants further investigation.

College students who form a subset of the world's population appear to be more vulnerable to sleep disturbance and mental distress due to the exhaustive routine of studies and extracurricular activities. Given that E-types are associated with many adverse effects on physical and mental health, we investigated the association of chronotypes with sleep disturbances and mental distress among Chinese college students. Therefore, we aimed to describe the contemporary chronotype distribution in a large sample of college students in the present work. We further aimed to describe sleep patterns, sleep disturbance, and mental distress with chronotypes in order to provide evidence for further prevention and control of sleep disturbance and mental distress in college students.

METHODS

Participants

This survey was part of a school-based cross-sectional study conducted at a university in Guangzhou from December 2019 to January 2020. Participants who met the following criteria were included in the study: (1) undergraduate students studying in the university; (2) WeChat users; (3) volunteers to participate in this survey. Using the method of convenient sampling, 1,607 college students in Guangzhou completed the questionnaires compiled by the Questionnaire Star platform relying on WeChat. This study has been approved by the Ethics Committee of Nanfang Hospital, Southern Medical University (QTEC-2019-101).

Instruments

Socio-Demographics, Lifestyles, and Health Conditions

At the first of the questionnaire, the socio-demographic data were collected, including gender, grade, ethnicity, place of residence, whether they are the only child or not, their parents' education level (tertiary education or above), and family incomes ($<$5,000 yuan/month or $\geq$5,000 yuan/month). Lifestyles and health conditions included body-mass index (BMI, $\geq$25 kg/m^2 or $<$25 kg/m^2), habitual napping ($\geq$3 days/week), habitual snoring ($\geq$3 days/week), chronic medical conditions, smoking, alcohol drinking, boarding in school, time spent on TV or Internet ($\geq$4 or $<$4 h/day), duration of mobile phone use before sleep ($\geq$1 or $<$1 h/day), perceived learning pressure (high or low), learning interest (high or low).

Sleep Patterns and Weekend Sleep Compensation

Sleep patterns were collected, including habitual bedtimes and wake-up times on weekdays and weekends. Weekend sleep compensation was calculated as the difference between time in bed on weekends and weekdays, and long weekend sleep compensation was defined as compensation $\geq$2 h (21).

Reduced Morningness-Eveningness Questionnaire (rMEQ)

The reduced Morningness-Eveningness Questionnaire (rMEQ), developed by Adan and Almirall, is the most convenient and commonly used method to assess chronotype. It extracted five items from the original MEQ (items 1, 7, 10, 18, and 19) (5, 22) to assess the morningness-eveningness preference. The overall scores range from 4 to 25, with lower scores meaning a stronger preference for E-types. Participants whose scores were higher than 17 and lower than 12 were classified as morning and evening types, respectively, and participants scoring between 12 and 17 were classified as I-types. The rMEQ has been verified in the Chinese population and was proved to have good reliability and validity (Cronbach's alpha = 0.74) (23, 24).

Insomnia Severity Index (ISI)

The ISI comprises seven items that evaluate insomnia subtypes and daytime dysfunction due to sleep difficulties in the past 2 weeks. The index is rated on a 5-point Likert scale (0 = completely ineffective, 4 = very serious), and the total scores range from 0 to 28 (25, 26). A total score of $\geq$8 is considered to

have insomnia symptoms. The internal reliability of the Chinese version of ISI was great (Cronbach's alpha = 0.8) (27).

Epworth Sleepiness Scale (ESS)

This scale assesses individuals' subjective daytime sleepiness and consists of seven items using a 4-point Likert scale. The sum score of the scale ranges from 0 (no chance of dozing) to 24 (highest chance of dozing). Excessive daytime sleepiness is defined as having a total score of 10 or higher (28). The Chinese version of ESS is reliable and well-validated (Cronbach's alpha = 0.81) (29).

Beck Depression Inventory-13 (BDI-13)

The BDI-13 is a 13-item scale evaluating the severity of depressive symptoms in the past week (30). A higher total score indicates a more severe depressive symptom. Each item is rated by a 4-point Likert scale (0 = none, 3 = severe), yielding a total score of 0 to 39. A total score of ≥5 was considered to experience depressive symptoms. The BDI-13 has been demonstrated good reliability and validity in previous studies of the Chinese population (Cronbach's alpha = 0.89) (31).

Zung Self-Rated Anxiety Scale (SAS)

The SAS is used to measure the anxiety symptoms in the past seven days (32). It consists of 20 items, each rated on a 4-point Likert scale (e.g., 1 = never or a little of the time, 4 = most of the time). The total score ranges from 25 to 100, multiplying the original score by 1.25. A total score of ≥50 was regarded as suffering from anxiety symptoms. The Chinese version of the questionnaire has been widely used and has satisfactory reliability and validity (Cronbach's alpha =0.78) (33).

Statistical Analysis

The characteristics and distribution of chronotypes were described by descriptive statistics. Continuous variables were expressed as the mean ± standard deviation (SD), and non-normally distributed variables were expressed as median (interquartile range [IQR]), while the discrete variables were reported as percentages. In univariate analyses, differences between categorical variables were assessed using the chi-squared test. Statistical intergroup differences were analyzed using the *t*-test, one-way ANOVA, and Kruskal–Wallis test, which examined the association of socio-demographics, lifestyles, health conditions with sleep patterns, sleep disturbances, and mental distress. The Bonferroni *post-hoc* test for multiple comparisons was used for statistical analysis when necessary. Those factors significantly associated with sleep disturbances and mental distress would be further controlled in binary logistic regression models. In multivariate analyses, after adjusting for age and gender using the ENTER method, as well as other socio-demographics, lifestyles, and health conditions that had a significant difference in univariate analyses by using the forward likelihood method, binary logistic regression was performed to determine the strengths of the relationships between chronotypes and sleep compensation, sleep disturbances, and mental distress.

RESULTS

General Characteristics of Participants

A total of 1607 questionnaires were received, among which 1,569 (97.6%) were valid for further analysis. **Table 1** shows the socio-demographic and lifestyle characteristic of all valid participants. The participants consisted of 681 males (43.4%) and 888 females (56.6%), with an average age of 19.86 ± 1.16 years old (15–27 years old). Based on the score of rMEQ, 14.9% of the participants were found to be M-types, 71.5% were I-types, and 13.6% were E-types. In comparison of these three groups, differences were found significant in only child situation, rural area, family incomes, time spent on TV or Internet, duration of mobile phone use before sleep, alcohol drinking, chronic medical conditions, and interest in study (all $p < 0.05$).

Sleep Patterns, Sleep Disturbances, and Mental Distress Among Different Chronotypes

As shown in **Table 2**, significant differences were found in time in bed and sleep-wake habits among three groups both on weekdays and weekends ($p < 0.001$). There were significant differences among the three on weekday bedtime and get-up time, weekend bedtime and get-up time, as well as sleep compensation during weekends ($p < 0.001$). E-types had later bedtime, shorter weekdays time in bed, and more sleep compensation than M-types, and I-types showed a sleep pattern between these two extremes. In addition, E-types had significantly higher scores in ISI, BDI-13, and SAS when compared with M-types and I-types (all $p < 0.001$). However, there was no difference in ESS total score among the three chronotypes ($p > 0.05$).

Comparisons of Sample Characteristics in Participants With Sleep Compensation, Sleep Disturbances, and Mental Distress

The relationships between the characteristics of participants and sleep compensation, sleep disturbances, and mental distress are presented in **Tables 3**, **4**. In socio-demographic factors, age was related to sleep compensation and insomnia symptoms ($p < 0.05$), and gender was related to sleep compensation, excessive daytime sleepiness (EDS), depressive and anxiety symptoms ($p < 0.001$). In addition, rural areas and family incomes (≥5,000 yuan/month) were significantly associated with EDS ($p < 0.05$), while parents' education level and family incomes (≥5,000 yuan/month) were significantly associated with depressive symptoms ($p < 0.05$). With respect to lifestyle and health condition, time spent on TV or Internet (≥4 h/day), duration of mobile phone use before sleep (≥1 h/day), chronic medical conditions, high study pressure, low interest in learning were correlated with sleep compensation, sleep disturbances, and mental distress ($p < 0.05$), except for duration of mobile phone use before sleep with EDS ($p = 0.238$) and chronic medical conditions for sleep compensation ($p = 0.09$). In addition, habitual napping (≥3 days/week) and smoking were correlated with depressive symptoms ($p < 0.05$). What is more, chronotypes were correlated with sleep compensation, insomnia, depressive

TABLE 1 | Demographic and lifestyle characteristics of participants stratified by chronotypes.

	Total (n = 1,569)	M-types (n = 233)	I-types (n = 1,122)	E-types (n = 214)	*P*
Socio-demographics					
Age, year, (Mean ± SD)	19.86 ± 1.16	19.80 ± 1.31	19.86 ± 1.13	19.96 ± 1.12	0.333
Gender, female, *n* (%)	681 (43.4)	94 (40.3)	485 (43.2)	102 (47.7)	0.289
Only child, *n* (%)	637 (40.6)	79 (33.9)	451(40.2)	107 (50.0)	0.002**
Rural area, *n* (%)	544 (34.7)	91 (39.1)	400 (35.7)	53 (24.8)	0.001**
Paternal education level (tertiary), *n* (%)	580 (37.0)	81 (34.8)	407 (36.3)	92 (43.0)	0.132
Maternal education level (tertiary), *n* (%)	483 (30.8)	66 (28.3)	344 (30.7)	73 (34.1)	0.410
Family income (≥5,000 yuan/month), *n* (%)	1,265 (80.6)	181 (77.7)	896 (79.9)	188 (87.9)	0.012*
Lifestyle and health condition					
BMI (≥25 kg/m^2), *n* (%)	106 (6.8)	18 (7.7)	72 (6.4)	16 (7.5)	0.695
Habitual napping (≥3 days/week), *n* (%)	1,477 (94.1)	220 (94.4)	1,060 (94.5)	197 (92.1)	0.378
Habitual snoring (≥3 days/week), *n* (%)	505 (32.2)	64 (27.5)	373 (33.2)	68 (31.8)	0.227
Boarding in school, *n* (%)	1,560 (99.4)	231 (99.1)	1,117 (99.6)	212 (99.1)	0.565
TV/Internet (≥4 h/day), *n* (%)	473 (30.1)	49 (21.0)	339 (30.2)	85 (39.7)	<0.001***
Mobile phone use before sleep (≥1 h/day), *n* (%)	303 (19.3)	33(14.2)	197(17.6)	73(34.1)	<0.001***
Smoking, *n* (%)	17 (1.1)	1 (0.4)	15 (1.3)	1 (0.5)	0.307
Drinking, *n* (%)	550 (35.1)	68 (29.2)	393 (35.0)	89 (41.6)	0.023*
Chronic medical conditions, *n* (%)	67 (4.3)	14 (6.0)	39 (3.5)	14 (6.5)	0.046*
High study pressure, *n* (%)	321 (20.5)	51 (21.9)	220 (19.6)	50 (23.4)	0.386
Low interest in learning, *n* (%)	1,090 (69.5)	127 (54.5)	786 (70.1)	177 (82.7)	<0.001***

*Chronotypes: E-types: reduced Morningness-Eveningness Questionnaire ≤11; I-types: 12 ≤reduced Morningness-Eveningness Questionnaire ≤17; M-types: reduced Morningness-Eveningness Questionnaire ≥18; *p < 0.05; **p < 0.01; ***p < 0.001.*

TABLE 2 | Comparisons of sleep patterns, sleep disturbances, and mental distress among different chronotypes.

Characteristic		Total (n = 1,569)	M-types (n = 233)	I-types (n = 1,122)	E-types (n = 214)	*P*	*Post-hoc*[a]
Sleep patterns[a]							
Weekday	Bedtime (hh:mm)	00:06 ± 00:46	23:40 ± 00:43	00:05 ± 00:40	00:41 ± 00:53	<0.001***	M < I < E
	Get-up time (hh:mm)	07:28 ± 00:36	07:10 ± 00:48	07:28 ± 00:43	07:49 ± 00:36	<0.001***	M < I < E
	Time in bed (h)	7.36 ± 0.79	7.5 ± 0.88	7.37 ± 0.72	7.12 ± 0.88	<0.001***	M = I>E
Weekend	Bedtime (hh:mm)	00:26 ± 00:58	23:55 ± 00:56	00:23 ± 00:50	01:17 ± 01:06	<0.001***	M < I < E
	Get-up time (hh:mm)	8:49 ± 01:14	08:03 ± 01:23	08:45 ± 01:02	09:56 ± 01:15	<0.001***	M <I < E
	Time in bed (h)	8.37 ± 1.15	8.13 ± 1.45	8.37 ± 1.07	8.65 ± 1.12	<0.001***	M < I < E
Sleep compensation (h)		0.92(0.25, 1.58)	0.5 (0, 1)	0.9(0.3,1.5)	1.5 (0.82, 2)	<0.001***	M < I < E
Sleep disturbances[b]							
ISI total score		4 (2, 7)	3 (2, 6)	4 (2, 7)	5.5 (3, 9)	<0.001***	M < I < E
ESS total score		7 (5,10)	7 (4, 9)	7 (5, 9)	8 (4, 10)	0.116	
Mental distress[b]							
BDI-13 total score		3 (0,7)	2 (0, 5.5)	3 (0, 6)	5 (1, 10)	<0.001***	M = I < E
SAS total score		38.75 (35.00, 43.75)	40 (35.00, 43.75)	38.75 (35.00, 42.50)	41.25 (36.25, 46.25)	<0.001***	I< M <E

[a]*Statistical differences among three or more groups were determined by one-way ANOVA, followed by LSD post-hoc analysis.*

[b]*Statistical analysis was performed by Kruskal–Wallis one-way ANOVA and the Bonferroni post-hoc test for multiple comparisons.*

*M, M-types; I, I-types; E, E-types; ISI, Insomnia Severity Index; ESS, Epworth Sleepiness Scale; BDI-13, Beck Depression Inventory-13; SAS, Zung Self-Rated Anxiety Scale. ***p < 0.001.*

and anxiety symptoms (p <0.001), while there was no significant difference between chronotypes and EDS (p =0.107). When compared with M-types and I-types, E-types were associated with long weekend sleep compensation as well as more insomnia symptoms, EDS, and depressive symptoms (p <0.05), while there was no significant difference between M-types and I-types in these outcomes (p <0.05). Significant differences only existed between I-types and E-types in anxiety symptoms after Bonferroni correction. Those characteristics significantly related to sleep compensation, sleep disturbances, and mental distress

TABLE 3 | Comparisons of sample characteristics in participants with and without sleep compensation and sleep disturbances.

