SLEEP AND PSYCHOLOGICAL TRAUMA OR STRESS

EDITED BY: Seog Ju Kim, Tobias Hecker and Heon-Jeong Lee
PUBLISHED IN: Frontiers in Psychiatry

frontiers Research Topics

frontiers

ISSN 1664-8714
ISBN 978-2-88976-526-3
DOI 10.3389/978-2-88976-526-3

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: frontiersin.org/about/contact

SLEEP AND PSYCHOLOGICAL TRAUMA OR STRESS

Topic Editors:
Seog Ju Kim, Sungkyunkwan University, South Korea
Tobias Hecker, Bielefeld University, Germany
Heon-Jeong Lee, Korea University, South Korea

Citation: Kim, S. J., Hecker, T., Lee, H.-J., eds. (2022). Sleep and Psychological Trauma or Stress. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88976-526-3

Table of Contents

frontiers | Frontiers in Psychiatry

EDITORIAL
published: 14 June 2022
doi: 10.3389/fpsyt.2022.951217

Editorial: Sleep and Psychological Trauma or Stress

*Seog Ju Kim**

Department of Psychiatry, Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, South Korea

Keywords: sleep, trauma, stress, posttraumatic stress disorder, depression

Editorial on the Research Topic

Sleep and Psychological Trauma or Stress

Restorative sleep plays a critical role in maintaining physical and mental health. Sleep disturbances frequently co-occur with trauma or stress related disorder such as posttraumatic stress disorder (PTSD). It has long been thought that interventions focusing on trauma itself would eventually reduce disturbed sleep. However, accumulating evidence have shown that sleep disturbances play a central role in both the development and maintenance of PTSD and therefore require clinical attention. As well as traumatic stress, stressful experiences are also associated with sleep (1). Stress can worsen the sleep quality, while poor sleep can also interfere with emotional processing of stressful experiences. The current Research Topic represents a collection of papers investigating the relationship between sleep abnormalities and psychological trauma or stress, as well as studies analyzing potential mechanisms connecting these pathologies.

In the current Research Topic, 1 review article and 1 original article on the association between PTSD and sleep were published. The review article by Lancel et al. introduced sleep disorders which have been suggested as predisposing, facilitating, and perpetuating factors of PTSD. This review also introduces non-pharmacological and pharmacological treatments for the four major sleep disorders commonly accompanying PTSD. Authors strongly recommended an initial comprehensive evaluation and timely treatment for comorbid sleep disorders for PTSD patients.

In the article by Denis et al., the relationship between sleep microarchitecture and symptom severity in trauma-exposed participants with and without PTSD were investigated. Contrary to previous studies, beta power was increased in trauma-exposed controls (TEC) compared to PTSD. Spectral power in the beta frequency was associated with reduced symptoms. Their results suggest an adaptive role of beta power during sleep for individuals exposed to trauma.

There are many stressful situations in hospital both for patients and health care workers, and these stressful situations can be associated with sleep. The current Research Topic covers the relationship between sleep and hospital-related stressful situations such as COVID-19, HIV infection, operation, and pregnancy. Cleper et al. reported that the influence of COVID-19 work-related stressors on sleep in physicians and nurses working in designated COVID-19 wards. COVID-19 frontline health care workers were more likely to report sleep difficulties compared to non-COVID-19 health care workers in the same hospital. In particular, the negative experiences, mainly witnessing patient's physical suffering or death, partially explained the association between COVID-19 work and sleep disturbances.

The reliability and validity of the Chinese version of Pittsburgh Sleep Quality Index (PSQI) in people living with HIV were assessed by Yan et al.. PSQI was used to measure sleep quality 5 years after HIV diagnosis. Sleep disturbances were associated with less income, higher CD4 counts, antiretroviral treatment initiation, exercise, depression, and higher stress levels. Authors reported that the Chinese version of PSQI is feasible for use among people living with HIV considering its internal consistency and the construct validity.

OPEN ACCESS

Edited and reviewed by:
Mehmet Y. Agargün, Yuzuncu Yil University, Turkey

***Correspondence:**
Seog Ju Kim
ksj7126@skku.edu

Specialty section:
This article was submitted to Sleep Disorders, a section of the journal Frontiers in Psychiatry

Received: *23 May 2022*
Accepted: *30 May 2022*
Published: *14 June 2022*

Citation:
Kim SJ (2022) Editorial: Sleep and Psychological Trauma or Stress. Front. Psychiatry 13:951217. doi: 10.3389/fpsyt.2022.951217

Applicability of intranasal dexmedetomidine (DEX) in the treatment of preoperative insomnia was reported by Zeng et al.. Patients with preoperative insomnia were divided into two groups of intranasal DEX and normal saline (NS). Intranasal DEX shorten sleep latency and lengthen total sleep time compared to intranasal NS. The intranasal DEX application also reduced insomnia and drowsiness. They suggest that intranasal DEX can improve preoperative insomnia, especially for patients who are reluctant to take sleeping pills before surgery.

Most women complained sleep disturbances during perinatal/postnatal period, which is associated with physiological and psychological change during pregnancy (2). Two papers on the association between sleep and perinatal/postnatal depression were reported by Bao et al.. Poor sleep trajectories during the perinatal period were related to postpartum depression. Authors suggest that screening for prenatal sleep problems would be helpful for identifying the onset of perinatal depression. Bao et al. also reported that patients with prenatal depression showed poor sleep quality and decision-making function especially when they had suicidal ideation. This study suggests that sleep disturbance and impaired decision-making function may be risk factors for suicidal ideation in prenatal depression.

The current Research Topic also covers the association between sleep and common psychological stress of young adults. Manzar et al. demonstrates that the interrelationship between psychological stress, poor sleep, inadequate sleep hygiene, and anxiety in university students. They suggest a need to address the various aspects of mental health and its diverse sleep correlates in university students.

Barbeau et al. investigated the impact of recent troubling experiences on dream characteristics. Individuals who experienced a recent troubling event reported a higher frequency of nightmares and more emotionally negative dream. Nightmare and oneiric dream were more common in young adults. Authors suggest that dysphoric dreams might serve as potential proxies of mental health status and developmental stages.

Taken together, this Research Topic covered several diverse of sleep disturbance and psychological trauma or stress, and can update readers with the latest research in the field of sleep medicine, psychosomatic medicine and psychiatry. These articles will provide insights to the clinicians and researchers, and help them to further explore the relationship between sleep and psychological trauma or stress with the goal of developing effective therapeutic strategies.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

FUNDING

This research was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (No. 2022R1A2C2008417), the Bio and Medical Technology Development Program of the National Research Foundation (NRF) funded by the Korean government (MSIT) (No. 2020M3E5D9080561), and a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI) funded by the Ministry of Health & Welfare, Republic of Korea (No. HR21C0885).

REFERENCES

1. Burgard SA, Ailshire JA. Putting work to bed: stressful experiences on the job and sleep quality. *J Health Soc Behav.* (2009) 50:476–92. doi: 10.1177/002214650905000407
2. Suzuki S, Dennerstein L, Greenwood KM, Armstrong SM, Satohisa E. Sleeping patterns during pregnancy in Japanese women. *J Psychosom Obstet Gynaecol.* (1994) 15:19–26. doi: 10.3109/01674829409025625

Conflict of Interest: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 28 May 2021
doi: 10.3389/fpsyt.2021.680890

Poor Sleep and Decision-Making Disturbance Are Associated With Suicidal Ideation in Pre-natal Depression

Ciqing Bao[1], Ling Xu[1], Weina Tang[2], Shiyu Sun[2], Wenmiao Zhang[3], Jincai He[4], Ke Zhao[5], Dongwu Xu[2]* and Xiaodan Ye[5]**

[1] Wenzhou Seventh People's Hospital, Wenzhou, China, [2] School of Mental Health, Wenzhou Medical University, Wenzhou, China, [3] Department of Obstetrics, First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China, [4] Department of Neurology, First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China, [5] The Affiliated Kangning Hospital of Wenzhou Medical University, Wenzhou, China

OPEN ACCESS

Edited by:
Seog Ju Kim,
Sungkyunkwan University,
South Korea

Reviewed by:
Rosalia Cesarea Silvestri,
University of Messina, Italy
Axel Steiger,
Ludwig Maximilian University of
Munich, Germany

***Correspondence:**
Xiaodan Ye
602401427@qq.com
Dongwu Xu
wzsdw@126.com
Ke Zhao
cherris@163.com

Specialty section:
This article was submitted to
Sleep Disorders,
a section of the journal
Frontiers in Psychiatry

Received: 15 March 2021
Accepted: 03 May 2021
Published: 28 May 2021

Citation:
Bao C, Xu L, Tang W, Sun S, Zhang W, He J, Zhao K, Xu D and Ye X (2021) Poor Sleep and Decision-Making Disturbance Are Associated With Suicidal Ideation in Pre-natal Depression. Front. Psychiatry 12:680890. doi: 10.3389/fpsyt.2021.680890

Although many risk factors for suicidal ideation have been identified, few studies have focused on suicidal ideation and pre-natal depression. The purpose was to investigate the relationship between decision-making (DM) dysfunction and sleep disturbance on suicidal ideation in pre-natal depression. Participants included 100 women in the third trimester of pregnancy, including pregnant women with pre-natal depression who had recent suicidal ideation ($n = 30$), pre-natal depression without SI ($n = 35$) and healthy controls ($n = 35$). The Iowa Gambling Task (IGT) was used to evaluate the DM function and the Pittsburgh Sleep Quality Index (PSQI) was used to assess the sleep index. The Edinburgh Post-natal Depression Scale (EPDS) was used to assess suicidal ideation and the seriousness of depression. Overall, the two groups with pre-natal depression showed worse sleep quality and decreased DM function compared with healthy controls. The pre-natal depression with suicidal ideation group showed a significantly higher score in subjective sleep quality and a lower score in block 5 of IGT than the pre-natal depression without suicidal ideation group. Further correlation analysis showed that suicidal ideation positively correlated with subjective sleep quality, sleep duration, and daytime function, and negatively correlated with IGT scores. Sleep disturbance and impaired DM function may be risk factors for suicidal ideation in pre-natal depression.

Keywords: sleep disturbance, antenatal depression, suicidal ideation, decision-making function, pregnancy

INTRODUCTION

Suicide in the perinatal period is an important public health problem, and suicidal ideation is, one of the most important risk factors for suicidal behavior. During pregnancy, the prevalence of suicidal ideation can reach between 5 and 14% (1–3) and there is a correlation between suicidal ideation and suicide attempts that can result in an elevated suicide risk at some point in the future (1, 4–7). There are many risk factors for suicidal ideation during pregnancy, including accidental pregnancy (8, 9), education level (10, 11), marital status (12, 13), and intimate partner violence (11, 14). Depression and anxiety may be the most important biological factors of perinatal suicide (15, 16). The incidence of perinatal depression is as high as 10–30%, and perinatal depression patients show a higher rate of suicide and self-injury than those with general depression (17).

There are few studies on the decision-making (DM) function of perinatal depression patients, even though DM dysfunction may be closely related to suicidal ideation in perinatal depression patients.

DM can be defined as the cognitive process that identifies and selects the best available solution for a given problem or challenging situation based on the value and preferences of the decision maker. The Iowa Gambling Task (IGT) is one of the most commonly used DM tasks (18), and was developed to simulate real-world DM processes in vague and dangerous situations. DM is impaired in various mental illnesses, including obsessive-compulsive disorder (19), schizophrenia (20), and depression (21, 22). Teenagers and adults with DM defects are more likely to display suicidal behavior (23), and more researches have shown that DM play a very important role in suicidal behavior (24). Neurobiological studies have found that the integrity of the orbital cortex/ventral medial PFC (OFC/VMPFC) determines the ability to make decisions. When the OFC/VMPFC is impaired, people suffer from false emotional signals, leading to neglect of unfavorable factors in the future and a focus on immediate interests (25). In depression, structural changes are found in the OFC and VMPFC, and these changes are thought to be closely related to the onset and severity of depression (26, 27).

A large proportion of patients with depression have sleep disturbance and, furthermore, sleep disturbance is more common in perinatal depression than in general depression because of the physiological changes associated with pregnancy (28). There are many studies that show a correlation between pre-natal depression and sleep disturbance (29–33). Jomeen et al. (34) found that about 26% of pregnant women had mild to moderate depressive symptoms, and the sleep quality of the depressed group was worse than that of the non-depressed group. Higher Pittsburgh Sleep Quality Index (PSQI)scores in early pregnancy predict an increase in the Beck depression index scores in the second trimester, and higher PSQI scores in the second trimester predict a higher Beck depression index score in the third trimester, suggesting that sleep quality in the first trimester of pregnancy can predict the clinical symptoms of depression in the third trimester of pregnancy (35). Studies have also shown that there is a correlation between suicidal ideation and sleep during pregnancy (36–38). In one study, in mid-pregnancy, women with high sleep reactivity report elevated symptoms of insomnia, depression, and anxiety, and were more likely to participate in suicidal ideation (39). Previous studies have also suggested that sleep may optimize emotion-guided DM. For example, Pace-Schott et al. reported that after uninterrupted sleep, subjects scores better in the IGT than those that had undergone interrupted sleep (40).

Although there are no studies on DM in pregnant women with pre-natal depression, there has been some research into pregnancy and post-natal cognitive performance and mood. Many studies have shown that there may be cognitive changes in perinatal depression patients (41–46). A Portuguese study found that more dysfunctional beliefs related with maternal responsibility, more frequent negative thoughts related with personal maladjustment and with the metacognitive appraisal of the thoughts' content, and less frequent positive thoughts were significantly associated with postpartum depression symptoms (47). Stress associated with pregnancy may contribute to postpartum mental illness and its associated symptoms by compromising structural plasticity in the mPFC (48). Women may show specific areas of cognitive changes during and after pregnancy, in particular, deficits in verbal learning and memory; mood appears to be impacted as well (46).

There are currently no studies on the association suicidal ideation and DM in patients with perinatal depression. The physiological and psychological mechanisms of high suicidal ideation in perinatal depression are currently unclear. In the present study, we hypothesized that high suicidal ideation in patients with perinatal depression is closely associated with sleep disorders and impaired DM during pregnancy. The purpose of this study was to determine if sleep quality and DM ability are associated with suicidal ideation in pre-natal women with depression compared to pre-natal women without depression.

METHODS

Participants

A total of 100 pregnant women in late pregnancy were recruited from the obstetrics clinic of the First Affiliated Hospital of Wenzhou Medical University. Three groups were as follows: Group SI included 30 pre-natal depression pregnant women with suicidal ideation (Edinburgh Post-natal Depression Scale (EPDS) >9 and the 10th item in the EPDS except "never"); Group NSI consisted of 35 pregnant women with antenatal depression, but no suicidal ideation (EPDS >9, item 10 in the EPDS was selected as "never"); Group CG was a control group consisting of 35 healthy pregnant women (EPDS $\leq$ 9, and item 10 in the EPDS was selected as "never"). Inclusion and exclusion criteria were based on clinical structured interviews and self-reports.

The inclusion criteria were: (1) adult ($\geq$18 years old); (2) late pregnancy (28–40 weeks); and (3) willing to sign informed consent.

The exclusion criteria were: (1) history of mental illness or brain disorders; (2) chronic diseases that require regular medical care; (3) intellectual disability; (4) obvious pregnancy complications; and (5) reading and writing dysfunction.

The researchers were composed of psychiatry and mental-health graduate students and physicians, who had undergone consistent training before the experiment began. Our trained researchers collected demographic and clinical information about all pregnant women in face-to-face interviews through standardized questionnaires, including age, height, weight, ethnicity, place of residence, marital status, level of education, monthly family income, history of mental illness, and family history of mental illness. And the standardized questionnaire consists of a demographic scale with consistent guidance and content.

Abbreviations: DM, decision-making; IGT, Iowa Gambling Task; PSQI, Pittsburgh Sleep Quality Index; EPDS, Edinburgh Post-natal Depression Scale; OFC, orbitofrontal cortex; VMPFC, ventromedial PFC.

TABLE 1 | Sociodemographic and clinical variables.

	Groups			Overall comparison	
	SI ($n = 30$)	**NSI ($n = 35$)**	**CG ($n = 35$)**	**Test statistic**	***P*-value**
Age (years)	28.2 (4.0)	29.5 (2.7)	28.8 (4.4)	$F = 1.16$	0.316
Years of education (years)	13.5 (2.0)	12.7 (3.4)	14.0 (2.5)	$F = 4.81$	0.090
%Han	100%	100%	100%	-	-
Marital status				-	-
Married	30 (100%)	35 (100%)	35 (100%)		
The others	0 (0%)	0 (0%)	0 (0%)		
Family monthly income (RMB)				$X^2 = 6.24$	0.397
<3,000	1 (3.3%)	0 (0%)	1 (2.9%)		
3,000–5,000	5 (16.7%)	12 (34.3%)	6 (17.1%)		
5,000–10,000	11 (36.7%)	14 (40.0%)	17 (48.6%)		
>10,000	13 (43.3%)	9 (25.7%)	11 (31.4%)		
Subjective occupational stress				$X^2 = 7.61$	0.107
Mild	18 (60.0%)	20 (57.1%)	29 (82.9%)		
Moderately severe	12 (40.0%)	14 (42.9%)	6 (17.1%)		
Number of children				$X^2 = 2.63$	0.622
0	16 (53.3%)	18 (51.4%)	20 (57.1%)		
1	12 (40.0%)	16 (45.7%)	15 (42.9%)		
2	2 (6.7%)	1 (2.9%)	0 (0.0%)		
Number of abortions				$X^2 = 4.27$	0.371
0	20 (66.7%)	16 (45.7%)	18 (51.4%)		
1–2	8 (26.7%)	16 (45.7%)	16 (45.7%)		
≥3	2 (6.7%)	3 (8.6%)	1 (2.9%)		

SI, Suicidal ideation group; NSI, Non-suicidal ideation group; CG,Control group; RMB, Chinese legal currency Age was analyzed by one-way analysis of variance, all other continuous variables by Kruskal-Wallis test, all categorical variables by Chi-square test.

Assessments

The Edinburgh Post-natal Depression Scale

In western countries, the EPDS (49) is a widely used depression assessment scale. And it is believed to be effective in multiple cultures during pregnancy (50–53) and postpartum. It has 10 items testing: mood, pleasure, guilt, anxiety, fear, insomnia, ability to cope, sadness, crying, and self-injury. In accordance with the severity of the relevant symptom, each item is divided into 0–3 points and the total score ranges from 0 to 30 points. The scale has good reliability and validity in populations in mainland China (54). In this experiment, a total score of >9 was classified as depression (55).

Suicidal Ideation

To evaluate suicidal ideation, we examined item 10 of the EPDS (presented as "The thought of harming myself has occurred to me") (56–58). Possible responses included "never" = 0, "hardly ever" = 1, "sometimes" = 2, or "quite often" = 3. Due to the particularity of China's national conditions, "never" is defined as "no suicidal ideation" and the other three are defined as "suicidal ideation."

The Pittsburgh Sleep Quality Index

The PSQI (59) was used to assess sleep quality over the previous month. The maximum total score of the PSQI is 21 points. Nineteen individual items generate seven component scores (range 0–3, with higher scores indicating worse sleep): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. This scale has good internal consistency, test-retest reliability, and validity (60). A score of >5 is indicative of clinically significant sleep disturbance.

Iowa Gambling Task

DM was assessed using the IGT (61). Participants completed the computerized version of the IGT consisting of four decks of cards labeled A, B, C, and D. The participants made 100 card selections. After each selection, a specified amount of facsimile money was awarded. At the top of the computer screen, a bar indicates wins and losses and changes according to the amount of money won or lost after each selection. Participants were told that the aim of the game is to win as much money as possible. They were also instructed that some decks were better than others and that they have to avoid the bad decks. The total net score on the IGT is the difference between the total number of cards selected from advantageous decks (decks $C' + D'$) and disadvantageous decks (decks $A' + B'$). Block scores were calculated for every 20 cards selected in the same manner. The total net scores range from −100 to 100 and block scores

TABLE 2 | Differences in scores of PSQI and EPDS among the three groups (SI, NSI, CG).

	Groups			Group comparison			
				Overall	Pairwise		
	SI ($n = 30$)	NSI ($n = 35$)	CG ($n = 35$)	*P*-value	SI vs. NSI *P*-value	SI vs. CG *P*-value	NSI vs. CG *P*-value
EPDS (SD)	13.57 (3.4)	11.63 (2.1)	5.6 (2.2)	<0.001	0.018	<0.001	<0.001
EPDS without suicidal ideation (SD)	12.27 (3.5)	11.63 (2.1)	5.6 (2.2)	<0.001	0.535	<0.001	<0.001
PSQI (SD)	9.27 (4.1)	7.66 (3.5)	5.97 (2.6)	0.002	0.074	0.001	0.048
Subjective sleep quality (SD)	1.67 (0.7)	1.31 (0.6)	1.14 (0.4)	0.005	0.05	0.001	0.185
Sleep latency (SD)	1.87 (0.9)	1.57 (1.0)	1.31 (0.8)	0.074	-	-	-
Sleep duration (SD)	0.87 (1.1)	0.54 (1.0)	0.31 (0.7)	0.091	-	-	-
Habitual sleep efficiency (SD)	1.13 (1.2)	0.89 (1.1)	0.80 (0.9)	0.671	-	-	-
Sleep disturbances (SD)	1.67 (0.6)	1.54 (0.5)	1.31 (0.4)	0.05	0.541	0.024	0.055
Use of sleeping medication (SD)	0	0	0	1.00	-	-	-
Daytime dysfunction (SD)	2.0 (0.9)	1.8 (0.7)	1.0 (0.9)	<0.001	0.161	<0.001	0.001

SI, Suicidal ideation group; NSI, Non-suicidal ideation group; CG,Control group; EPDS, The Edinburgh Post-natal Depression Scale; EPDS without suicidal ideation. The sum of the scores of the remaining nine items except the 10th item of EPDS; PSQI, The Pittsburgh Sleep Quality Index; Subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction are the seven sub-items of PSQI.

TABLE 3 | Differences in decision-making functions among three groups (SI, NSI, CG).

	Groups			Group comparison			
				Overall	Pairwise		
	SI ($n = 30$)	NSI ($n = 35$)	CG ($n = 35$)	*P*-value	SI vs. NSI *P*-value	SI vs. CG *P*-value	NSI vs. CG *P*-value
IGT (SD)	−15.13 (38.0)	−9.94 (21.2)	10.74 (27.2)	<0.001	0.191	<0.001	0.001
Block1 (SD)	−4.1 (7.0)	−4.2 (6.9)	−3.1 (6.2)	0.803	0.959	0.554	0.494
Block2 (SD)	−4.6 (9.0)	−3.6 (6.3)	−1.5 (8.5)	0.186	0.574	0.150	0.240
Block3 (SD)	−5.4 (8.4)	−2.2 (6.5)	2.7 (7.6)	<0.001	0.089	<0.001	0.005
Block4 (SD)	−2.6 (8.0)	−2.2 (7.0)	5.5 (8.1)	<0.001	0.855	<0.001	<0.001
Block5 (SD)	−2.3 (8.8)	2.3 (6.9)	7.1 (7.8)	<0.001	0.022	<0.001	0.008

IGT, Iowa gambling task; SI, Suicidal ideation group; NSI, Non-suicidal ideation group; CG, Control group.

range from −20 to 20. Positive net and block scores indicate advantageous decision-making.

Statistical Analysis

Comparison of the three groups (SI, NSI, and CG) with regard to sociodemographic and clinical variables were performed by means of one-way analysis of variance, Kruskal–Wallis test, and the Chi-square test, depending on the variable type (normally distributed, non-normally distributed and categorical, respectively). Checks for deviations from normality were performed by means of the Kolmogorov–Smirnov test. *Post-hoc* pairwise comparisons (by *t*-test, Mann–Whitney *U*-test, or Chi-square test, respectively) were conducted only if the overall group comparison yielded a significant result ($p < 0.05$). In the case of three groups, this sequential testing procedure allowed testing of group differences without adjustment for multiple comparisons.

The same procedure was also used to compare the three groups with PSQI and the DM task IGT. As the IGT consists of five consecutive blocks, we performed an additional repeated-measures analysis of variance with time as a within-subjects factor and group as a between-subjects factor to adjust for potential learning effects.

Spearman correlation analysis was used to analyze the correlations among sleep (PSQI and its seven component scores), DM function, and suicidal ideation in late pregnancy women.

RESULTS

A total of 100 participants (SI group, $n = 30$; NSI group, $n = 35$; CG group, $n = 35$) were included. Sociodemographic and clinical data are presented in **Table 1**. The three groups did not differ with respect to age, years of education, marital status, family monthly income, subjective occupational stress, the number of children, or the number of abortions.

Table 2 shows the results of the EPDS scores, EPDS scores without suicidal ideation, and PSQI between groups. Compared with the NSI group, the EPDS scores of the SI group were

TABLE 4 | Spearman correlation matrix of suicidal ideation, PSQI and IGT.

	Suicidal ideation	EPDS without suicidal ideation	IGT	PSQI	Subjective sleep quality	Sleep duration	Daytime dysfunction
Suicidal ideation	–	0.415***	−0.265**	0.289**	0.305**	0.212*	0.299**
EPDS without suicidal ideation		-	−0.365***	0.351***	0.251*	0.131	0.391***
IGT			–	−0.207*	−0.123	−0.123	−0.329**
PSQI				–	0.710***	0.707***	0.634***
Subjective sleep quality					–	0.444***	0.521***
Sleep duration						–	0.288**
Daytime dysfunction							–

Spearman correlation $^{*}p < 0.05$, $^{**}p < 0.01$,$^{***}p < 0.001$.

significantly increased, which was due to the higher score of the suicide ideation factor on the EPDS. There were significant differences between the three groups except for the PSQI scale and the EPDS scale without suicidal factor scores. There were also significant differences in subjective sleep quality, sleep disturbance, and daytime function in the PSQI scale. For the subjective sleep quality, the SI group showed a significantly higher score than the other two groups. This means that women with suicidal ideation had worse subjective sleep quality than women without suicidal ideation and healthy controls. No significant differences were found between the NSI and CG groups. The scores of sleep disturbances and daytime function in the SI group were significantly higher than those in the CG group.

There were significant differences of in the IGT scores and block3-block5 scores among the groups (**Table 3**). Among these differences, the block 5 group were significant after comparison. Repeated measures ANOVA revealed significant positive effects in the different groups of IGT ($F = 10.653$, $p < 0.001$) and significant learning effects from the first to fifth blocks of the IGT ($F = 17.905$, $p < 0.001$). In addition, test time interacted with the group ($F = 3.706$, $P = 0.001$).

Spearman correlation analysis (**Table 4**) showed that suicide ideation positively correlated with pre-natal depression ($r = 0.415$, $P < 0.001$), PSQI ($r = 0.289$, $P = 0.004$), subjective sleep quality ($r = 0.305$, $P = 0.002$), sleep duration ($r = 0.212$, $P = 0.034$), and daytime dysfunction ($r = 0.299$, $P = 0.002$), and negatively correlated with IGT total score ($r = -0.265$, $p = 0.008$).

DISCUSSION

To the best of our knowledge, this is the first study to assess DM and sleep in pre-natal depression patients with suicidal ideation. The risk-decision made by the suicidal ideation group in the fifth block of the IGT was significantly higher than that of the NSI group and the healthy control group, which indicates that people with DM defects have stronger suicidal ideation. Suicide ideation positively correlated with pre-natal depression, subjective sleep quality, sleep duration, and daytime dysfunction, and negatively correlated with DM function. The three groups in our study did not differ significantly in social demographics.

Our findings are generally consistent with the existing literature documenting the association of poor subjective sleep quality with the likelihood of suicidal ideation among men and non-pregnant women (62, 63). However, there are few studies on sleep and pre-natal depression and suicidal ideation during pregnancy. Among them, one study showed that poor subjective sleep quality was associated with an increased likelihood of suicidal ideation (36). The article mentioned that after adjusting for depression, the probability of suicidal ideation increases by 18% for every unit increase in the global PSQI score. The proportion of subjective sleep quality and suicidal ideation in patients with depression increased by 3.5-fold compared with patients without risk factors. Another study published in 2016 showed similar results (37).

Our study confirmed the correlation between suicidal ideation and subjective sleep quality, and the difference was also significantly related to sleep duration and daytime dysfunction. The causal relationship between sleep disorders and suicide in major depression is unclear, however, there is evidence that the activities of the three neurobiological systems play a key role in the pathophysiology of suicidal behavior, i.e., hyperactivity of the hypothalamus-pituitary-adrenal axis, dysfunction of the serotoninergic system and overactivity of the noradrenergic system. Not only the first and last systems appear to be involved in the response to stress events, the hyperactivity of the HPA axis and the dysfunction of the serotonergic system are also associated with changes in the sleep-wake cycle, such as insomnia (64–67). In depression, HPA hyperactivity can have many negative effects on sleep. It can lead to sleep fragmentation, decreased slow-wave sleep, and shortened sleep time (66). It can therefore be assumed that neurobiological dysfunction mediates the occurrence of suicidal behavior through the disturbed regulation of basic neuropsychological functions. The main clinical significance of suicidal ideation/sleep disturbance is that sleep assessment may help assess the risk of suicide in patients with antenatal depression.

Previous studies of DM and suicidal ideation have produced controversial results. Some studies have shown that IGT scores are significantly lower in people who currently have suicidal ideation compared with healthy controls (68). However, in contrast, some studies found no association between suicidal ideation and DM (69, 70). DM deficiencies were related to suicide

attempts in adolescents and adults, and the group differences in DM did not persist after controlling for current emotional problems and the use of psychotropic substances. In this study, there was no significant difference in the IGT net score between the SI group and the NSI group, but there was a significant difference compared with the healthy control, indicating that there was a decision deficit in the pre-natal depression groups with or without suicidal ideation. By comparing the net scores and their trends in different blocks, we analyzed the DM characteristics and strategy adjustment of the subjects in the income-loss situation (71). There was no significant difference in the net scores of blocks 1–2 between the three groups in this study. In blocks 3–4, both groups with depression had significantly lower scores than the healthy controls, while there was no significant difference between the SI and NSI groups. The two groups of pregnant women with pre-natal depression showed no difference in performance at the beginning and the middle stage. As the task progressed, the net scores of the two groups in the fifth block were different. The SI group scores were significantly lower than those in the NSI group, and the scores of both groups were lower than those of the healthy control group. These data shows that patients with pre-natal depression lack decision-making ability, have poor strategy adjustment, and do not show the "learning effect" of normal healthy people or improve the net score, while the DM function defects of pre-natal depression patients with suicidal ideation are more serious.

A previous study suggested that IGT performance was not mediated by the conscious knowledge of risk. Patients selected cards that brought higher immediate rewards despite more severe penalties, and patients with OFC/VMPFC lesions often showed this pattern of behavior (25, 72). Another study found that REM sleep in emotion-guided decision making plays a selective role, the subjects performed highly on the IGT, whose OFC/VMPFC regions were selectively activated in REM sleep (73). Sleep disturbances, including insomnia and sleep deprivation, can produce a labile mood (74), which may correspond with neural responses that suggest abnormal reward processing and autonomic hyperarousal (75), limbic overactivity (76), and loss of medial pre-frontal cortex connectivity (77). Having sleep disturbance could worsen the altered reward processes in mothers with depression and SI (78). We hypothesized that sleep inefficiency and daytime dysfunction would aggravate impairment of DM function in patients and the correlation results support our hypothesis.

Our study shows that suicidal ideation and depressive symptoms of pregnant women need to be carefully monitored, especially in those with poor sleep quality. Pregnant women often report poor sleep quality and those with poor subjective sleep quality should be evaluated for suicide ideation. Actively dealing with sleep problems may reduce suicide behavior of pregnant women. For example, investigators have noted that behavioral (e.g., sleep hygiene, stimulus control, and imagery rehearsal therapy) and pharmacological interventions may be particularly promising modalities for reducing the risk of suicidal ideation (79). This study suggests that the decision-making function impairment may be associated with pre-natal depression and suicidal ideation in pregnant women, However, further studies on the neuropathological mechanism are needed, such as functional magnetic resonance imaging (fMRI).

This study reports the DM profile of recent pre-natal depression subjects with suicidal ideation and confirms the existence of decision deficits in this population. The study also found correlations between antenatal depression, suicidal ideation and sleep disturbance. There is an urgent need to raise awareness of this issue and further longitudinal studies should be encouraged to examine other cognitive functions that may be related to suicide status.

There are several limitations in our study. Firstly, the sample size was relatively small ($n = 100$) and it will be necessary to study a larger sample size to reduce the type II error rate. Secondly, due to the nature of cross-sectional studies, we are not sure of the dynamic relationship between suicidal ideation and sleep in perinatal depression patients during pregnancy, nor can we infer the causal relationship between suicidal ideation and impaired DM function. Longitudinal studies are needed to address these questions and verify our findings. Thirdly, In this study, only the subjective scale (PSQI) was used to evaluate sleep, without using objective evaluation indicators, such as polysomnography test. Finally, due to the absence of brain imaging, in this study we do not know whether any neuroanatomical/functional changes in the patients' brains occurred.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Due to relevant data protection laws. Requests to access these datasets should be directed to baociqing@163.com.

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

CB and KZ conceived and designed the study and developed it in discussion with LX, WT, SS, and WZ. SS, WT, and LX were involved in the acquisition and analysis of the data. DX and XY provided research funding. CB wrote the first draft of the article. All authors participated in the interpretation of the data, contributed to critically revising the paper, read, and approved the final manuscript.

FUNDING

This work were supported by the Natural Science Foundation of Zhejiang Province (LQ18H090009 and LY19H090015). The preparation of the material scales were part of the funding of the fund.

ACKNOWLEDGMENTS

We wish to thank all the participants and medical staff of the First Affiliated Hospital of Wenzhou Medical University who supported our research. We thank all of the volunteers for their study participation and the support of the First Affiliated Hospital of WenZhou Medical University.

REFERENCES

1. Lindahl V, Pearson JL, Colpe L. Prevalence of suicidality during pregnancy and the postpartum. *Arch Women Ment Health*. (2005) 8:77–87. doi: 10.1007/s00737-005-0080-1
2. Bridge JA, McBee-Strayer SM, Cannon EA, Sheftall AH, Reynolds B, Campo JV, et al. Impaired decision making in adolescent suicide attempters. *J Am Acad Child Adolesc Psychiatry*. (2012) 51:394–403. doi: 10.1016/j.jaac.2012.01.002
3. Deisenhammer EA, Schmid SK, Kemmler G, Moser B, Delazer M. Decision making under risk and under ambiguity in depressed suicide attempters, depressed non-attempters and healthy controls. *J Affect Disord*. (2018) 226:261–6. doi: 10.1016/j.jad.2017.10.012
4. Joiner TE, Rudd D, Rouleau MR, Wagner KD. Parameters of suicidal crises vary as a function of previous suicide attempts in youth inpatients. *J Am Acad Child Adolesc Psychiatry*. (2000) 39:876–80. doi: 10.1097/00004583-200007000-00016
5. Swogger MT, Van Orden KA, Conner KR. The relationship of outwardly-directed aggression to suicidal ideation and suicide attempts across two high-risk samples. *Psychol Violence*. (2014) 4:184–95. doi: 10.1037/a0033212
6. Gelaye B, Kajeepeta S, Williams MA. Suicidal ideation in pregnancy: an epidemiologic review. *Arch Women Ment Health*. (2016) 19:741–51. doi: 10.1007/s00737-016-0646-0
7. Mbroh H, Zullo L, Westers N, Stone L, King J, Kennard B, et al. Double trouble: nonsuicidal self-injury and its relationship to suicidal ideation and number of past suicide attempts in clinical adolescents. *J Affect Disord*. (2018) 238:579–85. doi: 10.1016/j.jad.2018.05.056
8. Newport DJ, Levey LC, Pennell PB, Ragan K, Stowe ZN. Suicidal ideation in pregnancy: assessment and clinical implications. *Arch Women Ment Health*. (2007) 10:181–7. doi: 10.1007/s00737-007-0192-x
9. Ishida K, Stupp P, Serbanescu F, Tullo E. Perinatal risk for common mental disorders and suicidal ideation among women in Paraguay. *Int J Gynecol Obstet*. (2010) 110:235–40. doi: 10.1016/j.ijgo.2010.03.027
10. Coelho FM, Pinheiro RT, Silva RA, de Avila Quevedo L, de Mattos Souza LD, de Matos MB, et al. Parental bonding and suicidality in pregnant teenagers: a population-based study in southern Brazil. *Soc Psychiatry Psychiatr Epidemiol*. (2014) 49:1241–8. doi: 10.1007/s00127-014-0832-1
11. Alhusen JL, Frohman N, Purcell G. Intimate partner violence and suicidal ideation in pregnant women. *Arch Women Ment Health*. (2015) 18:573–8. doi: 10.1007/s00737-015-0515-2
12. Huang H, Faisal-Cury A, Chan YF, Tabb K, Katon W, Menezes PR. Suicidal ideation during pregnancy: prevalence and associated factors among low-income women in São Paulo, Brazil. *Arch Women Ment Health*. (2012) 15:135–8. doi: 10.1007/s00737-012-0263-5
13. Kim JJ, La Porte LM, Silver RK. Suicide risk among perinatal women who report thoughts of self-harm on depression screens reply. *Obstet Gynecol*. (2015) 126:217. doi: 10.1097/AOG.0000000000000941
14. Fisher J, Tran TD, Biggs B, Dang TH, Nguyen TT, Tran T. Intimate partner violence and perinatal common mental disorders among women in rural Vietnam. *Int Health*. (2013) 5:29–37. doi: 10.1093/inthealth/ihs012
15. Farias DR, Pinto Tde J, Teofilo MM, Vilela AA, Vaz Jdos S, Nardi AE, et al. Prevalence of psychiatric disorders in the first trimester of pregnancy and factors associated with current suicide risk. *Psychiatry Res*. (2013) 210:962–8. doi: 10.1016/j.psychres.2013.08.053
16. Eggleston AM, Calhoun PS, Svikis DS, Tuten M, Chisolm MS, Jones HE. Suicidality, aggression, and other treatment considerations among pregnant, substance-dependent women with posttraumatic stress disorder. *Compr Psychiat*. (2009) 50:415–23. doi: 10.1016/j.comppsych.2008.11.004
17. Ebeid E, Nassif N, Sinha P. Prenatal depression leading to postpartum psychosis. *J Obstet Gynaecol*. (2010) 30:435–8. doi: 10.3109/01443611003802321
18. Bechara A, Damasio AR, Damasio H, Anderson SW. Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition*. (1994) 50:7–15. doi: 10.1016/0010-0277(94)90018-3
19. Pushkarskaya H, Tolin D, Ruderman L, Kirshenbaum A, Kelly JM, Pittenger C, et al. Decision-making under uncertainty in obsessive-compulsive disorder. *J Psychiatr Res*. (2015) 69:166–73. doi: 10.1016/j.jpsychires.2015.08.011
20. Fond G, Bayard S, Capdevielle D, Del-Monte J, Mimoun N, Macgregor A, et al. A further evaluation of decision-making under risk and under ambiguity in schizophrenia. *Eur Arch Psy Clin N*. (2013) 263:249–57. doi: 10.1007/s00406-012-0330-y
21. Must A, Szabo Z, Bodi N, Szasz A, Janka Z, Keri S. Sensitivity to reward and punishment and the prefrontal cortex in major depression. *J Affect Disord*. (2006) 90:209–15. doi: 10.1016/j.jad.2005.12.005
22. Thames AD, Streiff V, Patel SM, Panos SE, Castellon SA, Hinkin CH. The role of HIV infection, cognition, and depression in risky decision-making. *J Neuropsychiatry Clin Neurosci*. (2012) 24:340–8. doi: 10.1176/appi.neuropsych.11110340
23. Richard-Devantoy S, Berlim MT, Jollant F. A meta-analysis of neuropsychological markers of vulnerability to suicidal behavior in mood disorders. *Psychol Med*. (2014) 44:1663–73. doi: 10.1017/S0033291713002304
24. Clark L, Dombrovski AY, Siegle GJ, Butters MA, Shollenberger CL, Sahakian BJ, et al. Impairment in risk-sensitive decision-making in older suicide attempters with depression. *Psychol Aging*. (2011) 26:321–30. doi: 10.1037/a0021646
25. Daurat A, Ricarrere M, Tiberge M. Decision making is affected in obstructive sleep apnoea syndrome. *J Neuropsychol*. (2013) 7:139–44. doi: 10.1111/j.1748-6653.2012.02039.x
26. Jalbrzikowski M, Larsen B, Hallquist MN, Foran W, Calabro F, Luna B. Development of white matter microstructure and intrinsic functional connectivity between the amygdala and ventromedial prefrontal cortex: associations with anxiety and depression. *Biol Psychiatry*. (2017) 82:511–21. doi: 10.1016/j.biopsych.2017.01.008
27. Klauser P, Fornito A, Lorenzetti V, Davey CG, Dwyer DB, Allen NB, et al. Cortico-limbic network abnormalities in individuals with current and past major depressive disorder. *J Affect Disord*. (2015) 173:45–52. doi: 10.1016/j.jad.2014.10.041
28. Krawczak EM, Minuzzi L, Simpson W, Hidalgo MP, Frey BN. Sleep, daily activity rhythms and postpartum mood: a longitudinal study across the perinatal period. *Chronobiol Int*. (2016) 33:791–801. doi: 10.3109/07420528.2016.1167077
29. Ko SH, Chang SC, Chen CH. A comparative study of sleep quality between pregnant and nonpregnant Taiwanese women. *J Nurs Scholarship*. (2010) 42:23–30. doi: 10.1111/j.1547-5069.2009.01326.x
30. Skouteris H, Germano C, Wertheim EH, Paxton SJ, Milgrom J. Sleep quality and depression during pregnancy: a prospective study. *J Sleep Res*. (2008) 17:217–20. doi: 10.1111/j.1365-2869.2008.00655.x
31. Kamysheva E, Skouteris H, Wertheim EH, Paxton SJ, Milgrom J. A prospective investigation of the relationships among sleep quality, physical symptoms, and depressive symptoms during pregnancy. *J Affect Disord*. (2010) 123:317–20. doi: 10.1016/j.jad.2009.09.015
32. Mellor R, Chua SC, Boyce P. Antenatal depression: an artefact of sleep disturbance?. *Arch Women Ment Health*. (2014) 17:291–302. doi: 10.1007/s00737-014-0427-6
33. Yang Y, Mao J, Ye Z, Zeng X, Zhao H, Liu Y, et al. Determinants of sleep quality among pregnant women in China: a cross-sectional survey. *J Matern Fetal Neonatal Med*. (2018) 31:2980–5. doi: 10.1080/14767058.2017.1359831