	Total (*n* = 1,569)	Short weekend sleep compensation (*n* = 1,292)	Long weekend sleep compensation (*n* = 277)	*P*	Without insomnia symptoms (*n* = 1,241)	With insomnia symptoms (*n* = 328)	P	Without excessive daytime sleepiness (*n* = 1,176)	With excessive daytime sleepiness (*n* = 393)	*P*
Socio-demographics										
Age, year, mean ± SD	19.86 ± 1.16	19.80 ± 1.13	20.15 ± 1.21	0.019*	19.81 ± 1.09	20.03 ± 1.35	0.040*	19.87 ± 1.31	19.84 ± 1.23	0.659
Gender, female, *n* (%)	681 (43.4)	704 (54.5)	184 (66.4)	<0.001***	694 (55.9)	194 (59.1)	0.295	636 (54.1)	252 (64.1)	0.001**
Only child, *n* (%)	637 (40.6)	518 (40.1)	119(43.0)	0.784	735 (59.2)	197 (60.1)	0.784	691 (58.8)	241 (61.3)	0.37
Rural area, *n* (%)	544 (34.7)	448 (34.7)	96 (34.7)	0.717	427 (34.4)	117 (35.7)	0.911	388 (21.9)	156 (39.7)	0.049*
Paternal education level (tertiary), *n* (%)	580 (37.0)	482 (37.3)	98 (35.4)	0.546	461 (37.1)	119 (36.3)	0.772	441 (37.5)	139 (35.4)	0.449
Maternal education level (tertiary), *n* (%)	483 (30.8)	403 (31.2)	80 (28.9)	0.450	385 (31.0)	98 (29.9)	0.689	377 (32.1)	106 (27.0)	0.059
Family income (≥5,000 yuan/month), n (%)	1,265 (80.6)	1,046 (81.0)	219 (79.1)	0.468	1,006 (81.1)	259 (79.0)	0.392	963 (81.9)	302 (76.8)	0.029*
Lifestyle and health condition										
BMI (≥25 kg/m^2), n (%)	106 (6.8)	88 (6.8)	18 (6.5)	0.815	82 (6.6)	24 (7.3)	0.649	81 (6.9)	25 (6.4)	0.719
Habitual napping (≥3 days/week), *n* (%)	1,477 (94.1)	1,222 (94.6)	255 (92.1)	0.105	1,167 (94.0)	310 (84.5)	0.745	1,104 (93.9)	373 (94.9)	0.45
Habitual snoring (≥3 days/week), *n* (%)	505 (32.2)	419 (32.4)	86 (31.0)	0.655	408 (32.9)	97 (29.6)	0.225	375 (31.9)	130 (33.1)	0.662
Boarding in school, *n* (%)	1,560 (99.4)	1,286 (99.5)	274 (98.9)	0.216	1,283 (99.8)	322 (98.2)	0.001**	1,173 (99.7)	387 (98.5)	0.004**
TV/Internet (≥4 h/day), *n* (%)	473 (30.1)	370 (28.6)	103 (37.2)	0.005**	342(27.6)	131(39.9)	<0.001***	592(50.3)	222(56.6)	0.035*
Mobile phone use before sleep (≥1 h/day), *n* (%)	303 (19.3)	218 (16.9)	85 (30.7)	<0.001***	208 (16.8)	95 (29.0)	<0.001***	219 (18.6)	84 (21.4)	0.238
Smoking, *n* (%)	17 (1.1)	12 (0.9)	5 (1.8)	0.202	13 (1.0)	4 (1.2)	0.776	14 (1.2)	3 (0.8)	0.585
Drinking, *n* (%)	550 (35.1)	440 (34.1)	110 (39.7)	0.073	438 (35.3)	112 (34.1)	0.698	400 (34)	150 (38.2)	0.135
Chronic medical conditions, *n* (%)	67 (4.3)	50 (3.5)	17 (12.6)	0.090	50 (3.5)	17 (12.6)	<0.001***	39 (3.1)	28 (8.5)	<0.001***
High study pressure, *n* (%)	321 (20.5)	254 (19.7)	67 (24.3)	<0.001***	207 (16.7)	114 (34.8)	<0.001***	217 (18.5)	104 (26.5)	0.001**
Low interest in learning, *n* (%)	1,090 (69.5)	877 (67.9)	213 (76.9)	0.003**	828 (66.7)	262 (79.9)	<0.001***	790 (67.2)	300 (76.3)	0.001**
Chronotypes				<0.001***			<0.001***			0.107
M-types	233 (14.9)	209 (16.2)[a]	24 (8.7)[a]		187 (15.1)[a]	46 (14.0)[a]		178 (15.1)	55 (14.0)	
I-types	1,122 (71.5)	942 (72.9)[a]	180 (65.0)[a]		914 (73.7)[a]	208 (63.5)[a]		850 (72.3)	272 (69.2)	
E-types	214 (13.6)	141 (10.9)[b]	73 (26.4)[b]		140 (11.3)[b]	74 (22.6)[b]		148 (12.6)	66 (16.8)	

*Short weekend sleep compensation: sleep compensation <2 h; Long weekend sleep compensation: sleep compensation ≥2 h; Insomnia symptoms: Insomnia Severity Index ≥8; Excessive daytime sleepiness: Epworth Sleepiness Scale ≥10. *p < 0.05, **p < 0.01, ***p < 0.001.*

[a,b]*There were significant differences between different letters within each column after Bonferroni correction.*

TABLE 4 | Comparisons of sample characteristics in participants with and without mental distress.

	Total (n = 1,569)	Without depressive symptoms (n = 970)	With depressive symptoms (n = 599)	*P*	Without anxiety symptoms (n = 1,434)	With anxiety symptoms (n = 135)	*P*
Socio-demographics							
Age, year, mean ± SD	19.86 ± 1.16	19.83 ± 1.18	19.93 ± 1.16	0.093	19.86 ± 1.15	19.91 ± 1.23	0.621
Gender, female, *n* (%)	681 (43.4)	520 (53.6)	368 (61.4)	0.002**	796 (55.5)	92 (68.1)	0.005**
Only child, *n* (%)	637 (40.6)	560 (57.7)	372 (61.1)	0.087	585 (40.8)	52 (38.5)	0.607
Rural area, *n* (%)	544 (34.7)	322 (33.2)	222 (37.1)	0.123	303 (21.1)	35 (25.9)	0.432
Paternal education level (tertiary), *n* (%)	580 (37.0)	380 (39.2)	200 (33.4)	0.021*	529 (36.9)	51 (37.8)	0.838
Maternal education level (tertiary), *n* (%)	483 (30.8)	319 (32.9)	164 (27.4)	0.022*	444 (31.0)	39 (28.9)	0.618
Family income (≥5,000 yuan/month), *n* (%)	1,265 (80.6)	802 (82.7)	463 (77.3)	0.009**	1,157 (80.7)	108 (80.0)	0.848
Lifestyle and health condition							
BMI (≥25 kg/m^2), *n* (%)	106 (6.8)	62 (6.4)	44 (7.3)	0.465	97 (6.8)	9 (6.7)	0.966
Habitual napping (≥3 days/week), *n* (%)	1,477 (94.1)	924 (95.3)	553 (92.3)	0.016*	1,354 (94.4)	123 (91.1)	0.118
Habitual snoring (≥3 days/week), *n* (%)	505 (32.2)	306 (31.5)	199 (33.2)	0.49	470 (32.8)	35 (25.9)	0.103
Boarding in school, *n* (%)	1,560 (99.4)	965 (99.5)	595 (99.3)	0.698	1,427 (99.5)	133 (98.5)	0.144
TV/Internet (≥4 h/day), n (%)	473 (30.1)	225 (26.3)	218 (36.4)	<0.001***	420 (29.3)	53 (39.3)	0.016*
Mobile phone use before sleep (≥1 h/day), *n* (%)	303 (19.3)	149 (15.4)	154 (25.7)	<0.001***	255 (17.8)	48 (35.6)	<0.001***
Smoking, *n* (%)	17 (1.1)	6 (0.6)	11 (1.8)	0.024*	14 (1.0)	3 (2.2)	0.175
Drinking, *n* (%)	550 (35.1)	327 (33.7)	223 (37.2)	0.156	501 (34.9)	49 (36.3)	0.752
Chronic medical conditions, *n* (%)	67 (4.3)	22 (2.3)	45 (7.5)	<0.001***	50 (3.5)	17 (12.6)	<0.001***
High study pressure, *n* (%)	321 (20.5)	121 (12.5)	200 (33.4)	<0.001***	261 (18.2)	60 (44.4)	<0.001***
Low interest in learning, *n* (%)	1,090 (69.5)	601 (62.0)	489 (81.6)	<0.001***	985 (68.7)	105 (77.8)	0.028*
Chronotypes				<0.001***			<0.001***
M-types	233 (14.9)	157 (16.2)[a]	76 (12.7)[a]		212 (14.8)[a,b]	21 (15.6)[a,b]	
I-types	1,122 (71.5)	404 (74.0)[a]	404 (67.4)[a]		1,041 (72.6)[b]	81 (7.2)[b]	
E-types	214 (13.6)	95 (9.8)[b]	119 (19.9)[b]		181 (12.6)[a]	33 (15.4)[a]	

*Depressive symptoms: Beck Depression Inventory-13 ≥5; Anxiety symptoms: Zung Self-Rating Anxiety Scale ≥50. *p < 0.05, **p < 0.01, ***p < 0.001.*
[a,b]There were significant differences between different letters within each column after Bonferroni correction.

TABLE 5 | Associations of chronotypes with sleep disturbances and mental distress.

	Coefficients B	*P*-value	Adjusted OR[a]	95% confidence interval for OR	
				Lower	Upper
Long weekend sleep compensation					
M-types	−0.473	0.045*	0.623	0.392	0.990
E-types	0.893	<0.001***	2.443	1.740	3.429
Insomnia symptoms					
M-types	0.163	0.392	1.177	0.810	1.710
E-types	0.693	<0.001***	2.000	1.428	2.801
Excessive daytime sleepiness					
M-types	−0.003	0.984	0.997	0.708	1.403
E-types	0.319	0.059	1.375	0.987	1.915
Depressive symptoms					
M-types	−0.064	0.702	0.938	0.675	1.303
E-types	0.727	<0.001***	2.068	1.496	2.858
Anxiety symptoms					
M-types	0.178	0.504	1.195	0.708	2.016
E-types	0.783	0.001**	2.188	1.387	3.451

[a]*Logistic regression model controlled for age, sex, and other socio-demographics significantly correlated with sleep disturbances and mental distress, as well as lifestyles and health conditions with statistical significance (forward likelihood ratio method). I-types as the reference category. E-types: reduced Morningness-Eveningness Questionnaire ≤11; I-types: 12 ≤reduced Morningness-Eveningness Questionnaire ≤17; M-types: reduced Morningness-Eveningness Questionnaire ≥18; Long weekend sleep compensation: sleep compensation ≥2 hours; Insomnia symptoms: Insomnia Severity Index ≥8; Excessive daytime sleepiness: Epworth Sleepiness Scale ≥10. Depressive symptoms: Beck Depression Inventory-13 ≥5; Anxiety symptoms: Zung Self-Rating Anxiety Scale ≥50. *p < 0.05, **p < 0.01, ***p < 0.001.*

were further controlled in multivariate analyses for chronotypes in these problems.

Multivariable Logistic Analyses

The binary logistic regression analysis results of the related factors of sleep disturbances and mental distress are shown in **Table 5**. After adjusting the socio-demographics, lifestyles, and health conditions, using the I-types as a reference, the E-types were found to indicate a higher risk of insomnia symptoms (adjusted OR 2.000, 95%CI 1.428–2.801), depressive symptoms (adjusted OR 2.068, 95%CI 1.496–2.858) and anxiety symptoms (adjusted OR 2.188, 95%CI 1.387–3.451). Compared with I-types, E-types were more likely to have long sleep compensation on weekends (adjusted OR 2.443, 95%CI 1.740–3.429), while M-types were the opposite (adjusted OR 0.623, 95%CI 0.392–0.990). Nonetheless, no significant associations were observed between chronotypes and EDS, except for E-types, which tended to have an association with EDS ($p = 0.059$).

DISCUSSION

This cross-sectional study attempted to investigate the distribution of chronotypes and the relationship between sleep disturbance and mental distress among college students. We identified that compared with I-types, E-types were positively associated with insomnia symptoms, sleep compensation, depressive symptoms, and anxiety symptoms, while M-types were negatively associated with sleep compensation.

In this study, we found that the most common chronotype of college students (71.5%) is I-type, which is consistent with previous studies (1, 34). In addition, the proportion of M-types (14.9%) was slightly higher than that of E-types (13.6%), which is consistent with a study in Hungary (35), but is different from an American study (36). Possible explanations for this discrepancy may include differences in the study sample size and population-related differences, such as the existence of socio-cultural diversity between the Chinese and Western populations.

We found that the E-type individuals were more likely to have sleep compensation on weekends, while those who were M-types were less likely to have sleep compensation on weekends. Several previous studies revealed that E-types generally go to bed and get up significantly later than M-types on both weekdays and weekends, which is consistent with our study (12, 37). Therefore, E-types are associated with a later bedtime and get-up time and a shorter time in bed during the weekdays when they are limited by the school schedule. However, on weekends, when there are less constrained by morning social demands, E-types may extend their sleep until a more favorable biological wake-up time to make up the deficit accumulated on weekdays (38). The need to get up at an earlier biological time to accommodate study and social demands on weekdays and frequently shift their sleep patterns between weekdays and weekends, producing a distinct phenomenon termed "social jetlag" (39, 40), might explain why E-types had more sleep compensation than other types.