34. Jomeen J, Martin CR. Replicability and stability of the multidimensional model of the Edinburgh Postnatal Depression Scale in late pregnancy. *J Psychiatr Ment Health Nurs*. (2007) 14:319–24. doi: 10.1111/j.1365-2850.2007.01084.x
35. Krawczak EM, Minuzzi L, Hidalgo MP, Frey BN. Do changes in subjective sleep and biological rhythms predict worsening in postpartum depressive symptoms? A prospective study across the perinatal period. *Arch Women Ment Hlth*. (2016) 19:591–8. doi: 10.1007/s00737-016-0612-x
36. Gelaye B, Barrios YV, Zhong QY, Rondon MB, Borba CPC, Sanchez SE, et al. Association of poor subjective sleep quality with suicidal ideation among pregnant Peruvian women. *Gen Hosp Psychiat*. (2015) 37:441–7. doi: 10.1016/j.genhosppsych.2015.04.014
37. Gelaye B, Addae G, Neway B, Larrabure-Torrealva GT, Qiu CF, Stoner L, et al. Poor sleep quality, antepartum depression and suicidal ideation among pregnant women. *J Affect Disord*. (2017) 209:195–200. doi: 10.1016/j.jad.2016.11.020
38. Sit D, Luther J, Buysse D, Dills JL, Eng H, Okun M, et al. Suicidal ideation in depressed postpartum women: associations with childhood trauma, sleep disturbance and anxiety. *J Psychiatr Res*. (2015) 66–67:95–104. doi: 10.1016/j.jpsychires.2015.04.021
39. Palagini L, Cipollone G, Masci I, Novi M, Caruso D, Kalmbach DA, et al. Stress-related sleep reactivity is associated with insomnia, psychopathology and suicidality in pregnant women: preliminary results. *Sleep Med*. (2019) 56:145–50. doi: 10.1016/j.sleep.2019.01.009
40. Pace-Schott EF, Nave G, Morgan A, Spencer RMC. Sleep-dependent modulation of affectively guided decision-making. *J Sleep Res*. (2012) 21:30–9. doi: 10.1111/j.1365-2869.2011.00921.x
41. Mazor E, Sheiner E, Wainstock T, Attias M, Walfisch A. The association between depressive state and maternal cognitive function in postpartum women. *Am J Perinatol*. (2019) 36:285–90. doi: 10.1055/s-0038-1667376
42. Meena PS, Soni R, Jain M, Jilowa CS, Omprakash. Cognitive dysfunction and associated behaviour problems in postpartum women: a study from North India. *East Asian Arch Psychiatry*. (2016) 26:104–8
43. Hampson E, Phillips SD, Duff-Canning SJ, Evans KL, Merrill M, Pinsonneault JK, et al. Working memory in pregnant women: relation to estrogen and antepartum depression. *Horm Behav*. (2015) 74:218–27. doi: 10.1016/j.yhbeh.2015.07.006
44. Logan DM, Hill KR, Jones R, Holt-Lunstad J, Larson MJ. How do memory and attention change with pregnancy and childbirth? A controlled longitudinal examination of neuropsychological functioning in pregnant and postpartum women. *J Clin Exp Neuropsychol*. (2014) 36:528–39. doi: 10.1080/13803395.2014.912614
45. Farrar D, Tuffnell D, Neill J, Scally A, Marshall K. Assessment of cognitive function across pregnancy using CANTAB: a longitudinal study. *Brain Cogn*. (2014) 84:76–84. doi: 10.1016/j.bandc.2013.11.003
46. Buckwalter JG, Buckwalter DK, Bluestein BW, Stanczyk FZ. Pregnancy and post partum: changes in cognition and mood. *Prog Brain Res*. (2001) 133:303–19. doi: 10.1016/S0079-6123(01)33023-6
47. Fonseca A, Canavarro MC. Cognitive correlates of women's postpartum depression risk and symptoms: the contribution of dysfunctional beliefs and negative thoughts. *J Ment Health*. (2020) 29:614–22. doi: 10.1080/09638237.2019.1581331
48. Leuner B, Fredericks PJ, Nealer C, Albin-Brooks C. Chronic gestational stress leads to depressive-like behavior and compromises medial prefrontal cortex structure and function during the postpartum period. *PLoS ONE*. (2014) 9:e89912. doi: 10.1371/journal.pone.0089912
49. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. *Br J Psychiatry*. (1987) 150:782–6. doi: 10.1192/bjp.150.6.782
50. Joshi U, Lyngdoh T, Shidhaye R. Validation of hindi version of Edinburgh postnatal depression scale as a screening tool for antenatal depression. *Asian J Psychiatr*. (2020) 48:101919. doi: 10.1016/j.ajp.2019.101919
51. Kozinszky Z, Dudas RB. Validation studies of the Edinburgh Postnatal Depression Scale for the antenatal period. *J Affect Disord*. (2015) 176:95–105. doi: 10.1016/j.jad.2015.01.044
52. Stewart RC, Umar E, Tomenson B, Creed F. Validation of screening tools for antenatal depression in Malawi–a comparison of the Edinburgh Postnatal Depression Scale and Self Reporting Questionnaire. *J Affect Disord*. (2013) 150:1041–7. doi: 10.1016/j.jad.2013.05.036
53. Zhao Y, Kane I, Wang J, Shen B, Luo J, Shi S. Combined use of the postpartum depression screening scale (PDSS) and Edinburgh postnatal depression scale (EPDS) to identify antenatal depression among Chinese pregnant women with obstetric complications. *Psychiatry Res*. (2015) 226:113–9. doi: 10.1016/j.psychres.2014.12.016
54. Wang Y, Guo X, Lau Y, Chan KS, Yin L, Chen J. Psychometric evaluation of the Mainland Chinese version of the Edinburgh Postnatal Depression Scale. *Int J Nurs Stud*. (2009) 46:813–23. doi: 10.1016/j.ijnurstu.2009.01.010
55. Gaynes BN, Gavin N, Meltzer-Brody S, Lohr KN, Swinson T, Gartlehner G, et al. Perinatal depression: prevalence, screening accuracy, and screening outcomes. *Evid Rep Technol Assess*. (2005) 119:1–8. doi: 10.1037/e439372005-001
56. Zhong QY, Gelaye B, Rondon MB, Sanchez SE, Simon GE, Henderson DC, et al. Using the Patient Health Questionnaire (PHQ-9) and the Edinburgh Postnatal Depression Scale (EPDS) to assess suicidal ideation among pregnant women in Lima, Peru. *Arch Women Ment Health*. (2015) 18:783–92. doi: 10.1007/s00737-014-0481-0
57. Toreki A, Ando B, Dudas RB, Dweik D, Janka Z, Kozinszky Z, et al. Validation of the Edinburgh Postnatal Depression Scale as a screening tool for postpartum depression in a clinical sample in Hungary. *Midwifery*. (2014) 30:911–8. doi: 10.1016/j.midw.2014.02.008
58. da Silva RA, da Costa Ores L, Jansen K, da Silva Moraes IG, de Mattos Souza LD, Magalhaes P, et al. Suicidality and associated factors in pregnant women in Brazil. *Commun Ment Health J*. (2012) 48:392–5. doi: 10.1007/s10597-012-9495-0
59. Buysse DJ, Reynolds CF, III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. (1989) 28:193–213. doi: 10.1016/0165-1781(89)90047-4
60. Tsai PS, Wang SY, Wang MY, Su CT, Yang TT, Huang CJ, et al. Psychometric evaluation of the Chinese version of the Pittsburgh Sleep Quality Index (CPSQI) in primary insomnia and control subjects. *Qual Life Res*. (2005) 14:1943–52. doi: 10.1007/s11136-005-4346-x
61. Bechara A, Tranel D, Damasio H. Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. *Brain*. (2000) 123:2189–202. doi: 10.1093/brain/123.11.2189
62. Agargun MY, Kara H, Solmaz M. Subjective sleep quality and suicidality in patients with major depression. *J Psychiatr Res*. (1997) 31:377–81. doi: 10.1016/S0022-3956(96)00037-4
63. Turvey CL, Conwell Y, Jones MP, Phillips C, Simonsick E, Pearson JL, et al. Risk factors for late-life suicide: a prospective, community-based study. *Am J Geriatr Psychiatry*. (2002) 10:398–406. doi: 10.1097/00019442-200207000-00006
64. Riemann D, Berger M, Voderholzer U. Sleep and depression - results from psychobiological studies: an overview. *Biol Psychol*. (2001) 57:67–103. doi: 10.1016/S0301-0511(01)00090-4
65. Buckley TM, Schatzberg AF. On the interactions of the hypothalamic-pituitary-adrenal (HPA) axis and sleep: normal HPA axis activity and circadian rhythm, exemplary sleep disorders. *J Clin Endocrinol Metab*. (2005) 90:3106–14. doi: 10.1210/jc.2004-1056
66. Steiger A. Neurochemical regulation of sleep. *J Psychiatr Res*. (2007) 41:537–52. doi: 10.1016/j.jpsychires.2006.04.007
67. Hatzinger M, Hemmeter UM, Brand S, Ising M, Holsboer-Trachsler E. Electroencephalographic sleep profiles in treatment course and long-term outcome of major depression: association with DEX/CRH-test response. *J Psychiatr Res*. (2004) 38:453–65. doi: 10.1016/j.jpsychires.2004.01.010
68. Westheide J, Quednow BB, Kuhn KU, Hoppe C, Cooper-Mahkorn D, Hawellek B, et al. Executive performance of depressed suicide attempters: the role of suicidal ideation. *Eur Arch Psychiatry Clin Neurosci*. (2008) 258:414–21. doi: 10.1007/s00406-008-0811-1
69. Keilp JG, Wyatt G, Gorlyn M, Oquendo MA, Burke AK, John Mann J. Intact alternation performance in high lethality suicide attempters. *Psychiatry Res*. (2014) 219:129–36. doi: 10.1016/j.psychres.2014.04.050
70. Sheftall AH, Davidson DJ, McBee-Strayer SM, Ackerman J, Mendoza K, Reynolds B, et al. Decision-making in adolescents with suicidal ideation: a case-control study. *Psychiatry Res*. (2015) 228:928–31. doi: 10.1016/j.psychres.2015.05.077

71. Bereczkei T. The manipulative skill: cognitive devices and their neural correlates underlying Machiavellian's decision making. *Brain Cogn*. (2015) 99:24–31. doi: 10.1016/j.bandc.2015.06.007
72. Beebe DW, Gozal D. Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. *J Sleep Res*. (2002) 11:1–16. doi: 10.1046/j.1365-2869.2002.00289.x
73. Neider M, Pace-Schott EF, Forselius E, Pittman B, Morgan PT. Lucid dreaming and ventromedial versus dorsolateral prefrontal task performance. *Conscious Cogn*. (2011) 20:234–44. doi: 10.1016/j.concog.2010.08.001
74. Zohar D, Tzischinsky O, Epstein R, Lavie P. The effects of sleep loss on medical residents' emotional reactions to work events: a cognitive-energy model. *Sleep*. (2005) 28:47–54. doi: 10.1093/sleep/28.1.47
75. Franzen PL, Buysse DJ. Sleep disturbances and depression: risk relationships for subsequent depression and therapeutic implications. *Dialogues Clin Neurosci*. (2008) 10:473–81. doi: 10.31887/DCNS.2008.10.4/plfranzen
76. Gujar N, Yoo SS, Hu P, Walker MP. Sleep deprivation amplifies reactivity of brain reward networks, biasing the appraisal of positive emotional experiences. *J Neurosci*. (2011) 31:4466–74. doi: 10.1523/JNEUROSCI.3220-10.2011
77. Yoo SS, Gujar N, Hu P, Jolesz FA, Walker MP. The human emotional brain without sleep - a prefrontal amygdala disconnect. *Curr Biol*. (2007) 17:R877–R8. doi: 10.1016/j.cub.2007.08.007
78. Walker MP, van der Helm E. Overnight therapy? The role of sleep in emotional brain processing. *Psychol Bull*. (2009) 135:731–48. doi: 10.1037/a0016570
79. Krakow B, Ribeiro JD, Ulibarri VA, Krakow J, Joiner TE, Jr. Sleep disturbances and suicidal ideation in sleep medical center patients. *J Affect Disord*. (2011) 131:422–7. doi: 10.1016/j.jad.2010.12.001

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.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 01 July 2021
doi: 10.3389/fpsyt.2021.677136

Anxiety Symptoms Are Associated With Higher Psychological Stress, Poor Sleep, and Inadequate Sleep Hygiene in Collegiate Young Adults—A Cross-Sectional Study

Md Dilshad Manzar[1], Ahmad H. Alghadir[2], Masood Khan[2], Mohammed Salahuddin[3,4], Abdulrhman Albougami[1], Jestoni D. Maniago[1], Brian A. Vasquez[1], Seithikurippu R. Pandi-Perumal[5] and Ahmed S. Bahammam[6,7]*

[1] Department of Nursing, College of Applied Medical Sciences, Majmaah University, Al Majmaah, Saudi Arabia, [2] Rehabilitation Research Chair, College of Applied Medical Sciences, King Saud University, Riyadh, Saudi Arabia, [3] Department of Pharmacy, College of Medicine and Health Sciences, Mizan-Tepi University (Mizan Campus), Mizan-Aman, Ethiopia, [4] Pharmacology Division, Department of BioMolecular Sciences, University of Mississippi, Oxford, MS, United States, [5] Somnogen Canada Inc., Toronto, ON, Canada, [6] The University Sleep Disorders Center, College of Medicine, King Saud University, Riyadh, Saudi Arabia, [7] National Plan for Science and Technology, College of Medicine, King Saud University, Riyadh, Saudi Arabia

OPEN ACCESS

Edited by:
Rafael Christophe Freire, Queen's University, Canada

Reviewed by:
Stephen McNevin, Queens University, Canada
Laiana Quagliato, Federal University of Rio de Janeiro, Brazil

***Correspondence:**
Masood Khan
raomasood22@gmail.com; mkhan4.c@ksu.edu.sa

Specialty section:
This article was submitted to Mood and Anxiety Disorders, a section of the journal Frontiers in Psychiatry

Received: *07 March 2021*
Accepted: *05 May 2021*
Published: *01 July 2021*

Citation:
Manzar MD, Alghadir AH, Khan M, Salahuddin M, Albougami A, Maniago JD, Vasquez BA, Pandi-Perumal SR and Bahammam AS (2021) Anxiety Symptoms Are Associated With Higher Psychological Stress, Poor Sleep, and Inadequate Sleep Hygiene in Collegiate Young Adults—A Cross-Sectional Study. Front. Psychiatry 12:677136. doi: 10.3389/fpsyt.2021.677136

Background: Anxiety symptoms, stress, poor sleep, and inadequate sleep hygiene are common in university students and these affect their learning and increase attrition. However, limited knowledge exists about the inter-relationship between these factors among university students in low-middle income countries. Therefore, this study aimed to investigate the prevalence of anxiety symptoms and their relationship with sleep quality, sleep hygiene practices, and psychological stress.

Materials and Methods: A cross-sectional study was conducted with a randomly selected sample of students in Mizan-Aman, Ethiopia. Participants completed a self-administered questionnaire, which included questions about socio-demographics, socio-economic factors, the Leeds Sleep Evaluation Questionnaire-Mizan, Sleep hygiene index, Perceived stress scale-10 (PSS-10), and Generalized anxiety disorder-7 scale (GAD-7).

Results: The prevalence of anxiety symptoms was about 22%. Multivariate regression analysis showed that both anxiety status $\chi^2[(13, N = 480) = 82.68, p < 0.001]$, and increasing levels of anxiety (model adjusted R2 = 0.204, $p < 0.001$) were associated with greater psychological stress, inadequate sleep hygiene practices, and poor sleep quality scores after adjusting for age, gender, attendance, substance use, years of university education, time spent in athletic activity every day, and frequency of tea/coffee consumption.

Conclusion: There was a high prevalence of anxiety symptoms in this study population, and this condition was associated with psychological stress, poor sleep, and inadequate sleep hygiene parameters. These results suggest a need to address the various aspects of mental health and its diverse sleep correlates in university students.

Keywords: anxiety, perceived stress, sleep quality, sleep hygiene, Leeds sleep evaluation questionnaire

INTRODUCTION

Anxiety is one of the common mental health disorders (global prevalence of 3.7%), associated with significant comorbidity and mortality (1). Anxiety is often comorbid with depression or other anxiety disorders, which renders its diagnosis and treatment complicated (2). As a result, anxiety remains undiagnosed and undertreated in most primary care settings (3). Anxiety has added indirect costs to the economic burden of countries owing to significant loss of personnel productivity and increased use of primary health care services (4). As such, it is important to identify anxiety for early diagnosis and treatment. This is more relevant for university students of the present-day world as mental health issues are common and usually associated with pressure to achieve higher academic grades, a transition to a higher level of studies, and pressure to succeed (5). Estimates vary but a large proportion of college-going students show stress (∼51–67%), and anxiety symptoms (∼34–56%) (6, 7).

Poor sleep quality adversely influences day-to-day activities and may predispose affected individuals to poor health and quality of life outcomes and mental health issues such as anxiety, depression, and other problems (8). There are pieces of evidence showing that anxiety is correlated with poor sleep quality in insomnia (9, 10). Inadequate sleep hygiene practices are correlated with measures of anxiety and stress in Saudi university students (11). However, the association was determined using bivariate analysis, and therefore it is desirable to further investigate this relationship in other populations using multivariate analysis. Sleep quality is associated with psychological distress and inadequate sleep hygiene among Iranian pre-clinical students (12). We recently found that insomnia is highly prevalent among university students and that it is associated with anxiety, and inadequate sleep hygiene practices (13). However, to the best of our knowledge, no study investigated anxiety, and its association with psychological stress, sleep quality and sleep hygiene.

Moreover, two recent studies in the Ethiopian population determined the prevalence and determinants of anxiety in healthcare workers (14) and women attending prenatal care (15). However, there are few reports which determined the prevalence of anxiety in the Ethiopian student population and studied its associated conditions. Therefore, this study was planned to investigate the prevalence of anxiety and its relationship with psychological stress, sleep quality, and sleep hygiene practices among Ethiopian university students.

MATERIALS AND METHODS

Study Design and Participants

A total of 17936 students were enrolled in both the campuses located at Mizan city and Tepi city of the Mizan-Tepi University (MTU) in regular and continuous programs in 2017–18 academic year. Haile et al. had reported a prevalence of 63.1% for common mental disorders especially anxiety and depressive symptoms in a similar setting of university students in Ethiopia (16). Therefore, a sample size of 598 was estimated using 5% as margin of error, confidence interval of 99%, population (all students of MTU), and 63.1% as expected response distribution. We randomly selected the Mizan campus for the recruitment of participants in this cross-sectional study. A list of 750 students was initially prepared by a simple random method. Of these students, 189 declined to participate or were absent on the day of the interview, 36 were excluded after screening for the exclusion criteria, and 26 responses were deleted because of person-level missing values, that is, missing responses for most of the items of the four standard questionnaires. Finally, analysis of a dataset of collegiate young adults ($n = 499$, age: 21.34 $\pm$ 2.76 years) is presented. The final sample size was deemed adequate because it was still more than a sample size (351) estimated using 5% as margin of error, confidence interval of 95%, population (all students of MTU), and 63.1% as expected response distribution. Respondents were asked to complete a self-administered questionnaire during in-person meetings with the research team. These meetings were scheduled during the semesters to avoid bias from the examination-related stress. Students who were pursuing higher education from Mizan-Tepi University, Mizan-Aman, Ethiopia were included in the study. Those with an idiosyncratic account of self-reported recollected complaints and those taking neuropsychiatric medications were excluded from the study. Institutional review committee approval from the College of Health Sciences, Mizan-Tepi University, Ethiopia was acquired. Before the collection of data, a precis of the intent and methodology to be implemented was explained to the respondents. The nature of participation was clarified to the respondents as voluntary and their right to terminate participation at any time-point was emphasized. There were no direct benefits for respondents and no risks or chances of harm. It was also communicated to the respondents that they will not receive any fee in exchange for participation. Stringent provisions for privacy and confidentiality were implemented. The study strictly conforms with the Helsinki declaration. Informed written consent for participation and publication were obtained. The study utilized five tools: (i) Generalized anxiety disorder-7 scale (GAD-7), (ii) Leeds Sleep Evaluation Questionnaire-Mizan, (iii) Perceived stress scale-10 (PSS-10), (iv) Sleep hygiene index, and (v) a semi-structured socio-demographics tool. Since the English language is the medium of instruction in all federal universities in Ethiopia, all the tools employed in this study were in English.

Measures

Generalized Anxiety Disorder – 7 Scale

GAD-7 scale is a succinct but scrupulously validated inventory to examine anxiety symptoms (17–19). It has been shown to have sufficient diagnostic validity for vetting a wide-array of anxiety-related disorders: "GAD, panic disorder, social phobia, and post-traumatic stress disorder" (18). A cut-point of 10 for GAD-7 is observed in this study to determine anxiety symptoms. A sensitivity of 68% and specificity of 88% were reported by Kroenke et al. at this cut-point. Seven items are scored using an ordinal scale (0–3) to account for the cumulative regularity of

Abbreviations: GAD, generalized anxiety disorder; PSS-10, perceived stress scale-10; SHI, sleep hygiene index; LSEQ-M, Leeds sleep evaluation questionnaire-Mizan; VAS, visual analog scale.

anxiety symptoms within the last 7 days (18). The GAD-7 total score, ranging from 0–21, is equal to the linear summation of all the 7-items (17, 18). The severity of the anxiety increases with the increment in the GAD-7 total score (17, 18). The GAD-7 is a valid instrument for screening anxiety in university students in Afro-Asian countries (19, 20).

Sleep Hygiene Index

SHI is a validated 13-item self-report measure of sleep hygiene (21). This study adapted the version with a slightly modified scoring system (dichotomized rating for each of the items: 0 = No; 1 = Yes). SHI total score is the summation of all the items ranging from 0–13, where a lower score infers good sleep hygiene practices and a higher score suggests the otherwise (21). The reliability of this version (dichotomized scoring) is sufficient as indicated by a GLB = 0.85 and Standardized $\alpha = 0.66$ (22). SHI is valid among university students (11).

Leeds Sleep Evaluation Questionnaire-Mizan

Manzar et al. (23) validated the modified version of the LSEQ (i.e., LSEQ-M) (24). The revision was composed to gauge the sleep complaints among the student populace. A 100 mm visual analog scale (VAS) was utilized to rate each of the 10-items (23, 25). Lower scores imply more severe sleep complaints (23). The scores (0–100 range) of each item are transformed into 0–10 range which when summed will yield an LSEQ-M total score ranging from 0–100 (23). LSEQ-M has requisite reliability, adequate internal homogeneity, construct validity, and structural validity in university students (23, 25).

Perceived Stress Scale-10

PSS-10 is a succinct (10-items) but scrupulously validated scale of psychological stress (26). PSS-10 is a self-report that appraises the stress experienced by the respondents throughout the month preceding the test. Each item is rated using a 4-point ordinal scale (0 = Never; 4 = Very Often), where higher scores would infer a cumulative regularity of stress-related complaints. The linear summation of all the 10-items will generate the total PSS-10 score (26). The higher the psychological stress level, the higher the PSS-10 total scores. Manzar et al. (27) reported that PSS-10 has adequate psychometric validity when utilized in assessing the psychological stress among Ethiopian university students.

Socio-Demographic Questionnaire

A concise questionnaire was utilized to register the socio-demographic characteristics of the respondents (e.g., age, gender, years of education, attendance (% of classes attended), substance use, daily athletic activity duration, and frequency of daily tea/coffee consumption). Substance use item recorded self-reported habitual consumption of alcohol and/or Khat and/or smoking.

Statistical Analysis

In this study, statistical analysis was performed using SPSS version 26.0. Participants' characteristics were presented using these: mean ± SD (continuous) and percentage and frequency (categorical variables). Chi-square test or Fisher's exact test (categorical variables) and Student's independent *t*-test (continuous variables) were employed for bivariate analysis.

Multivariate analysis was performed using binary logistic and multiple linear regression. Nineteen multivariate outliers [Mahalanobis distance criteria; X^2 (9) = 27.88, $p < 0.001$] and high leverage points and highly influential points (Cook's distance < 1.0) were removed for performing multivariate analysis. There were few univariate outliers in the attendance and age variables but these were not removed because those values were found to be correct and not arising out of data entry mistakes. Other assumptions for binary logistic regression like (i) independence of observations, (ii) absence of multicollinearity among independent variables as determined by the Spearman's correlation coefficients, and (iii) linear relationship with log odds of all independent variables were satisfied by the dataset. Additional assumptions for the multiple linear regression: (i) linear relation between outcome and independent variable as determined by scatterplot and partial regression plots, (ii) homoscedasticity as determined by studentized residuals plotted against the unstandardized predicted values, and (iii) normal distribution of the residual errors were satisfied by the dataset.

All the covariates and independent variables except gender, attendance, years of education, and frequency of daily tea/coffee consumption were significantly correlated with anxiety. However, gender, attendance, years of education, and frequency of daily tea/coffee consumption were used as covariates or predictors because earlier works have shown them to be associated with anxiety (28–31).

RESULTS

Participants' Characteristics

Most of the participants (80.6%) were males (**Table 1**). Three-fourth of the collegiate young adults (75%) were studying in the first 2 years of university education (**Table 1**). The average of attendance, PSS-10 total score, LSEQ-M total score, and SHI total score was 95.32 ± 6.87, 18.83 ± 6.43, 60.08 ± 21.19, and 6.44 ± 2.39, respectively (**Table 1**). The prevalence of anxiety symptoms was 21.6%, and the average GAD-7 total score was 7.2 ± 4.3 in the study sample.

Bivariate Analysis: The Relationship Between Anxiety and Participants' Characteristics

The bivariate analysis predicted that anxiety was more common in students with lower age (20.57 ± 1.47 vs. 21.55 ± 2.99, $p < 0.001$) and those who spent less time in athletic activities every day (28.15 ± 32.33 vs. 42.68 ± 40.85, $p < 0.001$) (**Table 1**). Both PSS-10 total score (22.82 ± 5.24 vs. 18.83 ± 6.43, $p < 0.001$) and SHI total score (7.47 ± 1.84 vs. 6.44 ± 2.39, $p < 0.001$) were higher in the anxiety group than normal (**Table 1**). Similarly, the anxiety group showed lower values for LSEQ-M total score (49.90 ± 19.18 vs. 60.08 ± 21.19, $p < 0.001$), indicating poorer sleep than the normal young adults (**Table 1**).

TABLE 1 | Participants' characteristics and their relationship (bivariate) with anxiety in Ethiopian collegiate young adults.

Characteristics	Mean ± SD /frequency (percentage)	Normal (n = 391) mean ± SD /frequency (percentage)	Anxiety symptoms (n = 108) mean ± SD /frequency (percentage)	Statistics	*P*-value
Age (yr)	21.34 ± 2.76	21.55 ± 2.99	20.57 ± 1.47	4.71[a]	<0.001
Gender					
Male	402 (80.6)	318 (81.3)	84 (77.8)	0.68[b]	0.41
Female	97 (19.4)	73 (18.7)	24 (22.2)		
Years of education					
1st	186 (37.3)	150 (38.4)	36 (33.3)	6.35[b]	0.18
2nd	188 (37.7)	140 (35.8)	48 (44.4)		
3rd	56 (11.2)	43 (11.0)	13 (12.0)		
4th	39 (7.8)	30 (7.7)	9 (8.3)		
5th	30 (6.0)	28 (7.2)	2 (1.9)		
Attendance	95.34 ± 6.92	95.32 ± 6.87	95.44 ± 7.13	−0.16[a]	0.88
Substance use*				0.45[b]	0.50
No	464 (93.0)	362 (92.6)	102 (94.4)		
Yes	35 (7.0)	29 (7.4)	6 (5.6)		
PSS-10 total score	19.69 ± 6.40	18.83 ± 6.43	22.82 ± 5.24	−6.65[a]	<0.001
LSEQ-M total score	57.88 ± 21.18	60.08 ± 21.19	49.90 ± 19.18	4.51[a]	<0.001
SHI total score	6.67 ± 2.32	6.44 ± 2.39	7.47 ± 1.84	−4.80[a]	<0.001
Daily athletic activity duration	39.53 ± 39.59	42.68 ± 40.85	28.15 ± 32.33	3.89[a]	<0.001
Frequency of tea/coffee consumption	1.15 ± 0.63	1.18 ± 0.63	1.06 ± 0.61	1.81[a]	0.07

**Substance use (self-reported habitual use of alcohol and/or Khat and/or smoking); Anxiety symptoms was screened by Generalized anxiety disorder-7 scale.*
SD, standard deviation; GAD-7, generalized anxiety disorder-7 scale; SHI, sleep hygiene index; LSEQ-M, an adapted and validated English version of the Leeds sleep evaluation questionnaire; PSS, perceived stress scale-10.
Statistics: Chi-square test/ Fisher's exact test for categorical variables and student's t-test for continuous variables; [a]: t statistic; [b]: chi-square statistic value.

Multivariate Analysis: Binary Logistic Regression-Association of Anxiety Disorder With the Level of Stress, Poor Sleep, and Inadequate Sleep Hygiene

A binary logistic regression was run to predict anxiety; this model was adjusted for age, gender, attendance (percentage of lectures attended), substance use (self-reported habitual use of alcohol and/or Khat and/or smoking), years of university education, time spent in athletic activity every day, and frequency of tea/coffee consumption. The model with three predictors, that is, PSS-10 total score, SHI total score, and LSEQ-M total score were significant in comparison to a model with only intercepts; $\chi^2(13, N = 480) = 82.68$, $p < 0.001$. The model with these predictors explained 24.1% of the variance in the classification of anxiety with an accuracy of 78.8%. Increasing scores of PSS-10 and SHI and the decreasing score of LSEQ-M were associated with anxiety status (**Table 2**).

TABLE 2 | Binary logistic regression: association of anxiety with psychological stress, poor sleep, and inadequate sleep hygiene in Ethiopian collegiate young adults.

Associated conditions	AOR (95 % CI)	*P*-value	COR (95 % CI)	*P*-value
LSEQ-M total score	0.97 (0.96–0.99)	<0.001	0.98 (0.97–0.99)	<0.001
SHI total score	1.16 (1.03–1.30)	0.01	1.22 (1.10–1.35)	<0.001
PSS total score	1.11 (1.06–1.16)	<0.001	1.12 (1.07–1.17)	<0.001

CI, confidence interval; AOR, adjusted odds ratio; COR, crude odds ratio.
Adjusted for age, gender, attendance (percentage of lectures attended), Substance use (self-reported habitual use of alcohol and/or Khat and/or smoking) and years of university education, time spent in athletic activity every day, frequency of tea/coffee consumption. Anxiety was screened by Generalized anxiety disorder-7 scale; LSEQ-M, an adapted and validated English version of the Leeds sleep evaluation questionnaire; SHI, sleep hygiene index; PSS: perceived stress scale-10.

Multivariate Analysis: Multiple Linear Regression-Association of Anxiety Level With the Level of Stress, Poor Sleep, and Inadequate Sleep Hygiene

Further, a multiple linear regression model assessed the extent to which inadequate sleep hygiene, poor sleep, and psychological stress predict changes in anxiety levels. Increasing severity of the anxiety (implied by increasing GAD-7 total score) was predicted by an increasing level of poor sleep (lower LSEQ-M total score), inadequate sleep hygiene (higher SHI total score), and increasing psychological stress (increasing PSS-10 total score) (model adjusted R2 = 0.204, $p < 0.001$) (**Table 3**).

DISCUSSION

In the present study, (i) a high prevalence of anxiety was found in the study population of Ethiopian university students, and

TABLE 3 | Multiple regression predictors of the anxiety level in Ethiopian collegiate young adults.

Independent variable	Beta coefficient	Standard error	*T*-values	*P*-values	Model unadjusted R2; adjusted R2; *P*-value
Age	−0.069	0.089	−1.525	0.128	0.219, 0.204, <0.001
Gender	0.001	0.468	0.03	0.976	
Attendance	−0.020	0.027	−0.477	0.633	
Daily athletic activity duration (min)	−0.067	0.005	−1.617	0.106	
Frequency of tea/coffee consumption	−0.097	0.307	−2.353	**0.019**	
SHI total score	0.120	0.084	2.726	**0.007**	
PSS-10 total score	0.307	0.03	7.097	**<0.001**	
LSEQ-M total score	−0.186	0.009	−4.359	**<0.001**	
Years of university education	0.006	0.169	0.134	0.894	
Intercept	8.818*	3.376	2.612	0.009	

**Unstandardized beta coefficient for the intercept, for all other independent variables standardized beta coefficient is shown.*
GAD-7, generalized anxiety disorder-7 scale; LSEQ-M, an adapted and validated English version of the Leeds sleep evaluation questionnaire; SHI, sleep hygiene index; PSS, perceived stress scale-10. Bold values indicate a significant relationship between an independent variable and the dependent variable.

(ii) both status of anxiety and an increasing level of anxiety were found to be associated with psychological stress, poor sleep quality, and inadequate sleep hygiene practices. To the best of our knowledge, this is the first study to demonstrate the status of having an anxiety and increasing level of anxiety to be associated with poor sleep, inadequate sleep hygiene practice, and psychological stress. The findings of the present study are strengthened by the fact that all the measures were standard questionnaires that have previously been validated in university students (11, 19, 23, 27). Furthermore, the results are reinforced by the fact that the relationship was significant in the multivariate models after adjusting for many of the known covariates (28–31).

The prevalence of anxiety (∼22%) in this study was slightly lower than that reported by a recent systematic review, that is, 24.5% based on a summarized finding of 48 articles from 40 countries (32). Ghrouz et al. (33) found a slightly higher level of anxiety symptoms using the GAD-7 scale (30%) in Indian university students (33). This concordance with the findings of a high prevalence rate of anxiety in Ethiopia and the rest of the world indicates a major global public health problem affecting university attending young adults (32, 33). The anxiety-sleep quality relationship in the present study is supported by previous reports. Poor sleep has been one of the consistent predictors of increased anxiety levels in collegiate young adults (33, 34). Zhang et al. reported that psychological stress mediates the relationship between poor sleep quality and anxiety levels among American nursing students (34). Ghrouz et al. (33) found that poor sleep quality was associated with anxiety in Indian university students (33). A recent systematic review summarized that sleep disturbances may aggravate the severity of anxiety symptoms, and thus, understanding comorbid anxiety and poor sleep may be important for the exploration of treatment strategies (35).

To the best of our knowledge, this is the first study to report a direct association of anxiety status, and anxiety level with inadequate sleep hygiene practices among young adults. However, thematically similar generalizations are entailed in some of the previous reports. Baroni et al. reported that an intervention called sleep course targeted to improve sleep hygiene practices also led to a decrease in anxiety levels in American college students (36). Similarly, Peltz et al. (37) using a moderator-mediator analysis found that (i) sleep hygiene was both directly and indirectly associated with anxiety levels in American adolescents whose school start time is before 8:30 am, and (ii) sleep hygiene was only directly associated with anxiety levels in American adolescents whose school start time was 8:30 am or later (37). A systematic review showed a constellation of poor sleep behaviors like inadequate sleep hygiene, and difficulty in initiating/maintaining sleep are common in children with anxiety disorders (38). Inadequate sleep hygiene practice is common in university students, due to continuous pressure to maintain a higher cumulative grade point average (cGPA), and personal socioeconomic position forcing some of them to work off-campus, all of these adds to their irregular sleeping schedules. Other evidence revealed that an increased co-sleeping tendency in anxious school-going children is found, with one in three children tending to co-sleep 2–4 times a week compared to non-anxious children (39). The use of portable electronic devices by children and adolescents before sleep has been proposed to cause displacement of time to sleep due to increased mental alertness, and psychological stimulation due to light exposure (40). To this end, inadequate sleep hygiene practice is common in university students, thus it is suggested that the universities should have appropriate advisory centers to provide specialized counseling tailored to improve sleep habits, and mental health.

Anxiety and increasing severity of anxiety were associated with psychological stress in the study population. Faravelli and Pallanti reported that distressing events in life lead to the development of anxiety symptoms (41). Perceived exam stress is common in university students with the fear of lower grades. Lower grades may consequently decrease prospects of finding jobs in the future, thoughts about this may increase the level of anxiety. Prolonged stress may impair the ability to perform well-during exams, and in the long-term makes an individual vulnerable to neuropsychiatric complications (42). Other aspects

that may potentially increase stress in students are adjustments to the new campus life, fulfilling academic requirements, and simultaneous maintenance of social and academic life.

Limitations of the Study

The study does not have an equal representation of females; nevertheless, the study satisfies the NIH mandate of inclusion of sex as a biological variable for reproducibility and replicability in science (43). Lesser female representation may also be related to the overall lower percentage of female students (about 30%) enrolled at MTU during the academic year. Similar studies involving Ethiopian university students also reported less participation from female students (16). It would be interesting to assess the relationship between courses of study and anxiety symptoms in future studies. Moreover, both regression models used in this study explained 20.4 and 24.1% of the variance. This is most plausibly explained by statistical consideration that some of the covariates associated with anxiety may have not been accounted for in the present study. This aspect should be further explored in future studies. Moreover, a clinical diagnosis of anxiety was not performed. However, it may not be out of place to mention that in the limited resource setting in which this study was performed, a comprehensive clinical neuropsychological assessment was not possible.

CONCLUSION

The study found a high prevalence of anxiety and psychological anxiety levels in the participating Ethiopian university students. Both the status of anxiety and the increasing severity were associated with higher psychological stress, poor sleep, and inadequate sleep hygiene. Screening of these correlates of anxiety may help in the early identification and management of mental health.

DATA AVAILABILITY STATEMENT

The dataset generated during and/or analyzed during the current study is available in the **Supplement File**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Human Institutional Ethics Review Committee, College of Medicine and Health Sciences, Mizan-Tepi University, Mizan. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MM, MS, JM, and BV conceptualized the study, methodology, and were involved in data collection and data curation. MM and MK did the data analysis and wrote and edited the manuscript. AHA, AA, SRP, and AB were involved in supervision. All authors contributed to the article and approved the submitted version.

FUNDING

This research is funded by Vice Deanship of Scientific Research Chairs, King Saud University. The authors extend their appreciation to the Deanship of Scientific Research at Majmaah University for funding this work under Project Number No (R-2021-134).

ACKNOWLEDGMENTS

The authors are grateful to the Deanship of Scientific Research, King Saud University for funding through Vice Deanship of Scientific Research Chairs. We are grateful to the participants of the study. The authors are grateful to the Deanship of Scientific Research at Majmaah University for funding this work under Project Number No (R-2021-134).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.677136/full#supplementary-material

REFERENCES

1. Stein DJ, Scott KM, de Jonge P, Kessler RC. Epidemiology of anxiety disorders: from surveys to nosology and back. *Dialogues Clin Neurosci.* (2017) 19:127–36. doi: 10.31887/DCNS.2017.19.2/dstein
2. Thibaut F. Anxiety disorders: a review of current literature. *Dialogues Clin Neurosci.* (2017) 19:87–8. doi: 10.31887/DCNS.2017.19.2/fthibaut
3. Wittchen HU, Kessler RC, Beesdo K, Krause P, Hofler M, Hoyer J. Generalized anxiety and depression in primary care: prevalence, recognition, and management. *J Clin Psychiatry.* (2002) 63 (Suppl 8):24–34.
4. Wittchen HU. Generalized anxiety disorder: prevalence, burden, and cost to society. *Depress Anxiety.* (2002) 16:162–71. doi: 10.1002/da.10065
5. Beiter R, Nash R, McCrady M, Rhoades D, Linscomb M, Clarahan M, et al. The prevalence and correlates of depression, anxiety, and stress in a sample of college students. *J Affect Disord.* (2015) 173:90–6. doi: 10.1016/j.jad.2014.10.054
6. Quek TT, Tam WW, Tran BX, Zhang M, Zhang Z, Ho CS, et al. The global prevalence of anxiety among medical students: a meta-analysis. *Int J Environ Res Public Health.* (2019) 16:2735. doi: 10.3390/ijerph16152735
7. Basudan S, Binanzan N, Alhassan A. Depression, anxiety and stress in dental students. *Int J Med Educ.* (2017) 8:179–86. doi: 10.5116/ijme.5910.b961
8. Mollaoglu M. Trigger factors in migraine patients. *J Health Psychol.* (2013) 18:984–94. doi: 10.1177/1359105312446773
9. Hertenstein E, Feige B, Gmeiner T, Kienzler C, Spiegelhalder K, Johann A, et al. Insomnia as a predictor of mental disorders: A systematic review and meta-analysis. *Sleep Med Rev.* (2019) 43:96–105. doi: 10.1016/j.smrv.2018.10.006
10. Baglioni C, Nanovska S, Regen W, Spiegelhalder K, Feige B, Nissen C, et al. Sleep and mental disorders: A meta-analysis of polysomnographic research. *Psychol Bull.* (2016) 142:969–90. doi: 10.1037/bul0000053
11. Anwer S, Alghadir A, Manzar MD, Noohu MM, Salahuddin M, Li H. Psychometric analysis of the sleep hygiene index and correlation with stress and anxiety among saudi university students. *Nat Sci Sleep.* (2019) 11:325–32. doi: 10.2147/NSS.S222440

12. Rezaei M, Khormali M, Akbarpour S, Sadeghniiat-Hagighi K, Shamsipour M. Sleep quality and its association with psychological distress and sleep hygiene: a cross-sectional study among pre-clinical medical students. *Sleep Sci.* (2018) 11:274–80. doi: 10.5935/1984-0063.20180043
13. Manzar MD, Noohu MM, Salahuddin M, Nureye D, Albougami A, Spence DW, et al. Insomnia symptoms and their association with anxiety and poor sleep hygiene practices among ethiopian university students. *Nat Sci Sleep.* (2020) 575–82. doi: 10.2147/NSS.S246994
14. Teshome A, Glagn M, Shegaze M, Tekabe B, Getie A, Assefa G, et al. Generalized anxiety disorder and its associated factors among health care workers fighting COVID-19 in Southern Ethiopia. *Psychol Res Behav Manage.* (2020) 13:907. doi: 10.2147/PRBM.S282822
15. Kassaw C, Pandey D. The prevalence of general anxiety disorder and its associated factors among women's attending at the perinatal service of Dilla University referral hospital, Dilla town, Ethiopia, April, 2020 in Covid pandemic. *Heliyon.* (2020) 6:e05593. doi: 10.1016/j.heliyon.2020.e05593
16. Haile YG, Alemu SM, Habtewold TD. Common mental disorder and its association with academic performance among Debre Berhan University students, Ethiopia. *Int J Ment Health Syst.* (2017) 11:1–1. doi: 10.1186/s13033-017-0142-6
17. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med.* (2006) 166:1092–7. doi: 10.1001/archinte.166.10.1092
18. Kroenke K, Spitzer RL, Williams JB, Monahan PO, Lowe B. Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. *Ann Intern Med.* (2007) 146:317–25. doi: 10.7326/0003-4819-146-5-200703060-00004
19. Alghadir A, Manzar MD, Anwer S, Albougami A, Salahuddin M. Psychometric properties of the generalized anxiety disorder scale among saudi university male students. *Neuropsychiatr Dis Treat.* (2020) 16:1427–32. doi: 10.2147/NDT.S246526
20. Manzar MD, Alghadir AH, Anwer S, Alqahtani M, Salahuddin M, Addo HA, et al. Psychometric properties of the general anxiety disorders-7 scale using categorical data methods: a study in a sample of university attending ethiopian young adults. *Neuropsychiatr Dis Treat.* (2021) 17:893. doi: 10.2147/NDT.S295912
21. Mastin DF, Bryson J, Corwyn R. Assessment of sleep hygiene using the Sleep Hygiene Index. *J Behav Med.* (2006) 29:223–7. doi: 10.1007/s10865-006-9047-6
22. Trizano-Hermosilla I, Alvarado JM. Best Alternatives to Cronbach's alpha reliability in realistic conditions: congeneric and asymmetrical measurements. *Front Psychol.* (2016) 7:769. doi: 10.3389/fpsyg.2016.00769
23. Manzar MD, Salahuddin M, Maru TT, Alghadir A, Anwer S, Bahammam AS, et al. Validation of the adapted Leeds sleep evaluation questionnaire in Ethiopian university students. *Health Qual Life Outcomes.* (2018) 16:49. doi: 10.1186/s12955-018-0876-0
24. Tarrasch R, Laudon M, Zisapel N. Cross-cultural validation of the Leeds sleep evaluation questionnaire (LSEQ) in insomnia patients. *Hum Psychopharmacol.* (2003) 18:603–10. doi: 10.1002/hup.534
25. Hameed UA, Al-Jarrah MD, Manzar MD, Nair C, Albougami A, Alrasheadi BA, et al. Leeds sleep evaluation questionnaire in Jordanian university students. A psychometric investigation using comparative confirmatory factor analysis. *Saudi Med J.* (2020) 41:746–52. doi: 10.15537/smj.2020.7.25146
26. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav.* (1983) 24:385–96. doi: 10.2307/2136404
27. Manzar MD, Salahuddin M, Peter S, Alghadir A, Anwer S, Bahammam AS, et al. Psychometric properties of the perceived stress scale in Ethiopian university students. *BMC Public Health.* (2019) 19:41. doi: 10.1186/s12889-018-6310-z
28. Kaczkurkin AN, Moore TM, Ruparel K, Ciric R, Calkins ME, Shinohara RT, et al. Elevated amygdala perfusion mediates developmental sex differences in trait anxiety. *Biol Psychiatry.* (2016) 80:775–85. doi: 10.1016/j.biopsych.2016.04.021
29. Abu Ruz ME, Al-Akash HY, Jarrah S. Persistent (anxiety and depression) affected academic achievement and absenteeism in nursing students. *Open Nurs J.* (2018) 12:171–9. doi: 10.2174/1874434601812010171
30. Naz N, Iqbal S, Mahmood A. Stress, anxiety and depression among the dental students of university college of medicine and dentistry Lahore; Pakistan. *Pak J Med Health Sci.* (2017) 11:1277–81.
31. Nymberg J, Vang Y, Clough N, Masters C. Does daily caffeine intake increase the risk of anxiety? *Evid Based Pract.* (2018) 21:E2. doi: 10.1097/01.EBP.0000541940.88000.28
32. de Paula W, Breguez GS, Machado EL, Meireles AL. Prevalence of anxiety, depression, and suicidal ideation symptoms among university students: a systematic review. *Braz J Health Rev.* (2020) 3:8739–56. doi: 10.34119/bjhrv3n4-119
33. Ghrouz AK, Noohu MM, Dilshad Manzar M, Warren Spence D, BaHammam AS, et al. Physical activity and sleep quality in relation to mental health among college students. *Sleep Breath.* (2019) 23:627–34. doi: 10.1007/s11325-019-01780-z
34. Zhang Y, Peters A, Chen G. Perceived stress mediates the associations between sleep quality and symptoms of anxiety and depression among college nursing students. *Int J Nurs Educ Scholarsh.* (2018) 15:1–9. doi: 10.1515/ijnes-2017-0020
35. Cox RC, Olatunji BO. A systematic review of sleep disturbance in anxiety and related disorders. *J Anxiety Disord.* (2016) 37:104–29. doi: 10.1016/j.janxdis.2015.12.001
36. Baroni A, Bruzzese JM, Di Bartolo CA, Ciarleglio A, Shatkin JP. Impact of a sleep course on sleep, mood and anxiety symptoms in college students: a pilot study. *J Am Coll Health.* (2018) 66:41–50. doi: 10.1080/07448481.2017.1369091
37. Peltz JS, Rogge RD, Connolly H, O'Connor TG. A process-oriented model linking adolescents' sleep hygiene and psychological functioning: the moderating role of school start times. *Sleep Health.* (2017) 3:465–71. doi: 10.1016/j.sleh.2017.08.003
38. Brown WJ, Wilkerson AK, Boyd SJ, Dewey D, Mesa F, Bunnell BE. A review of sleep disturbance in children and adolescents with anxiety. *J Sleep Res.* (2018) 27:e12635. doi: 10.1111/jsr.12635
39. Palmer CA, Clementi MA, Meers JM, Alfano CA. Co-sleeping among school-aged anxious and non-anxious children: associations with sleep variability and timing. *J Abnorm Child Psychol.* (2018) 46:1321–32. doi: 10.1007/s10802-017-0387-1
40. Hale L, Kirschen GW, LeBourgeois MK, Gradisar M, Garrison MM, Montgomery-Downs H, et al. Youth screen media habits and sleep: sleep-friendly screen behavior recommendations for clinicians, educators, and parents. *Child Adolesc Psychiatr Clin N Am.* (2018) 27:229–45. doi: 10.1016/j.chc.2017.11.014
41. Faravelli C, Pallanti S. Recent life events and panic disorder. *Am J Psychiatry.* (1989) 146:622–6. doi: 10.1176/ajp.146.5.622
42. Rasheed N. Prolonged stress leads to serious health problems: preventive approaches. *Int J Health Sci (Qassim).* (2016) 10:V–VI. doi: 10.12816/0031211
43. National Institutes of Health (NIH), (2015). *Consideration of Sex as a Biological Variable in NIH-Funded Research*. Available online at: https://grants.nih.gov/grants/guide/notice-files/not-od-15-102.html (accessed May 22, 2021).

Conflict of Interest: SRP reports non-financial support from Somnogen Canada Inc. and occasional royalties for the editorial contribution from Springer during the conduct of the study and is an employee of Somnogen Canada Inc.

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.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 06 July 2021
doi: 10.3389/fpsyt.2021.676022

Application of the Chinese Version of the Pittsburgh Sleep Quality Index in People Living With HIV: Preliminary Reliability and Validity

Dong-Qin Yan[1†], *Yun-Xiang Huang*[1,2†], *Xi Chen*[3], *Min Wang*[4], *Jie Li*[5] *and Dan Luo*[1*]

[1] Department of Social Medicine and Health Management, Xiangya School of Public Health, Central South University, Changsha, China, [2] Chinese Evidence-Based Medicine Center, West China Hospital, Sichuan University, Chengdu, China, [3] Hunan Provincial Center for Disease Prevention and Control, Changsha, China, [4] Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome Research Institute, The First Hospital of Changsha, Changsha, China, [5] Furong District Center for Disease Prevention and Control, Changsha, China

OPEN ACCESS

Edited by:
Seog Ju Kim,
Sungkyunkwan University,
South Korea

Reviewed by:
Daniela Adamo,
University of Naples Federico II, Italy
Lorenzo Tonetti,
University of Bologna, Italy

***Correspondence:**
Dan Luo
luodan_csu_2011@126.com

[†]These authors have contributed equally to this work

Specialty section:
This article was submitted to Sleep Disorders, a section of the journal Frontiers in Psychiatry

Received: 04 March 2021
Accepted: 24 May 2021
Published: 06 July 2021

Citation:
Yan D-Q, Huang Y-X, Chen X, Wang M, Li J and Luo D (2021) Application of the Chinese Version of the Pittsburgh Sleep Quality Index in People Living With HIV: Preliminary Reliability and Validity. Front. Psychiatry 12:676022. doi: 10.3389/fpsyt.2021.676022

Background: The Pittsburgh Sleep Quality Index (PSQI) has been a widely used instrument measuring sleep quality among people living with HIV (PLWH) in China while its psychometric properties have yet to be examined in this population. We aimed to assess the reliability and validity of the Chinese version of PSQI in PLWH and identify factors associated with sleep quality.

Methods: This study was based on a longitudinal study of newly diagnosed PLWH, among whom the PSQI was used to measure sleep quality 5 years after HIV diagnosis ($n = 386$). To evaluate internal consistency, Cronbach's alpha and corrected item-total correlation were calculated. To assess construct validity, Pearson's correlation coefficients were calculated between PSQI scores and depression, anxiety, stress, and health-related quality of life (HRQoL). Known group validity was evaluated by comparing PSQI scores between participants with probable depression and those without. Binary logistic regression was conducted to identify factors associated with sleep disturbances.

Results: The internal consistency Cronbach's alpha for the Chinese version of PSQI in PLWH was 0.713. Construct validity was established by significant relationships between PSQI and depression, anxiety, stress, and HRQoL. The PSQI scores in participants with probable depression were significantly higher than those without, indicating good known-group validity. Sleep disturbances were associated with less income, higher CD4 counts, antiretroviral treatment (ART) initiation, exercise, depression, and higher stress levels.

Conclusions: The Chinese version of PSQI is feasible for use among Chinese PLWH. Over a third of PLWH reported sleep disturbances. More attention should be given to individuals with less income and on ART. Intervention aimed at improving mental health or facilitating exercise may improve sleep quality.

Keywords: pittsburgh sleep quality index, reliability, validity, HIV, sleep disturbances, China

INTRODUCTION

Receiving diagnosis of HIV infection is considered as an extremely stressful experience for most individuals, accompanied with considerable stressors such as stigma, disclosure, emotional distress, medication side effects, and declines in physical function (1, 2), which are known to be strong predictors of sleep disturbances among people living with HIV (PLWH) (3, 4). PLWH are, therefore, more likely to be vulnerable to sleep problems (5). A meta-analysis estimating the prevalence of self-reported sleep disturbances among PLWH found that approximately more than half of PLWH report sleep disturbances after diagnosis (5), while PLWH complaining of poor sleep quality have been shown to be less likely to adhere to recommended treatment and more likely to suffer multiple mental disorders (6, 7), which may negatively impact the immune and virologic responses (8), leading to treatment failure (9) and, ultimately, influencing the quality of life in this population (10).

Given the significantly negative consequence of the poor sleep quality among PLWH, providing a reliable estimate of the prevalence of sleep disturbances has been increasingly important. Sleep quality is evaluated either by self-reported or interviewer-rated scales or objective measures (such as polysomnography and actigraphy) (11). Empirical evidence showed that self-reported measures are user-friendly, reliable, and sensitive to change in sleep pattern and quality (12). Of the different measures on sleep quality, the Pittsburgh Sleep Quality Index (PSQI) is the most widely used (5). The Chinese version of the PQSI was translated in 1996 by Liu et al. and have been subsequently examined in different populations including the civil servants, college students, and rural elderly (13), all indicating the Chinese version PSQI is a reliable and valid instrument for evaluating sleep quality (14–16).

Although previous studies have explored various psychometric properties of the Chinese-version PSQI across different clinical and non-clinical groups, its application in PLWH has yet to be examined. This study aimed to (1) examine the reliability and validity of the Chinese version of the PQSI in PLWH, and (2) assess the prevalence of poor sleep quality using PQSI and identify the factors associated with poor sleep quality among PLWH.

METHODS

Participants

Participants were HIV-infected patients enrolled since 2013 in a longitudinal study designed to evaluate mental health challenges, among people with newly diagnosed HIV infection. Relevant description on the study design is available in elsewhere (17). Briefly, individuals with newly diagnosed HIV were consecutively recruited from the Changsha Center for Disease Control and Prevention, Hunan Province, China. Individuals were eligible if they were (1) receiving HIV diagnosis for less than 1 month (newly diagnosed with HIV), (2) more than 18 years of age, and (3) having lived in Changsha city for more than 6 months. This study was approved by the Ethics Committee of Xiangya School of Public Health Central South University (ZYGW-2018-055). Written informed consent was obtained from each participant before participation.

A total of 855 people newly diagnosed with HIV met the inclusion criteria, among which 557 participants completed the baseline survey between March 1, 2013 and September 30, 2014. After 1 year, 410 participants continued to participate in the follow-up survey. Among the 557 individuals who completed the baseline survey, 386 agreed to participate in the 5-year follow-up survey which was conducted between August 1, 2018 and March 29, 2019. This study was based on data from 5-year follow-up survey in which the sleep quality was added as a new variable of interest.

Measures

Socio-Demographic Information

Demographic information included gender, age (18–29, 30–39, or ≥40), marriage status (single, married, or divorced/widowed), education (senior or below, college or above), employment (employed or unemployed), monthly income (≤4,000 Yuan or >4,000 Yuan), and exercise behavior (yes or no).

Sleep Quality

Sleep quality was assessed by the Chinese version of PSQI, which was translated and validated by Liu et al. in 1996 (13). The original scale was designed by Buysse et al. which was used to measure the sleep quality and disturbances over the past month (12). It includes 18 items consisting of seven components: subjective quality of sleep, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction. Each item is scored from 0 (not during the past month) to 3 (three or more times a week), with total score ranging from 0 to 21. A higher score suggests poorer sleep quality. A cut-off score of 5 has been recommended to screen for sleep disturbance by Buysse et al. (12).

Clinical Information

Clinical information including CD4 counts and antiretroviral treatment (ART) status were obtained from the Chinese HIV/AIDS Comprehensive Response Information Management System. In addition, participants were asked in questionnaire whether they had any other disease (except for HIV infection).

Depression

Depression was assessed by the 9-item Patient Health Questionnaire Depression Scale (PHQ-9) (18). Participants responded on a 4-point Likert-type scale ranging from 0 (not at all) to 3 (nearly every day). The total score of scare ranges from 0 to 27, with a score ≥10 being considered a cut-off screening for significant depressive symptoms (19). The Chinese version of the PHQ-9 shows good reliability and validity with a Cronbach's α coefficient of 0.86 (20).

Anxiety

Anxiety was measured by the 7-item Generalized Anxiety Disorder questionnaire (GAD-7) (21). Each item was rated on a 4-point Likert scale ranging from 0 (not at all) to 3 (nearly every day). The total score of scale ranges from 0 to 21. A score of 10 points or higher was usually used as cut-off to identify significant

anxiety symptoms (22). The Chinese version of GAD-7 shows good reliability and validity with a Cronbach's α coefficient of 0.88 (23).

Stress

The Chinese version of HIV/AIDS Stress Scale (CSS-HIV) was used to assess HIV-related stress (23). It was first developed by Pakenham et al. (24), and Niu et al. later translated it into Chinese version. This scale consists of three subscales: social stress, instrumental stress, and emotional stress. Participants were asked how much stress they had endured in the past month on a 5-point Likert-type scale. A higher score indicates higher levels of stress. In this study, the median score of the CSS-HIV ($P_{50} = 13$) was used as the cut-off to divide low and high stress. The CSS-HIV has good validity and reliability, with an overall Cronbach's α coefficient of 0.906 (23).

Health-Related Quality of Life

The health-related quality of life was measured using the Medical Outcomes Study HIV Survey (MOS-HIV) (25). The MOS-HIV includes 35 items with 11 dimensions containing general health, physical function, role function, cognitive function, pain, mental health, health distress, energy/fatigue, social function, overall quality of life, and health transition. Based on standard scoring procedures, a physical health summary score and a mental health summary score could be calculated. The Chinese version of the MOS-HIV has shown good validity and reliability among PLWH (26).

Statistical Analysis

The continuous variables were described as median with interquartile ranges (IQRs) and categorical variables were described as numbers with percentages. To evaluate the internal consistency, we calculated Cronbach's alpha for overall scale and corrected item-total correlation, with Cronbach's α ≥0.70 and corrected correlations ≥0.30 indicating adequate internal consistency (27). To evaluate construct validity, Pearson's correlation coefficients were calculated between PSQI scores and other theoretically related constructs, i.e., depression, anxiety, stress, and HRQoL. Known group validity was evaluated by comparing each component scores of PSQI between participants with probable depression (PHQ-9 ≥ 10) and without depression (PHQ-9 < 17) using independent sample *t* test. We hypothesized that depression is negatively associated with poor sleep quality. To identify the factors associated with sleep disturbances (defined as PSQI > 5), univariate logistical regression was conducted, with experiencing sleep disturbance or not as dependent variable, and sex, age, marital status, education, employment, monthly income, CD4 count, comorbidities, ART status, exercise, HIV-related stress, depressive, and anxiety symptoms as independent variables. Variables that were statistically associated with sleep disturbances with a $p \leq 0.2$ in the univariate logistic regression were further selected into the multiple logistic regression model. Odds ratios (OR) and 95% CIs were presented. All analyses were conducted using SPSS 22.0 (SPSS Inc., Chicago, IL, USA) with two-tailed $p < 0.05$ considered statistically significant.

RESULTS

Sample Characteristics

Of the 386 participants who completed the 5-year follow-up survey after diagnosis, 353 (91.5%) were male, with a median age of 34 (IQR: 30–43). The majority were single, employed, and had a monthly income of more than 4,000 Yuan. Nearly two-thirds of participants self-reported as homosexual or bisexual. The median CD4 counts 5 years after diagnosis were 512 cells/mm^3 (IQR: 368–656). Over one-third of individuals reported the presence of other disease except for HIV infection (**Table 1**).

Reliability

The corrected item-total correlation ranged from 0.131 for the use of sleep medication component to 0.702 for the subjective sleep quality component. The overall Cronbach's α was 0.719 and increased to 0.734 after excluding the use of sleep medication component (**Table 2**).

Validity

Construct Validity

Correlations between the PSQI scores and relevant variables are presented in **Table 3**. Theoretical related constructs such as depression, anxiety, stress, and HRQoL were all significantly correlated with the total score of the PSQI ($r \geq |0.360|$). Each component scores of the PSQI were significantly correlated with the depression, anxiety, and mental health summary scores of HRQoL ($|r| = 0.110$–0.526, $p < 0.05$). In addition, all components of the PSQI were correlated with the scores of stress the physical health summary scores of HRQoL ($|r| = 0.107$–0.369, $p < 0.05$), except for the component of sleeping medication use ($|r| = 0.042$–0.065, $p > 0.05$).

Known Group Validity

As hypothesized, the total score of the PSQI in individuals with probable depression (PHQ-9 ≥ 10, $n = 66$; mean = 6.42, $SD = 3.90$) was significantly higher than that in normal individuals with no depression (PHQ-9 < 10, $n = 320$; mean = 3.50, $SD = 3.50$) with $p < 0.001$ (**Table 4**). All of the PSQI components, except for two components, sleep efficiency and use of sleep medication, were significantly correlated with the depression ($p < 0.001$).

Sleep Quality Among PLWH

Prevalence and Severity of Symptoms

The global PSQI score for the 386 participants ranged from 0 to 18, with a median of 3 (IQR: 1–6). The overall prevalence rate of poor sleep quality was 37.0%, using a cut-off point of 5, as suggested by Buysse et al. (12).

Factors Associated With Sleep Quality in PLWH

In the multivariate regression analysis, we found participants with less income ($p = 0.002$), CD4 >350 cells/mm^3 ($p = 0.024$), ART initiation ($p = 0.047$), exercise behavior ($p = 0.008$), depressive symptoms ($p = 0.006$), and higher stress levels ($p = 0.032$) were more likely to experience sleep disturbances (**Table 5**).

TABLE 1 | Sample characteristics.

Variables	*n*	%
Sex		
Male	353	91.5
Female	33	8.5
Age, median (IQR)	34	(30–43)
18–29	94	24.4
30–39	171	44.3
≥40	121	31.3
Marital status		
Single	189	49.0
Married	138	35.8
Divorced/widowed	59	15.2
Education		
Senior or lower	215	55.7
College or higher	171	44.3
Employment		
Employed	318	82.4
Unemployed	68	17.6
Monthly income (Yuan), median (IQR)	5,000	(3,000–6,500)
≤4,000	179	46.4
>4,000	207	53.6
Exercise		
No	212	54.9
Yes	174	45.1
Sexual orientation		
Heterosexuality	142	36.8
Homosexuality	155	40.2
Bisexuality	89	23.1
CD4 count (cells/mm^3), median (IQR)	512	(368–656)
≤350	84	21.8
>350	302	78.2
Comorbidities		
No	265	68.7
Yes	121	31.3
ART		
No	36	9.3
Yes	350	90.7
Depressive symptoms		
No	320	82.9
Yes	66	17.1
Anxiety symptoms		
No	347	89.9
Yes	39	10.1

ART, antiretroviral treatment.

TABLE 2 | PSQI internal consistency data.

PSQI component	Corrected item-total correlation
Subjective sleep quality	0.702
Sleep latency	0.497
Sleep duration	0.462
Habitual sleep efficiency	0.380
Sleep disturbance	0.414
Sleep medication use	0.131
Daytime dysfunction	0.469
Cronbach's α	0.719

PSQI, Pittsburgh Sleep Quality Index.

TABLE 3 | Correlations between sleep measures and relevant variables.

PSQI component	Depression	Anxiety	Stress	HRQoL (PHS)	HRQoL (MHS)
Subjective sleep quality	0.426**	0.354**	0.317**	−0.301**	−0.439**
Sleep latency	0.319**	0.306**	0.255**	−0.236**	−0.332**
Sleep duration	0.266**	0.222**	0.177**	−0.211**	−0.329**
Habitual sleep efficiency	0.143**	0.130*	0.107*	−0.116*	−0.209**
Sleep disturbance	0.267**	0.219**	0.264**	−0.260**	−0.302**
Use of sleep medication	0.157*	0.179**	0.042	−0.065	−0.110*
Daytime dysfunction	0.456**	0.336**	0.316**	−0.334**	−0.455**
Total score of the PSQI	0.486**	0.409**	0.360**	−0.369**	−0.526**

$^*p < 0.05$; $^{**}p < 0.01$.
MHS, mental health summary score; PHS, physical health summary score; PSQI, Pittsburgh Sleep Quality Index.

TABLE 4 | PSQI scores according to the PHQ-9.

PSQI component	No depression		Probable depression		*t*	*p*
	Mean	SD	Mean	SD		
Subjective sleep quality	0.55	0.63	1.09	0.76	−6.077	<0.001
Sleep latency	0.82	0.99	1.33	1.19	−3.721	<0.001
Sleep duration	0.40	0.86	0.88	1.17	−3.857	<0.001
Habitual sleep efficiency	0.30	0.66	0.42	0.81	−1.365	0.173
Sleep disturbance	0.67	0.58	1.00	0.61	−4.163	<0.001
Use of sleep medication	0.03	0.22	0.08	0.40	−1.431	0.153
Daytime dysfunction	0.73	0.94	1.62	1.17	−6.647	<0.001
Total score of the PSQI	3.50	3.05	6.42	3.90	−6.741	<0.001

PHQ-9, 9-item Patient Health Questionnaire Depression Scale; PSQI, Pittsburgh Sleep Quality Index.

DISCUSSION

Although the PSQI has been frequently used in the studies of PLWH in China, the reliability and validity of the Chinese version in this population has yet to be examined. This is the first study to examine the psychometric efficiency of the PSQI among Chinese PLWH. We found that the Chinese version of the PSQI has adequate reliability and validity in PLWH. Over a third of PLWH reported sleep disturbances (defined as PSQI >5) in this study. Individuals who had a lower income, higher CD4 counts, ART initiation, exercise behavior, presence of depressive symptoms, and higher stress levels were more likely to experience sleep disturbances.

The reliability of PSQI in this study was supported by high internal consistency (Cronbach's α = 0.719), which was close to the result from studies by Buysse et al. (12). The component

TABLE 5 | Factors associated with sleep quality in PLWH.

Variables	Univariate		Multivariate	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Sex				
Male	Ref			
Female	1.12 (0.54–2.32)	0.770		
Age				
18–29	Ref			
30–39	0.84 (0.50–1.41)	0.503		
≥40	0.81 (0.47–1.42)	0.463		
Marital status				
Married	Ref		Ref	
Single	1.24 (0.78–1.97)	0.355	1.60 (0.93–2.73)	0.088
Divorced/widowed	1.74 (0.94–3.25)	0.081	1.93 (0.97–3.83)	0.060
Education				
Senior or lower	Ref			
College or higher	0.79 (0.52–1.19)	0.257		
Employment				
Unemployed	Ref		Ref	
Employment	0.65 (0.38–1.10)	0.110	1.08 (0.56–2.07)	0.824
Monthly income (Yuan)				
≤4,000	Ref		Ref	
>4,000	0.47 (0.31–0.72)	<0.001	0.44 (0.26–0.74)	0.002
CD4 count (cells/mm^3)				
≤350	Ref		Ref	
>350	1.63 (0.96–2.75)	0.071	2.00 (1.10–3.66)	0.024
Comorbidities				
No	Ref		Ref	
Yes	1.37 (0.88–2.13)	0.161	1.10 (0.66–1.82)	0.722
ART				
No	Ref		Ref	
Yes	2.23 (0.94–5.29)	0.070	2.63 (1.01–6.82)	0.047
Exercise				
No	Ref		Ref	
Yes	0.45 (0.29–0.69)	< 0.001	0.53 (0.33–0.85)	0.008
Depressive symptoms				
No	Ref		Ref	
Yes	4.47 (2.54–7.85)	<0.001	2.83 (1.34–5.98)	0.006
Anxiety symptoms				
No	Ref		Ref	
Yes	3.47 (1.74–6.92)	<0.001	1.43 (0.59–3.43)	0.427
HIV-related stress				
Low	Ref		Ref	
High	3.01 (1.96–4.63)	<0.001	1.75 (1.05–2.92)	0.032

ART, antiretroviral treatment; PLWH, people living with HIV.

on sleep medication use had an item-total correlation <0.3 in this study, indicating poor correlations for this component in the PSQI framework. After deleting the component on sleep medication use, the Cronbach's α coefficient of PSQI increased from 0.719 to 0.734. Such a result is consistent with several published studies (28, 29). Of note, removing the medication use component was based on psychometrical methods, whereas the best possible psychometrics may not always be the highest consideration.

The validity of PSQI was supported by good construct validity and known-group validity. Significant correlations between PSQI and theoretical related constructs such as depression, anxiety, stress, and HRQoL were found in this study. In addition, the total score of PSQI in individuals with probable depression (PHQ-9 $\geq$ 10) was found to be significantly higher than that of individuals with no depression (PHQ-9 < 10), compatible with our hypothesis that individuals with depression are more likely to experience poor sleep quality. The reliability and validity analyses of PSQI in this study suggest that the Chinese version of PSQI is a suitable and acceptable instrument for use in assessing sleep quality among Chinese PLWH.

Poor sleep quality was observed in 37% of participants in this study, which is much higher than that of the general population survey in China where the rate of sleep disturbances was found to be about 10% (30). This result, however, was lower than the rate of 43.1% reported by another study conducted among 4,103 HIV-infected individuals at 20 AIDS clinics across China (31). The different lengths of time since diagnosis may partially explain the discrepancy between the two studies. The median duration of diagnosis was 2.25 years in that study and 5 years in our sample, while the length of time since diagnosis has been associated with sleep disturbances, with shorter duration from diagnosis being associated with poor sleep quality (31). Nevertheless, the prevalence of sleep disturbances remains high even 5 years after diagnosis. Routinely assessing sleep quality over the course of the HIV infection should be taken into consideration. In accordance, identifying factors associated with sleep disturbances among PLWH is critical to inform strategies to improve sleep quality among this population.

In this study, PLWH on ART were more likely to report sleep disturbances. It is well-known that the morbidity and mortality rates among PLWH have declined dramatically with the scale-up of ART (32). However, side effects associated with ART have also been frequently reported by patients on ART, with sleep disturbances as a common side effect of treatment (33). A previous study investigating factors influencing adherence to ART mentioned that 56.4% of patients regarded insomnia as an adverse effect of ART, which further contribute to the non-adherence and discontinuation of treatment (34). Some antiretroviral medications (e.g., efavirenz) have been linked to adverse sleep effects, especially at higher plasma levels (35). Regularly monitoring adverse reactions to ART should be an important consideration in the management of HIV.

Our study found that individuals with higher CD4 counts (>350 cells/mm^3) have a higher rate of sleep disturbances when compared with those with lower CD4 counts (≤350 cells/mm^3). Conversely, findings from most HIV studies suggested higher CD4 counts were associated with better sleep quality (36, 37). It seems a more likely scenario as it would be expected that as patients decrease their viral load and improve their CD4 counts, their overall health would improve, together with sleep. However, a study in South Africa where 79% of the participants were women also reported a similar relationship between higher CD4 counts and poor sleep quality, arguing this may be related

to an underlying immune activation (38). In addition, a cross-sectional study conducted in France found that patients with CD4 count <500 cells/mm^3 were more likely to be long sleepers and less likely to experience insomnia. Insomnia and impaired sleep quality seem to be highly prevalent in well-controlled PLWH (39). Further investigation is needed to explore the relationship between CD4 counts and sleep quality.

5Poor immune function, serious symptoms, and antiretroviral side effects in the 1990s were broadly considered as the contributors of sleep disturbances in PLWH (40, 41), while even in the context of improved antiretroviral therapy and optimally controlled viral replication, PLWH still struggle with sleep disturbances, indicating that sleep disturbances among PLWH may be caused by additional factors related to psychosocial status other than HIV disease. Individuals would suffer from a myriad of stressors related to HIV after being diagnosed, such as disclosure concerns and infection-related stigma (2), which may make individuals with HIV infection be burdened further by depression and sleep disturbances (42, 43). Consistent with previous studies that depression is a major factor influencing sleep quality among PLWH (44, 45), we found that individuals with depression were more likely to experience sleep disturbances than those without. Considering the possible bidirectional association between sleep and depression (46), alleviating depressive symptoms among PLWH may improve sleep quality and vice versa.

In our study, less income was significantly associated with increased risk of sleep disturbances, and this variable is known to be an important factor associated with sleep whatever the medical condition (47). In addition, the beneficial effect of exercise on sleep has been commonly demonstrated among the general population or patients with other disease such as cancer survivors, and people with rheumatoid arthritis and mental illness (48–51), while less attention has been paid to PLWH. In this study, we found PLWH with exercise behavior were less likely to report sleep disturbances. Further research should investigate which type of exercise and exercise intensity is more effective for the sleep quality of PLWH.

Several limitations of this study should be acknowledged. First, consecutive sampling was used in this study to recruit participants, which may limit the generalizability of the findings. Second, other factors that may influence sleep quality were not included in this study, e.g., pain, alcohol assumption, smoking, and body mass index (BMI). These variables should be considered in future studies. Another limitation is that the sleep quality among PLWH in this study was based on one-time point assessment. Longitudinal studies tracking sleep disturbances among PLWH throughout the course of the disease could be valuable to characterize the impact of HIV infection on sleep.

CONCLUSIONS

The findings from this study supported the feasibility of the PSQI for use among Chinese PLWH. Over a third of PLWH reported sleep disturbances in this study, and participants with less income, higher CD4 counts, ART, exercise behavior, depressive symptoms, and higher stress levels were more likely to experience sleep disturbances. More attention should be given to the screening and treatment for sleep disturbances experienced by PLWH.

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 approved by the Ethics Committee of Xiangya School of Public Health Central South University (ZYGW-2018-055). Written informed consent was obtained from each participant before participation.

AUTHOR CONTRIBUTIONS

D-QY: investigation, data curation, formal analysis, visualization, writing—original draft, writing—review and editing. Y-XH: investigation, data curation, formal analysis, visualization, writing—original draft, writing—review and editing, supervision. DL: conceptualization, methodology, project administration, funding acquisition, writing—review and editing, supervision. XC: methodology, writing—review, and editing. MW and JL: methodology, writing—review and editing. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the Natural Science Foundation of Hunan Province (2019JJ40401), Development and Reform Commission of Hunan Province ([2019]875), and the National Natural Science Foundation of China (81202290).