This study also identified that E-types were more likely to have insomnia symptoms. Several previous studies revealed that E-type insomnia patients showed greater sleep-wake variability, more sleep-related dysfunctional cognitions, and less sleep hygiene knowledge than those with other chronotypes (41). It

has also been hypothesized that E-types, with maladaptive sleep-related cognitions and irregular sleep schedules, might be a risk factor for perpetuating insomnia symptoms (42).

Our findings indicate a tendency toward a significant relationship between E-types and EDS, which is consistent with previous research that found a higher complaint of EDS among college students with E-types (43). Similarly, a previous study confirmed a significant association between M-types and lesser EDS (38). However, a previous study reported the absence of a correlation between chronotype and EDS among college students (44). The possible explanation for this observed discrepancy might be the different study populations, socio-demographic characteristics, and socio-cultural characteristics. The existing findings between chronotypes and EDS in college students remain inconclusive; further investigation is required.

With respect to mental distress, the finding of this study indicates that E-types were positively associated with depressive symptoms and anxiety symptoms of college students after controlling for other predictors, which is consistent with many previous studies (45–47). Similar findings showed that the E-type was correlated with depressive symptoms in Chinese college students and Dutch (48, 49). Many factors might contribute to the increased mental distress risks among E-types in a complex way. Previous research showed that the main mechanism underlying chronotype and mood problems involved variations in biological clock genes (CLOCK, PER1, and PER2) (50). Moreover, previous studies suggested that chronotypes and sleep disruption may play an important role in susceptibility to mental distress and the precipitation of disorder symptoms (51, 52). Furthermore, people with E-types may increase the risk of mental health problems, including depression and anxiety due to disturbance of the sleep and wake cycle with melatonin and serotonin deficiency (53, 54).

The findings of the present study have important clinical and public health implications. Intervention and prevention strategies should be directed to target both the E-type and mental health in the context of psychopathology. Several positive and effective measures should be taken to avoid delay of the circadian rhythm of E-types, such as reducing the use of electronic devices with luminous screens (i.e., game consoles, tablets, computers, and mobile phones) before bedtime. Furthermore, they are supposed to get enough early light exposure by going outside early in the morning, which may help stabilize and advance their circadian rhythms. Therefore, it is important for school and health care providers to provide sleep hygiene education and necessary psychological intervention in time so as to prevent further exacerbations when detecting students with sleep disturbances and mental distress. Further prospective studies are warranted to examine the efficacy of interventions and prevention programs for circadian factors in improving sleep and mental health problems.

The advantages of the present study lie in its large sample size, which can make our findings convincing. Furthermore, to our best knowledge, there are few studies investigating the chronotypes and their relationships with sleep disturbances and mental distress among Chinese college students. Our study also has some limitations. Firstly, this cross-sectional survey cannot determine the causal relationship between chronotypes and their correlates. Secondly, data were collected through self-reported questionnaires rather than objective measures; this might lead to recall bias and social desirability bias. Physiological measurements of circadian rhythms (i.e., actigraphy) are more accurate methods to assess the chronotype, but these methods are too challenging and expensive for such a large sample as in this study, while the use of self-report questionnaires by online surveys can collect a large amount of data efficiently within a comparatively short time. However, research showed a strong correlation between subjective and objective measures of chronotypes and sleep durations. In addition, it was unable to calculate a response rate because the accurate number of students who received the message of the link was unknown. Finally, all of the participants were recruited from a single college, which may limit the finding's generalizability.

CONCLUSIONS

Our study showed a significant correlation between E-types and long weekend sleep compensation, symptoms of insomnia, depression, and anxiety among Chinese college students. Our findings emphasize the importance of early recognition and intervention of E-types and their accompanied sleep problems and mental distress.

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 Nanfang Hospital, Southern Medical University (QTEC-2019-101). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

JW and BZ: conceptualization. JW, SL, and BZ: methodology. JW: writing—original draft. JW, SL, and JG: formal analysis. SL, RX, JY, XL, YX, YZ, YC, YG, LC, and BZ: investigation, resources, and data curation. SL, JG, and BZ: writing—review and editing. SL and BZ: funding acquisition. BZ: supervision and project administration. All authors have approved the final manuscript.

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STUDY PROTOCOL
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Clinical Effect of Electroacupuncture on Acute Sleep Deprivation and Event-Related Potential Affecting the Inhibition Control of the Brain: Study Protocol for a Randomized Controlled Trial

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Background: Acute sleep deprivation (ASD) can effect mood, attention, memory, alertness and metabolism. Especially, it is often accompanied by cognitive impairment of the brain. Acupuncture is safe and effective for improving cognitive function, but its underlying mechanism is not fully understood. In this study, an event-related potential (ERP) technique will be employed to measure the behavioral, cognitive, and physiological changes produced by electroacupuncture intervention after ASD.

Methods: We will recruit 60 healthy subjects. The participants will be randomly divided into a treatment group, a control group, a sham electroacupuncture group and a blank group, at a 1:1:1:1 ratio. The primary outcome will be determined by the change from baseline to 36 h in the MoCA score. The secondary results include the amplitude and latency of ERP N2 and P3, Go-hit rates, Go-RTs, No-Go-FA rates, the WCST, the Digit Span Subtest of the WAIS, the ESS score and FS-14. The 15 healthy subjects will not receive acupuncture treatment and ASD, but will receive EEG records and cognition functions test at the beginning and end of the experiment. Electroacupuncture intervention will be performed for 30 min once every 12 h, a total of three times. ERP measurements and other tests will be performed after baseline and ASD, and the statistician and outcome evaluator will be blinded to treatment allocation.

Discussion: This study is expected to investigate the effectiveness of electroacupuncture in improving cognition for ASD.

Trial Registration: ChiCTR2200055999.

Keywords: electroacupuncture, cognition, acute sleep deprived, Go/No-Go, ERP

BACKGROUND

Acute sleep deprivation (ASD) is the elimination of sleep for a period of time (at least 24 h) to significantly prolong wakefulness (1). Inadequate sleep and sleep disorders have become an important public health problem. ASD can effect mood, attention, memory, alertness, cognitive performance and metabolism (2, 3). With the increasing pace of life, the incidence of sleep deprivation has increased significantly, which has attracted attention in the military field and many social sectors (such as aviation, navigation, medical treatment, and transportation). The common negative effects of sleep deprivation include feeling too sleepy during the day, accidents from lack of attention, mood changes, and changes in appetite (4). Insufficient sleep increases the risk of human error-related accidents (5). ASD affects cognition in many ways and can negatively impact alertness, learning, memory, and executive function (6–12). Since ASD has serious effects on human cognitive brain function, safety intervention studies on the effects of ASD, such as acupuncture, are increasingly popular in this field (13, 14).

Studies show that administration of caffeine may improve vigilance, alertness, mood and cognitive processes and enhance cognitive processing related to response selection and inhibition (15, 16). Compared with the central nervous system stimulant caffeine, acupuncture is a safe alternative therapy with minimal side effects (17). A Delphi expert consensus survey (18) shows that more than 80% of experts agree that acupuncture can be used to improve cognitive function, which has been underpinned by the results of previous studies (19, 20). Although acupuncture has been studied for a long time, there is still a lack of knowledge of the effects of acupuncture on the human brain. More research is necessary to better understand how brain activity is affected by acupuncture.

Executive function (also called executive control or cognitive control) is fundamental to human cognition (21). It is a top-down mental process needed when one has to concentrate and pay attention, when going on automatic or relying on instinct would be insufficient (22–24). There are three core executive functions: inhibition, working memory (WM), and cognitive flexibility (25, 26). The Go/No-go paradigm has been used to study the executive function (27). Event-related potential (ERP) has often been used to investigate the effects of sleep deprivation on neurocognitive functioning. It is non-invasive and simple to perform, and it does not entail discomfort for participants. Certain components of ERP have been found to reflect specific forms of information processing related to sensory, motor and/or cognitive functions (28). The visual Go/No-go task is often used to study response inhibition (29). There have been several reports supporting the hypothesis that the visual N2 reflects a frontal inhibition mechanism (30, 31), including cognitive control and response inhibition (32, 33). Furthermore, recent studies suggest that P3 may play an important role in the post-response stage, reflecting processes of cognitive processing, such as stimulus identification and evaluation (34, 35) or monitoring of inhibition (36, 37).

This high-quality randomized controlled trial (RCT) was designed *via* a pragmatic trial approach to objectively assess the efficacy of electroacupuncture for brain cognition using ERP. By comparing ERP related to response inhibition tasks before and after ASD, we can understand the effect of ASD on the brain's inhibition control and the effect of electroacupuncture on brain cognition function after ASD.

Objectives

The aim of this study is to assess the effect of electroacupuncture on brain inhibition control function.

METHODS/DESIGN

Study Setting

This study is a participant-, statistician-, and assessor-blinded parallel randomized control clinical trial. The study will follow the principles of the Consolidated Standards of Reporting Trials (CONSORT) as well as the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) statement for acupuncture. Sixty healthy college students will be randomly assigned to a treatment group, a sham electroacupuncture group and a blank group, at a 1:1:1:1 ratio. The control group will be set to evaluate the efficacy of electroacupuncture. The sham electroacupuncture group be set to rule out placebo effects. The study will be conducted at the Third Affiliated Hospital of Henan University of Traditional Chinese Medicine, Department of Acupuncture, Henan, China, following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT). For the participant timeline, see **Table 1**.

Sample Size

According to the pre-test study, the average MoCA scores in the treatment group, control group, and blank group are 26.70, 25.72, and 27.32, respectively, and the standard deviations are 1.03, 1.59, and 1.37, respectively. Using the sample size calculation method of multi-group mean, the sample size estimation [one-way analysis of variance (ANOVA)] *F*-test] method will use the test level $\alpha = 0.05$ (bilateral) and test efficiency $1 - \beta = 0.90$. The bilateral test will be used. The total sample size of 45 cases was estimated using PASS 15.0 software.

RECRUITMENT

All participants will be recruited through advertisements on websites and posters at colleges and universities near Henan University of Traditional Chinese Medicine. Treatment and measurements will be performed in quiet rooms. Participants will contact the recruitment staff by telephone or WeChat. Recruitment staff will be responsible for the enrollment of participants. If they meet the study criteria, they will be invited

Abbreviations: ASD, acute sleep deprivation; ERPs, event-related potentials; EHQ, Edinburgh Handedness Questionnaire; SCL-90, Symptom Checklist-90; PSQI, Pittsburgh Sleep Quality Index; MoCA, Montreal Cognitive Assessment; WCST, Wisconsin Card Sorting Test; DS, Digit Span of the Wechsler Adult Intelligence Scale; WAIS, Wechsler Adult Intelligence Scale; ESS, Epworth Sleepiness Scale; FS-14, Fatigue Scale-14; ANOVA, analysis of variance; IEC, Institutional Ethics Committee; EEG, electroencephalogram.

TABLE 1 | SPIRIT figure for schedule of enrollment, interventions and assessments.

	Study Period						
	Enrollment	Allocation	Post-allocation				Close-out
Timepoint	***−1 w***	**0**	***Baseline***	***12 h***	***24 h***	***36 h***	***48 h***
Enrollment							
Eligibility screen	X						
Informed consent	X						
Baseline assessment	X						
Allocation		X					
Interventions							
Treatment group				◆———	———	———◆	
Placebo group				◆———	———	———◆	
Control group				◆———	———	———◆	
Blank group							
Assessments							
EHQ	X						
Sleep log	X						
SCL-90	X						
PSQI	X						
MoCA			X			X	
WCST			X			X	
DS			X			X	
ESS			X			X	
FS-14			X			X	
EEG-record			X			X	
Adverse events			X	X	X	X	X

EHQ, Edinburgh Handedness Questionnaire; SCL-90, Symptom Checklist-90; PSQI, Pittsburgh Sleep Quality Index; MoCA, Montreal Cognitive Assessment; WCST, Wisconsin Card Sorting Test; DS, Digit Span of the Wechsler Adult Intelligence Scale; ESS, Epworth Sleepiness Scale; FS-14, Fatigue Scale-14; EEG, Electroencephalogram.

to the study. Eligible candidates will be asked to sign an informed consent form before the experiment begins. We will provide accommodation and meals during the experiment, and provide the participants a certain reward at the end of the experiment.

INCLUSION CRITERIA

Recruitment conditions are as follows: (1) male college student in good health after physical examination; (2) 18–24 years of age and right-hand according to the modified Edinburgh Handedness Questionnaire; (3) normal or corrected-to-normal visual acuity; (4) normal state of sleep awakening, with no unusual sleep schedule–that is, waking up unusually early or late–and no history of shift; the self-made "sleep log" table and interview show that the subjects have good sleep habits; (5) on Symptom Checklist 90 (Symptom List-90 SCL Mel 90), the total average score is <1, and the score of each factor is <1; (6) the score of the Pittsburgh Sleep Quality Index (PSQI) is <5; (7) no habit of drinking coffee, tea, or alcohol or smoking; (8) voluntarily signing an informed consent form. The participants will be contacted a few days later to determine whether they are interested in participating, and, if so, an appointment will be made for them to physical examination package at the Third Affiliated Hospital of Henan University of Traditional Chinese Medicine.

EXCLUSION CRITERIA

Participants with any of the following conditions will be excluded: (1) having taken sedative or sleep-aiding drugs, such as estazolam or alprazolam, in the past month; (2) having received acupuncture or moxibustion treatment in the past month; (3) severe heart, liver, or kidney disease, mental illness, or coagulation dysfunction; (4) family history of mental illness or history of infectious diseases; (5) allergies, especially to needles; (6) implantation of a cardiac pacemaker or implantable electronic equipment.

DROPOUT CRITERIA

(1) Those who do not fill in the cases in a timely and accurate manner or those who do not fill in the cases properly; (2) those who fail to follow the plan for treatment in the course of the trial; (3) subjects who automatically asked to withdraw.

RANDOMIZATION

Unrestricted (simple) randomization will be used to allocate participants to either the treatment group, control group, blank group. Participants will be randomized using sequentially numbered, opaque sealed envelopes (SNOSE) to maintain allocation concealment (38). Different personnel will carry out tasks such as assigning a sequence, recruiting subjects, or intervention.