REFERENCES

1. Martinez J, Lemos D, Hosek S. Stressors and sources of support: the perceptions and experiences of newly diagnosed Latino youth living with HIV. *AIDS Patient Care STDS*. (2012) 26:281–90. doi: 10.1089/apc.2011.0317
2. Huang Y, Luo D, Chen X, Zhang D, Huang Z, Xiao S. HIV-related stress experienced by newly diagnosed people living with HIV in China: a 1-year longitudinal study. *Int J Environ Res Public Health*. (2020) 17:2687. doi: 10.3390/ijerph17082681
3. Zimbardo PG, Pickren WE. *The Psychology Book: From Shamanism to Cutting-Edge Neuroscience, 250 Milestones in the History of Psychology* (2014).
4. Littlewood D, Kyle SD, Pratt D, Peters S, Gooding P. Examining the role of psychological factors in the relationship between sleep problems and suicide. *Clin Psychol Rev*. (2017) 54:1–16. doi: 10.1016/j.cpr.2017.03.009
5. Wu J, Wu H, Lu C, Guo L, Li P. Self-reported sleep disturbances in HIV-infected people: a meta-analysis of prevalence and moderators. *Sleep Med*. (2015) 16:901–7. doi: 10.1016/j.sleep.2015.03.027
6. Phillips KD, Mock KS, Bopp CM, Dudgeon WA, Hand GA. Spiritual well-being, sleep disturbance, and mental and physical health status in

HIV-infected individuals. *Issues Ment Health Nurs.* (2006) 27:125–39. doi: 10.1080/01612840500436917
7. Phillips KD, Moneyham L, Murdaugh C, Boyd MR, Tavakoli A, Jackson K, et al. Sleep disturbance and depression as barriers to adherence. *Clin Nurs Res.* (2005) 14:273–93. doi: 10.1177/1054773805275122
8. Gifford L, Bormann JE, Shively MJ, Wright BC, Richman DD, Bozzette SA. Predictors of self-reported adherence and plasma HIV concentrations in patients on multidrug antiretroviral regimens. *J Acquir Immune Defic Syndr.* (2000) 23:386–95. doi: 10.1097/00126334-200004150-00005
9. Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med.* (2000) 133:21–30. doi: 10.7326/0003-4819-133-1-200007040-00004
10. Phillips KD, Sowell RL, Boyd M, Dudgeon WD, Hand GA. Sleep quality and health-related quality of life in HIV-infected African-American women of childbearing age. *Qual Life Res.* (2005) 14:959–70. doi: 10.1007/s11136-004-2574-0
11. Abad VC, Guilleminault C. Diagnosis and treatment of sleep disorders: a brief review for clinicians. *Dialogues Clin Neurosci.* (2003) 5:371–88. doi: 10.31887/DCNS.2003.5.4/vabad
12. Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* (1989) 28:193–213. doi: 10.1016/0165-1781(89)90047-4
13. Liu XC, Tang MQ. Reliability and validity of the Pittsburgh sleep quality index. *Chinese J Psychiatry.* (1996) 29:29103–7.
14. Zheng B, Li M, Wang KL, Lv J. Analysis of the reliability and validity of the Chinese version of Pittsburgh sleep quality index among medical college students. *Beijing Da Xue Xue Bao Yi Xue Ban.* (2016) 48:424–8.
15. Spira AP, Beaudreau SA, Stone KL, Kezirian EJ, Lui L-Y, Redline S, et al. Reliability and validity of the Pittsburgh sleep quality index in older adults in rural area. *Modern Prevent Med.* (2016) 43:1835–8.
16. Zhao X, Lan M, Li H, Yang J. Study on reliability and validity of Pittsburgh sleep quality index in civil servants of Tianjin. *Tianjin Med J.* (2012) 40:316–9. doi: 10.1016/j.sleep.2020.05.021
17. Niu L, Luo D, Chen X, Wang M, Zhou W, Zhang D, et al. Longitudinal trajectories of emotional problems and unmet mental health needs among people newly diagnosed with HIV in China. *J Int AIDS Soc.* (2019) 22:e25332. doi: 10.1002/jia2.25332
18. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.* (2001) 16:606–13. doi: 10.1046/j.1525-1497.2001.016009606.x
19. Manea L, Gilbody S, McMillan D. A diagnostic meta-analysis of the Patient Health Questionnaire-9 (PHQ-9) algorithm scoring method as a screen for depression. *Gen Hosp Psychiatry.* (2015) 37:67–75. doi: 10.1016/j.genhosppsych.2014.09.009
20. Wang W, Bian Q, Zhao Y, Li X, Wang W, Du J, et al. Reliability and validity of the Chinese version of the Patient Health Questionnaire (PHQ-9) in the general population. *Gen Hosp Psychiatry.* (2014) 36:539–44. doi: 10.1016/j.genhosppsych.2014.05.021
21. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med.* (2006) 166:1092–7. doi: 10.1001/archinte.166.10.1092
22. Tong X, An D, McGonigal A, Park SP, Zhou D. Validation of the generalized anxiety disorder-7 (GAD-7) among Chinese people with epilepsy. *Epilepsy Res.* (2016) 120:31–6. doi: 10.1016/j.eplepsyres.2015.11.019
23. Niu L, Qiu Y, Luo D, Chen X, Wang M, Pakenham KI, et al. Cross-culture validation of the HIV/AIDS Stress Scale: the development of a revised Chinese version. *PLoS ONE.* (2016) 11:e0152990. doi: 10.1371/journal.pone.0152990
24. Pakenham K, Rinaldis M. Development of the HIV/AIDS Stress Scale. *Psychol Health.* (2002) 17:203–19. doi: 10.1080/08870440290013680
25. Wu W, Revicki DA, Jacobson D, Malitz FE. Evidence for reliability, validity and usefulness of the Medical Outcomes Study HIV Health Survey (MOS-HIV). *Qual Life Res.* (1997) 6:481–93. doi: 10.1023/a:1018451930750
26. Huang ZJ, Tian M, Dai SY, Ye DQ. Feasibility, reliability and validity of the Chinese simplified version of the MOS-HIV health survey among AIDS patients in China. *Qual Life Res.* (2013) 22:403–7. doi: 10.1007/s11136-012-0148-0
27. Cho E, Kim S. Cronbach's coefficient alpha: well-known but poorly understood. *Organ Res Methods.* (2015) 18:207–30. doi: 10.1177/1094428114555994
28. Zhang C, Zhang H, Zhao M, Li Z, Cook CE, Buysse DJ, et al. Reliability, validity, and factor structure of pittsburgh sleep quality index in community-based centenarians. *Front Psychiatry.* (2020) 11:573530. doi: 10.3389/fpsyt.2020.573530
29. Spira P, Beaudreau SA, Stone KL, Kezirian EJ, Lui LY, Redline S, et al. Reliability and validity of the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale in older men. *J Gerontol A Biol Sci Med Sci.* (2012) 67:433–9. doi: 10.1093/gerona/glr172
30. Xiang YT, Ma X, Cai ZJ, Li SR, Xiang YQ, Guo HL, et al. The prevalence of insomnia, its socio-demographic and clinical correlates, and treatment in rural and urban regions of Beijing, China: a general population-based survey. *Sleep.* (2008) 31:1655–62. doi: 10.1093/sleep/31.12.1655
31. Huang X, Li H, Meyers K, Xia W, Meng Z, Li C, et al. Burden of sleep disturbances and associated risk factors: a cross-sectional survey among HIV-infected persons on antiretroviral therapy across China. *Sci Rep.* (2017) 7:3657. doi: 10.1038/s41598-017-03968-3
32. Michaels SH, Clark R, Kissinger P. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med.* (1998) 339:405–6. doi: 10.1056/NEJM199808063390612
33. Clifford DB, Evans S, Yang Y, Acosta EP, Ribaudo H, Gulick RM. Long-term impact of efavirenz on neuropsychological performance and symptoms in HIV-infected individuals (ACTG 5097s). *HIV Clin Trials.* (2009) 10:343–55. doi: 10.1310/hct1006-343
34. Naidoo P. Factors influencing HAART adherence among private health care sector patients in a suburb of the Ethekwini Metro. *Afr J Prim Health Care Fam Med.* (2009) 1:12. doi: 10.4102/phcfm.v1i1.12
35. Gallego L, Barreiro P, Del RR, Gonzalez DRD, Rodriguez-Albarino A, Gonzalez-Lahoz J, et al. Analyzing sleep abnormalities in HIV-infected patients treated with Efavirenz. *Clin Infect Dis.* (2004) 38:430–2. doi: 10.1086/380791
36. Oshinaike O, Akinbami A, Ojelabi O, Dada A, Dosunmu A, John OS. Quality of sleep in an HIV population on Antiretroviral Therapy at an Urban Tertiary Centre in Lagos, Nigeria. *Neurol Res Int.* (2014) 2014:298703. doi: 10.1155/2014/298703
37. Seay JS, McIntosh R, Fekete EM, Fletcher MA, Kumar M, Schneiderman N, et al. Self-reported sleep disturbance is associated with lower CD4 count and 24-h urinary dopamine levels in ethnic minority women living with HIV. *Psychoneuroendocrino.* (2013) 38:2647–53. doi: 10.1016/j.psyneuen.2013.06.022
38. Redman KN, Karstaedt AS, Scheuermaier K. Increased CD4 counts, pain and depression are correlates of lower sleep quality in treated HIV positive patients with low baseline CD4 counts. *Brain Behav Immun.* (2018) 69:548–55. doi: 10.1016/j.bbi.2018.02.002
39. Faraut B, Malmartel A, Ghosn J, Duracinsky M, Leger D, Grabar S, et al. Sleep disturbance and total sleep time in persons living with HIV: a cross-sectional study. *AIDS Behav.* (2018) 22:2877–87. doi: 10.1007/s10461-018-2179-1
40. Norman SE, Chediak AD, Kiel M, Cohn MA. Sleep disturbances in HIV-infected homosexual men. *AIDS.* (1990) 4:775–81. doi: 10.1097/00002030-199008000-00009
41. Grandner MA, Patel NP, Gehrman PR, Xie D, Sha D, Weaver T, et al. Who gets the best sleep? Ethnic and socioeconomic factors related to sleep complaints. *Sleep Med.* (2010) 11:470–8. doi: 10.1016/j.sleep.2009.10.006
42. Garrido-Hernansaiz H, Alonso-Tapia J. Associations among resilience, posttraumatic growth, anxiety, and depression and their prediction from stress in newly diagnosed people living with HIV. *J Assoc Nurses AIDS Care.* (2017) 28:289–94. doi: 10.1016/j.jana.2016.12.005
43. Vosvick M, Gore-Felton C, Ashton E, Koopman C, Fluery T, Israelski D, et al. Sleep disturbances among HIV-positive adults. *J Psychosom Res.* (2004) 57:459–63. doi: 10.1016/j.jpsychores.2004.03.003
44. Ren J, Zhao M, Liu B, Wu Q, Hao Y, Jiao M, et al. Factors associated with sleep quality in HIV. *J Assoc Nurses AIDS Care.* (2018) 29:924–31. doi: 10.1016/j.jana.2018.04.006
45. Allavena C, Guimard T, Billaud E, De la Tullaye S, Reliquet V, Pineau S, et al. Prevalence and risk factors of sleep disturbance in a large HIV-infected adult population. *AIDS Behav.* (2016) 20:339–44. doi: 10.1007/s10461-015-1160-5

46. Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? *JAMA*. (1989) 262:1479–84. doi: 10.1001/jama.1989.03430110069030
47. Stamatakis KA, Kaplan GA, Roberts RE. Short sleep duration across income, education, and race/ethnic groups: population prevalence and growing disparities during 34 years of follow-up. *Ann Epidemiol.* (2007) 17:948–55. doi: 10.1016/j.annepidem.2007.07.096
48. Bennie JA, De Cocker K, Duncan MJ. Associations of muscle-strengthening and aerobic exercise with self-reported components of sleep health among a nationally representative sample of 47,564 US adults. *Sleep Health.* (2021) 7:281–8. doi: 10.1016/j.sleh.2020.08.004
49. Lederman O, Ward PB, Firth J, Maloney C, Carney R, Vancampfort D, et al. Does exercise improve sleep quality in individuals with mental illness? A systematic review and meta-analysis. *J Psychiatr Res.* (2019) 109:96–106. doi: 10.1016/j.jpsychires.2018.11.004
50. Hidde MC, Leach HJ, Marker RJ, Peters JC, Purcell WT. Effects of a clinic-based exercise program on sleep disturbance among cancer survivors. *Integr Cancer Ther.* (2020) 19:1534735420975852. doi: 10.1177/1534735420975852
51. McKenna SG, Donnelly AE, Esbensen BA, Fraser AD, Kennedy NM. The impact of exercise on sleep (time, quality, and disturbance) in patients with rheumatoid arthritis: a study protocol for a pilot randomised controlled trial. *Rheumatol Int.* (2018) 38:1191–8. doi: 10.1007/s00296-018-4052-y

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.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 19 November 2021
doi: 10.3389/fpsyt.2021.766647

Sleep Power Spectral Density and Spindles in PTSD and Their Relationship to Symptom Severity

Dan Denis[1†], Ryan Bottary[2,3,4†], Tony J. Cunningham[2,3,5], Shengzi Zeng[6], Carolina Daffre[4,7], Kaitlyn L. Oliver[4,7], Kylie Moore[4,7], Samuel Gazecki[4,7], Augustus Kram Mendelsohn[4,7], Uriel Martinez[4,7], Karen Gannon[8], Natasha B. Lasko[4,7] and Edward F. Pace-Schott[4,7,9]*

[1] Department of Psychology, University of Notre Dame, Notre Dame, IN, United States, [2] Department of Psychology and Neuroscience, Boston College, Chestnut Hill, MA, United States, [3] Division of Sleep Medicine, Harvard Medical School, Boston, MA, United States, [4] Department of Psychiatry, Massachusetts General Hospital, Charlestown, MA, United States, [5] Department of Psychiatry, Beth Israel Deaconess Medical School, Boston, MA, United States, [6] Department of Psychology, The University of Hong Kong, Pokfulam, Hong Kong SAR, China, [7] Department of Psychiatry, Harvard Medical School, Charlestown, MA, United States, [8] Department of Neurology, Massachusetts General Hospital, Charlestown, MA, United States, [9] Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA, United States

OPEN ACCESS

Edited by:
Tobias Hecker, Bielefeld University, Germany

Reviewed by:
Luigi De Gennaro, Sapienza University of Rome, Italy
Bozhidar Dimitrov Kolev, Retired, Sofia, Bulgaria

***Correspondence:**
Edward F. Pace-Schott
epace-schott@mgh.harvard.edu

[†]These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to Psychopathology, a section of the journal Frontiers in Psychiatry

Received: *29 August 2021*
Accepted: *26 October 2021*
Published: *19 November 2021*

Citation:
Denis D, Bottary R, Cunningham TJ, Zeng S, Daffre C, Oliver KL, Moore K, Gazecki S, Kram Mendelsohn A, Martinez U, Gannon K, Lasko NB and Pace-Schott EF (2021) Sleep Power Spectral Density and Spindles in PTSD and Their Relationship to Symptom Severity. Front. Psychiatry 12:766647. doi: 10.3389/fpsyt.2021.766647

Sleep disturbances are common in post-traumatic stress disorder (PTSD), although which sleep microarchitectural characteristics reliably classify those with and without PTSD remains equivocal. Here, we investigated sleep microarchitectural differences (i.e., spectral power, spindle activity) in trauma-exposed individuals that met ($n = 45$) or did not meet ($n = 52$) criteria for PTSD and how these differences relate to post-traumatic and related psychopathological symptoms. Using ecologically-relevant home sleep polysomnography recordings, we show that individuals with PTSD exhibit decreased beta spectral power during NREM sleep and increased fast sleep spindle peak frequencies. Contrary to prior reports, spectral power in the beta frequency range (20.31–29.88 Hz) was associated with reduced PTSD symptoms, reduced depression, anxiety and stress and greater subjective ability to regulate emotions. Increased fast frequency spindle activity was not associated with individual differences in psychopathology. Our findings may suggest an adaptive role for beta power during sleep in individuals exposed to a trauma, potentially conferring resilience. Further, we add to a growing body of evidence that spindle activity may be an important biomarker for studying PTSD pathophysiology.

Keywords: post-traumatic stress disorder, sleep, spectral power, sleep spindles, beta power

INTRODUCTION

Post-traumatic stress disorder (PTSD) is an emotional disorder characterized by the persistence of heightened reactivity 1 month or more after exposure to a traumatic event. Symptoms include intrusions, avoidance behaviors, and hyperarousal (1). Sleep disturbances are extremely common in PTSD, present in ∼70% of patients (2). Two meta-analyses have identified polysomnographic (PSG) findings common across multiple studies of PTSD including decreased total sleep time (TST) and sleep efficiency (SE) and increased wake time after sleep onset (WASO) (3), increased light (N1) sleep and reduced slow-wave (N3) sleep (3, 4), and increased rapid eye movement density (4). Certain moderators (e.g., age, sex) also reveal subgroup specific features relative to controls

and illustrate the heterogeneity but also the ubiquity of sleep disturbance in individuals with PTSD (4, 5). However, reliable microarchitectural markers of PTSD during sleep remain elusive (6). This is of critical importance as sleep macroarchitecture (i.e., time spent in different sleep stages) only provides a broad characterization of the sleeping brain that varies widely from night-to-night, potentially hindering their utility as reliable biomarkers of sleep in PTSD (7).

The quantification of sleep electroencephalography (EEG) signals through spectral power analysis allows for a more fine grained analysis of frequency-specific neural activity that is reflective of underlying brain states. Emerging evidence suggests that PTSD patients exhibit a reduction in low frequency (slow oscillation-delta band range; <4 Hz) power during non-rapid eye movement (NREM) sleep, and increased high frequency power (beta and gamma frequency range; >20 Hz) during both NREM and REM sleep (6, 8–12), though see (13, 14). In addition, trauma exposed individuals who do not go on to develop PTSD have been found to show higher REM theta (4–7 Hz) power compared to patients who did subsequently develop PTSD (15). These findings are hypothesized to indicate lower restorative functioning and increased hyperarousal during sleep in PTSD.

Another sleep oscillation that has been suggested as a potential pathophysiological biomarker are sleep spindles. These waxing and waning (∼9–16 Hz) oscillations are characteristic signatures of NREM sleep (16). Generated by the thalamic reticular nucleus (TRN), spindles travel to cortical regions via thalamocortical pathways (17, 18). A number of putative functions of sleep spindles have been suggested, including sleep maintenance, induction of synaptic plasticity, and memory consolidation [see (17) for detailed review]. Given their relatively well-understood generation by thalamo-cortical circuitry, scalp-EEG detected sleep spindles may provide an indirect, non-invasive readout of thalamocortical functioning during sleep (19). Unlike sleep macroarchitecture, sleep spindle properties are highly stable night-to-night, showing high test-retest reliability (20). Surprisingly, only two studies to date have examined sleep spindle activity in PTSD (6, 21), with one study suggesting a higher sleep spindle peak frequency in PTSD patients (21).

The aim of the present study was to compare NREM and REM sleep microarchitecture in PTSD patients to trauma-exposed individuals who did not go on to develop clinically diagnosed PTSD. We focused on differences in the NREM and REM power spectrum, and properties of sleep spindles. These were examined both in terms of group differences in sleep microarchitecture and correlations between sleep microarchitecture measures and psychiatric symptomatology. Our pre-registered hypotheses (https://osf.io/z6gfw) were as follows:

H1: PTSD patients would exhibit increased high frequency (>20 Hz) and decreased low frequency (<4 Hz) NREM spectral power compared to trauma-exposed controls (TEC).
H2: PTSD patients would exhibit increased high frequency (>20 Hz) and decreased theta (4–7 Hz) REM spectral power compared to TEC.
H3: PTSD patients would show higher frequency sleep spindles during NREM sleep compared to TEC.

Further exploratory analyses are described in sections below.

METHODS

We analyzed data from an existing dataset examining sleep and neuroimaging correlates of fear extinction learning in trauma exposed individuals. All reported analyses are novel, and the analysis plan was pre-registered on Open Science Framework (https://osf.io/z6gfw).

Participants

A total of 133 right-handed participants from the greater Boston metropolitan area were recruited via online and posted advertisements and passed initial telephone screening and had satisfied inclusion/exclusion criteria following clinical interviews (22, 23). All participants had experienced a DSM-V criterion-A traumatic event ("index trauma") within 1 month to 2 years of study participation. Current and lifetime histories of psychiatric disorders were assessed using the Structured Clinical Interview for DSM-IV-TR for Non-Patients [SCID 1/NP; (24)]. PTSD was diagnosed by a highly experienced interviewer (N.B.L.) using the Clinician-Administered PTSD Scale for DSM-5 [CAPS-5; (25)]. The PTSD Checklist for DSM-5 [PCL-5; (26)] was used to further assess symptom severity. In alignment with the National Institutes of Mental Health Research Domain Criteria (RDoC) Framework (27, 28), our study aimed to recruit participants across a range of post-traumatic symptomatology, including those with concurrent anxiety and depressive disorders. However, participants could not have a lifetime history of psychosis, bipolar disorder, autism spectrum or other neurodevelopmental disorder, suicide attempt or current or chronic suicidal ideation; neurologic conditions such as seizure, neurodegenerative disease, stroke, or other brain lesions; history of head trauma with concurrent loss of consciousness; severe medical conditions including cardiovascular or other systemic disease, chronic pain, or endocrine disorders. Participants could not have a current diagnosis of disorders known to influence sleep such as fibromyalgia, severe GERD, or chronic fatigue syndrome. However, participants were not excluded if they indicated a lifetime history of DSM-IV-TR Primary Insomnia, Insomnia Related to Another Mental Disorder or Nightmare Disorder. Participants could not meet criteria for current drug or alcohol abuse or dependence. To confirm presence of current drug use, participants completed a urine test, which identified commonly abused drugs (cocaine, THC, opiates, amphetamines, MDMA, PCP, benzodiazepines, barbiturates, methadone, tricyclic antidepressants, oxycodone, and buprenorphine). Participants treated with antidepressants were required to be on a stable dose and were accepted into the study on a case-by-case basis in consultation with the study physicians.

Of the 133 study participants, 68 participants met criteria for PTSD based on their CAPS-5 score. Sleep disorders were

screened using the Pittsburgh Structured Clinical Interview for Sleep Disorders (SCID-SLD), a widely used (29, 30), but unpublished, in-house instrument. Lastly, participants completed a urine toxicology screening for 11 abused substances. The present analysis included 114 participants who successfully completed a baseline night of polysomnographically-recorded sleep (see Procedures below). Of these participants, 17 were excluded due to having unusable EEG data (e.g., excessive noise, recording error, corrupted file). As such, a total of 97 participants (52 TEC, 45 PTSD) were included in this analysis. Participant characteristics are displayed in **Table 1**.

Procedure

Participants completed a ∼2-week sleep assessment period during which they continuously wore an Actiwatch-2 (Philips Respironics, Bend, OR) and filled out a sleep and nightmare diary. Over this period, participants also completed an online battery of questionnaires assessing trauma history, habitual sleep quality, circadian preference, anxiety, mood, and personality variables using the Research Electronic Data Capture (REDCap^{TM}) system (© 2013, Vanderbilt U). Approximately midway through the assessment period, participants completed a combined sleep-disorders-diagnostic and acclimation night of ambulatory polysomnography (PSG). This was followed by a second night of PSG recording ("baseline night"), a night prior to participants completing a fear conditioning and extinction protocol during functional magnetic resonance imaging followed by a third night of PSG-recorded sleep [see (23)]. Alcohol and recreational drugs were prohibited throughout the protocol. In the present analysis we focus solely on the baseline night of PSG. We chose to use this night for our analysis to avoid potential first-night effects as participants became acclimated to the PSG device during the acclimation/diagnostic night and the influence of learning on sleep physiology, as has been previously reported (31–33).

Ambulatory Polysomnography

Participants underwent three nights of ambulatory polysomnography (PSG) wearing the Somte-PSG recorder (Compumedics USA, Inc., Charlotte, NC). Electrodes were attached in the laboratory and participants were sent home to sleep. The montage included 6 EEG channels (F3, F4, C3, C4, O1, O2) with reference to contralateral mastoids (M1, M2), 2 electrooculogram (EOG) channels, 2 submental electromyogram (EMG) channels, and 2 electrocardiogram (ECG) channels (right clavicle and left 5th intercostal space). The first sleep recording was considered an acclimation and sleep-disorders screening night and included additional channels for respiration transducer belts, pulse-oximeter, nasal cannula, and tibialis movement sensors. Signals were recorded at 256 Hz, using high (0.16 Hz), and low (102 Hz) pass filters. Records were subsequently exported, with a 0.3–35 Hz band pass filter (plus 60 Hz notch filter) for sleep scoring. Records from the baseline PSG night (the focus of this analysis) were scored in 30-s epochs by an experienced, Registered Polysomnographic Technologist (K.G.) following American Academy of Sleep Medicine criteria (34). The acclimation night was examined by the same scorer for clinically significant obstructive sleep apnea and periodic limb movement disorder, though no participants in the current study met clinical criteria for a diagnosis of either of these disorders. The scored records from the baseline night were used to obtain sleep macroarchitecture measures (**Table 1**), and were exported as European Data Format files for further analysis of sleep microarchitecture. All subsequent analyses were carried out in MATLAB using custom code (35).

Artifact Detection

Artifactual epochs of PSG data were detected using an automated algorithm. For each EEG channel we calculated per-epoch summary metrics of three Hjorth parameters [signal activity, mobility, and complexity; (36)], and any epochs in which at least 1 channel was >3 standard deviations from the mean on any of the three parameters were marked as artifact and removed from subsequent analysis (37). Artifact detection was performed twice (in case of extreme outlying epochs), and performed separately for each sleep stage (given the inherent differences in the EEG signal between different sleep stages).

Power Spectral Density

Estimates of power spectral density (PSD) were obtained for both NREM (N2 + N3) and REM sleep at frontal (F3, F4) and central (C3, C4) electrodes. PSD was estimated using Welch's method with 5 s Hamming windows and 50% overlap. To minimize 1/f scaling, PSD estimates were derived from the derivative of the EEG time series (20). PSD estimates at each channel and sleep stage were then normalized within-subject by dividing power at each frequency between 0 and 30 Hz by the average power in the 0–30 Hz range [see (38) for a similar approach]. PSD estimates at the two frontal sites were averaged together to obtain a measure of frontal PSD activity, and PSD estimates at the two central sites were averaged together to obtain a measure of central PSD activity.

Sleep Spindles

Sleep spindles were automatically detected at frontal and central electrodes during NREM sleep using a previously-validated wavelet based detector (35, 39, 40). As a first step, individualized fast and slow spindle peak frequencies were identified through visual inspection of the NREM sleep power spectrum (using both frontal and central electrode sites, with PSD estimated using the same procedure described above). An individual's fast spindle peak was defined as the most prominent peak between 12.5 and 16 Hz, and a slow spindle peak was defined as the most prominent peak between 9 and 12.5 Hz. Any spindle peaks occurring at exactly 12.5 Hz were considered fast spindles. Detection of spindle peaks was performed blind to the patient group. Three participants did not show a clearly identifiable fast spindle peak, and 24 participants failed to exhibit a clearly defined slow spindle peak. Because the lack of a peak in the power spectrum does not necessarily indicate the lack of oscillatory activity (if those events are infrequent or of low amplitude), participants without a fast peak frequency had their fast spindle peak frequency set to 14 Hz, and participants without a slow peak frequency had their slow peak frequency set to 11 Hz. A sensitivity analysis, where

TABLE 1 | Sample characteristics.

	TEC ($n = 52$)	PTSD ($n = 45$)	Sig	Effect size
DEMOGRAPHICS				
Age (years)	23.8 (4.79)	24.2 (4.80)	0.66	0.09
Sex				
Female	28 (54%)	36 (80%)	**0.007**	
Male	24 (46%)	9 (20%)		0.25
Race				
American Indian or Alaskan Native	1 (2%)	2 (4%)		
Asian	6 (12%)	5 (11%)		
Black or African American	9 (17%)	7 (16%)		
More than one race	4 (8%)	5 (11%)		
White	30 (58%)	26 (58%)		
Prefer not to say/unreported	2 (4%)	0 (0%)		
Ethnicity				
Hispanic or Latino	3 (6%)	8 (18%)		
Not Hispanic or Latino	46 (88%)	37 (82%)		
Prefer not to say/unreported	3 (6%)	0 (0%)		
Marital status				
Married	4 (8%)	2 (4%)		
Separated	0 (0%)	1 (2%)		
Single	44 (84%)	40 (89%)		
Prefer not to say/unreported	4 (8%)	2 (4%)		
Highest level of education				
High school degree or equivalent	3 (6%)	0 (0%)		
Associate's degree	3 (6%)	1 (2%)		
Some college	22 (43%)	16 (36%)		
Bachelor's degree	15 (29%)	16 (36%)		
Graduate degree	4 (8%)	10 (22%)		
Prefer not to say/unreported	5 (10%)	2 (4%)		
Income				
<$20,000	10 (19%)	9 (20%)		
$20,000–$34,999	10 (19%)	10 (22%)		
$35,000–$49,999	7 (14%)	1 (2%)		
$50,000–$74,999	6 (12%)	5 (11%)		
$75,000–$99,999	3 (6%)	5 (11%)		
$100,000–$149,999	2 (4%)	3 (7%)		
$150,000–$199,999	1 (2%)	1 (2%)		
$200,000 +	6 (12%)	0 (0%)		
Prefer not to say/unreported	6 (12%)	6 (13%)		
Employment status				
Employed (1–39 h per week)	21 (40%)	20 (44%)		
Employed (40+ h per week)	14 (27%)	15 (33%)		
Not employed, looking for work	1 (2%)	2 (4%)		
Not employed, not looking for work	1 (2%)	1 (2%)		
Unemployed, looking for work	6 (12%)	3 (7%)		
Unemployed, not looking for work	4 (8%)	1 (2%)		
Prefer not to say/unreported	5 (10%)	3 (7%)		
PTSD SEVERITY				
Months from trauma to study	12.5 (6.99)	12.4 (6.34)	0.93	0.02
CAPS total	11.0 (6.31)	31.8 (7.87)	**<0.001**	2.92
CAPS hyperarousal	2.94 (2.53)	9.0 (3.36)	**<0.001**	2.04
PCL-5 total	18.1 (9.89)	40.5 (12.6)	**<0.001**	1.98

(Continued)

TABLE 1 | Continued

	TEC ($n = 52$)	PTSD ($n = 45$)	Sig	Effect size
PCL-5 hyperarousal	3.35 (2.63)	8.51 (3.75)	**<0.001**	1.60
PSYCHOPATHOLOGY MEASURES				
DASS	19.4 (17.5)	47.0 (23.6)	**<0.001**	1.32
DERS	109 (19.6)	85.4 (25.3)	**<0.001**	1.03
HVQ	22.7 (10.2)	32.3 (12.1)	**<0.001**	0.86
RETROSPECTIVE SLEEP MEASURES				
PSQI	5.68 (2.66)	8.34 (3.18)	**<0.001**	0.91
PSQI PTSD	4.22 (4.28)	6.95 (3.78)	**0.002**	0.68
ESS	6.66 (3.43)	9.14 (4.94)	**0.007**	0.58
MEQ	48.4 (8.79)	44.1 (9.24)	**0.02**	0.48
SLEEP DIARY MEASURES				
Total sleep time (min)	451 (56.7)	441 (59.7)	0.40	0.18
Sleep onset latency (min)	20.3 (13.9)	28.6 (18.9)	**0.021**	0.50
Sleep efficiency (%)	92.8 (6.50)	90.1 (6.12)	**0.037**	0.44
Number of nightmares	0.64 (1.03)	1.34 (1.90)	**0.033**	0.46
ACTIGRAPHY MEASURES				
Total sleep time (min)	423 (59.9)	429 (66.0)	0.64	0.10
Sleep onset latency (min)	32.3 (35.5)	26.7 (19.4)	0.35	0.20
Sleep efficiency (%)	86.5 (7.46)	87.3 (8.26)	0.63	0.10
BASELINE NIGHT POLYSOMNOGRAPHY MEASURES				
Total sleep time (min)	384 (105)	336 (136)	0.062	0.39
Sleep onset latency (min)	25.5 (32.8)	25.6 (39.7)	0.99	< 0.01
Sleep efficiency (%)	86.7 (9.26)	83.4 (14.2)	0.23	0.27
N1 %	6.85 (3.88)	5.11 (3.35)	**0.020**	0.48
N2 %	57.0 (7.42)	52.4 (13.0)	**0.042**[a]	0.43
N3 %	18.6 (9.56)	25.5 (16.7)	**0.017**[a]	0.51
REM %	17.9 (6.33)	17.4 (8.32)	0.74	0.07

All values reflect the mean (standard deviation) with the exception of sex through employment status, where frequency (percentage) are displayed. Significant differences between groups assessed using independent samples t-test with Cohen's d used as the measure of effect size, with the exception of sex, where differences were assessed using a chi-square test and Cramer's V measure of effect size. CAPS, Clinician Administered PTSD Scale; Higher score, greater symptomatology; PCL, PTSD checklist (self-report); Higher score, greater symptomatology; DASS, Depression Anxiety Stress Scales; A higher score, greater negative emotional states; DERS, Difficulties in Emotion Regulation Scale; A higher score, better able to regulate negative emotions; HVQ, hypervigilance questionnaire; A higher score, increased hypervigilance; PSQI, Pittsburgh Sleep Quality Index; A higher score indicates poorer overall sleep quality. PSQI PTSD, Pittsburgh Sleep Quality Index for Post-traumatic Stress Disorder; A higher score, higher frequency of sleep disturbances common to PTSD; ESS, Epworth Sleepiness Scale; A higher score, increased daytime sleepiness; MEQ, Morning Evening Questionnaire; A higher score indicates greater preference for mornings. Bold values indicate cases where $p < 0.05$ (uncorrected).

[a]*Group difference was not significant after controlling for total sleep time.*

all spindle based analyses were re-run excluding participants without a discernible peak, led to the same pattern of results (not reported).

After deriving each participant's individualized fast and slow spindle peaks, spindles were automatically detected using a wavelet-based detector. The raw, artifact-free, NREM EEG signal was subjected to a time-frequency decomposition using complex Morlet wavelets. The peak frequency of the wavelet was set to each individual's fast or slow spindle peak. In order to minimize overlap between fast and slow spindle ranges, the full-width half-max bandwidth was set as a 1.3 Hz window centered on the peak spindle frequency (35). Spindle detection was performed on the squared wavelet coefficients after being smoothed with a 100 ms moving average. A spindle was detected whenever the wavelet signal exceeded a threshold of six times the median signal amplitude for at least 400 ms (35, 41). Spindle detection was performed twice, once for fast spindles, and again for slow spindles.

For fast spindle analysis, fast spindle activity at central electrodes were averaged together for subsequent analyses. For slow spindles, activity at frontal electrodes were averaged. For both spindle types, the following parameters were extracted: Peak frequency (Hz), density (spindles/min), amplitude (μV), and duration (seconds).

Age Correction

Age can act as a confounding variable in sleep macro- and microarchitecture studies (42). Most notably, increasing age is linked to a reduction in slow wave sleep, and thus a reduction in low frequency spectral power. During study recruitment, an upper age limit of 40 was selected to ensure participants retained a measurable amount of slow wave sleep. However, because the

TEC and PTSD groups were not strictly age-matched, we tested for associations between age and our main sleep measures of interest (NREM spectral power, REM spectral power, and sleep spindle frequency). In all cases, no significant associations were observed between age and key sleep metrics (all r's < 0.16, all p's > 0.11).

Clinical Measures

Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). The CAPS-5 (25) is the "gold standard" clinical assessment for PTSD. Administration of the CAPS-5 involves clinician ratings for each of the 20 symptoms of PTSD on a 5-point severity scale ranging from 0 (absent) to 4 (extreme). Total scores range from 0 to 80.

The PTSD Checklist for DSM-5 (PCL-5). The PCL-5 (26) is a self-report scale that includes 20 questions based on the DSM-5 diagnostic criteria for PTSD. Participants rated symptom severity on 5-point scales. PCL-5 hyperarousal was the combined hyperarousal (Cluster E) PTSD symptoms on the PCL-5 excluding sleep item 20 ("Trouble falling or staying asleep").

Depression and Anxiety Stress Scale (DASS). The DASS (43) is a 42-item self-report scale which measures the three related negative emotional states of depression, anxiety and tension/stress.

Difficulties in Emotion Regulation Scale (DERS). The DERS (44) is a 36-item self-report scale which measures subjective emotion regulation by asking respondents to identify the frequency in which participants engage in adaptive and maladaptive emotion regulation strategies using a 5 point scale from 5 (almost never) to 1 (almost always). In this dataset, the DERS was reverse scored meaning a higher score indicates less difficulty regulating emotions.

Hypervigilance Questionnaire (HVQ). The HVQ (45) is an 11-item assessment of subjective hypervigilance in which participants rate items on a scale from 1 (not at all true) to 5 (*extremely true*) about their experience of hypervigilance symptoms.

Pittsburgh Sleep Quality Index (PSQI). The PSQI (46) is a 19 item self-report questionnaire that assesses several different aspects of sleep quality over a 1-month period including subjective sleep quality, sleep latency and duration, sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction.

Pittsburgh Sleep Quality Index for Post-traumatic Stress Disorder (PSQI PTSD). The PSQI PTSD (47) is a self-report instrument designed to assess the frequency of seven disruptive nocturnal behaviors including anxious nighttime thoughts and experiencing or acting out nightmares.

Epworth Sleepiness Scale (ESS). The ESS (48) is an 8-item self-report questionnaire in which respondents are asked to rate their usual chances of dozing off or falling asleep while engaged in different activities. Ratings are made on a 4-point scale from 0 (would never doze) to 3 (high chance of dozing).

Morning Evening Questionnaire (MEQ). The MEQ (49) is a 19-item self-report measure that identifies individuals' preference for a morning, evening or intermediate chronotype. Questions include preferred sleep and wake times and preferred times for daytime activities.

Statistical Analysis

Our *a priori* planned analyses can be found in the study pre-registration (https://osf.io/z6gfw). Group differences in PSD between TEC and PTSD were assessed using cluster-based permutation tests implemented in the FieldTrip toolbox for MATLAB (50). This approach allowed us to take the full power spectrum into account whilst also accounting for multiple comparisons. The *ft_statfun_indsamplesT* function was used with the following parameters: 10,000 iterations, a *clusteralpha* of 0.1 with the default *maxsum* method to determine cluster significance, and a significance threshold of 0.05. Separate tests were run for NREM and REM PSD. To test for significant associations between spectral power and symptomatology, our pre-registered *a priori* approach was to average PSD across each frequency in significant clusters to obtain a single value that could then be correlated with PCL hyperarousal score. In the absence of any significant group-differences, our unplanned *post-hoc* approach was to perform the spectrum-wide correlations with symptomatology utilizing the same cluster-based permutation approach, though with the *ft_statfun_correlationT* function. In this report, we focus on PSD at central electrode sites. Sensitivity analyses (not reported) using the frontal electrode sites revealed a highly similar pattern of results. Group differences in fast and slow spindle frequency was assessed using two independent samples t-tests.

As additional planned exploratory tests, we assessed group differences and symptomatology correlations for PSD estimates obtained separately for N2 and N3 sleep, and also for early and late NREM/REM periods. Here, early NREM/REM was defined as NREM or REM sleep occurring in the first half of the night. Late NREM/REM was defined as NREM or REM sleep occurring in the second half of the night. Similarly, we also examined group differences and symptomatology correlations for sleep spindle frequency during N2 and N3 sleep separately, as well as during early and late NREM sleep. Finally, exploratory analyses of group differences in spindle density, amplitude, and duration were performed, as well as exploratory correlations between these spindle properties and symptomatology. Additional, unplanned exploratory tests are highlighted in the results section as relevant.

RESULTS

Participant Characteristics

Demographic, psychometric, and sleep characteristics of the sample of participants included in this analysis are displayed in **Table 1.** There was no difference in age between the two groups [$t_{(87.2)} = 0.02$, $p = 0.98$, $d < 0.01$], however there was a difference in sex between groups [$X^2_{(1)} = 6.66$, $p = 0.010$, $V = 0.25$]. Sleep diary reported sleep onset latency was significantly shorter in the TEC group [$t_{(75.9)} = 2.37$, $p = 0.020$, $d = 0.50$], and diary reported sleep efficiency was significantly greater [$t_{(90.9)} = 2.12$, $p = 0.037$, $d = 0.44$] compared to the PTSD group. The frequency of nightmares during the diary reporting period was significantly higher in the PTSD group [$t_{(64.1)} = 2.18$, $p = 0.033$, $d = 0.46$]. The two groups did not differ on any actigraphy measures. On the baseline PSG night (the focus of this report), N1 and N2 percentage was both significantly greater in TEC

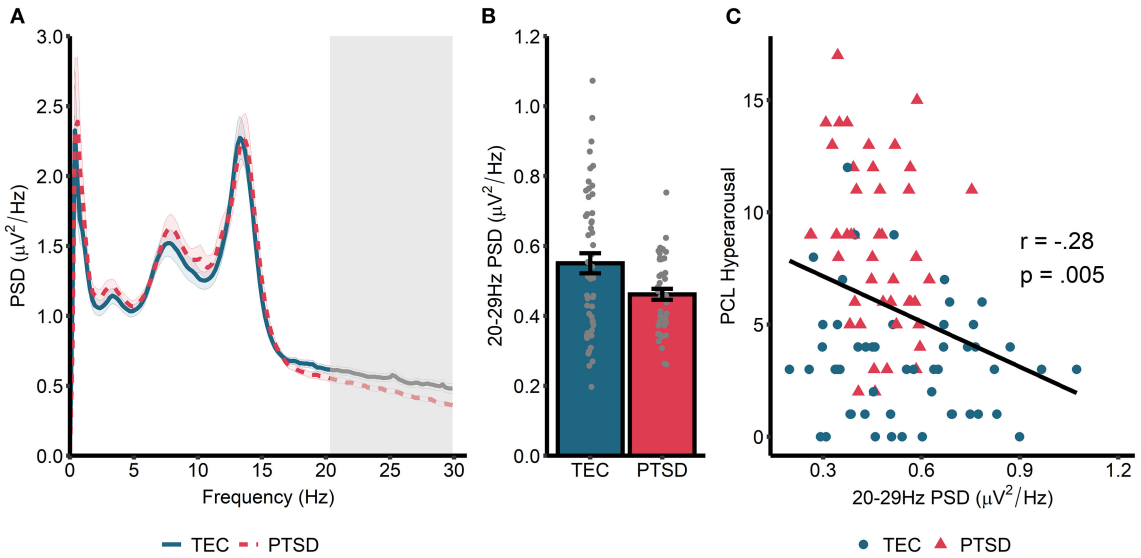

FIGURE 1 | Power spectral density during NREM sleep. **(A)** 0–30 Hz power spectrum during NREM sleep. Note that PSD at each frequency is relative to the average PSD in the 0–30 Hz range. Shaded area around lines denotes the standard error. Gray box marks frequencies showing significant group differences following cluster correction. **(B)** PSD averaged across frequencies in the significant cluster. **(C)** Correlation between spectral power (averaged across frequencies in the significant cluster in **A**) and symptoms of hyperarousal.

participants (p's < 0.043, d's > 0.42). Conversely, N3 percentage was significantly greater in the PTSD group [$t_{(68.1)} = 2.44$, $p = 0.017$, $d = 0.51$]. However, when controlling for total sleep time, only the difference in N1 percentage remained significant ($p = 0.038$). Sleep onset latency and sleep efficiency were also equivalent between groups (all p's > 0.30).