BLINDING

In this trial, outcome assessors, and data analysts will be blinded to the treatment allocation to minimize potential sources of bias and the clinical researcher, assessor, and statistician will not share study information with each other. After the end of the experiment, we will use a questionnaire to ask the participants if they know whether they received real acupuncture or sham acupuncture.

INTERVENTION

All practitioners in this trial are licensed TCM acupuncture therapists with at least 5 years of clinical experience, and they will be trained to master the study protocol. The acupuncturist will be asked to administer the standard manipulation.

TREATMENT GROUP

The treatment group will receive electroacupuncture and 36-h ASD. The choice of acupuncture points is based on a previous study (18). The acupoints will be Baihui (GV20), Sishencong (EX-HN1), and Shenting (GV24). Acupuncture at these acupoints mentioned above can regulate Qi of Governor Vessel, clear the mind, lift the spirits, nourish Yang based on Chinese acupuncture theory (39). Modern research shows that Baihui, Shenting and sishencong acupuncture can alleviates cognitive impairment (40–42).We will use sterile, disposable stainless-steel needles of the Hwato brand measuring 0.30 × 25 mm, with horizontal needling of 12–20 mm following an angle of 0–15°. After eliciting the Deqi response, the researcher will apply electroacupuncture by connecting an acupoint nerve stimulator (G6805-2A) to Baihui (GV20) and Shenting (GV24). The stimulation parameters are dense wave, frequency of 5 Hz, current of 1–5 mA, and needle retention for 30 min, with intervention performed every 12 h.

PLACEBO GROUP

Placebo group is intervened with sham electroacupuncture. The sham GV20 point is 0.5 cun (≈12.5 mm) lateral to GV20, the sham EX-HN1 point is 0.5 cun (≈12.5 mm) horizontal to EX-HN1 and the sham GV24 point is 0.5 cun (≈12.5 mm) horizontal to GV24, pierce of 3–5 mm following an angle of 0–15°. Procedures, electrode placements, and other treatment settings are the same as in the treatment group but with no electricity output and needle manipulation for de qi.

CONTROL GROUP

Participants in the control group will receive only 36-h ASD but will not receive electroacupuncture treatment.

BLANK GROUP

The healthy control group will not receive any intervention. They will keep normal work and rest time.

VISUAL GO/NO-GO TASK DESIGN

At the beginning of the visual Go/No-Go task, a small white cross (+) on a black background appears at the center of the screen for 100 ms before each trial, followed by the stimulus. Each stimulus is presented for a duration of 100 ms, with an inter-stimulus interval of 800 ms. The task has two blocks with 150 trials in each block. In one block, the subjects are asked to respond to the left arrow [target stimulus (Go)] and withhold responding to the right arrow [non-target stimulus (No-Go)], while in the other block, the response pattern is reversed. The Go stimuli occur with a one-third probability, and the sequence of Go/No-Go stimuli is pseudorandom to ensure that the No-Go stimuli do not appear in a continuous sequence. The participants will undergo a training session to ensure that they understand the Go/No-Go task and that their performance is above 90%.

The participants will arrive at the lab at 20:00 p.m. and perform a Go/No-Go task as a baseline. They will be asked to ensure that they get a full night's sleep (by wearing a wrist-operated sleep monitor and "sleep log" to ensure that they get at least 8 h of sleep), and the experiment will begin at 8:00 a.m. the next morning, taking the Go/No-Go task as 0 h. The participants will not be allowed to sleep for the next 36 h, during which time they will receive acupuncture every 11 h. After 36 h, the participants will be asked to complete the Go/No-Go task again. They will be accompanied and supervised by 10 staff members, and there will be two emergency doctors and nurses in the laboratory at all times. The participants will be asked to stay in the laboratory and will be allowed to talk, read, play computer games, and engage in other non-strenuous activities. They will not be allowed to smoke or drink coffee, tea, hot chocolate, wine, or other bladder-irritating drinks (**Figure 1**).

EEG RECORDING AND ERP ANALYSIS

The subjects will sit comfortably in a quiet room. Continuous EEG recordings will be obtained using Brain Vision recorder software. The sampling frequency will be 1,000 Hz, and the electrode impedances will be maintained below 5 kΩ. The electrodes will be placed according to the international 10–20 system; a total of 32 electrodes will be recorded in this study. ERP component analysis will be performed using Matlab 2018b and will include amplitudes and latencies. EEG data will be analyzed and collected by people who have received professional training.

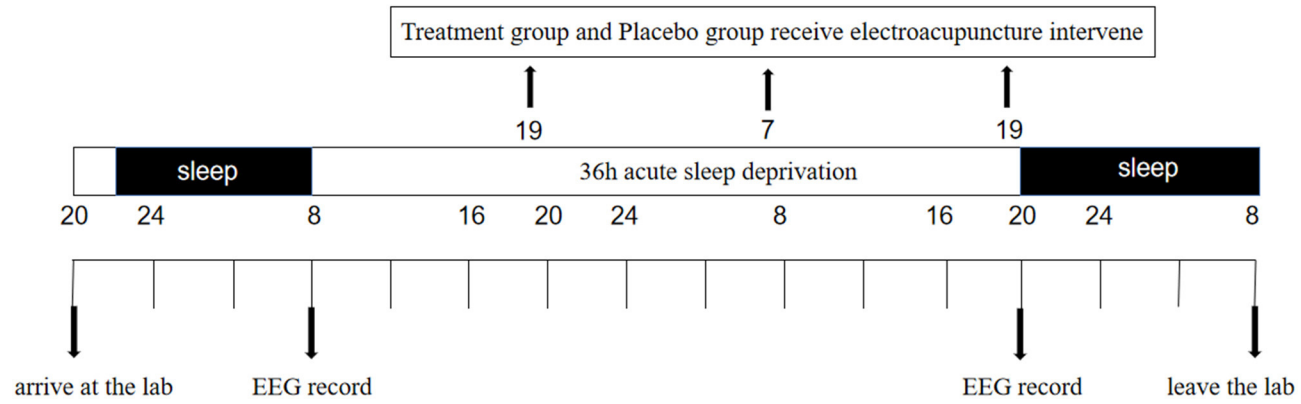

FIGURE 1 | Study protocol. In the study protocol, subjects will undergo 36 h periods of acute sleep deprivation (ASD). The black arrows indicate the time points of Electro- encephalogram (EEG) recordings and treatment group receive electroacupuncture treatment.

OUTCOMES

Primary Outcome

The primary outcome is the MoCA score. The cognitive areas assessed include attention and concentration, executive function, memory, language, visual structure skills, abstract thinking, calculation and orientation, with a total score of 30. The lower the score, the more severe the cognitive impairment.

Secondary Outcomes

The behavioral data and latency and amplitude of N2 and P3 amplitude will be used to evaluate the effect of sleep deprivation and the intervention effect of acupuncture. ERP component detection, such as N2 and P3, has been used for the measurement of brain activity (13) and as a reflection of brain executive function (30–37). The behavioral outcome variables include the mean RT for correct hits, hit rates (correct button presses for Go stimuli), and the percentage of false alarms (FAs, incorrect button presses in response to No-Go stimuli), which are used as indices of individual behavior performance. Executive function and working memory will be assessed with the Wisconsin Card Sorting Test (WCST). Working memory and the Digit Span (DS) of the Wechsler Adult Intelligence Scale (43). The Epworth Sleepiness Scale (ESS), also known as the Epworth Daytime Sleepiness Scale, developed by Johns (44), will be used to evaluate excessive drowsiness during the day. The maximum score on the scale is 24 points, with >6 points indicating drowsiness, >11 points indicating excessive drowsiness, and >16 points indicating dangerous drowsiness. The FS-14 was jointly compiled by a number of experts, including Chalder and Berelowitz, in the United Kingdom (45). The physical fatigue score is obtained by adding the scores of eight items (1–8), the mental fatigue score is obtained by adding the scores of six items (9–14), and the total fatigue score is the sum of physical and mental fatigue scores. The highest score of physical fatigue is 8, the highest score of mental fatigue is 6, and the highest total score is 14. The higher the score, the more serious the fatigue.

Other Outcomes

Participant characteristics such as age, weight, body mass index, blood pressure, heart rate, pulse, liver function, renal function, electrocardiogram, and back pain history will be collected using electronic case report forms.

Adverse Events

Any adverse event resulting from electroacupuncture in participants, such as headache, nausea, dizziness, localized infections, bleeding, or local subcutaneous hematoma, will be recorded, assessed, and reported. The occurrence time, cessation time duration, correlation with acupuncture, measures taken, and outcomes of adverse events will also be recorded. If serious adverse events occur, the Institutional Ethics Committee of the Third Affiliated Hospital of Henan University of Traditional Chinese Medicine will be informed, and the committee will decide whether to unblind and withdraw from the study.

Follow-Up

Twelve hours after the completion of the trial, a follow-up health checkup will be performed, and the participants will be asked if they are experiencing any physical discomfort. The trial work plan is summarized in **Figure 2.**

Data Management and Monitoring

Both paper files and electronic documents will be preserved for at least 5 years after publication. If readers have any questions, they can contact the corresponding author for access to the original data. Patient information will remain anonymous, including name, ID number, and telephone number. The protocol will be reviewed and revised by experts in acupuncture, emergency, methodology, and statistics. We will perform a pre-specified standard operating procedure, which includes screening patients, improving relevant inspection, acupuncture, filling out the CRF, assessing outcomes, and data management. Outcome assessments, completion of case report forms and data management will be closely supervised. We will be monitored by the IEC of the Third Affiliated Hospital of Henan University of Chinese Medicine, and it is independent from the investigators

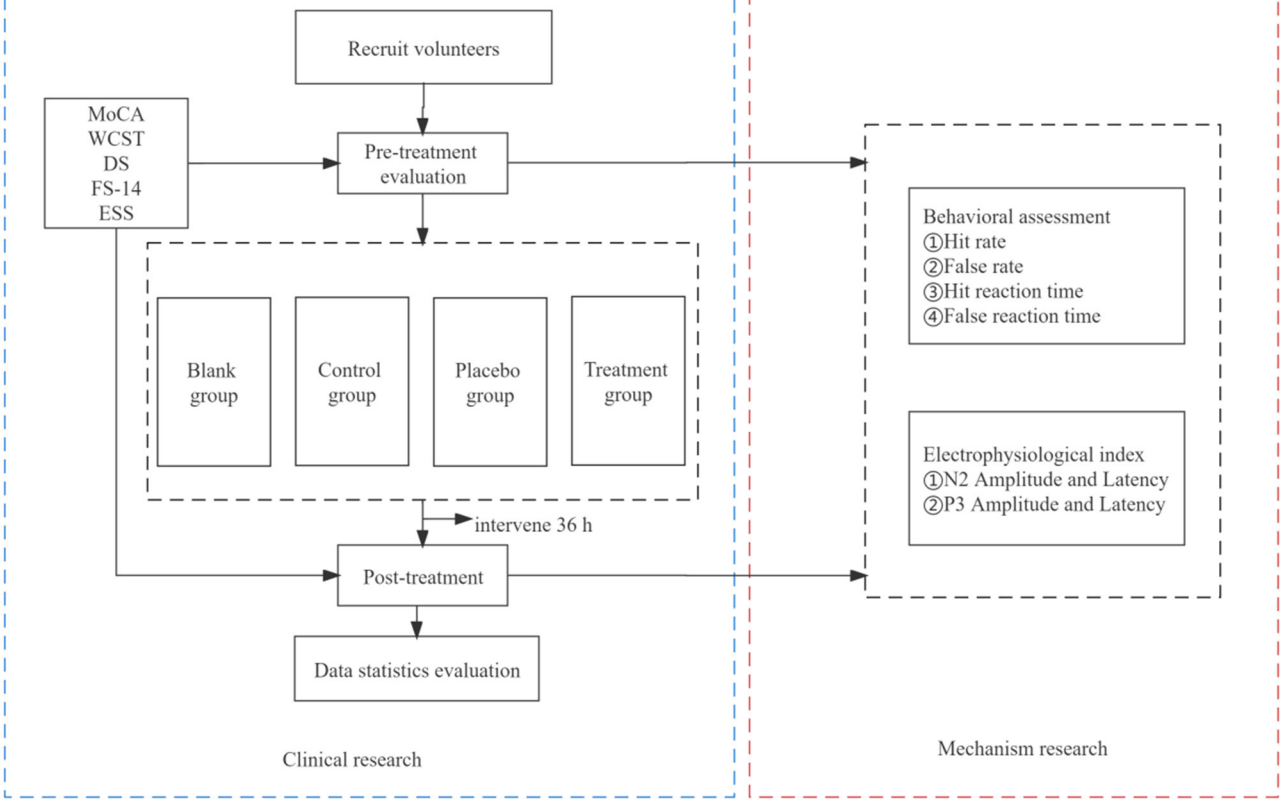

FIGURE 2 | Trial work plan. The primary outcome measure will be MoCA. The remaining outcome measures will be for secondary outcomes.

and sponsor which will audit trial conduct every 12 months. Any modifications and corrections to operation procedures will be fully documented using a breach report form, monitored, and submitted to the directors of the ethics committee and China Clinical Trial Registration.

Data Analysis

We will use SPSS software version 21.0 (IBM Corp, Armonk, New York, US) to perform data analysis. Demographic and baseline data will be analyzed with standard descriptive statistics. Data will be presented as the mean ± standard deviation (SD). A repeated measure ANOVA is employed to analyze the electroacupuncture effects and the time effects on the behavioral data. The repeated measure ANOVA is also used for the analysis of ERP indices. ANOVAs are performed on the N2 and P3 components of the scalp electrodes in the Go/No-Go task. The accepted level of significance for all analyses will be $P < 0.05$.

Ethics and Dissemination

All candidates who agree to participate and who meet all of the inclusion criteria and none of the exclusion criteria will be provided an informed consent form to provide them with full understanding of what the study participation will entail and the potential risks. Participants have the right to discontinue participation at any time. Data will be used in the aggregate only, and no identifying characteristics of individuals will be published or presented. In the consent form, the participants will be asked if they agree to the use of their data, should they choose to withdraw from the trial. The participants will also be asked for permission for the research team to share relevant data with people from the regulatory authorities, where relevant. This trial does not involve collecting biological specimens for storage. The study conforms to the principles of the Declaration of Helsinki. Ethical approval has been obtained from the IEC of the Third Affiliated Hospital of Henan University of Chinese Medicine. The trial protocol has been registered at the Chinese Clinical Trial Registry. The results will be disseminated through journal articles, a master's thesis, or conference presentations.

DISCUSSION

The purpose of this trial is to assess the impact of acupuncture on the management of brain cognition control. It is obvious that cognitive function is impaired after sleep deprivation. We intend to compare the effects of time (baseline and 36-h ASD) and intervention (electroacupuncture, sham electroacupuncture and non-electroacupuncture treatment) on executive brain function using a visual Go/No-Go task with simultaneous EEG recordings. Acupuncture is a non-toxic, economical intervention with minimal adverse effects (32) that has been shown to be effective after the therapy (11).

There are several methodological limitations to this study: (1) Due to the characteristics of acupuncture is the non-blinding of the acupuncturist. (2) Only young male subjects will be included; so, the findings may not be generalizable to women and older people. (3) The sample size is small. Despite these limitations, we will use rigorous methodology in this study, and we hope that the trial will help provide new insights into the value of acupuncture and evidence of ERP in executive brain function.

TRIAL STATUS

Recruiting will start in February 2022. The current protocol is version 1 of 27-12-2021. Patient recruitment is estimated to be completed around June 2022.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Third Affiliated Hospital of Henan University of Traditional Chinese Medicine. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XC is the principal investigator, conceived the study and led the proposal, protocol development, study design, and methodology. HL and MW drafted the manuscript and performed the trial registration. YW will perform electroacupuncture operation and provided critical revision of the manuscript. CX designed the statistical analysis. PL, RZ, and ZL participated in the data collection. All authors have read and approved the final manuscript.

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Prevalence of high-risk for obstructive sleep apnea in attention deficit hyperactivity disorder children referred to psychiatry clinic and impact on quality of life

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Objectives: To study the prevalence of high-risk obstructive sleep apnea (OSA) in attention deficit hyperactivity disorder (ADHD) children in a child and adolescent psychiatry clinic using the Thai version of the Pediatric Obstructive Sleep Apnea Screening Tool (POSAST) questionnaire. The secondary objective was to evaluate the quality of life and identify associated factors for high-risk OSA in ADHD children.

Study design: Prospective cross-sectional study.

Material and method: Caregivers of pediatric patients aged 5–18 years old and diagnosed with ADHD by child and adolescent psychiatrists were surveyed about their child's sleeping habits.

Results: Two hundred and seventy-four subjects were included. The patients' mean age was 10.4 ± 2.6 years, and 82.8% were males. There were 30 children (10.9%) diagnosed with obesity, 46 (16.8%) with chronic rhinitis, and 9 (3.3%) with asthma. The median duration of ADHD symptoms was 22.1 months. The prevalence of high-risk OSA was 18.2% and was associated with significantly reduced quality of life (adjusted OR = 4.46, 95% CI: 2.26–8.81, $P < 0.001$). A significant association between high-risk OSA and obesity also emerged (adjusted OR = 2.84, 95% CI: 1.17–6.88, $P = 0.021$).

Conclusion: An elevated prevalence of high-risk OSA is present among Thai children with ADHD, and significantly impacts quality of life. A significant

association between high-risk OSA and obesity is also detected in patients with ADHD. Therefore, screening for high-risk OSA in ADHD patients may likely facilitate early detection and treatment of OSA, and potentially prevent adverse consequences.

KEYWORDS

obstructive sleep apnea, sleep-disordered breathing, pediatric, questionnaire, attention deficit hyperactivity disorder, quality of life, Thailand

Introduction

Obstructive sleep apnea (OSA) is a common disorder in children and is characterized by prolonged partial obstruction and intermittent complete obstruction of the upper airway that disrupts normal ventilation during sleep and sleep continuity. The prevalence of habitual snoring in children is 1.5–27.6% of the pediatric population and the prevalence of OSA is 1–5% (1). In Thailand, two studies reported a prevalence of habitual snoring at 4.3 and 8.5%, while the prevalence of OSA was 0.69, and 1.3% (2, 3). Among the major end-organ morbidities of OSA in children, cardiometabolic dysfunction and neurobehavioral alterations manifesting as poor academic performance and especially ADHD-like behaviors, have been ultimately associated with reduced quality of life. Studies examining the association between snoring, OSA, and ADHD have consistently identifies significant relationships (4–10). In addition, a meta-analysis confirmed that OSA and ADHD tend to co-exist (11), with 20–30% of ADHD children suffering from OSA (12). In Thailand, the prevalence of snoring in children with ADHD was 19.8% (13). However, the prevalence of high-risk OSA in ADHD children and the impact on quality of life have not been explored in Thailand. Despite the consensus that the gold standard for diagnosis of OSA is overnight polysomnography (PSG), there are limitations to the implementation of such approach in Thailand, including high costs, long waiting times, and the need for sleep technologists and sleep medicine physicians. Instead, an easy-to-use screening questionnaire for OSA could provide an alternative approach in resource-constrained environments such as in Thailand. To explore these possibilities, we undertook the current study based on the hypothesis that an elevated proportion of children diagnosed with ADHD would test positively, i.e., be at high-risk for OSA, when screened with a previously validated OSA questionnaire. As such, the primary objective of the study was to assess the prevalence of high-risk OSA in ADHD children by using the Thai version of the Pediatric Obstructive Sleep Apnea Screening Tool (POSAST) in a child and adolescent psychiatry clinic of a tertiary care hospital. A secondary objective was to evaluate OSA-specific quality of life by using the OSA-18 questionnaire in children diagnosed with ADHD, and to identify the associated factors for high-risk OSA in ADHD children.

Materials and methods

Sample size calculation

Based on the study by Silvestri et al. (14) which revealed an estimated prevalence of sleep-disordered breathing (SDB) in ADHD children of 21%, we used the 95% confidence intervals and derived the estimated cohort size using the equation:

$$n = \frac{Z^2_{\alpha/2} P(1-P)}{d^2}$$

n = number of subjects.
P = expected proportion = 0.21.
α = type I error = 0.05,
2-sided (95% Confidence Interval, Z = 1.96).
d = distance from proportion to limit = 0.05.

$$n = (1.96)^2 \frac{(0.21)(1-0.21)}{(0.05)^2} = 255$$

Then, we added another 10% for possible drop-offs and attrition during the survey, such that 280 subjects were deemed necessary.

Study population

This study was performed after obtaining approval from Siriraj Institutional Review Board (SiRB), Protocol No. 379/2562(EC4). We consecutively recruited 280 subjects who were caregivers of pediatric patients aged 5–18 years old and diagnosed with ADHD in the child and adolescent psychiatry clinic of Siriraj Hospital, Bangkok, Thailand. The diagnosis of ADHD and other psychiatric comorbidities was conducted by child and adolescent psychiatrists using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria (15). We ascertained that all caregivers could read the Thai language. Recruitment spanned the period from

October 2019 to June 2020. Patients with a medical history of adenoidectomy, tonsillectomy, sinus surgery, Down syndrome, genetic syndromes, developmental delay, neuromuscular disorders, craniofacial anomalies, and chronic lung disease were excluded from the study.

Study design

This study was a prospective cross-sectional study. Caregivers were surveyed about their child's sleeping habits using a previously validated questionnaire. In addition to demographic information and significant medical history of their child, the Thai Version of both POSAST and OSA-18 questionnaires were administered for evaluation of the risk for OSA and quality of life, respectively.

Pediatric obstructive sleep apnea screening tool

There are several questionnaires used for OSA screening, but some have too many questions and unpredictable outcomes. Thus, this study was conducted by using a sensitive, short, and easy-to-use questionnaire named "Pediatric Obstructive Sleep Apnea Screening Tool (POSAST)" (16, 17). It is a validated 6-item questionnaire in which all questions are answered using a Likert-type response scale: "never" (0), "rarely" (once per week; 1), "occasionally" (twice per week; 2), "frequently" (three to four times per week; 3), and "almost always" (>4 times per week; 4), apart from the fifth question (i.e., mildly quiet = 0, medium loud = 1, loud = 2, very loud = 3, extremely loud = 4). The questions are Q1) Do you shake your child to breathe?, Q2) Have you witnessed an apnea during sleep?, Q3) Does your child struggle to breathe when asleep?, Q4) Do you have concerns about your child's breathing while asleep?, Q5) How loud does your child snore?, Q6) Does your child snore while asleep? The score derived from the POSAST is calculated as follows:

$A = (Q1 + Q2)/2$
$B = (A + Q3)/2$
$C = (B + Q4)/2$
$D = (C + Q5)/2$
Equation-derived score $= (D + Q6)/2$

A cut-off score of ≥ 1.9 rather than the original cut-off of ≥ 1.0 was used and indicative of high risk for the presence of moderate and severe OSA [correspond to an apnea-hypopnea index (AHI) ≥ 5 events per hour] according to the previously validated Thai version of the POSAST questionnaire (17, 18). A cut-off score of 1.9 yielded a sensitivity of 78.4%, a specificity of 50%, a positive predictive value of 76.3%, and a negative predictive value of 52.9%. In addition, we also implemented using the total additive score (Q1 + Q2 + Q3 + Q4 + Q5 + Q6) for diagnosing moderate and severe OSA [(AHI) ≥ 5 events per hour]. A cut-off of 8 yielded a sensitivity of 81.1%, a specificity of 52.8%, a positive predictive value of 77.9%, and a negative predictive value of 57.6% (18).

Thai version quality of life questionnaire (OSA-18) for pediatric obstructive sleep apnea

The Thai version of the Quality of Life Questionnaire (OSA-18) for Pediatric Obstructive Sleep Apnea (19) was also used to assess the quality of life in this study. The OSA-18 consists of 18 items grouped in five domains of sleep disturbance (4 items), physical suffering (4 items), emotional distress (3 items), daytime problems (3 items), and caregiver concerns (4 items). Each item is scored in a seven-point Likert scale (1 = none of the time, 2 = hardly any of the time, 3 = a little of the time, 4 = some of the time, 5 = good amount of the time, 6 = most of the time, and 7 = all of the time). The total maximal score is 126 points. The decrease in quality of life was defined as 'mild' if the score <60 points, "moderate" if the score was 60–80 points, and "severe" if the score > 80 points (20).

Outcomes

The primary outcome was the prevalence of high-risk group for OSA in ADHD patients based on the scores obtained from the Thai version of POSAST, while a secondary outcome was the quality of life of the patients with ADHD who had high risk for OSA.

Statistical analysis

Categorical data are presented as numbers and percentages. Continuous data are shown as mean ± standard deviation (SD) for normal distribution variables and median and interquartile range (IQR) for non-normal distribution variables. The Chi-Square test was used to compare the counts of categorical responses between two independent groups. Comparison of continuous data between groups was conducted by using unpaired *t*-tests for normal distribution variables and Mann-Whitney U test for non-normal distribution variables. A univariate analysis of associated factors for high risk OSA in ADHD children was performed. All variables with *P*-value < 0.25 on univariate analysis were included in the multivariate analysis. All statistical analyses were performed using PASW Statistics version 18.0 (SPSS Inc, Chicago, Illinois). A *P*-value < 0.05 was considered statistically significant.

TABLE 1 Demographic and clinical characteristics of the pediatric ADHD cohort ($n = 274$).

Characteristic	Value
Age, mean ± SD, year	10.4 ± 2.6
Sex, *n* (%)	
Male	227 (82.8)
Female	47 (17.2)
Nutritional status[a], *n* (%)	
Normal	188 (68.6)
Overweight	56 (20.5)
Obesity	30 (10.9)
ADHD duration, median (IQR), months	22.1 (9.89, 45.45)
Associated psychiatric diseases, *n* (%)	
Specific learning disorder	136 (49.6)
Oppositional defiant disorder	22 (8.0)
Autism spectrum disorder	5 (1.8)
Cognitive deficits	4 (1.5)
Vocal tic disorder	4 (1.5)
Anxiety disorder	4 (1.5)
Bipolar disorder	2 (0.7)
Obsessive compulsive disorder	2 (0.7)
Psychiatric medication	
Methylphenidate	211 (77.0)
Methylphenidate and anti-psychotics	47 (17.2)
Methylphenidate and fluoxetine	9 (3.3)
Methylphenidate and clonidine	5 (1.8)
No psychiatric medication	2 (0.7)

ADHD, attention-deficit hyperactivity disorder; SD, standard deviation; IQR, interquartile range. [a]Nutritional status was defined by weight for height normative reference values in Thai children. (21) Normal, % weight- for-height ≤ 120; overweight, % weight-for-height > 120–140; obesity, % weight-for-height > 140.

Results

Two hundred and eighty caregivers of children diagnosed with ADHD were included in this study. Six subjects were excluded based on a history of previous adenotonsillectomy for symptoms of sleep disordered breathing. Therefore, 274 subjects were included in the final analyses. The patients' mean age was 10.4 ± 2.6 years, and they were predominantly males (82.8%). Overweight was present among 56 patients (20.5%), while 30 (10.9%) responders were obese. There were 46 patients (16.8%) diagnosed with chronic rhinitis and 9 children (3.3%) diagnosed with asthma. The median duration of ADHD was 22.1 (9.9, 45.5) months, and 49.6% had associated specific learning disorders. The demographic, nutritional status (21), and clinical characteristics of the patients are shown in Table 1. The prevalence of high-risk OSA was 18.2% when using the equation-derived score cut-off of 1.9 points, and 16.4% when using the total additive score cut-off of 8 points (Table 2).

TABLE 2 Prevalence of high-risk OSA in ADHD children ($n = 274$).

OSA	Equation-derived score		Total additive score	
	Cut-off score	Prevalence, *n* (%)	Cut-off score	Prevalence, *n* (%)
Low risk	<1.9	224 (81.8)	<8	229 (83.6)
High risk	≥1.9	50 (18.2)	≥8	45 (16.4)

OSA, obstructive sleep apnea; ADHD, attention-deficit hyperactivity disorder.

TABLE 3 Quality of life in ADHD children ($n = 274$).