Power Spectral Density

Spectral power during non-rapid eye movement (NREM) sleep is displayed in **Figure 1A**. A cluster-based permutation test revealed a significant group difference in spectral power at 20.31–29.88 Hz ($t_{sum} = 122.77$, $p = 0.015$, $d = 0.56$). Spectral power in this band was higher in TEC participants ($M = 0.55$, $SD = 0.03$) compared to PTSD patients ($M = 0.46$, $SD = 0.02$; **Figure 1B**). As planned exploratory analyses, we tested whether these group differences would be seen in both N2 and N3 sleep, and in both early and late NREM sleep. For N2 sleep, we observed a similar significant cluster differentiating groups in frequencies spanning 24.41–29.88 Hz ($t_{sum} = 75.07$, $p = 0.034$). No significant clusters differentiating groups emerged for N3 sleep PSD. Conversely, when we compared early (which typically contains more N3 sleep) and late (which typically contains more N2 sleep) NREM, a non-significant cluster emerged differentiating groups during early NREM (23.63–29.88 Hz; $t_{sum} = 70.80$, $p = 0.056$). A significant cluster differentiating groups emerged during late NREM sleep (23.24–29.88 Hz; $t_{sum} = 98.21$, $p = 0.018$). In all cases, TEC participants showed increased spectral power relative to PTSD participants.

Next, we correlated cluster-averaged spectral power with PCL hyperarousal symptomatology (**Figure 1C**). Across all participants, we observed a significant *negative* correlation ($r = -0.27$, $p = 0.008$), indicating that increased 20–30 Hz power was associated with fewer hyperarousal symptoms. Correlations were not significant when run separately within the TEC ($r = -0.13$, $p = 0.34$) and PTSD ($r = -0.23$, $p = 0.14$) groups. A similar magnitude correlation was found when the total PCL was used (all participants: $r = -0.20$, $p = 0.047$; TEC: $r = 0.06$, $p = 0.68$; PTSD: $r = -0.17$, $p = 0.27$), and also when correlated with CAPS-measured hyperarousal (all participants: $r = -0.27$, $p = 0.008$; TEC: $r = -0.13$, $p = 0.37$; PTSD: $r = -0.13$, $p = 0.42$) and CAPS total score (all participants: $r = -0.26$, $p = 0.01$; TEC: $r = -0.08$, $p = 0.56$; PTSD: $r = -0.11$, $p = 47$).

We next turned our attention to rapid eye movement (REM) sleep (**Figure 2A**). For REM sleep, no significant clusters emerged when we compared the REM power spectrum between the TEC and PTSD groups (all $p > 0.23$). Similarly, no group differences were found when groups were compared during early and late REM sleep separately (all $p > 0.21$). As such, we performed spectrum-wide correlations across all participants, again using a cluster-based permutation test. Here, we found a significant *negative* correlation between spectral power in a band ranging from 23.24 to 29.88 Hz and PCL measured hyperarousal ($t_{sum} = -81.35$, $p = 0.026$, cluster-averaged $r = -0.27$; **Figures 2A,B**). This same pattern was observed during early (25–29.88 Hz; $t_{sum} = -64.89$, $p = 0.042$) but not late ($p = 0.18$) REM sleep. As with NREM sleep, correlations were not significant when run within the two groups separately (TEC: $r = -0.17$, $p = 0.34$; PTSD: $r = -0.22$, $p = 0.18$). The pattern of results remained unchanged when using the PCL total score (all participants: $r = -0.22$, $p = 0.035$; TEC: $r = -0.08$, $p = 0.58$; PTSD: $r = -0.14$, $p = 0.41$) and when using CAPS-measured hyperarousal (all participants: $r = -0.28$,

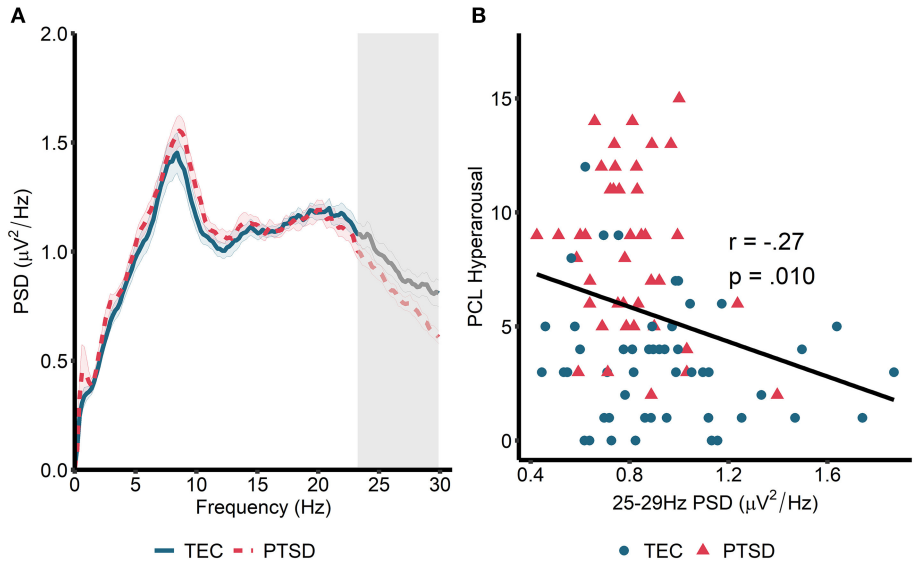

FIGURE 2 | Power spectral density during REM sleep. **(A)** 0–30 Hz power spectrum during REM sleep. Note that PSD at each frequency is relative to the average PSD in the 0–30 Hz range. Gray box marks frequencies showing significant correlations with hyperarousal symptomatology across all participants following cluster correction. Shaded area around lines denotes the standard error. Note that no overall group differences were observed. **(B)** Scatterplot visualizing the relationships between cluster-averaged spectral power and hyperarousal symptomatology.

$p = 0.007$; TEC: $r = -0.18$, $p = 0.20$; PTSD: $r = -0.22$, $p = 0.18$) and CAPS total score (all participants: $r = -0.30$, $p = 0.004$; TEC: $r = -0.20$, $p = 0.16$; PTSD: $r = -0.25$, $p = 0.12$). These results suggest a pattern of increased spectral power in high (>20 Hz) frequencies being associated with reduced PTSD symptomatology.

To supplement these unexpected results, we next performed unplanned exploratory tests directly comparing high frequency spectral power in participants who were asymptomatic-to-low levels of symptomatology (defined as a score of 10 or less on the CAPS, $n = 28$) with those exhibiting moderate-to-severe symptoms (defined as a score of >22 on the CAPS, $n = 44$). NREM high frequency power was defined as PSD averaged between 20.31 and 29.88 Hz. REM high frequency power was defined as PSD averaged between 23.24 and 29.88 Hz (i.e., we averaged across frequencies in the significant clusters that emerged in our primary analyses; **Figures 1**, **2**). In this analysis, high frequency spectral power was significantly higher in asymptomatic-to-mild symptoms participants compared to moderate-to-severe participants for both NREM [$t_{(39.3)} = 2.74$, $p = 0.01$, $d = 0.70$] and REM [$t_{(38.2)} = 2.79$, $p = 0.009$, $d = 0.72$] sleep (**Figure 3A**). Within-groups, there were no significant correlations with either PCL or CAPS hyperarousal scores (all p's > 0.063) or PCL or CAPS total score (all p's > 0.16).

Heightened spectral power in the 20–30 Hz range has previously been linked to hyperarousal in insomnia patients. Although the current dataset lacked a validated measure of insomnia symptoms, we were able to examine how spectral power differed between generally good and poor sleepers, as defined using the Pittsburgh Sleep Quality Index (PSQI). As an unplanned exploratory analysis, we divided the sample into participants with either good or poor sleep quality. Those with good sleep quality were defined as participants with a PSQI score in the bottom two quintiles of the distribution of PSQI scores ($M = 3.96$, $SD = 1.36$, $n = 27$). Those with poor sleep were defined as participants with a PSQI score in the top two quintiles ($M = 10.6$, $SD = 1.78$, $n = 28$). We again defined high frequency power by averaging across frequencies in the significant clusters that emerged in our primary analyses (**Figures 1**, **2**). We did not see any differences between good and poor sleepers with regards to either NREM [$t_{(52)} = 0.93$, $p = 0.35$, $d = 0.25$] or REM [$t_{(48.2)} = 0.83$, $p = 0.41$, $d = 0.23$] spectral power (**Figure 3B**).

This set of results, that high frequency spectral power is *inversely* associated with PTSD symptomatology, directly contradicting our original hypotheses. To better understand these findings, we next performed unplanned exploratory correlations between high frequency PSD and other measures of psychopathology and well-being. In particular, we focused on symptoms of depression, anxiety, and stress (as measured by the DASS), ability to regulate emotions [as measured by the DERS, on the basis of other research linking oscillatory EEG activity during wake is related to emotion regulation PTSD; (51)] and nightmare frequency [on the basis that nightmares in PTSD have been theorized to reflect hyperarousal; (52, 53)]. High frequency power during NREM sleep showed a trend toward being associated with lower overall DASS-measured psychopathology ($r = -0.20$, $p = 0.054$) along with significantly better emotion regulation ($r = 0.23$, $p = 0.027$) and significantly fewer nightmares ($r = -0.26$, $p = 0.011$; **Figure 4**). For REM sleep, high frequency PSD was associated with lower overall psychopathology ($r = -0.24$, $p = 0.028$) and better emotion regulation ($r = 0.23$, $p = 0.033$; **Figure 4**). No other correlations were significant.

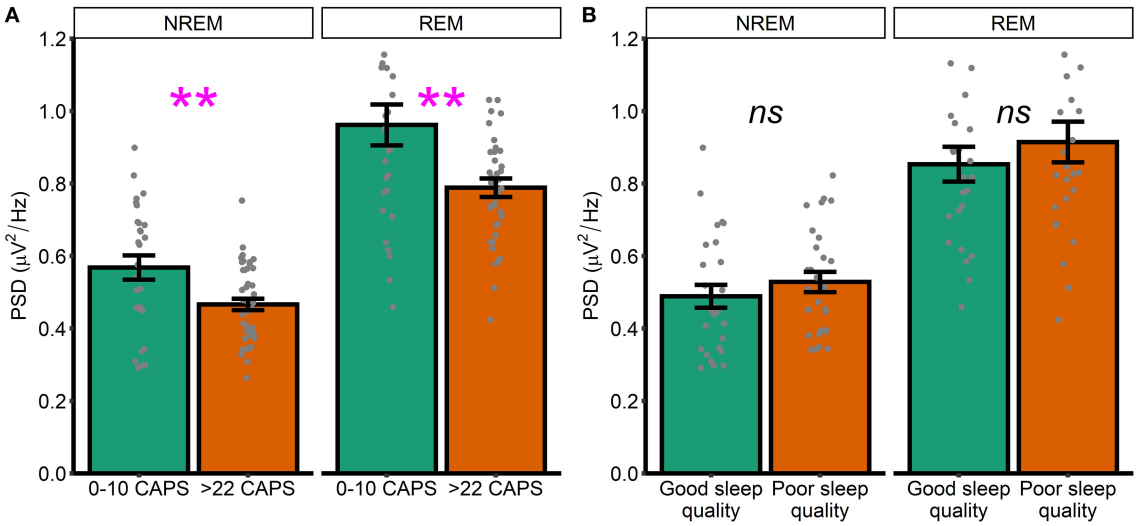

FIGURE 3 | High and low symptomatology participants. **(A)** High frequency spectral power in low and high PTSD symptomatology participants, as defined by CAPS scores. **(B)** High frequency spectral power participants with good and poor sleep quality, as defined by global PSQI score. Note that PSD at each frequency is relative to the average PSD in the 0–30 Hz range Error bars = standard error. $^{**}p < 0.01$, *ns*, not significant.

TABLE 2 | Correlations between sleep spindle properties and symptomatology.

	PCL hyperarousal	PCL total
Fast spindle frequency	$r = 0.09$ $p = 0.38$	$r = 0.05$ $p = 0.66$
Slow spindle frequency	$r = -0.08$ $p = 0.44$	$r = -0.11$ $p = 0.27$
Fast spindle density	$r = -0.10$ $p = 0.32$	$r = -0.14$ $p = 0.16$
Slow spindle density	$r = 0.06$ $p = 0.53$	$r = 0.03$ $p = 0.80$
Fast spindle amplitude	$r = 0.06$ $p = 0.53$	$r = 0.13$ $p = 0.19$
Slow spindle amplitude	**$r = 0.24$** **$p = 0.02$**	**$r = 0.25$** **$p = 0.01$**
Fast spindle duration	$r = -0.09$ $p = 0.38$	$r = -0.11$ $p = 0.29$
Slow spindle duration	$r = 0.04$ $p = 0.70$	$r = 0.12$ $p = 0.23$

Bold values indicate cases where $p < 0.05$ (uncorrected).

Sleep Spindles

Group differences in sleep spindle properties are displayed in **Figure 5**. Our pre-registered *a priori* hypothesis was that sleep spindle peak frequency would be faster in PTSD patients compared to TEC. For fast spindles, a small but significant difference was observed [$t_{(94.94)} = 2.51$, $p = 0.014$, $d = 0.51$] with spindle peak frequency being slightly faster in PTSD ($M = 13.56$ Hz, $SD = 0.57$ Hz) compared to TEC ($M = 13.28$ Hz, $SD = 0.52$ Hz). No difference in peak frequency was found for slow spindles [$t_{(94.53)} = 0.77$, $p = 0.44$, $d = 0.15$]. The same pattern of results were observed when fast spindle frequency was examined during N2 [$t_{(94.87)} = 2.52$, $p = 0.013$, $d = 0.51$], N3 [$t_{(94)} = 2.31$, $p = 0.023$, $d = 0.47$], early NREM [$t_{(95)} = 2.53$, $p = 0.013$, $d = 0.51$], or late NREM [$t_{(94.84)} = 2.52$, $p = 0.016$, $d = 0.50$] sleep. One possibility is that a higher spindle frequency is a by-product of faster EEG activity. To test this hypothesis, we correlated fast spindle frequency with high frequency power (20.31–29.88 Hz, frequencies derived from our primary analysis; see Power spectral density results). We did not find a significant correlation either across all participants ($r = -0.16$, $p = 0.12$), or when TEC ($r = -0.09$, $p = 0.51$) and PTSD ($r = -0.21$, $p = 0.17$) were assessed separately.

We next ran planned exploratory tests on other spindle properties. The only significant difference (uncorrected) was reduced fast spindle density in PTSD ($M = 6.14$, $SD = 1.75$) relative to TEC [$M = 6.82$, $SD = 1.54$; $t_{(94.94)} = 2.05$, $p = 0.043$, $d = 0.42$]. We note that the difference in fast spindle density was no longer significant after controlling for multiple comparisons. All other comparisons were non-significant (all p's > 0.36, all d's < 0.19). Correlations between spindle properties and PTSD symptomatology are shown in **Table 2**. The only (uncorrected) significant results were a positive correlation between slow spindle amplitude and symptomatology.

DISCUSSION

In this report, we investigated the relationship between sleep microarchitecture (power spectral density and spindles) and psychopathology symptom severity in trauma-exposed participants with and without diagnosed PTSD. Contrary to our hypothesis, we observed elevated beta spectral power activity for TEC compared to PTSD participants during both NREM and REM sleep. We did not replicate prior reports implicating REM theta power for PTSD resilience. Beta power was further associated with reduced hyperarousal, decreased nightmare

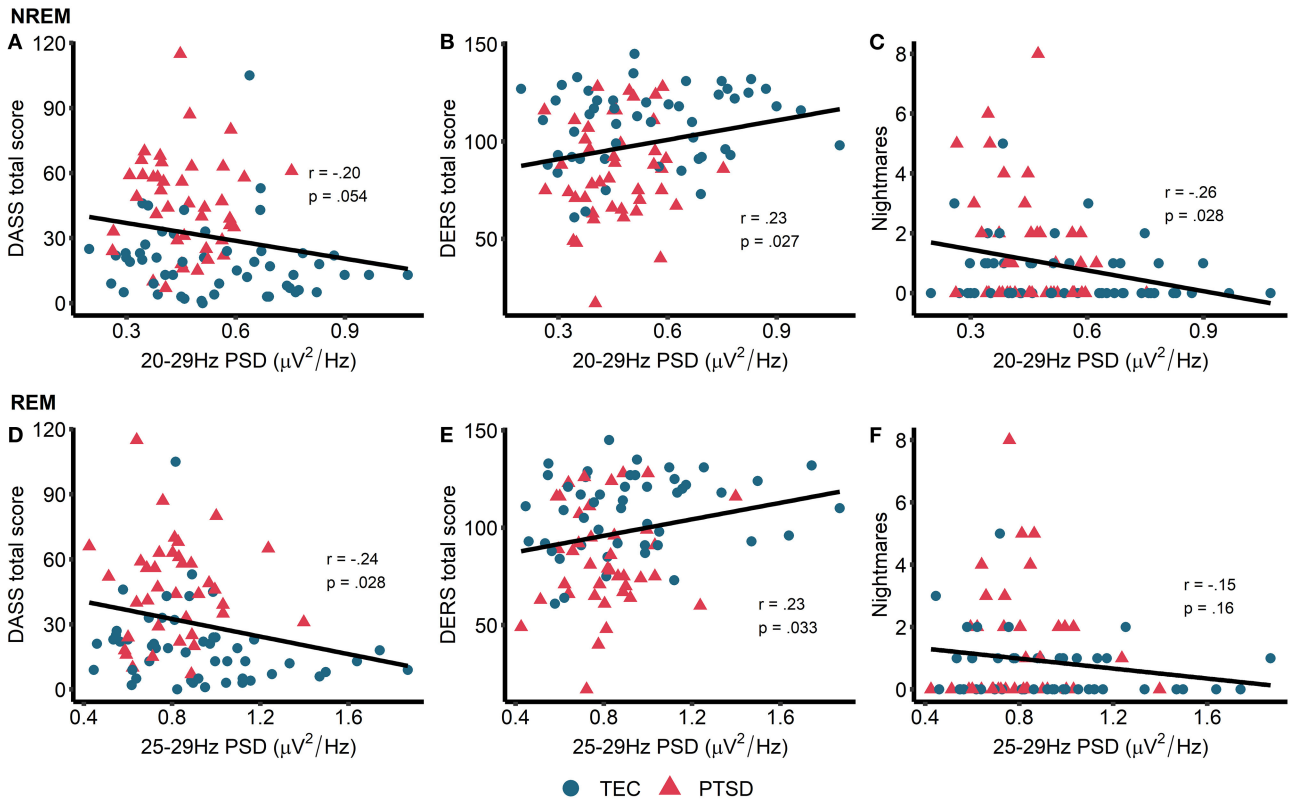

FIGURE 4 | Exploratory correlations. Top row: correlations between NREM high frequency power and general psychopathology (higher score = more symptoms of depression, anxiety, and stress) **(A)**, emotion regulation (higher score = better able to regulate emotions) **(B)**, and nightmare frequency **(C)**. Bottom row: correlations between REM high frequency power and general psychopathology **(D)**, emotion regulation **(E)**, and nightmare frequency **(F)**. Note that PSD at each frequency is relative to the average PSD in the 0–30 Hz range.

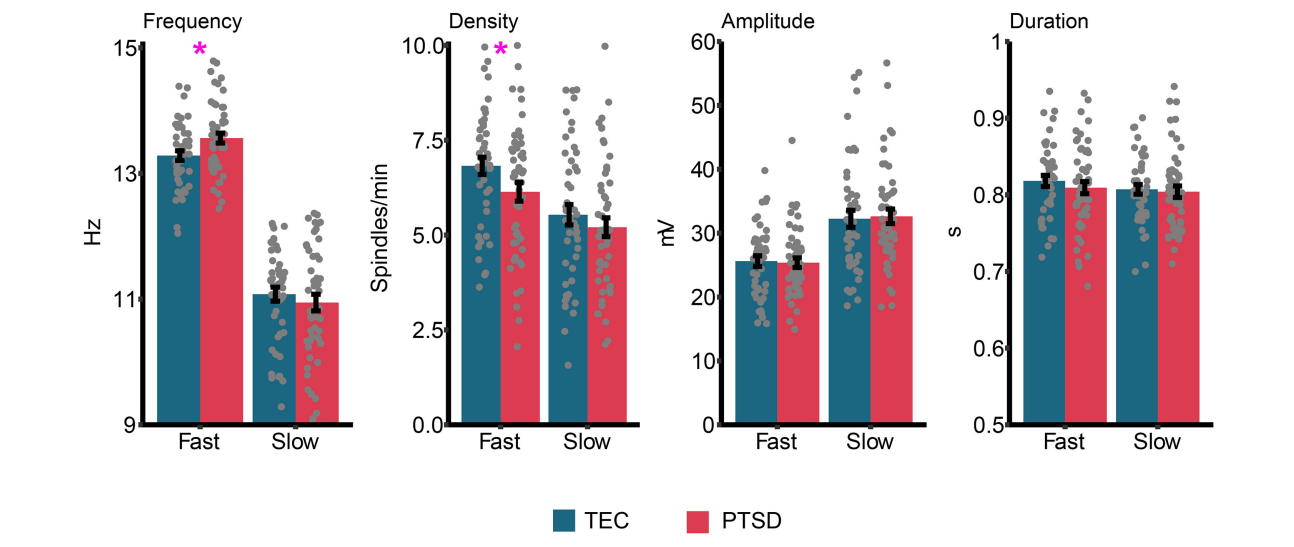

FIGURE 5 | Group differences in sleep spindle properties. Gray dots represent individual data points, and error bars indicate the standard error. *$p < 0.05$.

frequency, decreased depression, anxiety and stress, and better ability to regulate emotions. Interestingly, we also observed fewer, but higher frequency fast sleep spindles in PTSD compared to TEC participants while slow spindle amplitude was positively

associated with hyperarousal. The following sections aim to interpret these findings.

Beta Spectral Power Decreased in PTSD

High frequency EEG rhythms (e.g., beta rhythms) during sleep are theorized to be a component of a hyperarousal syndrome present in Insomnia Disorder [(54–60); though see (61) who failed to detect this in a large meta-analytic study], a condition commonly comorbid with anxiety and traumatic-stress disorders, such as PTSD. However, associations between elevated beta power and PTSD symptomatology remains mixed. For example, in PTSD compared to non-PTSD controls, some studies have observed higher waking beta EEG power (62), higher beta power across a whole night of sleep (8, 9), higher REM-NREM sleep beta power ratios (12), and greater high frequency activity (including beta power) during NREM sleep (63). Nonetheless, others have failed to observe such group differences (13, 14).

Here, we surprisingly observed that beta power was increased in trauma-exposed non-PTSD participants compared to participants that met criteria for PTSD. Inconsistencies among studies of sleep beta activity in PTSD may be explained by a number of factors. First, it is unclear whether beta power represents a biomarker of trauma exposure as opposed to a marker of hyperarousal or PTSD severity. In support of the former interpretation, NREM beta power has been shown to be positively associated with prior combat exposure in those with PTSD (13). Second, beta power may be an indicator of adaptive emotional processing (64). For example, a prospective study linked increased REM beta power soon after a trauma to decreased PTSD and nightmare severity at a follow-up 2 months later (14). We similarly observed a negative association between beta power and PTSD symptomatology, including self-reported hyperarousal and nightmare frequency, albeit during NREM sleep. These associations gain convergent validity by the fact that the DASS, DERS, and nightmare frequency varied with PTSD symptomatology in the same manner. To our knowledge, no prospective studies have assessed whether beta power is a trait vulnerability factor or a marker of PTSD pathogenesis. While we recognize such a study might be difficult to perform, others have studied baseline sleep and subsequent PTSD development in groups with a high likelihood of experiencing subsequent trauma [e.g., military personnel; (65)]. Third, studies to date differ as to when sleep was measured relative to the index trauma, with some measuring sleep in close proximity to the traumatic event [e.g., (14)] and others measuring sleep decades after trauma exposure [e.g., (12)]. We report here associations between current sleeping patterns and psychopathology in individuals with a relatively recent (1 month to 2 years) index trauma. Future work might focus on prospectively mapping trajectories of sleep microarchitecture over the course of PTSD development and maintenance.

Another potential reason for heterogeneity among prior reports may be that whereas beta power may be a marker of insomnia severity, a sleep disorder commonly comorbid to PTSD and associated with a daytime hyperarousal syndrome (66), it may not reflect PTSD-specific hyperarousal over and above trauma exposure itself. While we did not directly measure insomnia severity in the present study, we did not find that poorer sleep quality (measured by comparing widely separated PSQI scores) were associated with greater beta power. Interestingly, a prospective treatment study for patients experiencing insomnia found that improvements in psychopathology and insomnia severity were associated with increased beta power during NREM sleep (64). Contrary to earlier theories (58), beta power appears to be adaptive to regulating emotions or learning emotion control techniques. Further, other studies have failed to find an association between beta power during sleep and insomnia symptomatology (63) or subjective hyperarousal symptoms (12). Nonetheless, current evidence is far from definitive and requires further exploration.

Lastly, several studies to date likely lack the power to detect consistent sleep microarchitectural features related to PTSD symptomatology owing to small sample sizes, and underpowered studies are highly susceptible to Type 2 error (67). To our knowledge, our study constitutes the largest sample size to date that spans the full spectrum of post-traumatic stress symptomatology. Increasing power through meta-analytic techniques is a practical and important next step to update current trends in the literature related to sleep spectral power and PTSD symptomatology.

Sleep Spindle Frequency Differences in PTSD

Here, we report increased fast spindle frequency during NREM sleep in PTSD compared to TEC. This aligns with recent reports of sleep spindle morphology differences in PTSD (6, 21, 63). We found that spindle peak frequency was not correlated with activity at faster frequencies (>20 Hz), suggesting that the group difference in spindle frequency was independent to EEG activity at faster frequencies.

While we did not find that these group differences predicted symptom severity, other reports have found that spindle activity predicted daytime intrusive symptoms (63) and fragmented sleep (21). Interestingly, several other reports have linked NREM sigma power (the frequency band encompassing sleep spindles) with increased susceptibility to post-traumatic symptomatology in rodent models (68) and humans (12, 69). Specifically, human studies have shown a positive association between NREM sigma activity and subjective hyperarousal (12) as well as intrusive symptoms (69) in those with PTSD.

While speculative, fast spindle activity, when coupled with cortical slow oscillations and hippocampal sharp-wave ripples, has been linked to enhanced consolidation of fear memories in rodent models of PTSD (70). This aligns with targeted memory reactivation studies in humans showing that fear memory cueing during post-learning NREM sleep alters subsequent conditioned-fear responses (71, 72). Moreover, consolidation of extinction memories may be impaired when fear reminders are presented during slow wave sleep following extinction learning (73). However, like beta power, it remains unknown whether changes in spindle morphology in PTSD is an indicator of disorder pathogenesis or a trait vulnerability factor.

While spindle activity has been shown to be stable across multiple nights of sleep (37), associative learning (including fear conditioning) has been shown to increase NREM sleep post-learning in rodents (74) and sleep spindle density in humans (32). An important next step will be to determine whether spindle activity alone, or spindles specifically coupled with slow oscillations [which have been predictive of emotional memory consolidation; e.g., (31, 70, 75, 76)], alters the processing of conditioned fear and extinction memories both in healthy participants as well as those with anxiety and traumatic stress disorders.

Limitations

The current study was limited in a number of ways. First, the study is cross-sectional, including analysis of only a single night of recorded sleep. We therefore could not investigate some key questions addressed above including whether specific sleep oscillatory rhythms are trait vulnerability factors, diagnostic of PTSD disorder sequelae or a combination of the two. We limited our analysis to a single night in order to reduce potential confounds from first night effects (i.e., not analyzing the acclimation/diagnostic recording) and learning (i.e., not analyzing the post-fear conditioning night). Second, our sleep recordings took place in participants' own homes, reducing experimental control. However, we believe this approach was a strength as such recordings may be more indicative of the typical sleep our participants obtain on a nightly basis. Thirdly, the stored PSG files limited our ability to look beyond 30 Hz activity, into the gamma frequency range. Gamma activity during sleep has been associated with reduced overnight emotional processing [as indexed by behavioral responses and functional brain activity in emotional brain regions; (77)] and has been shown to be increased in PTSD (6), and could be an interesting range to investigate in future research. Fourthly, because antidepressant treatment is extremely common among those with moderate to severe PTSD, individuals receiving a stable dose of an antidepressant were accepted into the study on a case-by-case basis and these drugs may have influenced EEG spectral power in certain participants.

Conclusions

In a large sample of trauma-exposed participants expressing a wide range of post-traumatic symptomatology, we found NREM beta power to be decreased and fast spindle peak frequency increased in participants meeting criteria for PTSD compared to trauma-exposed participants without PTSD. Contrary to several prior reports, beta power was associated with better, rather than poorer mental health on a variety of measures. Whether these sleep rhythms may be protective from PTSD pathogenesis remains to be determined.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: the data underlying this article will become available in the future in the NIMH Data Archive (NDA) at https://nda.nih.gov, and can be accessed following instructions at https://nda.nih.gov/get/access-data.html. Requests to access these datasets should be directed to https://nda.nih.gov/get/access-data.html.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Massachusetts General Hospital Internal Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DD, RB, TC, SZ, and EP-S conceived the hypotheses and analysis plan. DD analyzed the data. RB and DD wrote the paper. TC, SZ, and EP-S read and edited drafts of the paper. CD, KO, KM, and SG collected the data. CD, KO, KM, SG, AK, and UM carried out data reduction, management, and initial processing. KG performed the sleep scoring. NL performed the diagnostic clinical interviews. All authors contributed to the article and approved the submitted version.

FUNDING

This project was supported by NIMH grants R01MH109638 and R21MH115279 to EP-S. RB and TC were funded by the Research Training Program in Sleep, Circadian and Respiratory Neurobiology (NIH T32 HL007901) through the Division of Sleep Medicine at Harvard Medical School and Brigham & Women's Hospital. Research was carried out at the Athinoula A. Martinos Center for Biomedical Imaging, Charlestown MA, and the Massachusetts General Hospital, Department of Psychiatry, Psychiatric Neuroimaging Division.

ACKNOWLEDGMENTS

We would like to thank Dr. Michael Goldstein for his helpful comments during the drafting of this manuscript.

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. Arlington, VA: American Psychiatric Association (2013). doi: 10.1176/appi.books.9780890425596
2. Ohayon MM, Shapiro CM. Posttraumatic stress disorder in the general population. *Comprehens Psychiatry*. (2000) 41:469–78. doi: 10.1053/comp.2000.16568
3. Zhang Y, Ren R, Sanford LD, Yang L, Zhou J, Zhang J, et al. Sleep in posttraumatic stress disorder: a systematic review and meta-analysis of polysomnographic findings. *Sleep Med Rev*. (2019) 48:101210. doi: 10.1016/j.smrv.2019.08.004
4. Kobayashi I, Boarts JM, Delahanty DL. Polysomnographically measured sleep abnormalities in PTSD: a meta-analytic review. *Psychophysiology*. (2007) 44:660–9. doi: 10.1111/j.1469-8986.2007.537.x
5. Germain A. Sleep disturbances as the hallmark of PTSD: where are we now? *AJP*. (2013) 170:372–82. doi: 10.1176/appi.ajp.2012.12040432

6. Wang C, Ramakrishnan S, Laxminarayan S, Dovzhenok A, Cashmere JD, Germain A, et al. An attempt to identify reproducible high-density EEG markers of PTSD during sleep. *Sleep.* (2020) 43:zsz207. doi: 10.1093/sleep/zsz207
7. Lewandowski A, Rosipal R, Dorffner G. On the individuality of sleep EEG spectra. *J Psychophysiol.* (2013) 27:105–12. doi: 10.1027/0269-8803/a000092
8. Germain A, Hall M, Shear MK, Nofzinger EA, Buysse DJ. Ecological study of sleep disruption in PTSD. *Ann N Y Acad Sci.* (2006) 1071:438–41. doi: 10.1196/annals.1364.038
9. Germain A, Hall M, Shear MK, Nofzinger EA, Buysse DJ. Sleep disruption in PTSD: a pilot study with home-based polysomnography. *Sleep Biol Rhythms.* (2006) 4:286–9. doi: 10.1111/j.1479-8425.2006.00230.x
10. Neylan TC, Lenoci M, Maglione ML, Rosenlicht NZ, Metzler TJ, Otte C, et al. Delta sleep response to metyrapone in post-traumatic stress disorder. *Neuropsychopharmacology.* (2003) 28:1666–76. doi: 10.1038/sj.npp.1300215
11. Richards A, Metzler TJ, Ruoff LM, Inslicht SS, Rao M, Talbot LS, et al. Sex differences in objective measures of sleep in post-traumatic stress disorder and healthy control subjects. *J Sleep Res.* (2013) 22:679–87. doi: 10.1111/jsr.12064
12. Woodward SH, Murburg MM, Bliwise DL. PTSD-related hyperarousal assessed during sleep. *Physiol Behav.* (2000) 70:197–203. doi: 10.1016/S0031-9384(00)00271-7
13. Cohen DJ, Begley A, Alman JJ, Cashmere DJ, Pietrone RN, Seres RJ, et al. Quantitative electroencephalography during rapid eye movement (REM) and non-REM sleep in combat-exposed veterans with and without post-traumatic stress disorder. *J Sleep Res.* (2013) 22:76–82. doi: 10.1111/j.1365-2869.2012.01040.x
14. Mellman TA, Pigeon WR, Nowell PD, Nolan B. Relationships between REM sleep findings and PTSD symptoms during the early aftermath of trauma. *J Traum Stress.* (2007) 20:893–901. doi: 10.1002/jts.20246
15. Cowdin N, Kobayashi I, Mellman TA. Theta frequency activity during rapid eye movement (REM) sleep is greater in people with resilience versus PTSD. *Exp Brain Res.* (2014) 232:1479–85. doi: 10.1007/s00221-014-3857-5
16. Fogel SM, Smith CT. The function of the sleep spindle: a physiological index of intelligence and a mechanism for sleep-dependent memory consolidation. *Neurosci Biobehav Rev.* (2011) 35:1154–65. doi: 10.1016/j.neubiorev.2010.12.003
17. Fernandez LMJ, Lüthi A. Sleep spindles: mechanisms and functions. *Physiol Rev.* (2020) 100:805–68. doi: 10.1152/physrev.00042.2018
18. Klinzing JG, Niethard N, Born J. Mechanisms of systems memory consolidation during sleep. *Nat Neurosci.* (2019) 22:1598–610. doi: 10.1038/s41593-019-0467-3
19. Manoach DS, Stickgold R. Abnormal sleep spindles, memory consolidation, and schizophrenia. *Ann Rev Clin Psychol.* (2019) 15:451–79. doi: 10.1146/annurev-clinpsy-050718-095754
20. Cox R, Schapiro AC, Manoach DS, Stickgold R. Individual differences in frequency and topography of slow and fast sleep spindles. *Front Hum Neurosci.* (2017) 11:433 doi: 10.3389/fnhum.2017.00433
21. Wang C, Laxminarayan S, David Cashmere J, Germain A, Reifman J. Inter-channel phase differences during sleep spindles are altered in veterans with PTSD. *Neuroimage Clin.* (2020) 28:102390. doi: 10.1016/j.nicl.2020.102390
22. Mäder T, Oliver KI, Daffre C, Kim S, Orr SP, Lasko NB, et al. Autonomic activity, posttraumatic and nontraumatic nightmares, and PTSD after trauma exposure. *Psychol Med.* (2021). doi: 10.1017/S0033291721002075. [Epub ahead of print].
23. Seo J, Oliver KI, Daffre C, Moore KN, Lasko NB, Pace-Schott EF. In trauma-exposed individuals, self-reported hyperarousal and sleep architecture predict resting-state functional connectivity in frontocortical and paralimbic regions. *Biol Psychiatry.* (2019) 4:1059–69. doi: 10.1016/j.bpsc.2019.06.013
24. First MB. *Structured Clinical Interview for DSM-IV Axis I Disorders.* Washington, DC: Biometrics Research Department (1997).
25. Weathers FW, Blake DD, Schnurr PP, Kaloupek DG, Marx BP, Keane TM. *The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5).* National Center for PTSD (2013). p. 6. Available online at: www ptsd va gov. (accessed August 29, 2021).
26. Weathers FW, Litz BT, Keane TM, Palmieri PA, Marx BP, Schnurr PP. *The PTSD Checklist for DSM-5 (PCL-5).* The National Center for PTSD (2013). p. 10. Available online at: www ptsd va gov. (accessed August 29, 2021)
27. Cuthbert BN. The RDoC framework: facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. *World Psychiatry.* (2014) 13:28–35. doi: 10.1002/wps.20087
28. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am Psychiatric Assoc.* (2010) 167:748–51. doi: 10.1176/appi.ajp.2010.09091379
29. Insana SP, Hall M, Buysse DJ, Germain A. Validation of the Pittsburgh Sleep Quality Index Addendum for posttraumatic stress disorder (PSQI-A) in U.S. male military veterans. *J Traum Stress.* (2013) 26:192–200. doi: 10.1002/jts.21793
30. Stocker RPJ, Paul BTE, Mammen O, Khan H, Cieply MA, Germain A. Effects of blast exposure on subjective and objective sleep measures in combat veterans with and without PTSD. *J Clin Sleep Med.* (2016) 12:49–56. doi: 10.5664/jcsm.5392
31. Cairney SA, Guttesen AÁV, El Marj N, Staresina BP. Memory consolidation is linked to spindle-mediated information processing during sleep. *Curr Biol.* (2018) 28:948–54.e4. doi: 10.1016/j.cub.2018.01.087
32. Gais S, Mölle M, Helms K, Born J. Learning-Dependent increases in sleep spindle density. *J Neurosci.* (2002) 22:6830–4. doi: 10.1523/JNEUROSCI.22-15-06830.2002
33. Wilhelm I, Diekelmann S, Molzow I, Ayoub A, Mölle M, Born J. Sleep selectively enhances memory expected to be of future relevance. *J Neurosci.* (2011) 31:1563–9. doi: 10.1523/JNEUROSCI.3575-10.2011
34. Iber C, Ancoli-Israel S, Chesson A, Quan S. The AASM manual for the scoring of sleep and associated events: Rules, terminology and technical specifications. *Am Acad. Sleep Med.* (2007).
35. Denis D, Mylonas D, Poskanzer C, Bursal V, Payne JD, Stickgold R. Sleep spindles preferentially consolidate weakly encoded memories. *J Neurosci.* (2021) 41:4088–99. doi: 10.1523/JNEUROSCI.0818-20.2021
36. Hjorth B. EEG analysis based on time domain properties. *Electroencephalogr Clin Neurophysiol.* (1970) 29:306–10. doi: 10.1016/0013-4694(70)90143-4
37. Purcell SM, Manoach DS, Demanuele C, Cade BE, Mariani S, Cox R, et al. Characterizing sleep spindles in 11,630 individuals from the National Sleep Research Resource. *Nat Commun.* (2017) 8:15930. doi: 10.1038/ncomms15930
38. Cunningham TJ, Bottary R, Denis D, Payne JD. Sleep spectral power correlates of prospective memory maintenance. *Learn Mem.* (2021) 28:291–9. doi: 10.1101/lm.053412.121
39. Mylonas D, Tocci C, Coon WG, Baran B, Kohnke EJ, Zhu L, et al. Naps reliably estimate nocturnal sleep spindle density in health and schizophrenia. *J Sleep Res.* (2019) 29:e12968. doi: 10.1111/jsr.12968
40. Wamsley EJ, Tucker MA, Shinn AK, Ono KE, McKinley SK, Ely AV, et al. Reduced sleep spindles and spindle coherence in schizophrenia: mechanisms of impaired memory consolidation? *Biol Psychiatry.* (2012) 71:154–61. doi: 10.1016/j.biopsych.2011.08.008
41. Djonlagic I, Mariani S, Fitzpatrick AL, Van Der Klei VMGTH, Johnson DA, Wood AC, et al. Macro and micro sleep architecture and cognitive performance in older adults. *Nat Hum Behav.* (2021) 5:123–45. doi: 10.1038/s41562-020-00964-y
42. Muehlroth BE, Werkle-Bergner M. Understanding the interplay of sleep and aging: methodological challenges. *Psychophysiology.* (2020) 57:e13523. doi: 10.1111/psyp.13523
43. Lovibond PF, Lovibond SH. The structure of negative emotional states: comparison of the Depression Anxiety Stress Scales (DASS) with the beck depression and anxiety inventories. *Behav Res Ther.* (1995) 33:335–43. doi: 10.1016/0005-7967(94)00075-U
44. Gratz KL, Roemer L. Multidimensional assessment of emotion regulation and dysregulation: development, factor structure, and initial validation of the difficulties in emotion regulation scale. *J Psychopathol Behav Assess.* (2004) 26:41–54. doi: 10.1023/B:JOBA.0000007455.08539.94
45. Kimble MO, Fleming K, Bennion KA. Contributors to hypervigilance in a military and civilian sample. *J Interpers Violence.* (2013) 28:1672–92. doi: 10.1177/0886260512468319
46. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res.* (1989) 28:193–213. doi: 10.1016/0165-1781(89)90047-4
47. Germain A, Hall M, Krakow B, Katherine Shear M, Buysse DJ. A brief sleep scale for posttraumatic stress disorder: Pittsburgh sleep