Impact on quality of life	*n* (%)
Mild (<60 points)	217 (79.2)
Moderate (60–80 points)	47 (17.2)
Severe (>80 points)	10 (3.6)

ADHD, attention-deficit hyperactivity disorder.

Quality of life findings are shown in Table 3. Most of the participants (79.2%) reported mild decreases in quality of life, and 20.8% had moderate to severe reductions in quality of life. High-risk OSA among ADHD children was significantly associated with reduced quality of life (OR = 4.24, 95% CI: 2.18–8.25, $P < 0.001$; Table 4). Among 30 ADHD subjects with overweight/obesity, there were 10 children (33.3%) who had a high-risk for OSA. In addition, univariate analysis across multiple potential confounders revealed a significant association between high-risk OSA and obesity (OR = 2.55, 95% CI: 1.11–5.86, $P = 0.023$) as shown in Table 4. In the multivariate analysis, factor loading of variables with univariate association P-values < 0.25, namely obesity, asthma, and quality of life revealed a significant independent association between high-risk OSA and obesity (adjusted OR = 2.84, 95% CI: 1.17–6.88, $P = 0.021$), and high-risk OSA and quality of life (adjusted OR = 4.46, 95% CI: 2.26–8.81, $P < 0.001$). Regarding asthma, a significant association emerged in the univariate analysis, but was not retained in the multivariate analysis (Table 5).

Discussion

Our study demonstrated a relatively elevated prevalence of high-risk OSA among Thai children diagnosed with ADHD (18.2%) by using the previously validated POSAST questionnaire. According to previous publications, the prevalence of OSA in community Thai children was estimated at 0.69–1.3% (2, 3). Several previous studies have identified an association between OSA and ADHD around the world (4, 11, 12). The current study has uncovered that the validated POSAST sleep questionnaire can be used as a screening tool to identify the children with high-risk for OSA in a pediatric

TABLE 4 Univariate analysis of associated factors for high-risk OSA in ADHD children ($n = 274$).

Factors	Low Risk OSA, ($n = 224$) n (%)	High Risk OSA, ($n = 50$) n (%)	OR (95% CI)	P-value
Age, mean ± SD, year[a]	10.40 ± 2.61	10.36 ± 2.50	-	0.920
Sex[b]				0.810
Male	185 (82.6)	42 (84.0)	1	
Female	39 (17.4)	8 (16.0)	0.90 (0.39, 2.08)	
Asthma[b]				0.230
No	218 (97.3)	47 (94.0)	1	
Yes	6 (2.7)	3 (6.0)	2.32 (0.56, 9.61)	
Chronic rhinitis[b]				0.800
No	187 (83.5)	41 (82.0)	1	
Yes	37 (16.5)	9 (18.0)	1.11 (0.50, 2.48)	
Obesity[b,d]				**0.023**
No	204 (91.1)	40 (80.0)	1	
Yes	20 (8.9)	10 (20.0)	2.55 (1.11, 5.86)	
ADHD duration, median (IQR), month[c]	22.24 (9.61, 46.81)	21.39 (10.87, 36.83)	-	0.855
Quality of life[e]				**<0.001**
Mild	189 (84.4)	28 (56.0)	1	
Moderate to severe	35 (15.6)	22 (44.0)	4.24 (2.18, 8.25)	

OSA, obstructive sleep apnea; ADHD, attention-deficit hyperactivity disorder; OR, odds ratio; CI, confidence interval; SD, standard deviation; IQR, interquartile range. The data was analyzed by using: [a]Unpaired T-test, [b]Chi-Square Test, [c]Mann-Whitney U Test. [d]Obesity was defined by % weight-for-height > 140. [e]Impact on quality of life was defined as "mild" if the OSA-18 questionnaire score < 60 points, and "moderate to severe" if the score ≥ 60 points. Bold values indicate statistical significance.

psychiatry clinic. Accordingly, ADHD children at high-risk for OSA based on the POSAST instrument should be referred to specialists for further evaluation. Our findings are in close concordance with a systematic review that revealed an estimated prevalence of OSA in ADHD children between 20 and 30% (12). Although the mechanisms underlying the increased prevalence of OSA among children with ADHD remain unknown, previous work in rodent models (22, 23) has led to the assumption that intermittent hypoxia and disrupted sleep induced by upper airway dysfunction during sleep might impose an adverse impact on brain structure and function (24–26), as well as on cognitive function (5, 27, 28), leading to inattention and hyperactivity in developing subjects (5, 28, 29). The presence of high-risk OSA was also associated with an increased risk for reduced quality of life, similar to the findings reported by a meta-analysis by Baldassari et al. (30) From the results of 10 separate studies, 3 studies compared the quality of life in children with OSA and healthy children using the Child Health Questionnaire (CHQ), and found that children with OSA had poorer quality of life. In the other 7 publications, 369 children with OSA undergoing adenotonsillectomy were evaluated using the OSA-18 questionnaire. The total OSA-18 score and each of the domain scores showed significant improvements after adenotonsillectomy and remained improved during long-term follow-up (30). Furthermore, in the only randomized controlled study to date, the CHAT study, significant improvements in quality of life emerged in the group undergoing adenotonsillectomy when compared to the group assigned to watchful waiting (31). Since the prevalence of high-risk OSA in children with ADHD was high and significantly associated with reduced quality of life, screening for OSA in ADHD patients is recommended. Screening for pediatric OSA in children with ADHD or other risk groups by using a questionnaire such as POSAST is easy and cost-effective.

TABLE 5 Multivariate analysis of associated factors for high-risk OSA in ADHD children ($n = 274$).

Factors	Adjusted OR (95% CI)	P-value
Obesity	2.84 (1.17, 6.88)	**0.021**
Asthma	2.49 (0.52, 11.87)	0.251
Quality of life	4.46 (2.26, 8.81)	**< 0.001**

OSA, obstructive sleep apnea; ADHD, attention-deficit hyperactivity disorder; CI, confidence interval. Bold values indicate statistical significance.

Similar to previous studies (32, 33), the current study uncovered a significant association between OSA and obesity. We found the prevalence of high-risk OSA in obese children was 33.3%. This result was in accordance with the previous study with the prevalence of OSA among obese children was 44.6% (32, 33). We should also point out that children suffering from ADHD are also at higher risk of being overweight or obese. The odds ratio for obesity in ADHD children with high-risk OSA was 2.55, which is similar to the previous study that demonstrated the odds ratio for obesity in children with OSA was 4.69 (32, 33). Moreover, the presence of somnolence in children with ADHD

may be facilitated by the underlying presence of concurrent obesity and OSA (34, 35).

Several studies have explored the potential relationships between asthma and sleep-disordered breathing. Most of the studies have uncovered a substantial risk afforded by the presence of asthma on OSA-related risk (36–38). In a large multicentric cross-sectional study involving 22,478 children aged 5–12 years, the authors reported that the prevalence of SDB and asthma were 12 and 3.5%, respectively and that habitual snoring and OSA were significantly associated with asthma with corresponding odds ratios of 1.28 and 1.92 (39). Such findings are remarkably similar to the current study. However, although the association between asthma and OSA in patients with ADHD was statistically significant in the univariate analysis, it did not persist in the multivariate analysis, possibly due to the relatively small number of patients diagnosed with asthma in our study.

There were limitations in this study. First, the diagnosis of OSA in this study was done by using POSAST, which is considered a subjective tool. Because of limitations of the resources for using PSG, which is the gold standard for the diagnosis of OSA, we considered using the questionnaire as a screening tool for identifying patients with high risk for moderate and severe OSA. Then, these patients should be referred to specialists for further management. Second, the risk for OSA in patients who had a POSAST score less than the cut-off could not be ruled out. Follow-up is recommended and if there are persistent symptoms or signs suggestive of OSA, the patients should also be referred to specialists for further evaluation. Third, this study did not include patients with specific underlying conditions who are at high risk for OSA, such as Down syndrome, craniofacial anomalies, or neuromuscular diseases. We also included only pediatric patients aged 5 years and older in this study because of the difficulty for diagnosis of ADHD in a younger age group. Hence, a high index of suspicion of OSA in ADHD patients at a younger age is recommended.

Conclusion

The prevalence of high-risk OSA in children with ADHD is high and appears to impose a significant detrimental effect on the quality of life. Therefore, screening for OSA among ADHD patients is recommended and should enable early detection along with timely treatment ultimately aiming at the prevention of the adverse consequences of OSA.

Data availability statement

The datasets presented in this article are not readily available because no potential identifiable data was provided. Requests to access the datasets should be directed to archwin.tan@mahidol.ac.th.

Ethics statement

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

Author contributions

TP, AT, and TH contributed to conception and design of the study. TP organized the database and wrote the first draft of the manuscript. TP and AT performed the statistical analysis. AT, KU, and DG contributed to manuscript revision. All authors contributed to read and approved the submitted version.

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Conflict of interest

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

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Thematic trends and knowledge structure on cognitive behavior therapy for insomnia: A bibliometric and visualization analysis

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Objective: To find publications trend about cognitive behavior therapy for insomnia (CBTI) using bibliometric and visualization analysis. In this study, the authors sought to identify the publication trends of peer-reviewed articles about CBTI.

Materials and methods: Analyses were focused on the past 18 years from 2004 to 2021. All searches were performed on the Web of Science Core Collection database. The search was repeated to include structural cognitive behavior therapy for insomnia. Quantitative analysis was assessed using the bibliometric tool. Visualization analysis was carried out using VOSviewer.

Results: In the 736 articles reviewed, the number of publications has been increasing every year for the past 18 years. Behavioral sleep medicine and sleep were the most active journals published on CBTI. The United States and Canada had the highest scientific publications in the field. Morin CM and Espie CA were the most active authors. The study type mostly observed were randomized controlled trials, meta-analyses, and epidemiological. Publications on digital-based cognitive behavior therapy and accessibility to primary care settings represent the future trends of research on CBTI.

Conclusion: Possible explanations for CBTI publication trends were discussed, including the emergence of the evidence-based therapy, feasibility, and scalability. Potential CBTI publications trends in the future and clinical implications were also discussed.

KEYWORDS

cognitive behavior therapy, insomnia, visualization, psychotherapy, bibliometric

Introduction

Cognitive Behavior Therapy for Insomnia (CBTI) is a psychotherapeutic approach to treating insomnia that includes cognitive, behavioral, and educational components (1). Cognitive content in CBTI attempts to change dysfunctional beliefs about sleep often termed cognitive restructuring. Behavioral content in CBTI consist of relaxation training (such as deep breathing exercises, progressive muscle relaxation, hypnosis, and/or meditation), stimulus control (changing the association of bedtime habit making sleep difficulties, like eating, watching TV, or using a cell phone or computer) (2), and sleep restriction (limits time spent in bed during the day and/or night to reestablish a consistent sleep schedule). Psychoeducation about the connection between feelings, thoughts, behaviors, and sleep is central to CBTI which is often aided by a sleep diary. Although CBTI lasts between 6–8 sessions (3), the length may vary according to the provider and person's needs. Treatment may be as short as two sessions when given by a primary care provider (4), furthermore, there were reports of single-shot CBTI and its effectiveness in literature. Although cognitive therapy and behavioral therapy alone are effective, patients will experience the greatest benefit when all components of CBTI are combined with an 8-week course (5).

Insomnia is a major public health concern with a prevalence of about 10–20% (6). There are both pharmacological (such as benzodiazepines, z-drugs, melatonin, antidepressants, antipsychotics, and antihistamines) and non-pharmacological treatments (sleep hygiene, cognitive behavior therapy, relaxation therapy, multicomponent therapy, and paradoxical intention) available for insomnia (7). CBTI is one of the effective non-pharmacological treatments which can be applied to primary insomnia or comorbid insomnia in chronic conditions without the fear of drug interaction. However, due to the lack of trained clinicians, the uneven geographic distribution of knowledgeable professionals, and high costs, CBTI is an effective but underutilized treatment for insomnia (8).

Bibliometrics is a statistical method which provides researchers with qualitative and quantitative characteristics of literature by analyzing measurement indicators such as countries, journals, institutions, authors, and keywords, to describe current trends and discover the field hotspots. Bibliometric analysis has made a great contribution to the development of treatment and clinical guidelines (9). Therefore, this study intends to use bibliometrics to analyze the research status and research hotspots of CBTI, to lead the direction for related fields in the future.

Materials and methods

The criteria for considering studies for this bibliometric analysis are described below.

Study design

The papers published between the years 2004 and 2021 relevant to cognitive behavior therapy for insomnia were included. A detailed search strategy was developed for this study, and two researchers (QX and DP) in the field conducted article screening. Having more than one screener ensures the elimination of bias and errors in methodology resulting in data of high quality. The bibliometric and visualization analysis was done.

The current study aimed to examine possible trends in the volume of peer-reviewed publications on cognitive behavioral interventions for insomnia across time and to assess the evolution of such trends.

Data source and retrieval strategies

Data retrieval for this study was conducted on March 30, 2022. Data are drawn from the Web of Science Core Collection (WOSCC) using the Science Citation Index Expanded, the Social Science Citation Index, the Arts, and Humanities Citation Index, and the Emerging Sources Citation Index (SCIE, SSCI, AHCI, and ESCI) for the period of 18 years (2004–2021). Documents for analysis were restricted to original academic journal contributions (i.e., articles and reviews) which we will refer to as "papers." **Figure 1** shows the adapted Prisma flow diagram for the study (10).

After multiple iterations and using wildcards the following 2 concepts were used as topic search terms: concept 1, Cognitive Behavior Therapy (TS = ("cogniti* behavio* therap*") OR Behavior Therapy (TS = ("behavio* therap*" OR "behavio* psychotherap*") AND Cognitive Therapy (TS = ("cogniti* therap*" OR "cogniti* psychotherap*") AND concept 2, insomnia (TS = (insomnia OR sleep Initiation and maintenance disorder* OR disorder* of initiating and maintaining sleep OR primary insomnia OR transient insomnia OR chronic insomnia OR secondary insomnia OR sleeplessness OR insomnia disorder* OR sleep wake disorder* OR sleep initiation dysfunction)).