quality index addendum for PTSD. *J Anxiety Disord.* (2005) 19:233–44. doi: 10.1016/j.janxdis.2004.02.001
48. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep.* (1991) 14:540–5. doi: 10.1093/sleep/14.6.540
49. Horne JA, Östberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *Int J Chronobiol.* (1976) 4:97–110. doi: 10.1037/t02254-000
50. Oostenveld R, Fries P, Maris E, Schoffelen J-M. FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Comput Intell Neurosci.* (2011) 2011:156869. doi: 10.1155/2011/156869
51. Cohen JE, Shalev H, Admon R, Hefetz S, Gasho CJ, Shachar LJ, et al. Emotional brain rhythms and their impairment in post-traumatic patients. *Hum Brain Mapp.* (2013) 34:1344–56. doi: 10.1002/hbm.21516
52. Germain A, Nielsen TA. Sleep pathophysiology in posttraumatic stress disorder and idiopathic nightmare sufferers. *Biol Psychiatry.* (2003) 54:1092–8. doi: 10.1016/S0006-3223(03)00071-4
53. Blaskovich B, Reicher V, Gombos F, Spoormaker VI, Simor P. Hyperarousal captured in increased number of arousal events during pre-REM periods in individuals with frequent nightmares. *J Sleep Res.* (2020) 29:e12965. doi: 10.1111/jsr.12965
54. Hall M, Thayer JF, Germain A, Moul D, Vasko R, Puhl M, et al. Psychological stress is associated with heightened physiological arousal during NREM sleep in primary insomnia. *Behav Sleep Med.* (2007) 5:178–93. doi: 10.1080/15402000701263221
55. Krystal AD. NREM sleep EEG frequency spectral correlates of sleep complaints in primary insomnia subtypes. *Sleep.* (2002) 25:630–40. doi: 10.1093/sleep/25.6.626
56. Merica H, Blois R, Gaillard JM. Spectral characteristics of sleep EEG in chronic insomnia. *Eur J Neurosci.* (1998) 10:1826–34. doi: 10.1046/j.1460-9568.1998.00189.x
57. Merica H, Gaillard J-M. The EEG of the sleep onset period in insomnia: a discriminant analysis. *Physiol Behav.* (1992) 52:199–204. doi: 10.1016/0031-9384(92)90258-4
58. Perlis ML, Merica H, Smith MT, Giles DE. Beta EEG activity and insomnia. *Sleep Med Rev.* (2001) 5:365–76. doi: 10.1053/smrv.2001.0151
59. Riedner BA, Goldstein MR, Plante DT, Rumble ME, Ferrarelli F, Tononi G, et al. Regional patterns of elevated alpha and high-frequency electroencephalographic activity during nonrapid eye movement sleep in chronic insomnia: a pilot study. *Sleep.* (2016) 39:801–12. doi: 10.5665/sleep.5632
60. Spiegelhalder K, Regen W, Feige B, Holz J, Piosczyk H, Baglioni C, et al. Increased EEG sigma and beta power during NREM sleep in primary insomnia. *Biol Psychol.* (2012) 91:329–33. doi: 10.1016/j.biopsycho.2012.08.009
61. Zhao W, Van Someren EJW, Li C, Chen X, Gui W, Tian Y, et al. EEG spectral analysis in insomnia disorder: a systematic review and meta-analysis. *Sleep Med Rev.* (2021) 59:101457. doi: 10.1016/j.smrv.2021.101457
62. Jokić-Begić N, Begić D. Quantitative electroencephalogram (qEEG) in combat veterans with post-traumatic stress disorder (PTSD). *Nordic J Psychiatry.* (2003) 57:351–5. doi: 10.1080/08039480310002688
63. de Boer M, Nijdam MJ, Jongedijk RA, Bangel KA, Olff M, Hofman WF, et al. The spectral fingerprint of sleep problems in post-traumatic stress disorder. *Sleep.* (2020) 43:zsz269. doi: 10.1093/sleep/zsz269
64. Goldstein MR, Turner AD, Dawson SC, Segal ZV, Shapiro SL, Wyatt JK, et al. Increased high-frequency NREM EEG power associated with mindfulness-based interventions for chronic insomnia: preliminary findings from spectral analysis. *J Psychosom Res.* (2019) 120:12–9. doi: 10.1016/j.jpsychores.2019.02.012
65. Gehrman P, Seelig AD, Jacobson IG, Boyko EJ, Hooper TI, Gackstetter GD, et al. Predeployment sleep duration and insomnia symptoms as risk factors for new-onset mental health disorders following military deployment. *Sleep.* (2013) 36:1009–18. doi: 10.5665/sleep.2798
66. Kalmbach DA, Cuamatzi-Castelan AS, Tonnu CV, Tran KM, Anderson JR, Roth T, et al. Hyperarousal and sleep reactivity in insomnia: current insights. *Nat Sci Sleep.* (2018) 10:193–201. doi: 10.2147/NSS.S138823
67. Button KS, Ioannidis JP, Mokrysz C, Nosek BA, Flint J, Robinson ES, et al. Power failure: why small sample size undermines the reliability of neuroscience. *Nat Rev Neurosci.* (2013) 14:365–76. doi: 10.1038/nrn3475
68. Vanderheyden WM, George SA, Urpa L, Kehoe M, Liberzon I, Poe GR. Sleep alterations following exposure to stress predict fear-associated memory impairments in a rodent model of PTSD. *Exp Brain Res.* (2015) 233:2335–46. doi: 10.1007/s00221-015-4302-0
69. van der Heijden AC, Hofman WF, de Boer M, Nijdam MJ, van Marle HJ, Jongedijk RA, et al. Sleep spindle dynamics suggest over-consolidation in post-traumatic stress disorder. *bioRxiv [Preprint].* (2021). doi: 10.1101/2021.07.29.453342
70. Latchoumane C-FV, Ngo H-VV, Born J, Shin H-S. Thalamic spindles promote memory formation during sleep through triple phase-locking of cortical, thalamic, and hippocampal rhythms. *Neuron.* (2017) 95:424–35.e6. doi: 10.1016/j.neuron.2017.06.025
71. Hauner KK, Howard JD, Zelano C, Gottfried JA. Stimulus-specific enhancement of fear extinction during slow-wave sleep. *Nat Neurosci.* (2013) 16:1553–5. doi: 10.1038/nn.3527
72. He J, Sun H-Q, Li S-X, Zhang W-H, Shi J, Ai S-Z, et al. Effect of conditioned stimulus exposure during slow wave sleep on fear memory extinction in humans. *Sleep.* (2015) 38:423–31. doi: 10.5665/sleep.4502
73. Ai S-Z, Chen J, Liu J-F, He J, Xue Y-X, Bao Y-P, et al. Exposure to extinction-associated contextual tone during slow-wave sleep and wakefulness differentially modulates fear expression. *Neurobiol Learn Mem.* (2015) 123:159–67. doi: 10.1016/j.nlm.2015.06.005
74. Hellman K, Abel T. Fear conditioning increases NREM sleep. *Behav Neurosci.* (2007) 121:310–23. doi: 10.1037/0735-7044.121.2.310
75. Alger SE, Kensinger EA, Payne JD. Preferential consolidation of emotionally salient information during a nap is preserved in middle age. *Neurobiol Aging.* (2018) 68:34–47. doi: 10.1016/j.neurobiolaging.2018.03.030
76. Kaestner EJ, Wixted JT, Mednick SC. Pharmacologically increasing sleep spindles enhances recognition for negative and high-arousal memories. *J Cognit Neurosci.* (2013) 25:1597–610. doi: 10.1162/jocn_a_00433
77. van der Helm E, Yao J, Dutt S, Rao V, Saletin JM, Walker MP. REM sleep depotentiates amygdala activity to previous emotional experiences. *Curr Biol.* (2011) 21:2029–32. doi: 10.1016/j.cub.2011.10.052

Conflict of Interest: Praxis Precision Medicines, Inc. provides partial salary support to EP-S.

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.

frontiers in Psychiatry

PERSPECTIVE
published: 24 November 2021
doi: 10.3389/fpsyt.2021.767760

Disturbed Sleep in PTSD: Thinking Beyond Nightmares

Marike Lancel[1,2]*, *Hein J. F. van Marle*[3,4], *Maaike M. Van Veen*[1] and *Annette M. van Schagen*[5]

[1] Centre of Expertise on Sleep and Psychiatry, GGZ Drenthe Mental Health Institute, Assen, Netherlands, [2] Department of Clinical Psychology and Experimental Psychopathology, University of Groningen, Groningen, Netherlands, [3] Department of Psychiatry, Amsterdam Neuroscience, Vrije Universiteit, Amsterdam UMC, Amsterdam, Netherlands, [4] GGZ InGeest Specialized Mental Health Care, Amsterdam, Netherlands, [5] ARQ Centrum'45, Oegstgeest, Netherlands

Sleep disturbances frequently co-occur with posttraumatic stress disorder (PTSD). Insomnia and nightmares are viewed as core symptoms of PTSD. Yet, relations between disturbed sleep and PTSD are far more complex: PTSD is linked to a broad range of sleep disorders and disturbed sleep markedly affects PTSD-outcome. This article provides a concise overview of the literature on prevalent comorbid sleep disorders, their reciprocal relation with PTSD and possible underlying neurophysiological mechanisms. Furthermore, diagnostic procedures, standard interventions—particularly first choice non-pharmacological therapies—and practical problems that often arise in the assessment and treatment of sleep disturbances in PTSD are described. Finally, we will present some perspectives on future multidisciplinary clinical and experimental research to develop new, more effective sleep therapies to improve both sleep and PTSD.

Keywords: PTSD, sleep, sleep disorders, nightmares, insomnia, sleep apnea, assessment, treatment

OPEN ACCESS

Edited by:
Seog Ju Kim,
Sungkyunkwan University,
South Korea

Reviewed by:
David Neubauer,
Johns Hopkins University,
United States
Michael Nadorff,
Mississippi State University,
United States

***Correspondence:**
Marike Lancel
m.lancel@rug.nl

Specialty section:
This article was submitted to Sleep Disorders, a section of the journal Frontiers in Psychiatry

Received: *31 August 2021*
Accepted: *02 November 2021*
Published: *24 November 2021*

Citation:
Lancel M, van Marle HJF, Van Veen MM and van Schagen AM (2021) Disturbed Sleep in PTSD: Thinking Beyond Nightmares. Front. Psychiatry 12:767760. doi: 10.3389/fpsyt.2021.767760

INTRODUCTION

Sleep disturbances frequently occur in posttraumatic stress disorder (PTSD) and are reported by 70–90% of patients (1). Nightmares (intrusions) and difficulties sleeping (hyperarousal) are specifically included in the diagnostic (DSM-5) criteria of the disorder (2). In addition, various other sleep disorders are common in PTSD [e.g., (3, 4)]. It has long been thought that interventions focusing on trauma itself would eventually reduce disturbed sleep, but accumulating evidence shows that sleep disorders play a central role in both the development and maintenance of PTSD [e.g., (5, 6)] and therefore require particular clinical attention.

In this paper we provide an overview of prevalent sleep disorders in PTSD, the reciprocal association of sleep disturbances and PTSD and its underlying mechanisms, as well as information on accurate assessment and treatment of disturbed sleep tailored to the PTSD patient population. Finally, our perspectives for future research directed at more effective sleep-targeted interventions and integrated treatment strategies are described. Our aim is to enhance awareness of clinical practitioners of the importance of targeting sleep in PTSD treatment.

PTSD AND SLEEP DISTURBANCES

The majority of patients with PTSD, about 50–70%, suffer from recurrent distressing nightmares (see **Table 1** for an overview of the most frequently occurring sleep disorders in PTSD, their characteristics, ways of assessment and treatment). These can be exact replications or more symbolic representations of traumatic experiences, and primarily occur during rapid eye movement sleep (REMS) (7). Insomnia symptoms, reported by ∼70% of patients (8), are often related to increased autonomic arousal and fear of sleep: fear of loss of control and/or of having nightmares (9, 10). PTSD is also associated with obstructive sleep apnea (OSA), concerning 40–90% of PTSD patients (11). The repeated OSA events lead to frequent oxygen desaturations and arousals. Insomnia, nightmares and OSA may trigger and exacerbate each other, forming a vicious cycle (1, 4). In addition, multiple studies found a high proportion (around 33%) of periodic limb movement disorder (PLMD) in PTSD patients (12). The limb movements during sleep are associated with arousals/awakenings. Also relatively prevalent in PTSD are periods of sleep paralysis, typically occurring during (REM) sleep-wake transitions, which are often accompanied by distressing experiences, referred to as hypnagogic or hypnopompic hallucinations (13). Although the exact frequency is unclear, PTSD is also linked to remarkable disruptive nocturnal behaviors, including abnormal vocalizations and complex body movements. These parasomnias are generally thought to occur during non-REMS (confusional arousals, night terrors, sleepwalking), but may also take place during REMS, implying REMS behavior disorder (RBD)-like periods of REMS without the usual muscle atonia (RWA) with dream enactment. Mysliwiec et al. (14) proposed a distinct trauma-associated sleep disorder (TASD), conceptualized as a parasomnia encompassing nightmares, disruptive nocturnal behaviors as well as RWA [see (15) for an illustrative case study]. In support of this idea, a recent study in a large sample of veterans found self-reported dream enactment in nearly 40%. However polysomnography (PSG) showed no RWA in 80% of this group, indicating a non-REMS parasomnia, rather than a REMS phenomenon (16). Furthermore, in those veterans with RWA, RBD appeared related to PTSD (prevalence rate 15%) and even more so to the combination of PTSD and traumatic brain injury (prevalence rate 21%). Therefore, it is still controversial whether TASD really represents a separate sleep disorder (17, 18).

INTERRELATIONS BETWEEN PTSD AND SLEEP DISTURBANCES

Research strongly indicates that disturbed sleep is not merely a symptom or consequence of PTSD, but constitutes a predisposing, precipitating and perpetuating factor for PTSD. Sleep disturbances prior to and/or shortly after trauma increase the risk for PTSD (5, 12). For instance, in patients admitted to an emergency department after a motor vehicle collision both pre-trauma insomnia and nightmares predicted subsequent PTSD development (19). Furthermore, sleep disturbances affect the clinical course of PTSD: poor sleep quality is associated with reduced responsiveness to trauma-focused therapy [e.g., (20, 21)], while interventions targeting insomnia, nightmares or OSA improve sleep quality and ameliorate daytime PTSD symptoms (22). For example, Kanady et al. (9) observed that cognitive behavioral treatment of insomnia (CBT-I) in patients with PTSD and insomnia significantly decreased hypervigilance as well as PTSD symptom severity, and both were related to persistent reductions in fear of sleep. Moreover, sleep disturbances often persist after trauma-focused therapy (10). For example, Walters et al. (23) recently showed that prolonged exposure therapy improved daytime PTSD symptoms, but did not ameliorate insomnia and nightmares in veterans with PTSD. Residual insomnia has been shown to be an important risk factor for the development of and relapse in diverse mental disorders [e.g., (24)].

The reciprocal relations between sleep disturbances and PTSD suggest that disturbed sleep constitutes a causal factor in PTSD (25, 26). This causality is partly based on sleep's role in memory consolidation and emotion regulation (27, 28). While memory consolidation takes place during both slow wave sleep (SWS; deep non-REMS) and REMS, the processing of emotional memories is thought to happen primarily during REMS (29). In PTSD, traumatic memories arise in part from a failure in extinction learning, i.e., learning that the previously conditioned stimulus no longer represents a threat (30, 31). It is postulated that REMS disturbances, resulting from the noradrenergic hyperactivation typical of PTSD, hamper the consolidation of extinction memory, leading to a failure of the extinction memory to persist and generalize (32). So far the experimental support for this idea is limited, but nonetheless growing. Sleep disturbances following a traumatic event, including fragmented REMS, predict the development of PTSD (33–35). In polysomnographic studies, PTSD is characterized by reduced SWS and increased REM density (36, 37) as well as REMS fragmentation (38). These characteristics may well result from increased noradrenergic tone during (REM) sleep in PTSD patients (39, 40). Focusing on the role of sleep in the treatment of PTSD, a recent study found that the level of SWS and REM density positively predict treatment outcome (41). This and other clinical studies point toward an additional role of non-REMS disturbances, particularly a shortage of SWS, in the development and perpetuation of PTSD. Furthermore, shared neuromodulatory pathways may also underlie the relationship between PTSD and disturbed sleep. Especially (hyperactive) noradrenergic projections from the locus coeruleus (LC), as part of both the sleep-wake and PTSD-related circuitry, could form a final common pathway in generating the state of hyperarousal typical for both PTSD and disturbed sleep (32). Insomnia (42), nightmares (26) and most other sleep disorders discussed in this perspective are characterized by hyperarousal, frequent disruptions in REMS and aberrant LC-firing. In case of OSA, trauma-related hyperarousal may promote sleep disordered breathing (43). Vice versa, untreated OSA may contribute to development of PTSD, being a continuous stressor leading to sympathetic overactivity and disruption of sleep (44). As OSA events often occur during REMS, it is the brain's

TABLE 1 | Overview of frequently occurring sleep disorders in PTSD: characteristics, assessment and treatments.

Sleep disorder	Timing and sleep-phase	Duration	Behavior during	Behavior after	Recollection of the event	Provocative factors	Assessment	PSG changes	Treatment
Non-REMS									
Confusional arousals (CA)	First third of the night, first bout of slow wave sleep (SWS)	Seconds to minutes	Sudden arousal, followed by confusion, disorientation, eyes open	Confusion	Amnesia	Sleep deprivation, fever, anxiety, stress, sleep apnea, sleep-related movement disorder, caffeine	Observations by bed partner, video observation, PSG optional	Arousal out of SWS, return to sleep	Avoidance of provocative factors, sleep hygiene
Sleepwalking (somnambulism)	See CA	1–10 mins	Abrupt arousal, motor activity outside the bed, possibility of confusion/agitation when suddenly interrupted	Sleeping again	Amnesia	See CA. Hypnotic zolpidem	See CA	See CA	See CA. Safety measures for protection: remove sharp objects, lock windows and doors. If dangerous, consider pharmacotherapy
Night terrors (pavor nocturnus)	See CA	Seconds to minutes	Sudden arousal with intense screaming, inconsolable crying or agitation, and increased autonomic discharge	If awake: being anxious	Amnesia	See CA	See CA	Sudden and incomplete arousal from SWS	See CA. Also psycho-education to parents/partners and patients that episodes are transient and patient should not be awakened. Installation of fixed wake-up times prior to episode, stress reduction training.

(Continued)

TABLE 1 | Continued

Sleep disorder	Timing and sleep-phase	Duration	Behavior during	Behavior after	Recollection of the event	Provocative factors	Assessment	PSG changes	Treatment
Periodic limb movements (PLMs)	Non-REMS	Seconds	Repetitive cramping or jerking of the legs during sleep	Continue sleeping, possible short arousal	Amnesia / no recollection	Somatic disease (including iron deficiency), smoking, caffeine, medication use, sleep apnea	Observations by bed partner, video observation, PSG	Consecutive bursts of activity in leg muscles, with or without arousals	Sleep hygiene, avoidance of possible triggers, when severe with frequent arousals: pharmacological treatment
REMS									
Sleep paralysis	Transition from REMS to wakefulness	< 1 min	Enduring muscle atonia: not being able to talk and move body and limbs when waking up (less frequently when falling asleep), anxiety	Sometimes anxious reaction, paranormal sensations	Recollection	Sleep deprivation, schedule disruption, alcohol ingestion	Self-report, possible PSG	Persistence of consciousness and alpha activity intruding into the otherwise desynchronized REMS EEG	Psycho-education and reassurance. Paralysis usually resolves in < 1 min and/or after sensory stimulation (touch). Focus on small movements, such as breathing and eye movement
Nightmares/ nightmare disorder	During REMS, last third of the night	Seconds to minutes	Vivid and extended extremely dysphoric dreams, with a strong negative emotional tone, typically involving threats to security, physical and/or emotional integrity; muscle atonia	Sudden and violent awakening, often accompanied by anxiety, sometimes shortness of breath. Fear of going back to sleep	Clear recollection of dream content and storyline	Sleep deprivation, fever, stress, major (traumatic) events, medications such as antihypertensives, antidepressants, and dopamine agonists	Self-report, nightmare logs	Densely packed eye movements during REMS	Sleep hygiene, stress reduction, imagery rehearsal therapy (IRT): rescripting of nightmares, imaginal exposure to nightmare content, consider pharmacotherapy: prazosin

(Continued)

TABLE 1 | Continued

Sleep disorder	Timing and sleep-phase	Duration	Behavior during	Behavior after	Recollection of the event	Provocative factors	Assessment	PSG changes	Treatment
REMS behavior disorder (RBD)	During REMS, last third of the night	Seconds to minutes	Loss of REMS atonia. Dream enactment motor activity: usually trying to prevent an attack, and any behavior that could occur during a dream, possibility of injuring themselves and/or bed partner	Awakening often accompanied by anxiety, sometimes shortness of breath. Fear of going back to sleep, fear of hurting bed partner	Vivid recollection of the dream, correlating with observed behavior	Acute phase: medication induced: tricyclic antidepressants, monoamine oxidase inhibitors, and serotonin reuptake inhibitors; alcohol withdrawal, benzodiazepine withdrawal	Self-report, observations by bed partner, PSG	REMS without atonia (RWA)	Bedroom safety principles, removing provocative factors, consider pharmacotherapy: melatonin, clonazepam
Other									
Sleep-related hallucinations	When falling asleep (hypnagogic) or waking up (hypnopompic)	Seconds to 1 minute	Hallucinations with visual, auditory, tactile, olfactory, and/or kinetic properties, possible paranormal sensations, sometimes in combination with sleep paralysis	Sometimes fear, paranormal beliefs	Recollection	Sleep deprivation, daytime naps, psychoactive substances: opiates, cannabis, amphetamines, cocaine, hypnotics, and zopiclone	Self-report	Not known	Psycho-education
Sleep talking (somniloquy)	Mostly in non-REMS, also in REMS	Seconds to minutes	Talking in own language or nonsense, one word or an extensive dialogue	Sleep continues	Amnesia	Anxiety, sleep deprivation and fever	See CA	Occurring in both non-REMS and REMS	Psycho-education, sleep hygiene and stress reduction

(Continued)

TABLE 1 | Continued

Sleep disorder	Timing and sleep-phase	Duration	Behavior during	Behavior after	Recollection of the event	Provocative factors	Assessment	PSG changes	Treatment
Insomnia	Entire night	1–8 h	Lying awake, unrest, rumination	Daytime fatigue, concentration problems, impaired emotion and trauma regulation	Recollection	Arousal, negative thoughts, fear of nightmares, trauma-related triggers, such as bed, bedroom, nighttime, darkness	Self-report, sleep diary, possible PSG	Longer periods of wakefulness, frequent awakenings. REMS fragmentation with very short arousals	CBT-I
Obstructive sleep apnea syndrome (OSAS)	Entire night	1–8 h	Short breathing stops, and arousals without conscious awakening	Continue sleeping, daytime fatigue, non-refreshing sleep, possible development of insomnia	Amnesia	Obesity, snoring, smoking, use of alcohol or other sedating substances/ medication	Observations by bed partner, audio/video recording, PSG	Recurrent partial or complete cessation of air flow, with hypoxia and arousals/sleep fragmentation	Weight loss, sleep hygiene, avoidance of possible triggers, CPAP, MRA, position trainer, ENT surgery
Restless legs syndrome (RLS)	Prior to sleep	Minutes–hours	Uncomfortable sensations in legs (sometimes arms) while awake; irresistible urge to move limbs	Awake	Recollection	Somatic disease (including Iron deficiency), smoking, caffeine, medication use	Self-report	Longer sleep onset latency, often co-occurring PLMs during sleep	Sleep hygiene, avoidance of possible triggers, pharmacological treatment

capacity to process negative emotions during REMS that is most likely affected.

ASSESSMENT OF SLEEP DISTURBANCES IN PTSD

Sleep disturbances can be screened and assessed with a clinical interview and objectified with other measures such as actigraphy and PSG. An actigraph and/or smartwatch can be helpful in detecting nightly arousals and limb movements, as well as daily rhythms in sleep and activity, and estimating sleep onset latency, total sleep time and sleep efficiency (45). PSG (with/without overnight video recording) provides an accurate picture of multiple physiological parameters related to sleep and wakefulness. PSG is less suitable as a screening tool, because it is an elaborate measurement which might not be readily accessible and financially feasible.

For an accurate diagnosis of PTSD according to DSM-5 criteria (2), the Clinician Administered PTSD Scale (CAPS-5) (46) can be used. It is a structured interview to diagnose current and life-time PTSD. However, the CAPS-5 is not sufficient for assessing the presence of sleep disorders, as it contains only two questions regarding sleep problems, considering nightmares and sleep disturbance in general. Diagnoses of sleep disorders are easily missed if specific diagnostic criteria are not inquired about. Therefore an accurate clinical assessment according to the International Classification of Sleep Disorders 3 (ICSD-3) (47) of sleep history, present sleep quality, sleep-wake behavior (preferably including information from the bedpartner to get a more accurate report of nightly behaviors) and screening for sleep disorders is essential.

We recommend an extensive clinical interview as there is no comprehensive questionnaire for screening diverse sleep disturbances in PTSD available. The diagnostic procedure should include an assessment of daily routines, diet, substance (ab)use, medication, mental state, presence of diseases and/or pain (or other physical limitations that compromise sleep), activity levels during night and day, and sleep behaviors including fear of sleep (10) [see (48) for a comprehensive review of the assessment and treatment guidelines of insomnia].

In PTSD the following events should be evaluated. (1) Presence of trauma-related triggers associated with sleep, the bedroom, nighttime and/or darkness, as these triggers might maintain a high arousal level, thereby hampering sleep onset and sleep maintenance. (2) Evaluation of circadian rhythm sleep-wake disorders in (uniformed) personnel working irregular hours (military personnel, police officers, fire-fighters, first responders). (3) Presence of parasomnias and distinguishing the different parasomnias, which is important for psychoeducation as well as treatment indication. For the detection of nightmares, which occur primarily during REMS, screening questionnaires such as the Nightmare Disorder Index (NDI) might be useful (49). However, both patients with PTSD and clinicians tend to misinterpret all nightly behaviors/experiences as nightmares. As the NDI does not cover other parasomnias, the clinician should always ask further about the experiences. Non-REMS parasomnias, such as confusional arousals, night terrors and sleepwalking, are often misdiagnosed as nightmares. Experiences during non-REMS parasomnias are generally not remembered well. The associated emotional distress can therefore be different from nightmares that are typically remembered vividly. It is important to ask patients to describe their nightmares in detail: What is the story in the dream? Is this trauma-related or more symbolic? What is the emotional intensity? Other parasomnias, such as sleep paralysis with or without hypnagogic and/or hypnopompic hallucinations, can be distressing, but they are not the same as nightmares. (4) Patient and bedpartner need to be asked about snoring, breathing stops, arousals and other symptoms to screen for OSA. One should take into account that the usually reported excessive daytime sleepiness is often not experienced by PTSD patients with OSA, possibly due to hyperarousal, yielding low scores on a screening questionnaire such as the Epworth Sleepiness Scale (50). An overnight audio-recording can be a useful tool to screen for sleep-related breathing problems. However, a PSG is the most objective measurement to assess OSA and its severity (51). (5) Patients and bedpartner can be asked about movements during sleep, and if present these movements can be objectified and interpreted with video-assisted PSG.

NON-PHARMACOLOGICAL TREATMENT OF SLEEP DISTURBANCES IN PTSD

With or without PTSD, non-pharmacological interventions are first choice in the treatment of insomnia, nightmares and other (non-REMS) parasomnias (48, 52–54). In line with this, a recent meta-analysis on studies in PTSD patients found that PTSD symptoms and sleep both improve across all PTSD and sleep treatments. Yet, sleep improved the most after sleep-focused interventions, especially psychotherapy approaches (55).

Insomnia

For insomnia CBT-I has shown the most evidence of efficacy (56). CBT-I consists of several therapeutic components targeting different aspects of the sleep disorder: psychoeducation about sleep and sleep hygiene, relaxation training, behavioral interventions such as stimulus control (focus on re-connection of bed/bedroom with sleep) and sleep restriction (focus on reduction of time in bed to total sleep time), and cognitive therapy (48). Drawn from clinical experience and the cognitive behavioral model of PTSD, the following interventions within CBT-I require specific attention in PTSD: relaxation training because of hyperarousal (57); treatment of trauma-related triggers associated with sleep, the bed and/or bedroom, with exposure *in vivo*, EMDR and/or cognitive therapy. Furthermore, other interventions promoting the feeling of safety, such as a photograph of a loved one next to the bed, sleeping with a dim light, soothing music or white noise can be helpful. An increasing number of studies in patients with both PTSD and insomnia show positive effects of CBT-I on sleep efficiency, time awake after sleep onset, self-reported insomnia severity and fear of sleep

(58). Another practice based intervention is the use of weighted blankets, some patients benefit from it. It is a simple non-invasive intervention and a first trial shows promising results (59). However, the presence of OSA is a contra-indication.

Nightmares

If nightmares are particularly prominent and perpetuate fear of sleep and insomnia, one can decide to treat nightmares before starting trauma-focused therapy. Most evidence is found for imagery rehearsal therapy, a technique for rescripting the nightmare story toward a better ending (60). The new dream is subsequently rehearsed through imagination. Imaginal exposure to the nightmare story is another effective, however, less studied intervention (53). There are no studies on EMDR for nightmares, even though it can be argued that desensitization of the nightmare image might be helpful.

Night Terrors or Arousals

If the patient has night terror-induced arousals, the bedpartner can sooth the patient with a soft and low voice, directing him/her back to bed and to sleep. Do not force awakening, ensure safety and trust that the patient will have no recollection of the event. If the arousals occur often and generally at the same time of the night it can be helpful to awaken the patient 15–30 mins before the expected arousal to prevent its occurrence (61).

Obstructive Sleep Apnea

Continuous positive airway pressure (CPAP) and mandibular repositioning appliance (MRA) can be used, and show most evidence in the treatment of OSA syndrome. CPAP has been shown to successfully reduce PTSD symptoms, including nightmare frequency, possibly by stabilizing the arousal system (43). In veterans with subclinical PTSD, non-compliance to CPAP therapy leads to increased PTSD symptoms, implying that optimal OSA-treatment prevents progression to clinical PTSD (44). If OSA-treatment adherence, e.g., wearing a CPAP-mask or MRA, is complicated by trauma-related anxiety, this needs to be specifically addressed, for example with cognitive therapy or EMDR. Other treatment options may be considered, such as weight reduction.

Timing of Sleep Interventions

There is no guideline available for the timing of sleep-targeted interventions in PTSD in relation to trauma-focused therapy. Because of the reciprocal relation between PTSD and sleep disturbances one can argue that the sequence of interventions should be determined by the most prominent symptoms. Moreover, regarding the heterogeneity of PTSD symptoms, it is unlikely that a "one size fits all" treatment will be found. Therefore, we recommend focusing the treatment on the most distressing symptoms and/or administer two different treatments, e.g., EMDR for PTSD and CBT-I for sleep disturbances, side by side. Through monitoring the treatment process, the treatment plan can be adjusted when necessary.

PHARMACOLOGICAL TREATMENT OF SLEEP DISTURBANCES IN PTSD

Several types of drugs have been specifically evaluated in PTSD-related sleep disorders (51). Alpha1-receptor antagonists such as prazosin are best supported by evidence, showing improvement in nightmares as well as insomnia (62, 63). Both sedating antipsychotics and antidepressants have been found beneficial in the treatment of PTSD, including specific positive effects on sleep quality and nightmares, but need close monitoring of negative effects such as hang-over, metabolic dysregulation, and induction/elevation of restless legs syndrome (RLS), PLMD and nightmares (64). The use of benzodiazepine-receptor agonists is controversial in patients with PTSD, not just because of generally known adverse effects, but specific negative outcomes such as worse therapy outcomes and increased risk of developing PTSD when used directly following trauma (65). Considering current evidence, pharmacological treatment of insomnia and nightmares in PTSD should be regarded as temporary and additional, rather than alternative, to psychological interventions.

CONCLUSIONS AND PERSPECTIVES

Research convincingly demonstrates that PTSD is frequently associated with multiple and diverse sleep disorders that impact both PTSD development, maintenance and recovery. Thus, an early and comprehensive assessment of comorbid sleep disorders as well as their timely treatment is of high clinical relevance for patients with trauma and PTSD. In our opinion, centers providing (mental) health care to patients with PTSD should, therefore, include at least one clinician trained in sleep medicine and establish close collaboration with a sleep center for accurate assessment and (interdisciplinary) treatment of co-occurring sleep disorders.

Yet, there are clear gaps in the knowledge on the links between PTSD and sleep and to optimize PTSD-outcome further research and innovations are warranted. For both research and clinical practice, it would be helpful to develop a screening instrument to more accurately assess all sleep disturbances and contributing factors relevant in PTSD populations, ultimately leading to a guideline for the assessment of sleep disorders in PTSD. Prospective studies of large, naturalistic cohorts suffering from trauma implementing both subjective and objective sleep measures, would be highly informative for instance with respect to delineating the sleep-related protective as well as risk factors in the development of PTSD. Furthermore, evidence on the efficacy of integrated PTSD and sleep treatment is limited to small samples, specific patient groups (veterans) and only a few sleep disorders (insomnia and nightmares) and interventions. Research needs to be expanded to include larger and more diverse groups of traumatized/PTSD patients (to entangle general and population-specific factors) and diverse, both pharmacological and non-pharmacological, treatment strategies for all relevant sleep disorders. Moreover, novel developments in the neuroscience of sleep may also guide PTSD treatment.

Combining for instance trauma-focused treatment with new EEG-based techniques to deepen and lengthen SWS (66, 67) could have a synergistic effect through enhanced consolidation of the traumatic memories altered in therapy. Due to faster and more complex oscillatory dynamics, such sleep-based interventions are harder to perform during REMS. Alternatively, novel behavioral methods to strengthen memories during sleep (known as targeted memory reactivation, TMR) (68, 69) could in theory be used in PTSD during post-treatment sleep to augment treatment outcome (70).

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

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

REFERENCES

1. Lewis C, Lewis K, Kitchiner N, Isaac S, Jones I, Bisson JI. Sleep disturbance in post-traumatic stress disorder (PTSD): a systematic review and meta-analysis of actigraphy studies. *Eur J Psychotraumatol.* (2020) 11:1767349. doi: 10.1080/20008198.2020.1767349
2. American Psychiatric Association APA. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Press (2013).
3. Krakow B, Moore B, Ulibarri VA. Sleep-disordered breathing and posttraumatic stress disorder. In: Vermetten E, Germain A, Neylan TC, editors. *Sleep and Combat-Related Post Traumatic Stress Disorder*. New York, NY: Springer New York (2018), p. 243–52.
4. Pigeon WR, Gallegos AM. Posttraumatic stress disorder and sleep. *Sleep Med Clin.* (2015) 10:41–8. doi: 10.1016/j.jsmc.2014.11.010
5. Germain A, McKeon AB, Campbell RL. Sleep in PTSD: Conceptual model and novel directions in brain-based research and interventions. *Curr Opinion Psychol.* (2017) 14:84–9. doi: 10.1016/j.copsyc.2016.12.004
6. Hertenstein E, Feige B, Gmeiner T, Kienzler C, Spiegelhalder K, Johann A, et al. Insomnia as a predictor of mental disorders: a systematic review and meta-analysis. *Sleep Med Rev.* (2019) 43:96–105. doi: 10.1016/j.smrv.2018.10.006
7. Gieselmann A, Ait Aoudia M, Carr M, Germain A, Gorzka R, Holzinger B, et al. Aetiology and treatment of nightmare disorder: state of the art and future perspectives. *J Sleep Res.* (2019) 28:e12820. doi: 10.1111/jsr.12820
8. Ohayon MM, Shapiro CM. Sleep disturbances and psychiatric disorders associated with posttraumatic stress disorder in the general population. *Compr Psychiat.* (2000) 41:469–78. doi: 10.1053/comp.2000.16568
9. Kanady JC, Talbot LS, Maguen S, Straus LD, Richards A, Ruoff L, et al. Cognitive behavioral therapy for insomnia reduces fear of sleep in individuals with posttraumatic stress disorder. *J Clin Sleep Med.* (2018) 14:1193–203. doi: 10.5664/jcsm.7224
10. Werner GG, Riemann D, Ehring T. Fear of sleep and trauma-induced insomnia: a review and conceptual model. *Sleep Med Rev.* (2021) 55:101383. doi: 10.1016/j.smrv.2020.101383
11. Khazaie H, Ghadami MR, Masoudi M. Sleep disturbances in veterans with chronic war-induced PTSD. *J Inj Violence Res.* (2016) 8:99–107. doi: 10.5249/jivr.v8i2.808
12. Brownlow JA, Miller KE, Gehrman PR. Treatment of sleep comorbidities in posttraumatic stress disorder. *Curr Psychiat Rep.* (2020) 7:301–16. doi: 10.1007/s1190-015-0587-8
13. Solomonova E. Sleep paralysis: phenomenology, neurophysiology, and treatment. In: Christoff K, Fox KCR, editors. *The Oxford Handbook of Spontaneous Thought: Mind-Wandering, Creativity, and Dreaming*. Oxford: Oxford University Press (2018), p 435–56.
14. Mysliwiec V, Brock MS, Creamer JL, O'Reilly BM, Germain A, Roth BJ. Trauma associated sleep disorder: a parasomnia induced by trauma. *Sleep Med Rev.* (2018) 37:94–104. doi: 10.1016/j.smrv.2017.01.004
15. Feemster JC, Smith KL, McCarter SJ, St Louis EK. Trauma-associated sleep disorder: a posttraumatic stress/rem sleep behavior disorder mash-up? *J Clin Sleep Med.* (2019) 15:345–9. doi: 10.5664/jcsm.7642
16. Elliott JE, Opel RA, Pleshakov D, Rachakonda T, Chau AQ, Weymann KB, et al. Posttraumatic stress disorder increases the odds of REM sleep behavior disorder and other parasomnias in Veterans with and without comorbid traumatic brain injury. *Sleep.* (2020) 43:237. doi: 10.1093/sleep/zsz237
17. Rachakonda TD, Balba NM, Lim MM. Trauma-associated sleep disturbances: a distinct sleep disorder? *Curr Sleep Med Rep.* (2018) 4:143–8. doi: 10.1007/s40675-018-0119-2
18. Barone DA. Dream enactment behavior-a real nightmare: a review of post-traumatic stress disorder, REM sleep behavior disorder, and trauma-associated sleep disorder. *J Clin Sleep Med.* (2020) 16:1943–8. doi: 10.5664/jcsm.8758
19. Neylan TC, Kessler RC, Ressler KJ, Clifford G, Beaudoin FL, An X, et al. Prior sleep problems and adverse post-traumatic neuropsychiatric sequelae of motor vehicle collision in the AURORA study. *Sleep.* (2021) 44:zsaa200. doi: 10.1093/sleep/zsaa200
20. Kartal D, Arjmand H-A, Varker T, Cowlishaw S, O'Donnell M, Phelps A, et al. Cross-lagged relationships between insomnia and posttraumatic stress disorder in treatment-receiving veterans. *Behav Ther.* (2021) 52:982–94. doi: 10.1016/j.beth.2020.12.006
21. Sullan MJ, Crocker LD, Thomas KR, Orff HJ, Davey DK, Jurick SM, et al. Baseline sleep quality moderates symptom improvement in veterans with comorbid PTSD and TBI receiving trauma-focused treatment. *Behav Res Therapy.* (2021) 143:103892. doi: 10.1016/j.brat.2021.103892
22. Miller KE, Brownlow JA, Gehrman PR. Sleep in PTSD: treatment approaches and outcomes. *Curr Opinion Psychol.* (2020) 34:12–7. doi: 10.1016/j.copsyc.2019.08.017
23. Walters EM, Jenkins MM, Nappi CM, Clark J, Lies J, Norman SB, et al. The impact of prolonged exposure on sleep and enhancing treatment outcomes with evidence-based sleep interventions: a pilot study. *Psychol Trauma.* (2020) 12:175–85. doi: 10.1037/tra0000478
24. Lancel M, Boersma GJ, Kamphuis J. Insomnia disorder and its reciprocal relation with psychopathology. *Curr Opinion Psychol.* (2021) 41:34–9. doi: 10.1016/j.copsyc.2021.02.001
25. Pace-Schott EF, Germain A, Milad MR. Sleep and REM sleep disturbance in the pathophysiology of PTSD: the role of extinction memory. *Biol Mood Anxiety Disord.* (2015) 5:3. doi: 10.1186/s13587-015-0018-9
26. Spoormaker VI, Montgomery P. Disturbed sleep in post-traumatic stress disorder: secondary symptom or core feature? *Sleep Med Rev.* (2008) 12:169–84.
27. Rasch B, Born J. About sleep's role in memory. *Physiol Rev.* (2013) 93:681–766. doi: 10.1152/physrev.00032.2012
28. Goldstein AN, Walker MP. The role of sleep in emotional brain function. *Annu Rev Clin Psychol.* (2014) 10:679–708. doi: 10.1146/annurev-clinpsy-032813-153716
29. van der Helm E, Yao J, Dutt S, Rao V, Saletin JM, Walker MP, et al. sleep depotentiates amygdala activity to previous emotional experiences. *Curr Biol.* (2011) 21:2029–32. doi: 10.1016/j.cub.2011.10.052
30. Yehuda R, LeDoux J. Response variation following trauma: a translational neuroscience approach to understanding PTSD. *Neuron.* (2007) 56:19–32. doi: 10.1016/j.neuron.2007.09.006
31. Lebois LAM, Seligowski AV, Wolff JD, Hill SB, Ressler KJ. Augmentation of extinction and inhibitory learning in anxiety and trauma-related disorders. *Annu Rev Clin Psychol.* (2019) 15:257–84. doi: 10.1146/annurev-clinpsy-050718-095634

32. Richards A, Kanady JC, Neylan TC. Sleep disturbance in PTSD and other anxiety-related disorders: an updated review of clinical features, physiological characteristics, and psychological and neurobiological mechanisms. *Neuropsychopharmacol.* (2020) 45:55–73. doi: 10.1038/s41386-019-0486-5
33. Mellman TA, Bustamante V, Fins AI, Pigeon WR, Nolan B. REM sleep and the early development of posttraumatic stress disorder. *Am J Psychiat.* (2002) 159:1696–701. doi: 10.1176/appi.ajp.159.10.1696
34. Koren D, Arnon I, Lavie P, Klein E. Sleep complaints as early predictors of posttraumatic stress disorder: a 1-year prospective study of injured survivors of motor vehicle accidents. *Am J Psychiat.* (2002) 159:855–7. doi: 10.1176/appi.ajp.159.5.855
35. van Liempt S. Sleep disturbances and PTSD: a perpetual circle? *Eur J Psychotraumatol.* (2012) 3(Suppl3):19142. doi: 10.3402/ejpt.v3i0.19142
36. Kobayashi I, Boarts JM, Delahanty DL. Polysomnographically measured sleep abnormalities in PTSD: a meta-analytic review. *Psychophysiology.* (2007) 44:660–9. doi: 10.1111/j.1469-8986.2007.537.x
37. Zhang Y, Ren R, Sanford LD, Yang L, Zhou J, Zhang J, et al. Sleep in posttraumatic stress disorder: A systematic review and meta-analysis of polysomnographic findings. *Sleep Med Rev.* (2019) 48:101210. doi: 10.1016/j.smrv.2019.08.004
38. Habukawa M, Uchimura N, Maeda M, Kotorii N, Maeda H. Sleep findings in young adult patients with posttraumatic stress disorder. *Biol Psychiat.* (2007) 62:1179–82. doi: 10.1016/j.biopsych.2007.01.007
39. Insana SP, Hall M, Buysse DJ. Germain A. Validation of the Pittsburgh Sleep Quality Index Addendum for posttraumatic stress disorder (PSQI-A) in US male military veterans. *J Trauma Stress.* (2013) 26:192–200. doi: 10.1002/jts.21793
40. Mellman TA, Kumar A, Kulick-Bell R, Kumar M, Nolan B. Nocturnal/daytime urine noradrenergic measures and sleep in combat-related PTSD. *Biol Psychiat.* (1995) 38:174–9. doi: 10.1016/0006-3223(94)00238-x
41. Kobayashi I, Mellman TA, Altaee D, Howell MK, Lavela J. Sleep and processing of trauma memories. *J Trauma Stress.* (2016) 29:568–71. doi: 10.1002/jts.22137
42. Riemann D, Spiegelhalder K, Feige B, Voderholzer U, Berger M, Perlis M, et al. The hyperarousal model of insomnia: a review of the concept and its evidence. *Sleep Med Rev.* (2010) 14:19–31. doi: 10.1016/j.smrv.2009.04.002
43. Zhang Y, Ren R, Yang L, Zhou J, Sanford LD, Tang X. The effect of treating obstructive sleep apnea with continuous positive airway pressure on posttraumatic stress disorder: a systematic review and meta-analysis with hypothetical model. *Neurosci Biobehav Rev.* (2019) 102:172–83. doi: 10.1016/j.neubiorev.2019.03.019
44. Ullah MI, Campbell DG, Bhagat R, Lyons JA, Tamanna S. Improving PTSD symptoms and preventing progression of subclinical PTSD to an overt disorder by treating comorbid OSA with CPAP. *J Clin Sleep Med.* (2017) 13:1191–8. doi: 10.5664/jcsm.6770
45. Tsanas A, Woodward E, Ehlers A. Objective characterization of activity, sleep, and circadian rhythm patterns using a wrist-worn actigraphy sensor: insights into posttraumatic stress disorder. *JMIR MHealth UHealth.* (2020) 8:e14306. doi: 10.2196/14306
46. Weathers FW, Blake DD, Schnurr PP, Kaloupek DG, Marx BP, Keane TM. *The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) [Clinical interview]*. Available online at: https://www.ptsd.va.gov/professional/assessment/adult-int/caps.asp
47. American Academy of Sleep Medicine AASM. *International Classification of Sleep Disorders* (ICSD-3). 3 edn. Darien, IL: American Academy of Sleep Medicine (2014).
48. Riemann D, Baglioni C, Bassetti C, Bjorvatn B, Dolenc Groselj L, Ellis JG, et al. European guideline for the diagnosis and treatment of insomnia. *J Sleep Res.* (2017) 26:675–700. doi: 10.1111/jsr.12594
49. Dietch JR, Taylor DJ, Pruiksma K, Wardle-Pinkston S, Slavish DC, Messman B, et al. The Nightmare Disorder Index: development and initial validation in a sample of nurses. *Sleep*. (2021) 44:zsaa254. doi: 10.1093/sleep/zsaa254
50. Fabbri M, Beracci A, Martoni M, Meneo D, Tonetti L, Natale V. Measuring subjective sleep quality: a review. *Int J Environ Res Public Health.* (2021) 18:1082. doi: 10.3390/ijerph18031082
51. Colvonen PJ, Straus LD, Stepnowsky C, McCarthy MJ, Goldstein LA, Norman SB. Recent advancements in treating sleep disorders in co-occurring PTSD. *Curr Psychiat Rep.* (2018) 20:48. doi: 10.1007/s11920-018-0916-9
52. Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD; Clinical Guidelines Committee of the American College of Physicians. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* (2016)165:125–33. doi: 10.7326/M15-2175
53. Morgenthaler TI, Auerbach S, Casey KR, Kristo D, Maganti R, Ramar K, et al. Position paper for the treatment of nightmare disorder in adults: an American academy of sleep medicine position paper. *J Clin Sleep Med.* (2018) 14:1041–55. doi: 10.5664/jcsm.7178
54. Hrozanova M, Morrison I, Riha RL. Adult NREM parasomnias: an update. *Clocks Sleep.* (2018) 1:87–104. doi: 10.3390/clockssleep1010009
55. Maher AR, Apaydin EA, Hilton L, Chen C, Troxel W, Hall O, et al. Sleep management in posttraumatic stress disorder: a systematic review and meta-analysis. *Sleep Med.* (2021). doi: 10.1016/j.sleep.2021.08.016
56. Benz F, Knoop T, Ballesio A, Bacaro V, Johann AF, Rücker G, et al. The efficacy of cognitive and behavior therapies for insomnia on daytime symptoms: a systematic review and network meta-analysis. *Clin Psychol Rev.* (2020) 80:101873. doi: 10.1016/j.cpr.2020.101873
57. Kelly MR, Robbins R, Martin JL. Delivering cognitive behavioral therapy for insomnia in military personnel and veterans. *Sleep Med Clin.* (2019) 14:199–208. doi: 10.1016/j.jsmc.2019.01.003
58. Ho FY, Chan CS, Tang KN. Cognitive-behavioral therapy for sleep disturbances in treating posttraumatic stress disorder symptoms: a meta-analysis of randomized controlled trials. *Clin Psychol Rev.* (2016) 43:90–102. doi: 10.1016/j.cpr.2015.09.005
59. Ekholm B, Spulber S, Adler M. A randomized controlled study of weighted chain blankets for insomnia in psychiatric disorders. *J Clin Sleep Med.* (2020) 16:1567–77. doi: 10.5664/jcsm.8636
60. Waltman SH, Shearer D, Moore BA. Management of post-traumatic nightmares: a review of pharmacologic and nonpharmacologic treatments since 2013. *Curr Psychiatry Rep.* (2018) 20:108. doi: 10.1007/s11920-018-0971-2
61. Ntafouli M, Galbiati A, Gazea M, Bassetti CLA, Bargiotas P. Update on nonpharmacological interventions in parasomnias. *Postgrad Med.* (2020) 132:72–9. doi: 10.1080/00325481.2019.1697119
62. Yücel DE, Emmerik AAP, Souama C, Lancee J. Comparative efficacy of imagery rehearsal therapy and prazosin in the treatment of trauma-related nightmares in adults: a meta-analysis of randomized controlled trials. *Sleep Med Rev.* (2019) 50:101248. doi: 10.1016/j.smrv.2019.101248
63. Zhang Y, Ren R, Sanford LD, Yang L, Ni Y, Zhou J, et al. The effects of prazosin on sleep disturbances in post-traumatic stress disorder: a systematic review and meta-analysis. *Sleep Med.* (2020) 67:225–31. doi: 10.1016/j.sleep.2019.06.010
64. de Jong J, Vermetten E. Medication for sleep problems in posttraumatic stress disorder. In: Vermetten E, Germain A, Neylan TC, editors. *Sleep and Combat-Related Post Traumatic Stress Disorder*. New York: Springer Science+Business Media LLC (2018), p. 325-48.
65. Guina J, Rossetter SR De RB, Nahhas RW, Welton RS. Benzodiazepines for PTSD: a systematic review and meta-analysis. *J Psychiatr Pract.* (2015) 21:281–303. doi: 10.1097/pra.0000000000000091

66. Marshall L, Helgadóttir H, Mölle M, Born J. Boosting slow oscillations during sleep potentiates memory. *Nature.* (2006) 444:610–3. doi: 10.1038/nature05278
67. Ngo HV, Martinetz T, Born J, Mölle M. Auditory closed-loop stimulation of the sleep slow oscillation enhances memory. *Neuron.* (2013) 78:545–53. doi: 10.1016/j.neuron.2013.03.006
68. Cellini N, Capuozzo A. Shaping memory consolidation via targeted memory reactivation during sleep. *Ann N Y Acad Sci.* (2018). doi: 10.1111/nyas.13855
69. Paller KA, Creery JD, Schechtman E. Memory and Sleep: How sleep cognition can change the waking mind for the better. *Annu Rev Psychol.* (2021) 72:123–50. doi: 10.1146/annurev-psych-010419-050815
70. van der Heijden A, van den Heuvel O, van der Werf Y, Talamini L, van Marle H. Targeted Memory Reactivation to augment TRAUMA therapy during sleep (TMR-TRAUMA study). *Dutch Trial Register*. (2017). Available online at: https://www.trialregister.nl/trial/6455

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.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 03 March 2022
doi: 10.3389/fpsyt.2022.770380

Dissociated Effects of Age and Recent Troubling Experiences on Nightmares, Threats and Negative Emotions in Dreams

Kheana Barbeau[1†], *Alexandre Lafrenière*[2†], *Hanae Ben Massaoud*[1], *Emma Campbell*[2] *and Joseph De Koninck*[1*‡]

[1] School of Psychology, University of Ottawa, Ottawa, ON, Canada, [2] Department of Psychology, Université de Montréal, Montreal, QC, Canada

Several studies have highlighted associations between adverse life events and the dysphoric character of dream experiences. This degree of continuity between waking-life and dream content seems partly attributed to the emotional and personal attachment linked to the incorporated waking experiences. Numerous changes in the processing of emotion-related stimuli are also reported across different human developmental stages. Therefore, we were interested in testing whether age would modulate the impact of recent troubling experiences on dream characteristics. Two hundred sixty participants, evenly distributed in five developmental stages, matched for gender and their exposure to a troubling experience, were selected from a large sample collected for a previous normative study of dreams of Canadians. Participants completed a dream questionnaire from which independent judges subsequently scored the dreams. We observed no interactions between the experience of troubling events and age. However, individuals who experienced a recent troubling event reported a higher frequency of nightmares and their dreams were more emotionally negative. Participants who experienced a moderately severe troubling event were also more likely to experience a dream whose maximal threat severity was of moderate intensity. Adolescents and young adults had dreams with a higher level of oneiric threats compared to older adults (>40 years old). Young adults also reported a higher frequency of nightmares compared to older adults. Our findings have implications for modern dream theories. They also suggest that dysphoric dreams might serve as potential proxies of mental health status and developmental stages. Future studies are now needed to explore the implications of these findings for psychological adaptation.

Keywords: dreams, troubling experiences, nightmares, emotions, dream formation, neurocognitive model of nightmares, threat simulation theory, continuity hypothesis

OPEN ACCESS

Edited by:
Seog Ju Kim,
Sungkyunkwan University,
South Korea

Reviewed by:
Michael Schredl,
University of Heidelberg, Germany
Sérgio Arthuro Mota-Rolim,
Federal University of Rio Grande do Norte, Brazil

***Correspondence:**
Joseph De Koninck
jdekonin@uottawa.ca

[†] *These authors share first authorship*

[‡] *These authors share senior authorship*

Specialty section:
This article was submitted to Sleep Disorders, a section of the journal Frontiers in Psychiatry

Received: *03 September 2021*
Accepted: *18 January 2022*
Published: *03 March 2022*

Citation:
Barbeau K, Lafrenière A, Ben Massaoud H, Campbell E and De Koninck J (2022) Dissociated Effects of Age and Recent Troubling Experiences on Nightmares, Threats and Negative Emotions in Dreams. Front. Psychiatry 13:770380. doi: 10.3389/fpsyt.2022.770380

INTRODUCTION

There is evidence for a certain degree of continuity between waking-life and dream content. It is postulated that dream features reflect waking-life experiences and/or that dreams impact psychological adaptation. The former concern dream formation theories and the latter dream function theories. Several specific proposals on how this occurs have been formulated and fall under

the umbrella of what is best known as the continuity hypothesis (CH) of dreams [see an overview by (1)]. Research so far suggests that the reflection of waking life in dreams is mostly selective, distorted and that features, such as reading and writing (i.e., mundane tasks), very seldomly find their way into dreams (2). More specifically, continuity between dream content and waking life was observed within complex individual characteristics, such as personality (3, 4), physical health (5), social roles (6) and individual concerns (7, 8). It was also found that changes in psychological well-being are correlated with similar changes in emotional dream content (9) and significant life experiences such as pregnancy can be well represented with distortions in dreams (10). Schredl (11) has proposed a mathematical model of families of influencing factors and their interactions that mediate incorporation into dreams. Of overall interest is the observation that, once the proper physiological substrate and cognitive capacity are achieved, dream construction prioritizes emotional waking-life experiences and concerns with a negative bias (12, 13).

Along the same line, stressful life experiences have been shown to be preferentially incorporated into dreams (14, 15). There is strong evidence of this effect in those who have experienced a traumatic or severe adverse life event and subsequently suffered from post-traumatic nightmares (16, 17). Indeed, several studies have found a relationship between traumatic experiences during waking-life and the subsequent development of dysphoric dreams and chronic nightmares (18–21). Interestingly, current research examining the impact of the 2019 Coronavirus (COVID-19) has reported increased nightmares, anxiety, and threats in dreams (22–25). Mounting evidence supports the idea that personally and emotionally difficult waking experiences, which may vary in temporal proximity, can have a long-lasting impact on the everyday oneiric experience. For example, a history of severe childhood trauma in undergraduate women was associated with more frequent disturbing dreams, higher nightmare distress and augmented psychopathology (26). Similarly, a recent study reported that the dreams of war prisoners during World War II had long-lasting incorporations of war-related themes, threatening elements, and negative emotions (27). Adverse life events may thus be overrepresented in dreams because they continue to represent real-life concerns and are of personal significance (28). From a dream construction perspective, these two elements have been identified as factors that affect the degree of continuity between waking-life and dream content (28).

According to the Threat Simulation Theory (TST), dreaming is thought to have evolved as an adaptive mechanism to simulate oneiric threats drawn from waking-life experiences, and the repetition of these threats in dreams were thought to improve survival skills (29). Although the TST was proposed to explain the evolutionary function of dreaming in our previous human ancestors, the theory has been investigated in modern life and societies. For instance, those who have a more active threat simulation system (TSS), such as those who have endured a trauma, have been shown to report more severe dream threats (30). Other studies have also found that the frequency and severity of waking-life threatening events are associated with the severity and frequency of dream threats (31, 32). Additionally, pre-sleep negative emotions were shown to be associated with threats in dreams (31), suggesting that waking life emotional experiences influence the menacing characteristics of dreams. In sum, the CH and the TST offer an explanation for the incorporation of waking-life events into dreams. The TST goes further by postulating that dreams served an evolutionary biological function in ancestral times (33). This phylogenetic function is impossible to directly test in modern days, as recognized by the TST (33, 34). However, what can be tested is whether threatening dreams form following adverse life experiences.

Nightmares are defined as elaborated and highly dysphoric dreams whose content is threatening and accompanied by intense negative emotions (35). While several recent models of nightmare formation have been developed from a psychological (36) to a neurochemical (37) perspective, a predominant view of interest for the current study stems from the neurocognitive model of nightmares [NMN; (38)]. It proposes that nightmares result from a dysfunction in a network of affective processes that typically serve the adaptive function of fear-memory extinction during dreaming (38). Thus, "normal dreaming" would facilitate fear-memory extinction through memory-element activation (e.g., deconstruction of memories into isolated elements); memory-element recombination (e.g., new elements are combined with isolated memory-specific elements to be inconsistent with real memories and offer novelty for enhanced emotional processing); and emotional expression [e.g., attentional focus on dream imagery to downregulate negative emotional arousal; (38)]. The link between adverse life experiences and nightmares is thus explained by a disruption in these dream processes caused by the accumulation of stress and negative affect from these life events (i.e., high affective load). This would ultimately lead to more incorporation of distressing memories into dreams. The relationship between adverse life events and nightmares may also be modulated by age. For example, it was reported that early life exposure to negative adverse events is associated with later nightmares and dysphoric dream experiences (26, 39–41). Moreover, the frequency of nightmares also changes with age. The direction of this change remains, however, to be clarified, as some cross-sectional studies observed with advancing age an increase (39, 42), a decrease (43–46), or no changes (47) for the frequency of nightmares. Nevertheless, more studies seem to point in the direction of a general decline in nightmares frequency with advancement in age. Congruently, in a study investigating non-trauma exposed adults, it was shown that the younger the participants were, the higher were the frequency of dream threats (48). To date, our understanding of the potential age-related effects on dysphoric characteristics of dreams in those who experienced a negative adverse event is limited and has not been investigated in an ontogenetic manner.

Although there are no theories to explain these age-related differences, neurodevelopmental changes associated with brain maturation and aging may explain differences in perceptual processing and memory storage of negative stimuli. For

instance, compared to older adults, adolescents demonstrate greater activity in areas of the brain responsible for processing emotions, specifically areas implicated in the fear response (e.g., amygdala), when viewing negative stimuli (49–51). These findings suggest that adolescents are more emotionally reactive to negative stimuli than older adults. Additionally, older adults demonstrate lower activation in these regions (52, 53) or a stronger coupled activation with prefrontal areas of the brain compared to younger adults when viewing negative stimuli (54), signifying better emotion regulation and less negative emotionality. Adolescents and young adults may demonstrate higher fear responses when viewing negative stimuli because their limbic structures, such as their amygdala, are more developed than prefrontal structures during this life stage, and thus functional connectivity between these regions in the brain are weaker, limiting the capacity for emotion regulation (55). These differences in fear responses when viewing negative stimuli are also associated with biases in memory retrieval. Indeed, younger adults are more likely to recall negative stimuli (56), while older adults are more likely to recall positive stimuli (57–59). Taken together, these findings suggest that neurodevelopmental processes may underlie age-related differences in experiencing threatening and dysphoric elements in dreams and nightmares. More specifically, adolescents and younger adults may be more likely to perceive situations or elements of their environment as more threatening and be more likely to recall these events, leading to higher incorporation of these memories into their dreams. Furthermore, some of their affective processes are limited, such as emotion regulation, due to brain immaturity in frontal regions, which may impede the facilitation of fear-extinction processes that naturally occur during "normal dreaming," resulting in fear-enhancing dreams (i.e., nightmares).

Although associations have been found between adverse life events and the disturbing and threatening nature of dreams, it remains unclear if those who have experienced a common (e.g., a death, a separation, interpersonal difficulties, an accident) and recent (i.e., within the past year) troubling personal event would report more nightmares, have a higher level of threat and negative emotions in their dreams. Furthermore, the degree to which there is continuity between the severity of recent adverse events and the threat severity of dreams remains unclear in a community-based population. Finally, despite observations of age-related differences in negative dream characteristics, studies have yet to take a developmental approach.

The main objective of the current study was thus to investigate the potential interaction between age and the experience of a recent troubling event on the dysphoric characteristics of dreams. In terms of dream characteristics, we were interested in the frequency of nightmares, the "threatening tone" of dreams, and the level of positive and negative dream emotions. We selected these variables as they measure the dysphoric experience of dreams at the level of monthly occurrence, actual threatening content, and emotions, respectively. Finally, our last objective was to assess which relevant dream theory (i.e., CH, TST, NMN) would best explain our findings.

HYPOTHESES AND PREDICTIONS

The CH (11) and TST (33) posit a certain degree of continuity between waking negative experiences and subsequent dream content. Thus, we predicted that, compared to participants who did not experience a recent troubling event, those who did will have more dysphoric dreams, which will manifest through a higher frequency of nightmares, higher level of oneiric threat, higher negative dream emotions and lower positive emotions. We also predicted that the severity of troubling events will be associated with the severity of dream threats: minor troubling experiences will be associated with minor oneiric threats, moderately troubling experiences will be associated with moderate oneiric threats, and severe troubling experiences will be associated with severe oneiric threats. It should be noted that, for the current study, the predictions drawn from the CH and TST cannot be differentiated.

The NMN (21, 38) proposes that the accumulation of stressful and negative emotional experiences (i.e., affect load) during wakefulness can entail the experience of disturbing dreams. Consequently, we predict that, compared to participants who did not experience a recent troubling event, those who did will have a higher frequency of nightmares and a higher level of negative emotions in their dreams. Of note, the NMN postulates that dreams regulate fear-related emotions by recombining fear-memories with non-fearful mnemonic elements into dreams. Therefore, we propose that this mechanism could be observed at the level of dream emotions, where the positive and negative emotions would tend toward a "relative" equilibrium in their intensities to regulate the impact of negative dream emotions. Thus, compared to individuals who did not experience a recent troubling event, those who did should have either a comparable or higher level of positive emotions in their dreams to match or outmatch their expected higher level of negative emotions. To the best of our knowledge, this prediction has never been tested before.

The neurodevelopmental paradigm highlights multiple changes in the perception and processing of emotion-related stimuli from adolescence to older ages (60–63), and the dream formation literature points to a link between waking-life and dream experiences (11, 33, 38). Moreover, age-related differences have been found in the frequency of nightmares (43–47) and oneiric threats (48). Collectively, these led to the prediction that adolescents and younger adults will report a higher frequency of nightmares and level of dream threats compared to middle-aged and older adults. This effect will be magnified in those who had a recent troubling experience.

METHOD

Participants and Protocol Overview

Two hundred sixty participants were selected from a large sample collected between 2004 and 2017 for a normative study of the dreams of Canadians (64, 65). Therefore, it was completed before the COVID 19 pandemic. Participants were between the ages of 12–90 years old (Mean = 38.0, SD = 21.3) and were devised into five age groups according to key developmental stages:

adolescence (12–17 years old), early adulthood (18–24 years old), adulthood (25–39 years old), middle adulthood (40–64 years old), and late adulthood (65 years old and older). There were 52 participants who were matched for gender and exposure to a recent troubling experience within the past year in each age group ($N = 260$, men = 127; women 133; exposed = 129; non-exposed = 129). Of those who experienced a recent troubling event over the past year, most experiences were categorized as psychological, social, or economic adverse events ($n = 79$, 61%), followed by minor events ($n = 32$, 25%), deadly ($n = 13$, 10%), and physical ($n = 5$, 4%). All age groups included 52 participants who were matched for gender (men = 127; women = 133) and their exposure to a troubling experience within the past year (non-exposed = 131; exposed = 129). Chi-square tests confirmed that the proportion of gender ($\chi^2_{(4)} = 0.25$, $p = 0.99$) and exposure to a troubling experience ($\chi^2_{(4)} = 3.45$, $p = 0.49$) were similar across age groups. The study was approved by the Research Ethics Boards (REB) at the University of Ottawa.

Participants were recruited using the following approaches: through personal contacts at school boards, advertisements displayed at a Canadian university, advertisements on social media, at public presentations and conferences, at retiree associations, and word of mouth. All participants were unaware of the purposes of the study and provided written consent. After obtaining participant's consent, they were instructed to complete a dream questionnaire using pen and paper until at least two dreams were reported, for a maximum period of ten days. The dream questionnaire (DQ) included several sections, some of them described below are based on existing questionnaires, most notably on dream recall and nightmare frequency. No new validation procedure was applied. It was developed for the Normative Study of the dreams of Canadians that has led to several publications [see (64–66)]. The first section contained the consent form and instructions regarding how to fill out the questionnaire. The other sections contained sociodemographic questions and subsections about the characteristics of their dreams. The subsections of the questionnaire used in the current study are described below.

Measures

Sociodemographics and Troubling Events

The DQ included a sociodemographic questionnaire in which the participants were asked to provide a detailed account regarding general information about them (e.g., age, gender, marital status, profession, education). Participants also had to report whether they had experienced any troubling events (e.g., a death, a separation, interpersonal difficulties, an accident) over the past year and, if so, to describe them.

Frequency of Nightmares

Next, the questionnaire required the participants to self-report their monthly frequency of nightmares, similar to the one for dream recall frequency, by checking one of the following categories: Less than once a month, Approximately once a month, Approximately once every two weeks, Approximately once a week, Many times a week, and Almost every night. These categories were recoded from 1 (i.e., less than once a month) to 6 (i.e., almost every night) and were used to conceptualize the frequency of nightmares.

Dream Reports and Emotions

Following this, participants filled out the morning section of the DQ and describe the narrative of their dream as soon as they wake up in the morning. The mean word count of dream narratives was 145.18 (range: 50–531; $SD = 84.68$). After describing the dream, they were instructed to assess the degree of joy, happiness, apprehension, anger, sadness, confusion, fear and anxiety [the dream emotion categories used by Hall et al. (67)] experienced in their dream on a four-point Likert scale (1 = not at all, 2 = a little, 3 = moderate, 4 = a lot). Participants' ratings of their dream emotions were recoded to range between 0 and 3, such that the level "not at all" started with a value of "0" to denote the absence of emotional experience. Then, the ratings of apprehension, anger, sadness, fear, and anxiety were averaged to form a mean intensity measure of the dream's negative emotions. The ratings of joy and happiness were averaged to produce the mean level of the dream's positive emotions. Cronbach's alpha of the positive and negative emotion scores were 0.91, 0.67, respectively.

Dream Threat Scale and Threat Severity Scale

For evaluating participant's threats in dreams, the third section of the Dream Threat Scale was used (68), which relates to the severity of the threats for the self. As in previous studies (31, 32), the definitions of this subscale (Life-threatening event; socially, psychologically or financially severe threat; physically severe threat; and a minor threat) were used for the identification of threats in the DQ. The level of threat severity was further rated on a four-point scale (0 = not threatening, 1 = somewhat threatening, 2 = moderately threatening, 3 = highly threatening). This allowed the assessment of the dream threats severity regardless of its qualitative nature. A similar scale was used in a previous study investigating aggressions in dreams of soldiers, gamers, and control participants (69). Given the relationship between the frequency of dream components and the reports length (64, 65), the frequency of dream threats were divided by the word count for the purpose of the analyses. Moreover, the most severe dream threat was selected as the measure of threat severity. A global measure of the dream's "threatening tone" was computed by conducting a z-transformation of the threat severity and frequency scores. After this transformation, both scores were averaged to create a threats composite score with higher values reflecting more severe and frequent dream threats. Cronbach's alpha was 0.81 for the threat composite score.

Scoring Procedure of Threat Characteristics of Adverse Events and Dreams

All participant's dreams were coded for the presence of oneiric threats. The dreams were coded by two independent judges who received instructions on how to identify the threats in the reports and how to evaluate their severity. The judges were trained on reports from other sources before starting the scoring of the participant's dreams. The threatening components in dreams were considered as such on the basis that both

judges had identified the same elements as menacing using the aforementioned definitions in the DTS. If both judges disagreed on the threatening nature of an event, the scoring of this event was discussed until they reached an agreement. The inter-rater reliability was evaluated for the level of threats severity using the intraclass correlation coefficient's (ICC) average measure parametrized for an absolute agreement definition. All ICC values ranged from 0.90 to 0.94, suggesting excellent reliability between the judge's scoring. The same procedure was undertaken for the scoring of the troubling events experienced within the past year. The ICC for the severity level of threats was 0.78, suggesting good reliability. Following the scoring phase, the first dream containing a minimum of 50 words and a maximum of 550 words was retained for analyses. Five participants (1.92%) were excluded from analyses as they reported dreams with an insufficient word count. Therefore, 255 participants were retained and included in the main analyses.

Data Analytical Plan

For the main analysis, a series of 2 (recent troubling event: yes or no) by 5 (age group: 12–17 years old; 18–24 years old; 25–39 years old; 40–64 years old; and 65 years or older) between-subjects ANOVAs were conducted to examine the relationship between experiences of recent troubling events and age on the threatening tone of dreams, frequency of nightmares, and emotional levels of dreams (positive and negative). Bonferroni adjustments were applied to *post-hoc* tests. To examine whether the severity of a recent troubling event is associated with severity of oneiric threats, a 3 by 3 (somewhat threatening, moderately threatening, and highly threatening) chi-square test of independence was conducted in those who experienced a recent troubling event and had dreams that contained threatening events. Only those with a threatening dream were included in this analysis as we were interested in whether the severity of troubling events during wakefulness was associated with the maximal severity of threatening events in dreams. This allowed us to test the degree of continuity between the severity of threatening experiences during wakefulness and dreaming. Bonferroni corrections were applied to *post-hoc* comparisons (0.05/3 = 0.0166). All statistical analyses were conducted using IBM SPSS v27 (SPSS, 2021) and figures were created using GraphPad Prism v9 (2021) for Windows.

For a between-subjects ANOVA with two factors, an a priori power analysis using G*Power (70) recommended a sample size of 223 participants for detecting a medium effect size with power of 0.70 and an alpha of 0.05, thus our goal was to reach this sample size. For a two-tailed 3 by 3 Chi-square test of independence, an a priori power analysis using G*Power (70) recommended a sample size of 108 participants for detecting a medium effect size with a power of 0.70 and an alpha of 0.05.

RESULTS

Preliminary Analyses

Regarding data cleaning, missing data were not imputed; therefore, participants with missing data were omitted from certain ANOVA analyses ($n = 4$ excluded; three from the exposed group and one from the non-exposed group; $N = 255$ for the final sample). Some participants were missing data due to variations in questionnaire packages over the duration of the data collection period for the normative study and thus did not have the opportunity to self-report on all outcomes of interest in the current study. Univariate outliers were winsorized. There were no multivariate outliers. Assumptions for the 2 (recent troubling event) by 5 (age group) between-subjects ANOVAs for the main analyses for normality and homogeneity of variance were examined through scatterplots and tests of homogeneity of variance. The assumption for homogeneity of variance was met across all outcomes. There were minor violations of normality; however, transformations were not applied considering that analysis of variance tests are robust to non-normality (71), especially in cases where group variances are similar (72). Means and standard deviations for all outcomes of interest are displayed in **Table 1**.

Main Analyses

Differences in the Threatening Tone of Dreams: Threats Composite Score

A 2 (recent troubling event) by 5 (age group) ANOVA demonstrated a non-significant main effect of recent troubling event, $F_{(1,245)} = 0.55$, $p = 0.815$, $\eta_p^2 = 0.000$, a significant main effect of age group, $F_{(4,245)} = 8.94$, $p = < 0.001$, $\eta_p^2 = 0.127$, and a non-significant interaction between recent troubling event and age group, $F_{(4,245)} = 1.31$, $p = 0.269$, $\eta_p^2 = 0.021$, for the composite score of oneiric threats. As shown in **Figure 1**, pairwise comparisons revealed that 12–17 year old's significantly had more severe and frequent oneiric threats compared those who were 40 years old or older (40–64 years old: $p = < 0.001$; 65 years old or older: $p = <0.001$). Similarly, 18–24 year old's had significantly more severe and frequent oneiric threats compared those who were 40 years old or older (40–64 years old: $p = 0.004$; 65 years old or older: $p = 0.009$). No other age differences emerged.

Differences in Frequency of Nightmares

A 2 (recent troubling event) by 5 (age group) ANOVA demonstrated a significant main effect of recent troubling event, $F_{(1,240)} = 4.74$, $p = 0.030$, $\eta_p^2 = 0.019$, a significant main effect of age group, $F_{(4,240)} = 5.66$, $p = <0.001$, $\eta_p^2 = 0.086$, and a non-significant interaction between recent troubling event and age group, $F_{(4,240)} = 0.67$, $p = 0.614$, $\eta_p^2 = 0.011$, for the monthly frequency of nightmares. Pairwise comparisons revealed that those who experienced a recent troubling event reported a higher frequency of nightmares compared to those who did not ($p = 0.030$; see **Figure 2A**). Additionally, as depicted in **Figures 2B**, 18–24 year old's had significantly more nightmares compared to those who were 40 years old or older (40–64 years old: $p = 0.005$; 65 years old or older: $p = 0.002$). No other age differences emerged.

Differences in Positive Dream Emotions

A 2 (recent troubling event) by 5 (age group) ANOVA demonstrated a non-significant main effect of recent troubling event, $F_{(1,243)} = 1.22$, $p = 0.270$, $\eta_p^2 = 0.005$ (see **Figure 3A**), a non-significant main effect of age group, $F_{(4,243)} = 1.00$,

TABLE 1 | Descriptive statistics stratified by adverse event exposure within the past year (AE) and age group.

Group	12–17 AE	12–17 No AE	18–24 AE	18–24 No AE	25–39 AE	25–39 No AE	40–64 AE	40–64 No AE	65 + AE	65+ No AE
Mean (*SD*) severity of AE	2.31 (0.65)	–	2.00 (0.82)	–	2.25 (0.79)	–	1.93 (0.98)	–	2.10 (0.94)	–
Mean (*SD*) nightmare frequency	2.10 (1.19)	1.86 (1.00)	2.62 (1.56)	2.13 (1.00)	2.13 (1.51)	1.77 (1.14)	1.48 (0.94)	1.58 (0.99)	1.69 (1.11)	1.05 (0.23)
Mean (*SD*) positive emotions in dreams	1.18 (1.23)	1.02 (1.02)	0.74 (0.96)	0.78 (0.89)	0.63 (0.77)	0.90 (1.12)	1.04 (1.04)	0.60 (0.90)	1.18 (1.17)	0.74 (1.09)
Mean (*SD*) negative emotions in dreams	1.11 (0.57)	0.91 (0.64)	1.23 (0.61)	0.96 (0.65)	0.91 (0.81)	0.98 (0.80)	0.91 (0.74)	0.66 (0.68)	0.94 (0.92)	0.53 (0.60)
Mean (*SD*) threatening tone of dreams	0.28 (0.91)	0.64 (1.13)	0.26 (0.85)	0.21 (0.74)	0.15 (0.79)	−0.14 (0.77)	−0.43 (0.84)	−0.30 (0.75)	−0.20 (0.83)	−0.47 (0.76)
Mean (*SD*) max severity of threats in dreams	2.11 (0.76)	2.29 (0.75)	2.00 (0.91)	1.92 (0.74)	1.95 (0.89)	1.88 (0.81)	1.92 (0.86)	1.47 (0.74)	1.76 (0.83)	2.00 (0.87)

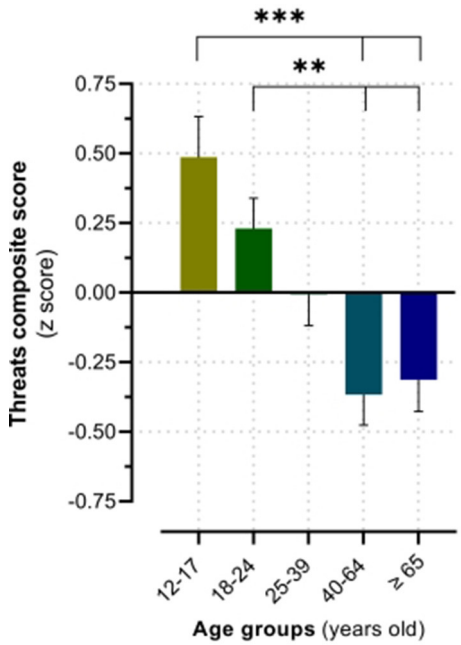

FIGURE 1 | Age group differences in the threatening tone of dreams. The values are expressed as means ± SEM, $N = 255$. $^{**}p < 0.01$, $^{***}p < 0.001$.

$p = 0.407$, $\eta_p^2 = 0.016$, and a non-significant interaction between recent troubling event and age group, $F_{(4,243)} = 1.12$, $p = 0.348$, $\eta_p^2 = 0.018$, for positive emotions felt in dreams. Pairwise comparisons were not examined due to non-significant main effects.

Differences in Negative Dream Emotions

A 2 (recent troubling event) by 5 (age group) ANOVA demonstrated a significant main effect of recent troubling event, $F_{(1,243)} = 5.55$, $p = 0.019$, $\eta_p^2 = 0.022$, a non-significant main effect of age group, $F_{(4,243)} = 2.23$, $p = 0.067$, $\eta_p^2 = 0.035$, and a non-significant interaction between recent troubling event and age group, $F_{(4,243)} = 0.71$, $p = 0.588$, $\eta_p^2 = 0.011$, for negative emotions experienced in dreams. Pairwise comparisons revealed that those who experienced a recent troubling event had a significantly higher level of negative emotions in their dreams than those who did not have a recent troubling experience, $p = 0.046$ (see **Figure 3B**).