Eligibility criteria

Criteria for inclusion of a paper were as follows: (a) the main problem statement was insomnia (primary or comorbid), (b) the type of study was empirical, replication or review, and (c) the treatment condition used or main theme of the review was therapy consisting of both cognitive and behavioral in content.

As such the final included papers are relevant to cognitive behavior therapy for insomnia (CBTI). And those articles comparing behavior therapy and cognitive therapy for insomnia populated with boolean search strategies were excluded.

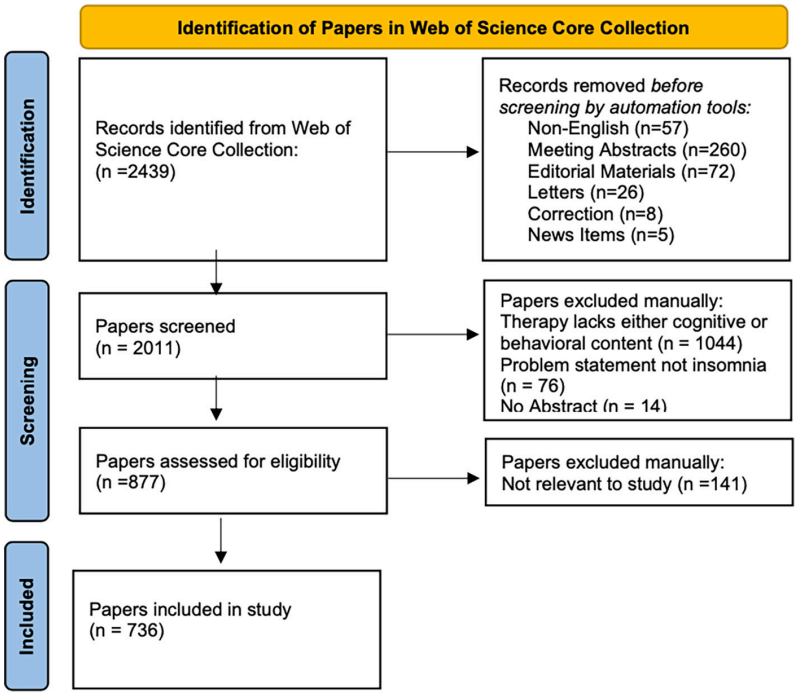

FIGURE 1
Flow diagram.

Study variables

Dependent variable

Papers on Cognitive Behavior Therapy for insomnia.

Independent variable

Number of publications, distribution of journals, the contribution of authors, institutions, and countries, top-cited papers, and keyword co-occurrences.

Quantitative and visualization tools

The Bibliometrix (11), an R package for bibliometric analysis was used to analyze the annual scientific productions, citation counting, journal, author, institution, and country distribution. The VOSviewer is visualization software that constructs a visualization network map from the co-occurrence of keywords (12).

Results

Number of publications

The study included a total of 736 papers on CBTI. The number of annual publication papers increased every year, from 11 papers in 2004 to 138 in 2021. The study included papers on randomized clinical/controlled trials (RCT) (307), original research other than RCT (234), meta-analysis with systematic reviews (32), meta-analyses (19), systematic reviews (31) and reviews other than systematic reviews and meta-analysis (113). Figure 2 shows yearly trends and top 10 journals publishing CBTI papers from 2004 to 2021.

Distribution of journals

Cognitive behavior therapy for insomnia papers were distributed in 236 journals. Sleep published the most papers (62/736, 8.42%), followed by Behavioral Sleep Medicine (52/736, 7.07%). The highest impact factors (IF) and h-index were observed with Sleep (IF: 5.849, h-index: 35) and Sleep Medicine Reviews (IF:11.609, h-index:21) (Table 1). Table 1 listed the top 10 journals according to volumes of publications on CBTI.

Contribution of authors, institutions, and countries

There were 957 institutions that participated in the CBTI papers. Table 2 presented the top 10 institutions that contributed papers on CBTI. The University of Laval published

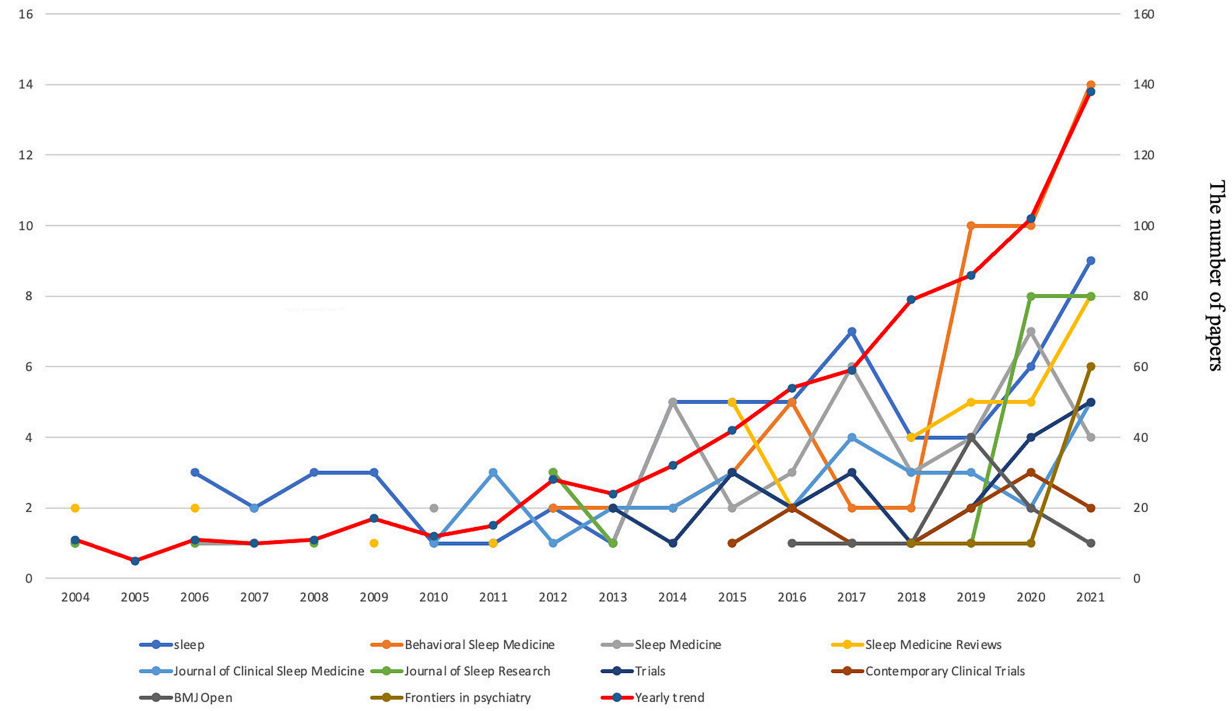

FIGURE 2
Yearly trends and top 10 journals publishing CBTI papers from 2004–2021.

TABLE 1 Top 10 journals publishing papers on CBTI.

Rank	Journal	*n* (%)*	IF	Mean IF**	H-index
1	Sleep	62 (8.42)	5.849	5.0566	35
2	Behavioral Sleep Medicine	52 (7.07)	2.964	2.7614	13
3	Sleep Medicine	42 (5.71)	3.492	3.3352	17
4	Sleep Medicine Reviews	37 (5.03)	11.609	10.2598	21
5	Journal of Clinical Sleep Medicine	33 (4.48)	4.062	3.5858	17
6	Journal of Sleep Research	26 (3.53)	3.981	3.5456	11
7	Trials	23 (3.13)	2.279	2.0346	8
8	Contemporary Clinical Trials	12 (1.63)	2.226	2.2182	5
9	BMJ Open	10 (1.36)	2.692	2.4692	4
10	Frontiers in Psychiatry	9 (1.22)	4.157	3.3112	1

*Denominator = Total number of papers on CBTI retrieved from Web of Science Core Collection from 2004 to 2021 (N = 736); **Mean IF = Five-year mean impact factor for 2017–2021.

the most papers (79/736, 10.73%), followed by the University of Pennsylvania (68/736, 9.24%) (Table 3).

Only 33 countries around the globe contributed to papers on CBTI. Table 3 shows the top 10 countries that published papers on CBTI. The United States published the most articles (296/736,40.22%), followed by Canada (62/736,8.42%) (Table 3).

The study identified 2,783 authors contributing to CBTI papers. Table 2 presented the top 10 authors with the highest yields of CBTI studies. Morin CM had the most papers (38/736,

TABLE 2 Top 10 authors in terms of publications on CBTI.

Rank	Author	Country	*n* (%)*	Citations	Average citations**	H-index
1	Morin CM	Canada	38 (5.16)	801	21.08	19
2	Espie CA	United Kingdom	34 (4.62)	674	19.82	21
3	Ritterband LM	United States	22 (2.99)	418	19.00	11
4	Savard J	Canada	22 (2.99)	359	16.32	13
5	Garland SN	Canada	18 (2.45)	114	6.33	11
6	Manber R	United States	18 (2.45)	276	15.33	15
7	Perlis ML	United States	18 (2.45)	233	12.94	14
8	Lack L	Australia	17 (2.31)	86	5.06	9
9	Van Straten A	Netherlands	17 (2.31)	223	13.12	10
10	Edinger JD	United States	16 (2.17)	512	32.00	14

*Denominator = Total number of papers on CBTI retrieved from Web of Science Core Collection from 2004 to 2021 (N = 736); **Average citations = Citation number divided by the number of journals publishing papers.

TABLE 3 Top 10 countries and institutions contributing papers on CBTI.

Ranks	Country	*n* (%)*	Institutions	Country	*n* (%)*
1	United States	296 (40.22)	University of Laval	Canada	79 (10.73)
2	Canada	62 (8.42)	University of Pennsylvania	United States	68 (9.24)
3	Australia	61 (8.29)	University of Oxford	United Kingdom	63 (8.56)
4	China	53 (7.20)	Karolinska Institute	Sweden	56 (7.61)
5	United Kingdom	52 (7.07)	Vrije University Amsterdam	Holland	51 (6.93)
6	Netherlands	34 (4.62)	University of Sydney	Australia	49 (6.66)
7	Sweden	30 (4.08)	Flinders University	Australia	39 (5.30)
8	Germany	27 (3.67)	University of Rochester	United States	37 (5.03)
9	Japan	19 (2.58)	University of Michigan	United States	36 (4.89)
10	Korea	18 (2.45)	University of Pittsburgh	United States	36 (4.89)

*Denominator = Total number of papers on CBTI retrieved from Web of Science Core Collection from 2004 to 2021 (N = 736).

5.16%), followed by Espie CA (34/736, 4.62%). Espie CA and Morin CM had the highest h-index of 21 and 19, respectively (Table 2).

Top cited papers

Out of the top 10 cited papers in this study (Table 4), four were practical recommendations for the management of insomnia. One was a pilot study done on depression co-morbidity. One was a review on the relationship between sleep and pain. Two were meta-analyses on cognitive behavior therapy for insomnia. And two were a randomized controlled trial on CBT vs. z-drug (viz Zopiclone and Zolpidem) for insomnia.

Keywords co-occurrence and visual analysis

The research directions of CBTI publications collected by WoS were divided into five clusters (Figure 3). The top ten keywords as detected by VOSviewer were insomnia (n = 460), cognitive behavioral therapy (n = 358), sleep (n = 227), depression (n = 174), meta analysis (n = 167), efficacy (n = 161), validation (n = 131), older-adults (n = 121), severity index (n = 114) and randomized controlled trial (n = 102).

The visual analysis shows the research trends. Most of the participants were adolescents, adults, older adults, veterans, and women. The study type mostly observed were randomized controlled trials, meta-analyses, and epidemiological. CBTI has been used in comorbid conditions both physical and psychiatric conditions such as stress, post-traumatic stress disorder, anxiety, depression, pain, fatigue, and cancer. It can be drawn that measurement tools used to test the effectiveness of CBTI were insomnia severity index, sleep quality index, hospital anxiety depression scale, quality of life, polysomnography, and actigraphy. The appearance of words like the internet and online shows the digital adoption of cognitive behavior therapy in recent years.

Excluded papers

Most of the papers excluded were about Cognitive behavior therapy for other disorders, notably CBT for tinnitus,

TABLE 4 Top 10 most cited papers on CBTI during study period.

Rank	Title	Author	Journal	Year	Citations
1	Psychological and behavioral treatment of insomnia:update of the recent evidence (1998–2004)	Morin CM	Sleep	2006	749
2	Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians	Qaseem A	Ann Intern Med	2016	663
3	How do sleep disturbance and chronic pain inter-relate? Insights from the longitudinal and cognitive-behavioral clinical trials literature	Smith MT	Sleep Med Rev	2004	542
4	Cognitive behavioral therapy for insomnia enhances depression outcome in patients with comorbid major depressive disorder and insomnia	Manber R	Sleep	2008	521
5	Practice parameters for the psychological and behavioral treatment of insomnia: An update. An American Academy of Sleep Medicine Report	Morgenthaler T	Sleep	2006	496
6	Cognitive behavioral therapy, singly and combined with medication, for persistent insomnia: a randomized controlled trial	Morin CM	Jama-J Am Med Assoc	2009	414
7	Cognitive Behavioral Therapy for Chronic Insomnia: A Systematic Review and Meta-analysis	Trauer JM	Ann Intern Med	2015	401
8	Dealing with sleep problems during home confinement due to the COVID-19 outbreak: Practical recommendations from a task force of the European CBT-I Academy	Altena E	J Sleep Res	2020	348
9	Cognitive behavioral therapy vs. zopiclone for treatment of chronic primary insomnia in older adults: a randomized controlled trial	Sivertsen B	Jama-J Am Med Assoc	2006	342
10	Comparative meta-analysis of behavioral interventions for insomnia and their efficacy in middle-aged adults and in older adults 55+years of age	Irwin MR	Health Psychol	2006	322

cancer, pain, hypertension, and psychiatric disorders. The pharmacological management articles were also excluded.

Discussion

Global trend on cognitive behavior therapy for insomnia

This study found that the number of annual publication papers on CBTI increased every year. Sleep and Behavioral Sleep Medicine were the top journals of CBTI publications, among the top 10 authors who published CBTI papers, four are from the United States and three are from Canada. The University of Laval and the University of Pennsylvania were the top institutions that published papers on CBTI, and the United States and Canada were the top countries that published papers on CBTI.

This study found that the authors in an institution from countries in North America and Europe contribute more to CBTI research. China, Japan, and Korea taking a lead in Asian Continent. In the identified publications, the United States, Canada, Australia, and China were currently leaders in CBTI. And the study found that, among the top 10 authors who published CBTI papers, four are from the United States and three are from Canada. Four of the top 10 institutions on CBTI papers were from the United States, and another five were from Canada, Sweden, the United Kingdom, Australia, and Holland. This might be due to the better economic and scientific status of each country or territory and better communication among them similar to another bibliometric analysis study (13).

The changes in the number of scholarly publications in a field were an important indicator of trends in the field (14). The journal with higher publication frequency provides researchers with guidelines for paper publication. The study found that Sleep and Behavioral Sleep Medicine had a high frequency of CBTI publications. Nowadays, researchers are probing on metabolic, hormonal, genetic, cellular, and subcellular effects of sleep disturbances (15). However, CBTI research is still in the early stage, and the cooperation between authors is still limited. Facilitating collaboration between authors, institutions and countries will increase the number of authors who regularly publish in the field and contribute to a more effective exchange of experiences on CBTI research to improve the quality of treatment methods for insomnia.

Hot topics on cognitive behavior therapy for insomnia

The study found that CBTI has been widely used in comorbid conditions both physical and psychiatric conditions such as stress, post-traumatic stress disorder, anxiety, depression, pain, fatigue, and cancer. Co-occurrence can be drawn that the study type mostly observed were randomized controlled trials, meta-analyses, and epidemiological, and measurement tools used to test the effectiveness of

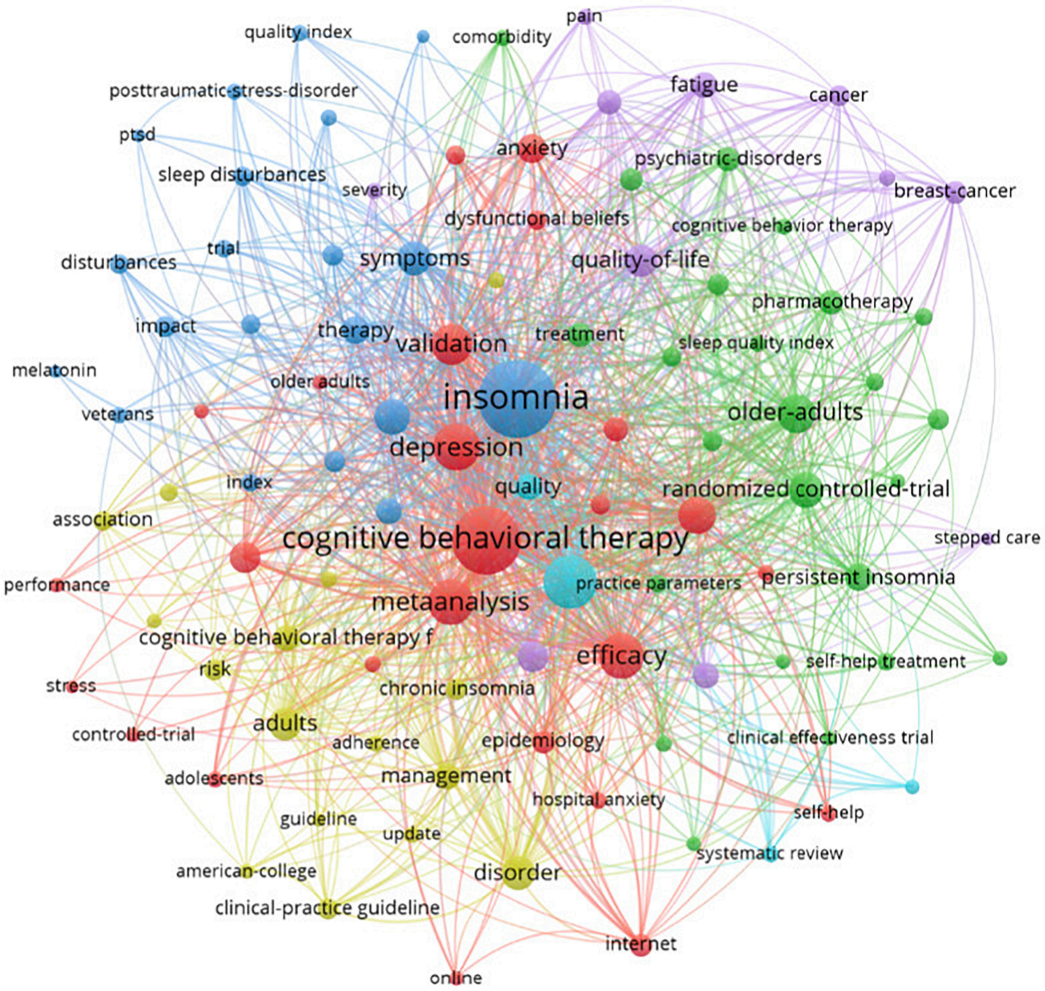

FIGURE 3
Network visualization map of co-occurrence on top 100 keywords. Each node is represented by a circle with labels for different words. Larger circles represent more frequently used words. The thickness and length of the lines linked between nodes represent the strength of the association between the corresponding nodes.

CBTI were insomnia severity index, sleep quality index, polysomnography among others.

Cognitive behavior therapy for insomnia has been accepted as a first-line treatment, and American Academy of Sleep Medicine (AASM) guidelines also recommend CBTI as standard psychological and behavioral therapy for chronic insomnia. In addition, The National Institute for Health and Care Excellence (NICE) guidelines and the latest European Sleep Research Association guidelines also recommend CBTI as an initial treatment for chronic insomnia in any age group (16). Numerous previous studies have shown that CBTIs were effective in reducing the severity of insomnia, also in primary care settings (17). Results from previous studies on the effectiveness of CBTI have shown response rates over 60%, with good initial responses maintained after 6 months (18). Silversten et al. compared CBTI, Zopiclone (a drug treatment), and placebo in a sample of 46 older adults diagnosed with chronic insomnia. They found that over just 6 weeks, patients who received CBTI reported more improvements in sleep efficiency, slow-wave sleep, middle of the night awakenings, compared with patients who received the drug or a placebo. These results persisted even at 6 months, with patients receiving CBTI reporting greater improvements in sleep efficiency than those receiving Zopiclone (19).

Cognitive behavior therapy for insomnia also has a good effect on insomnia with comorbid conditions, especially depression and anxiety. Anxiety disorders are the most common mental health disorder worldwide, with a prevalence of 25%, and people with anxiety disorders often experience poor sleep quality, and further exacerbate anxiety. Molecular imaging evidence also suggests that there are specific neurotransmitter mechanisms of sleep-wake regulation associated with anxiety

(20). It is known that there is a benefit of CBTI not only for insomnia but also for comorbid anxiety disorder (20). A report of ten studies examining the effect of CBTI on depressive outcomes in patients with co-occurring depression and insomnia reported that CBTI may be an appropriate stand-alone treatment for co-occurring depression and insomnia, or in combination with antidepressants (21). Several other meta-analyses have similar results (22). Apart from anxiety and depression, CBTI has been applied to the treatment of comorbid insomnia in pain, migraine, fatigue, chronic obstructive pulmonary disease, asthma, Parkinson's disease, and other neurological as well as psychiatric disorders (23).

Subjective-objective sleep differences have long been a difficult problem in sleep medicine practice, which is because sleep is a subjective perceptual experience of a person, so subjective sleep parameters are often inconsistent with objective sleep parameters measured by polysomnography or actigraphy. The measurement tools or indicators like polysomnography, actigraphy, and insomnia severity index (ISI) are being widely used in the field of sleep (24). Polysomnography was considered the "gold standard" for assessing sleep characteristics and stages. An advantage of actigraphy is that it can assess sleep outcomes over multiple nights, allowing an assessment of sleep patterns and variability (25). ISI is particularly useful in population and clinical settings where more than one condition needs to be measured at a time without overburdening the patient (26). With the help of psychometric tools and technologies available, studies have found that CBTI is effective regardless of whether the subjective-objective sleep differences are large or small (27).

Most potential areas of cognitive behavior therapy for insomnia

With keywords co-occurrence, it can be drawn that digital CBTI is a research hotspot in recent years. CBTI is recommended as a first-line treatment. However, some doctors were difficult to carry out CBTI due to a lack of professional knowledge, sufficient time, qualified psychologists, high cost, and other reasons (28).

The number of trained CBTI practitioners is scarce. Most patients learn about sleeping tablets than CBTI due to prescribing physicians and advertisements and misconceptions about CBTI (8). Health care workers and physicians play an important role in the dissemination of CBTI (8). In addition, there is an optimistic view regarding CBTI utilization. Even primary healthcare workers can deliver 6-session CBT to insomnia patients without the involvement of physicians and with minimal supervision (29). Furthermore, reports showed that brief CBT can be delivered with teleconsultation and self-help materials (30). These findings suggest that brief and effective CBTI can be developed to suit primary care settings. In primary care settings, with limited resources, various modifications of CBTI have been investigated such as group CBTI, and brief CBTI (4). Several CBTI modifications are effective and comparative to standard CBTI in routine care settings (31).

Furthermore, the application of digital CBTI may bridge the gap. Digital CBTI can be divided into different types including internet, phone, email, and mobile app-based CBTI. Compared with face-to-face CBTI, online CBTI is a cost-effective and time-effective, scalable, and accessible, meanwhile interactive web design, animation technology, automated multimedia web applications coupled with effective clinical support can greatly improve patient motivation and outcomes (32). Espied et al. (33) found that the online CBT was related to adherence to some therapists' guidance in patients with co-morbid insomnia and depression. The results of sleep onset latency and sleep efficiency of verbally contacted telephone-based CBTI were suboptimal, possibly because therapist-patient interaction may play a key role in the success of digital CBTI. Online CBTI with therapists significantly improved several sleep metrics, including self-reported total sleep time (compared to phone-based CBTI), wake after sleep onset (compared to mobile app-based CBTI, phone-based CBTI, and web-based CBTI without a therapist), and sleep efficiency (compared to online CBTI without a therapist). In addition, a meta-analysis of assessment methods analyzing digital CBTI found that compared with face-to-face therapy, digital CBTI prolonged self-reported total sleep time, shortened sleep onset latency, shortened wake after sleep onset, and better sleep efficiency (32). Online CBTI combined with virtual therapists is preferred considering better treatment outcomes, offering promising results, scalability, and addressing the lack of real therapists in the future (32). At the same time, future research should focus on raising the awareness of primary care providers (general practitioners, primary care nurses, etc.) about CBTI, optimizing CBTI online courses (for example, doing some preparation before each CBTI meeting, having a specific agenda, and schedule the meeting at a time when the primary care provider is less tiring), increased training of primary care providers (such as more thorough discussion of the different components of CBTI treatment, negotiate with the patient on the goals of each session, regular phone calls to actively follow up with the patient) and providing patients with some relevant paper materials (34), and explore other new behavioral treatments such as population-specific CBTI or combination therapy. Digital CBTI will help provide immediate evidence-based care to individuals in rural/remote areas during the current COVID-19 pandemic and social distancing in the future (35).

Limitation

There are some limitations of our bibliometric study. Firstly, the data was searched from the database of WOSCC and only

papers published in the English language were selected. The strategy might have missed some important literature in the field. Secondly, the citation of the same paper in different databases is different, and the citation of WOSCC is different than that of google scholar. Although the variable contributions of authors include co-authors, the possibility of co-authorship and their contribution to the field could not be ascertained. These issues should be addressed in future studies.

Conclusion

This research systematically and comprehensively analyzes the research characteristics and trends of the CBTI paper. The field of CBTI is maturing, with great potential and broad prospects. The quality of research in this field is high. The top journals can be used by researchers as target journals for publications on CBTI. Additionally, the topics of special interest and novel studies in this field are indicative of the future directions in CBTI research. Over the past 18 years, CBTI has dominated the professional literature. CBTI was applied to insomnia as well as comorbid conditions with insomnia. New approaches like digital-based CBTI have emerged, likely influenced by the increase in the use of digital platforms. Future research should focus on creating new delivery models for CBTI that emphasize the prevention of insomnia and the scalability of treatments.

Data availability statement

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

Author contributions

QX and DP worked with KA to formulate the search formula, identify the search library, literature search, and data analysis. LC, YY, and SZ helped draft the manuscript and screen the data. DP visualized and revised the manuscript. HY and BZ helped with the conception and revision of the full text. All authors contributed to the article and approved the submitted version.

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Conflict of interest

DP was employed by the company Mental Health and Yoga Pvt., Ltd.

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

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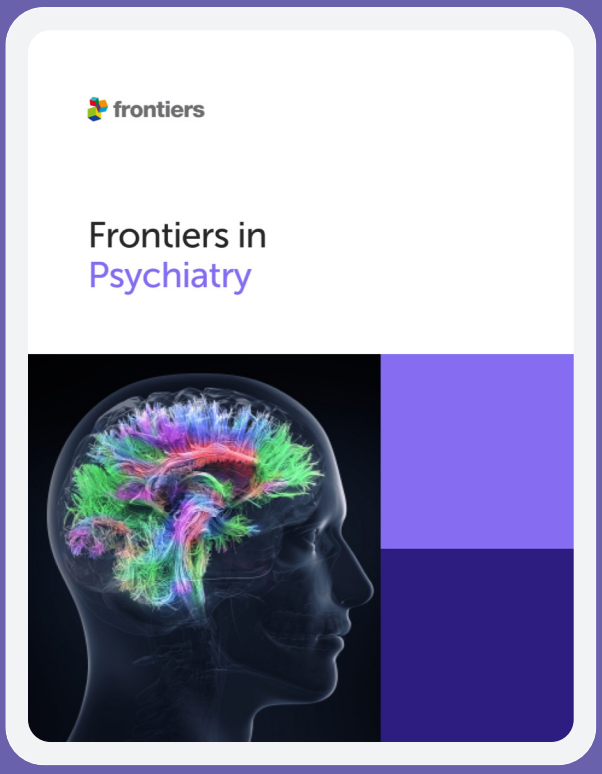

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