Associations Between Severity of a Recent Troubling Event and Severity of Oneiric Threats

In those who recently experienced a troubling event and had a threatening dream ($N = 125$), a 3 (severity of troubling event) by 3 (severity of oneiric threat) chi-square test of independence was conducted to examine the association between severity of the event and maximal severity of threats in dreams. This analysis revealed that the severity of a recent troubling event and severity of threats in dreams are significantly associated, $X^2_{(4)} = 11.09$, $p = 0.026$. *Post-hoc* comparisons demonstrated that recently experiencing a moderately threatening event during waking was

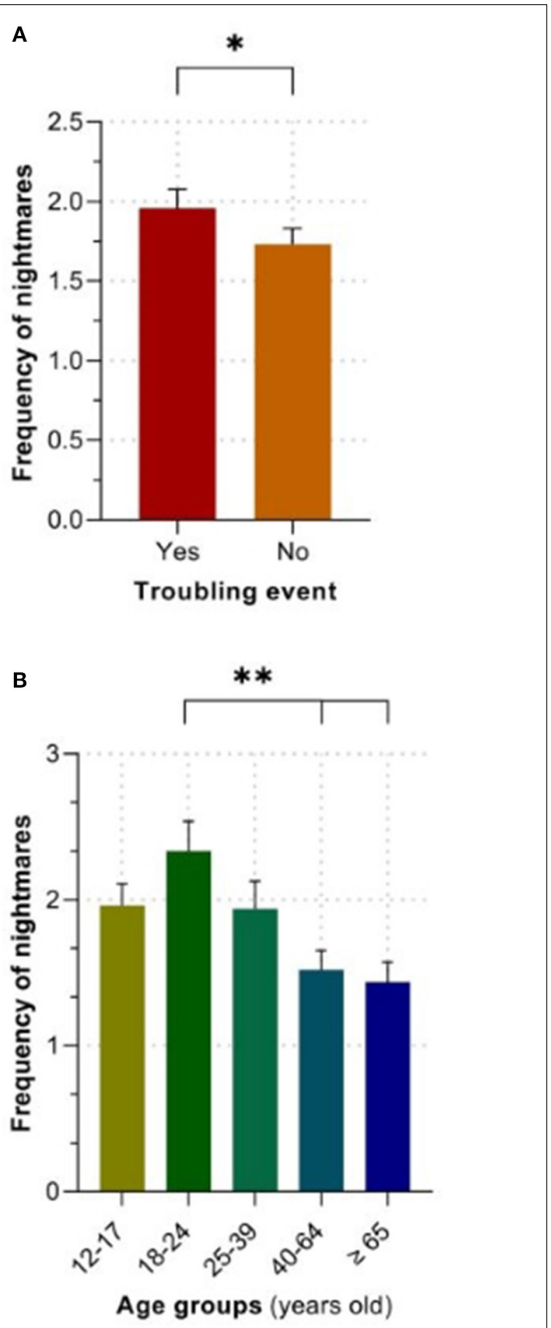

FIGURE 2 | Group differences in the frequency of nightmares. **(A)**. Main effect of the experience of troubling events over the past year. **(B)**. Main effect of age. The values are expressed as means ± SEM, $N = 250$. *$p < 0.05$; **$p < 0.01$; ***$p < 0.01$.

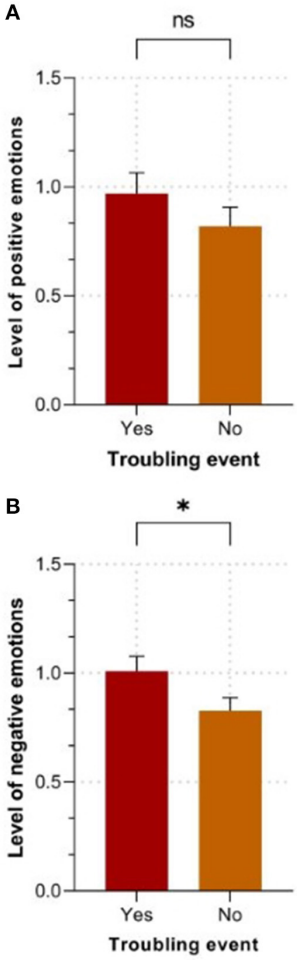

FIGURE 3 | Main effect of the experience of a recent troubling event on emotion levels in dreams. **(A)**. Level of positive emotions. **(B)**. Level of negative emotions. The values are expressed as means ± SEM, $N = 253$. *$p < 0.05$, ns = $p > 0.05$.

significantly associated with moderate severity for the maximal threat in dreams, $p = 0.002$ (see **Figure 4**).

DISCUSSION

In the context of recent dream formation theories, the objective of the current study was to examine whether common and recent adverse events were related to dysphoric dream characteristics. Given that the perception and processing of emotion-related stimuli undergo several changes from adolescence to older ages (60–63), we were also interested in examining whether age would modulate the influence of recent adverse experiences on subsequent dream characteristics. Aligned with our hypotheses, our results suggest that having a recent troubling experience is associated with reporting more nightmares monthly and experiencing a higher level of negative dream emotions. However, these adverse experiences were not related to the experience of dreams with a higher threatening tone. Additionally, we only observed a small degree of continuity between the severity of troubling events experienced within the last year and severity of threats in dreams, as this relationship was only present when the adverse event and dream threat were of moderate intensity. Furthermore, adolescents and younger adults had a higher level of threats in dreams compared to older age groups. Younger adults also self-reported a higher

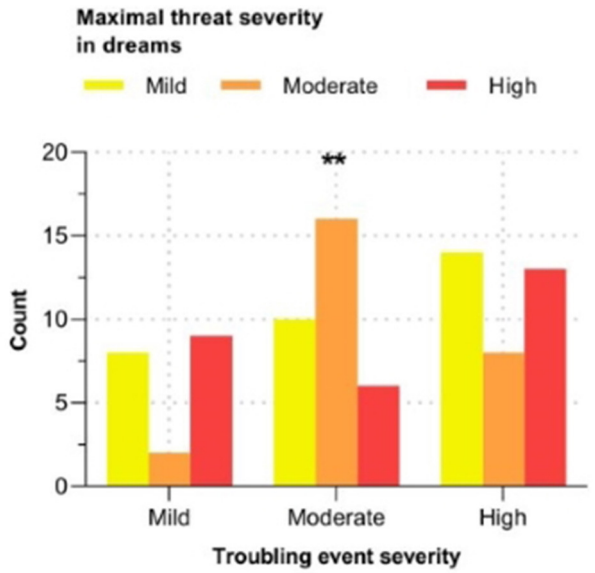

FIGURE 4 | Associations between the severity of a recent troubling event and severity of oneiric threats. The values are expressed as count. $N = 125$. $^{**}p < 0.01$.

frequency of nightmares than adults older than 40 years old. Contrary to our hypotheses and predictions, no interactions between the experience of troubling personal events and age group were observed for any dream characteristic. The absence of significant interactions in the presence of both factors' significant main effects thus suggests a dissociation between these variables, which show specific and different impacts on the dreaming experience. Results are more thoroughly discussed and interpreted through the lens of three relevant modern dream theories in the following sections.

Effects of Recent Troubling Events on Dream Characteristics

The NMN (21, 38) postulates that a higher level of affect load during wakefulness could precipitate the occurrence of disturbing dreams. One could safely speculate that experiencing a troubling event within the previous year may manifest through dysphoric emotions and stress levels experienced in daily life. Thus, as predicted by the NMN, we observed that individuals who experienced a recent troubling event self-reported a higher frequency of nightmares compared to those who did not report such an experience. Although this result aligns with the literature on trauma and nightmares (16), our results add to the latter by showing that even the experience of common and recent troubling events can significantly increase the monthly frequency of nightmares in a community-based sample. Moreover, the NMN (38) proposes that dreams regulate fear-infused emotions by a recombination of fearful memories with non-fearful mnestic elements into dreams. Another contribution of our study was to show that, compared to individuals who did not report a recent experience of troubling event, those who did had a higher level of negative emotions with a similar level of positive ones (see **Figure 3A**). This mixture of emotional intensity could reflect an attempt to down-regulate negative emotions and memories through dreaming. Indeed, maintaining a "normal level" of positive emotions in the presence of an increased level of negative affects could dilute the latter within the global emotional tone of dreams, allowing their down-regulation as proposed by Perlis and Nielsen (73) and Menz et al. (74). Thus, our findings seem coherent and add to the literature on the NMN and the emotional regulation theory of dream (75).

Both the CH (11) and TST (33, 76) predict that the exposition to adverse life events would lead to more dysphoric characteristics in dreams, such as a higher frequency of nightmares, higher level of oneiric threats, and higher level of negative dream emotions. Thus, the increased frequency of nightmares and higher level of negative oneiric emotions in those who experienced a recent troubling event lends some support to both theories, but the fact that such afflicting events did not affect the threatening tone of dreams does not. Additionally, when specifically looking at dreams containing threats, the only significant associations was found for individuals having experienced a moderately severe troubling event who were more likely to experience a dream whose maximal threat severity was of moderate intensity. This suggests that, following moderately severe troubling events, the dream-production system would generate dreams with a symmetrical level of threat severity between waking and oneiric experiences. This is consistent with the TST proposing that the intensity of the oneiric threat simulations should be proportional to the magnitude of personal threat experienced during waking-life events (33). However, the fact that this association was only found for moderately, and not highly, severe troubling events does not completely align with the TST. Indeed, highly adverse experiences are postulated to be most relevant for the activation of the TSS, entailing more severe and persistent threatening dreams. This finding regarding the association between moderately threatening troubling events and moderately threatening oneiric threats also partly supports the CH due to the continuity between waking-life experiences and dream experiences. However, according to this theory, we would have expected to observe similar patterns for the other troubling events' severities, which was not the case. However, as proposed by the CH (11), the incorporation rate of waking-life experiences into dreams may depend on the time interval between both. Because the troubling event reported by our participants could have happened anytime within the last year preceding the dream report, this varying delay might have limited the degree of continuity between the waking-life troubling events and dream experiences in our study. Overall, the effects of recent troubling events on the distressing character of dream experiences seem best explained by the NMN, and offer mixed support for the TST and CH.

Effects of Age on Dream Characteristics

No theories of dreaming have specifically addressed the ontogenetic patterns of dream experiences. For this reason, our results regarding the effects of age on dream features will be interpreted in relation to previous relevant findings. Some evidence supports a progressive declining pattern of

the disturbing character of dreams across life. For instance, a linear decrease from adolescence to older age was reported for the frequency of nightmares (45), which is consistent with a previous study comparing young and older adults (46). This is congruent with our findings such that young adults reported a higher frequency of nightmares compared to older adults (>40 years old). Furthermore, our group (64, 65) previously investigated the ontogenetic patterns of several components of dream content, such as the characters, interactions, activities, and emotions of both men and women. One consistent result was the significant decrease across the lifespan of the frequency of aggressive interactions in dreams. Similarly, a study found that younger participants reported a higher frequency of dream threats, although in their study few participants were older than 40 years old ($n = 11$) (18). Together, these findings suggest a possible decrease in the frequency of oneiric threats with advancing age. Consistent with this hypothesis, we observed that adolescents and young adults reported dreams containing a higher level of oneiric threats compared to older adults (>40 years old).

Collectively, our findings suggest that the disturbing character of dreams, at the occurrence- and content-level, seem to deplete with aging. One could nonetheless speculate that the reduction in dream recall observed with advancing age (77) might explain the lower frequency of nightmares of older adults. However, it would not explain the previous and current findings of the less threatening nature of dreams in the older age groups. As it was recently proposed that dream mentation could mirror neurocognitive development across the lifespan (78, 79), one could hypothesize that such developmental processes might influence the content of dreams at different levels. For example, numerous changes pertaining to the perception of emotions, emotional processing, and regulation are incurred with advancing age. These might result from changes in the trajectories of personality traits (80), structural and functional brain changes (55, 60, 63), and coping strategies (81, 82), to name a few. Future studies will thus be required to investigate whether these developmental changes in the processing of emotion-related stimuli might relate to the declining experience of dysphoric dreams with aging. Such inquiries can bring valuable insights to theories of dreaming, shedding light on the possible mechanisms underlying their formation and function.

Limitations and Future Directions

The main limitation of our study is the fact that the participants were not required to report the date of when the troubling experience took place in the preceding year. Therefore, it was not possible to control for the potential acute effect of the recency of the adverse experience on dream features. Future studies could thus specifically assess how the level of recency of troubling experiences progressively influences subsequent dreams' dysphoric nature and the temporal sources of these dreams (32). Additionally, we did not score the troubling events according to their nature. Instead, they were scored based on their severity as a threatening experience. Thus, we cannot determine whether the troubling events' nature could have modulated the effects observed in our study. Future studies should consider the nature of different common adverse life events and determine whether it influences the dysphoric characteristics of dreams. Another limitation is that we did not assess participant's personality traits, which may have influenced the perception of dream threats, their severity, and the negative affect elicited by them. Given that the experience of a troubling event was self-reported, individuals with a dispositional susceptibility to emotional reactivity and distress might have been more prone to report both a troubling life event and more distressing dreams (83). Indeed, it was previously shown that trait-like factors were associated with the frequency of nightmares (84, 85), oneiric threats (48) and the emotional tone (86) of dreams. Future research should incorporate questionnaires assessing personality traits and test their influence on the relationship between adverse life events and dreams. Finally, as we were interested in the potential interaction between age and the experience of a troubling personal event, and to maximize statistical power, we did not focus on the effect of gender on our results. Although previous research highlighted an impact of gender on dream characteristics (66, 87), we minimized this potential confounding effect by gender-matching our groups.

CONCLUSION

Our findings lend partial support to the CH and TST but seem to favor the NMN with respect to dream formation. One exciting result is the observation of a specific mixture of oneiric emotional intensities in individuals having experienced a troubling personal event within the past year. This mixture, composed of a heightened level of negative emotions with a "normal" level of positive emotions, could serve an adaptive emotion regulation function. Future studies should investigate whether such an emotional mixture in dreams would predict better outcomes for this population's following morning mood. Furthermore, our findings may have implications beyond the understanding of dream formation to the mental health and developmental fields. Indeed, we highlighted the impact of experiencing common and recent troubling events on oneiric negative emotions and the monthly occurrence of nightmares. The recurrence of nightmares can induce waking-life distress during the following day (3). However, some evidence suggests that lucid dreaming techniques might serve as a potential intervention to reduce nightmares' occurrence (88), representing a promising avenue for future studies aiming to treat nightmare disorders. We also validated emerging evidence suggesting a decline of the disturbing character of dream experiences accompanying the advancement in age. We propose that such decline could depict the well-detailed changes in the processing of emotion-related stimuli across the human lifespan. Future studies are thus needed to further explore the potential implications of these findings for psychological adaptation in the context of adverse life events and development.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the University of Ottawa. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

AL, JD, KB, and HB all contributed to the conception and design of the study. AL, HB, and EC carried out the analyses of the dreams. HB wrote an Honors Thesis in French on the basis of part of this study and collated the data in preparation of the statistical analyses. KB, AL, and HB carried out the statistical analyses. AL, KB, and JD prepared the final manuscript. JD obtained the funding for the study and acted as mentor the work. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by a grant from the Social Sciences and Humanities Research Council of Canada.

REFERENCES

1. Schredl M. Continuity hypothesis of dreaming. In: Valli K, Hoss R, editiors. *Dreams: Understanding Biology, Psychology, And Culture*. Santa Barbara: ABC-CLIO (2019). p. 88–94.
2. Domhoff GW. *The Emergence of Dreaming:Mind-Wandering, Embodied Simulation, and the Default Network*. New York, NY: Oxford University Press (2018). p. 64–7.
3. Busby K, De Koninck J. Short-term effects of strategies for self-regulation on personality dimensions and dream content. *Percept Mot Skills.* (1980) 50:751–65. doi: 10.2466/pms.1980.50.3.751
4. Hartmann E, Elkin R, Garg M. Personality and dreaming: the dreams of people with very thick or very thin boundaries. *Dreaming.* (1991) 1:311–24. doi: 10.1037/h0094342
5. King DB, DeCicco TL. The relationships between dream content and physical health, mood, and self-construal. *Dreaming.* (2007) 17:127–39. doi: 10.1037/1053-0797.17.3.127
6. Lortie-Lussier M, Schwab C, De Koninck J. Working mothers versus homemakers:Do dreams reflect the changing roles of women? *Sex Roles.* (1985) 12:1009–21. doi: 10.1007/BF00288101
7. Delorme MA, Lortie-Lussier M, De Koninck J. Stress and coping in the waking and dreaming states during an examination period. *Dreaming.* (2002) 12:171–83. doi: 10.1023/A:1021128326940
8. Halliday G. Examination dreams. *Percept Mot Skills.* (1993) 77:489–90. doi: 10.2466/pms.1993.77.2.489
9. Pesant N, Zadra A. Dream content and psychological well-being: a longitudinal study of the continuity hypothesis. *J Clin Psychol.* (2006) 62:111–21. doi: 10.1002/jclp.20212
10. Sabourin C, Robidoux R, Pérusse A, De Koninck J. Dream content in pregnancy and post-partum:Refined exploration of continuity between waking and dreaming. *Dreaming.* (2018) 28:122–39. doi: 10.1037/drm0000070
11. Schredl M. Continuity between waking and dreaming: a proposal for a mathematical model. *Sleep and Hyp.* (2003) 5:38–52.
12. De Koninck J. Sleep, dreams and dreaming. In: Espie CA, Morin CM, editiors. *The Oxford Handbook Of Sleep And Sleep Disorders*. New York, NY: Oxford (2012). p. 150–71. doi: 10.1093/oxfordhb/9780195376203.013.0009
13. Domhoff W. The neurocognitive theory of dreaming. In: Valli K, Hoss R, editiors. *Dreams: Understanding Biology, Psychology, and Culture*. Santa Barbara: ABC-CLIO (2019). p. 95–9.
14. Koulack, D. Dreams and adaptation to contemporary stress. In: A. Moffitt, M. Kramer, & R. Hoffmann, edition. The functions of dreaming. New York, NY: State University of New York Press (1993). p. 321–40.
15. Picchioni D, Goeltzenleucher B, Green DN, Convento MJ, Crittenden R, Hallgren M, et al. Nightmares as a coping mechanism for stress. *Dreaming.* (2002) 12:155–69. doi: 10.1023/A:1020118425588
16. Mysliwiec V, Brock MS, Creamer JL, O'Reilly BM, Germain A, Roth BJ. Trauma associated sleep disorder:a parasomnia induced by trauma. *Sleep Med Rev.* (2018) 37:94–104. doi: 10.1016/j.smrv.2017.01.004
17. Phelps AJ, Forbes D, Creamer M. Understanding posttraumatic nightmares: an empirical and conceptual review. *Clin Psych Rev.* (2008) 28:338–55. doi: 10.1016/j.cpr.2007.06.001
18. Duval M, Zadra A. Frequency and content of dreams associated with trauma. *Sleep Med Clin.* (2010) 5:249–60. doi: 10.1016/j.jsmc.2010.01.003
19. Gieselmann A, Ait M, Michelle A, Anne C, Gorzka R, Holzinger B, et al. Aetiology and treatment of nightmare disorder : state of the art and future perspectives. *J Sleep Res.* (2019) 28:e12820. doi: 10.1111/jsr.12820
20. Hartmann E, Hartmann E. Nightmare after trauma as paradigm for all dreams : a new approach to the nature and functions of dreaming nightmare. *Psychiatry.* (2016) 61:223–38. doi: 10.1080/00332747.1998.11024834
21. Levin R, Nielsen TA. Disturbed dreaming, posttraumatic stress disorder, and affect distress:a review and neurocognitive model. *Psychol Bull.* (2007) 133:482–528. doi: 10.1037/0033-2909.133.3.482
22. Kilius E, Abbas NH, McKinnon L, Samson DR. Pandemic nightmares:COVID-19 lockdown associated with increased aggression in female university students' dreams. *Front Psychol.* (2021) 12:644636. doi: 10.3389/fpsyg.2021.644636
23. Schredl M, Bulkeley K. Dreaming and the COVID-19 pandemic: a survey in a US sample. *Dreaming.* (2020) 30:189–98. doi: 10.1037/drm0000146
24. Barrett D. Dreams about COVID-19 versus normative dreams: trends by gender. *Dreaming.* (2020) 30:216–21. doi: 10.1037/drm0000149
25. Fränkl E, Scarpelli S, Nadorff MR, Bjorvatn B, Bolstad CJ, Chan NY, et al. How our dreams changed during the COVID-19 pandemic: effects and correlates of dream recall frequency - a multinational study on 19,355 adults. *Nat Sci Sleep.* (2021) 13:1573–91. doi: 10.2147/NSS.S324142
26. Duval M, Mcduff P, Zadra A. Nightmare frequency, nightmare distress, and psychopathology in female victims of childhood mistreatment. *J Nerv Ment Dis.* (2013) 201:767–72. doi: 10.1097/NMD.0b013e3182a214a1
27. Bergman M, Macgregor O, Olkoniemi H, Owczarski W, Revonsuo A, Valli K. The holocaust as a lifelong nightmare: posttraumatic symptoms and dream content in polish Auschwitz survivors 30 Years after World War II. *Am J Psychol.* (2020) 133:143–67. doi: 10.5406/amerjpsyc.133.2.0143
28. Malinowski J, Horton CL. Evidence for the preferential incorporation of emotional waking-life experiences into dreams. *Dreaming.* (2014) 24:18–31. doi: 10.1037/a0036017
29. Revonsuo A. The reinterpretation of dreams: an evolutionary hypothesis of the function of dreaming. *Behav Brain Sci.* (2000) 23:877–901. doi: 10.1017/S0140525X00004015
30. Valli K, Revonsuo A, Pälkäs O, Ismail KH, Ali KJ, Punamäki RL. The threat simulation theory of the evolutionary function of dreaming: evidence from dreams of traumatized children. *Conscious Cogn.* (2005) 14:188–218. doi: 10.1016/S1053-8100(03)00019-9
31. Bradshaw S, Lafrenière A, Amini R, Lortie-lussier M, De Koninck J. Threats in dreams, emotions and the severity of threatening experiences in waking. *Int J Dream Res.* (2016) 9:102–9. doi: 10.11588/IJODR.2016.2.27214
32. Lafrenière A, Lortie-lussier M, Dale A, Robidoux R, Koninck J De. Autobiographical memory sources of threats in dreams. *Conscious Cogn.* (2018) 58:124–35. doi: 10.1016/j.concog.2017.10.017

33. Valli K, Revonsuo A. The threat simulation theory in light of recent empirical evidence: a review. *Am J Psychol.* (2009) 122:17–38. doi: 10.2307/27784372
34. Valli K, Revonsuo A. Recurrent dreams: recurring threat simulations? *Conscious Cogn.* (2006) 15:464–9. doi: 10.1016/j.concog.2005.05.001
35. American Psychiatric Association. *Diagnostic And Statistical Manual Of Mental Disorders* 5th ed. Arlington: American Psychiatric Association (2013). doi: 10.1176/appi.books.9780890425596
36. Hartmann E. T*he Nightmare: The Psychology And Biology Of Terrifying Dreams*. E Hartmann, edition New York, NY: Basic Books (1984).
37. Sikkis IG. The possible mechanism of the appearance of nightmares in post-traumatic stress disorder and approaches to their prevention. *Neurochem J.* (2019) 13:320–34. doi: 10.1134/S1819712419030127
38. Levin R, Nielsen T. Nightmares, bad dreams, and emotion dysregulation: a review and new neurocognitive model of dreaming. *Curr Dir Psychol Sci.* (2009) 18:84–8. doi: 10.1111/j.1467-8721.2009.01614.x
39. Csóka S, Simor P, Szabó G, Kopp MS, Bódizs R. Early maternal separation, nightmares, and bad dreams: results from the hungarostudy epidemiological panel. *Attach Hum Dev.* (2011) 13:125–40. doi: 10.1080/14616734.2011.553991
40. Nielsen T, Carr M, Picard-Deland C, Marquis LP, Saint-Onge K, Blanchette-Carrière C, et al. Early childhood adversity associations with nightmare severity and sleep spindles. *Sleep Med.* (2019) 56:57–65. doi: 10.1016/j.sleep.2019.03.004
41. Nielsen T. The stress acceleration hypothesis of nightmares. *Front Neurol.* (2017) 8:201. doi: 10.3389/fneur.2017.00201
42. Sandman N, Valli K, Kronholm E, Ollila HM, Revonsuo A, Laatikainen T, et al. Nightmares: prevalence among the Finnish general adult population and war veterans during 1972-2007. *Sleep.* (2013) 36:1041–50. doi: 10.5665/sleep.2806
43. Schredl M. Nightmare frequency in a representative German sample. *Intern J Dream Res.* (2013) 6:565–70. doi: 10.11588/ijodr.2013.2.11127
44. Schredl M, Lahl O, Göritz AS. Nightmare frequency and femininity/masculinity. *Percept Mot Skills.* (2010) 111:60–4. doi: 10.2466/02.09.PMS.111.4.60-64
45. Nielsen TA, Stenstrom P, Levin R. Nightmare frequency as a function of age, gender, and September 11, 2001: findings from an internet questionnaire. *Dreaming.* (2006) 16:145–58. doi: 10.1037/1053-0797.16.3.145
46. Salvio M, Wood JM, Eichling PS, Schwartz J. Nightmare prevalence in the healthy elderly. *Psychol Aging.* (1992) 7:324–3255. doi: 10.1037/0882-7974.7.2.324
47. Schredl M. Nightmare frequency and nightmare topics in a representative German sample. *Eur Arch Psychiatry Clin Neurosci.* (2010) 260:565–70. doi: 10.1007/s00406-010-0112-3
48. Mathes J, Schredl M. Threats in dreams: are they related to waking- life? *Int J Dream Res.* (2016) 9:58–66. doi: 10.11588/ijodr.2016.1.27499
49. Ernst M, Nelson EE, Jazbec S, Mcclure EB, Monk CS, Leibenluft E, et al. Amygdala and nucleus accumbens in responses to receipt and omission of gains in adults and adolescents. *Neuroimage.* (2005) 25:1279–91. doi: 10.1016/j.neuroimage.2004.12.038
50. Guyer AE, Monk CS, Mcclure-tone EB, Nelson EE, Roberson-nay R, Adler AD, et al. Developmental examination of amygdala response to facial expressions. *J Cogn Neurosci.* (2008) 20:1565–82. doi: 10.1162/jocn.2008.20114
51. Monk CS, Mcclure EB, Nelson EE, Zarahn E, Bilder RM, Leibenluft E, et al. Adolescent immaturity in attention-related brain engagement to emotional facial expressions. *Neuroimage.* (2003) 20:420–8. doi: 10.1016/S1053-8119(03)00355-0
52. Mather M, Canli T, English T, Whitfield S, Wais P, Ochsner K, et al. Amygdala responses to emotionally valenced stimuli in older and younger adults. *Psychol Sci.* (2004) 15:259–63. doi: 10.1111/j.0956-7976.2004.00662.x
53. Reed AE, Carstensen LL. The theory behind the age-related positivity effect. *Front Psychol.* (2012) 3:339. doi: 10.3389/fpsyg.2012.00339
54. Jacques PS, Dolcos F, Cabeza, R. Effects of aging on functional connectivity of the amygdala during negative evaluation: a network analysis of fMRI data. *Neurobiol Aging.* (2010) 31:315–27. doi: 10.1016/j.neurobiolaging.2008.03.012
55. Somerville LH, Jones RM, Casey B. A time of change:Behavioral and neural correlates of adolescent sensitivity to appetitive and aversive environmental cues. *Brain Cogn.* (2010) 72:124–33. doi: 10.1016/j.bandc.2009.07.003
56. Kensinger EA, Garoff-eaton RJ, Schacter DL. Effects of emotion on memory specificity in young and older adults. *J Gerontol Psychol Sci.* (2007) 62:208–15. doi: 10.1093/geronb/62.4.P208
57. Emery L, Hess TM. Viewing instructions impact emotional memory differently in older and young adults. *Am Psychol Assoc.* (2008) 23:2–12. doi: 10.1037/0882-7974.23.1.2
58. Kensinger EA, Schacter DL. Memory and emotion. In: Lewis M, Haviland-Jones JM, Barrett LF, editors. *Handbook of Emotions*. New York, NY: The Guilford Press (2008). p. 601–17.
59. Ziaei M, Fischer H. Emotion and aging: the impact of emotion on attention, memory, and face recognition in late adulthood. In: Absher JR, Cloutier J, editors. *Neuroimaging Personality, Social Cognition, And Character*. Elsevier Academic Press (2016). p. 259–78. doi: 10.1016/B978-0-12-800935-2.00013-0
60. Casey BJ. Beyond simple models of self-control to circuit-based accounts of adolescent behavior. *Annu Rev Psychol.* (2015) 66:295–319. doi: 10.1146/annurev-psych-010814-015156
61. Casey BJ, Heller AS, Gee DG, Cohen AO. Development of the emotional brain. *Neurosci Lett.* (2019) 693:29–34. doi: 10.1016/j.neulet.2017.11.055
62. Mather M. The affective neuroscience of aging. *Annu Rev Psychol.* (2016) 67:213–38. doi: 10.1146/annurev-psych-122414-033540
63. Martin RE, Ochsner KN. The neuroscience of emotion regulation development:Implications for education. *Curr Opin Behav Sci.* (2017) 10:142–8. doi: 10.1016/j.cobeha.2016.06.006
64. Dale A, Lafrenière A, Koninck J De. Dream content of Canadian males from adolescence to old age:An exploration of ontogenetic patterns. *Conscious Cogn.* (2017) 49:145–56. doi: 10.16/j.concog.2017.01.008
65. Dale A, Lortie-Lussier M, Koninck J De. Ontogenetic patterns in the dreams of women across the lifespan. *Conscious Cogn.* (2015) 37:214–24. doi: 10.16/j.concog.2015.09.008
66. Dale A, Lortie-Lussier M, Wong C, De Koninck J. Dreams of Canadian students:Norms, gender differences, and comparison with American norms. *J Cross Cult Psychol.* (2016) 47:941–55. doi: 10.1177/0022022116655788
67. Hall CS, Van De Castle RL. *The Content Analysis Of Dreams*. New York: Appleton-Century-Crofts. (1966).
68. Revonsuo A, Valli K. Dreaming and consciousness: Testing the threat simulation theory of the function of dreaming. *Psyche*. (2000) 6:8.
69. Dale A, Murkar A, Miller N, Black J. Comparing the effects of real versus simulated violence on dream imagery. *Cyberpsychol Behav Soc Netw*. (2014) 17:536–41. doi: 10.1089/cyber.2013.0494
70. Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods.* (2007) 39:175–91. doi: 10.3758/BF03193146
71. Blanca MJ, Alarcon R, Arnau J, Bono R, Bendayan R. Non-normal data: is ANOVA still a valid option? *Psicotherma.* (2017) 29:552–7. doi: 10.7334/psicothema2016.383
72. Kirk RE. *Experimental Design: Procedures for the Behavioral Sciences* 4th ed. Thousand Oaks: Sage Publications (2013). doi: 10.4135/9781483384733
73. Perlis ML, Nielsen TA. Mood regulation, dreaming and nightmares: evaluation of a desensitization function for REM sleep. *Dreaming.* (1993) 3:243–57. doi: 10.1037/h0094383
74. Menz MM, Rihm JS, Buchel C. REM sleep is causal to successful consolidation of dangerous and safety stimuli and reduces return of fear after extinction. *J Neurosci.* (2016) 36:2148–60. doi: 10.1523/JNEUROSCI.3083-15.2016
75. Malinowski JE, Horton CL. Emotion regulation in dreaming. In: Vall K, Hoss R, editiors. *Dreams: Understanding Biology, Psychology, and Culture*. Santa Barbara: ABC-CLIO (2019). p. 105–12.
76. Revonsuo A, Valli K. How to test the threat-simulation theory. *Conscious Cogn.* (2008) 17:1292–6. doi: 10.1016/j.concog.2008.01.007
77. Nielsen T. Variations in dream recall frequency and dream theme diversity by age and sex. *Front Neurol.* (2012) 3:106. doi: 10.3389/fneur.2012.00106
78. Mangiaruga A. Spotlight on dream recall : the ages of dreams. *Nat Sci Sleep.* (2018) 10:1. doi: 10.2147/NSS.S135762
79. Scarpelli S, Bartolacci C, D'Atri A, Gorgoni M, De Gennaro L. Mental sleep activity and disturbing dreams in the lifespan. *Int J Environ Res Public Health.* (2019) 16:3658. doi: 10.3390/ijerph16193658
80. Costa PT, Mccrae RR, Corinna EL. Personality across the life span. *Annu Rev Psychol.* (2019) 70:423–48. doi: 10.1146/annurev-psych-010418-103244

81. Amirkhan J, Auyeung B. Coping with stress across the lifespan: absolute vs. relative changes in strategy. *J Appl Dev*. (2007) 28:298–317. doi: 10.1016/j.appdev.2007.04.002
82. Isaacowitz DM, Livingstone KM, Castro VL. Aging and emotions:experience, regulation, and perception. *Curr Opin Psychol*. (2017) 17:79–83. doi: 10.1016/j.copsyc.2017.06.013
83. Nielsen T, Levin R. Nightmares: a new neurocognitive model. *Sleep Med*. (2007) 11:295–310. doi: 10.1016/j.smrv.2007.03.004
84. Schredl M, Goeritz AS. Nightmare frequency and nightmare distress: socio-demographic and personality factors. *Sleep Sci*. (2019) 12:178–84. doi: 10.5935/1984-0063.20190080
85. Schredl M, Goritz AS. Stability of nightmare frequency and its relation to neuroticism: a longitudinal study. *J Sleep Res*. (2020) 30:e13126. doi: 10.1111/jsr.13126
86. Samson-Daoust E, Julien SH, Beaulieu-Prévost D, Zadra A. Predicting the affective tone of everyday dreams: a prospective study of state and trait variables. *Sci Rep*. (2019) 9:14780. doi: 10.1038/s41598-019-50859-w
87. Schredl M, Reinhard I. Gender differences in nightmare frequency: a meta-analysis. *Sleep Med Rev*. (2011) 15:115–21. doi: 10.1016/j.smrv.2010.06.002
88. de Macêdo TCF, Ferreira GH, de Almondes KM, Kirov R, Mota-Rolim SA. My dream, my rules:can lucid dreaming treat nightmares? *Front Psych*. (2019) 10:2618. doi: 10.3389/fpsyg.2019.02618

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.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 31 March 2022
doi: 10.3389/fpsyt.2022.762719

Trajectories and Depressive Symptoms During the Perinatal Period: A Longitudinal Population-Based Study in China

Ciqing Bao[1], Dongzhen Jin[2], Shiyu Sun[3], Ling Xu[1], Chaoyue Wang[3], Weina Tang[4], Wenmiao Zhang[5], Yin Bao[5], Dongwu Xu[3], Siyao Zhou[3], Xin Yu[3]* and Ke Zhao[3]**

[1] Wenzhou Seventh People's Hospital, Wenzhou, China, [2] Department of Preventive Medicine, School of Public Health and Management, Wenzhou Medical University, Wenzhou, China, [3] School of Mental Health, Wenzhou Medical University, Wenzhou, China, [4] Shaoxing 7th People's Hospital, Shaoxing, China, [5] Department of Obstetrics, First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China

OPEN ACCESS

Edited by:
Heon-Jeong Lee,
Korea University, South Korea

Reviewed by:
Giulia Avvenuti,
IMT School for Advanced Studies Lucca, Italy
Ngan Yin Chan,
The Chinese University of Hong Kong, China

***Correspondence:**
Siyao Zhou
zsy950823@163.com
Xin Yu
yuxin@bjmu.edu.cn
Ke Zhao
cocozk1986@163.com

Specialty section:
This article was submitted to Sleep Disorders, a section of the journal Frontiers in Psychiatry

Received: 22 August 2021
Accepted: 02 February 2022
Published: 31 March 2022

Citation:
Bao C, Jin D, Sun S, Xu L, Wang C, Tang W, Zhang W, Bao Y, Xu D, Zhou S, Yu X and Zhao K (2022) Trajectories and Depressive Symptoms During the Perinatal Period: A Longitudinal Population-Based Study in China. Front. Psychiatry 13:762719. doi: 10.3389/fpsyt.2022.762719

Most women in the perinatal period face sleep issues, which can affect their mental health. Only a few studies have focused on sleep trajectories and depressive symptoms of women during the perinatal period in China. This study aims to explore the development trajectory of sleep quality by classifying pregnant women according to the changes in their sleep quality during pregnancy and postpartum and investigate the correlation between different sleep quality trajectory groups and depressive symptoms. The Pittsburgh Sleep Quality Index (PSQI) was used to assess the sleep quality, and the Edinburgh Postnatal Depression Scale (EPDS) was used to assess the symptoms of depression. Participants ($n = 412$) completed the assessment of sleep quality, depressive symptoms, and some sociodemographic and obstetric data at 36 weeks of gestation, 1 week after delivery, and 6 weeks after delivery. The group-based trajectory model (GBTM) was used to complete the trajectory classification, and logistic regression was used to analyze the predictive factors of postpartum depressive symptoms. Four different sleep quality trajectories were determined: "stable-good," "worsening," "improving," and "stable-poor" groups. The results demonstrate that poor sleep trajectories, social support and parenting experience during the perinatal period are related to postpartum depression. Screening for prenatal sleep problems is crucial for identifying the onset of perinatal depressive symptoms.

Keywords: depression, social support, perinatal, sleep quality trajectory, parenting experience

INTRODUCTION

Perinatal depression is characterized by the occurrence of depressive episodes during pregnancy and the perinatal period with its international prevalence rates ranging from 8 to 36% (1). This disorder is related to many adverse outcomes for women's maternal and physical health. It can interfere with normal maternal–infant relationships and may adversely affect child development (2). However, the specific cause of depression is yet to be determined, especially during the perinatal

period. Many risk factors, such as stressful life events in the past 12 months, lack of family support during pregnancy, and low socioeconomic status, among others affect the occurrence of perinatal depression (3, 4).

Countless changes are introduced during the perinatal period. An important but often overlooked change is the increased risk of sleep disorders. In total, 66–94% of pregnant women reported sleep disturbances, resulting mainly from significant changes in their physiology and psychology during pregnancy (5, 6). Most studies demonstrate that decline in sleep quality and night awakenings occur during the third trimester (7–9) and after delivery (10, 11). Sleep gradually worsens with the progression of pregnancy (11–13), usually lasting until the postpartum period and reaching its peak within 1 month after delivery (14). Previous studies show that sleep disturbance may be a risk factor for postpartum depression (13, 15). Dørheim et al. conducted a study on 2,816 women in the 32nd week of pregnancy and found that depressive symptoms were closely related to insomnia in the third trimester of pregnancy (16). Likewise, Skouteris et al. supports the view that sleep disturbance is related to an increase in depressive symptoms during pregnancy (17). Besides this, Park et al. also conducted objective and subjective assessments of sleep quality from the third trimester to the postpartum period. They used the General Sleep Disturbance Scale to evaluate subjective sleep quality and the Edinburgh Postnatal Depression Scale to evaluate depression and found that sleep quality was highly correlated with depressive symptoms (18). The hypothalamic–pituitary–adrenal (HPA) axis may explain the potential biological mechanism between sleep quality and depression. The HPA axis is a physiological system that can be activated by stress, which leads to the release of corticotropin (ACTH) from the pituitary gland and cortisol from the adrenal glands. In general, cortisol levels have a significant circadian rhythm in humans with higher levels in the morning and lower levels in the evening (19). People with poor sleep quality can activate the responsiveness of the HPA axis to physical and psychosocial stressors. The HPA axis is also related to depression (20). Researchers have found significantly increased plasma corticosterone levels in the classic depression model of rodents (21). Thus, an abnormal HPA axis may participate in the manifestation of sleep disturbance and depression. Moreover, psychosocial factors can also impart variability in this association between sleep disturbance and depression. The postpartum period is a special period for new mothers when they may not be able to adapt to the role change for a while. They may find it difficult to take care of the newborn. Difficult infant temperaments are recognized as important stressors for mothers throughout the postpartum period (22), and these can impair the sleep quality experienced by mothers. Mothers with insufficient sleep may feel more pessimistic, thus underestimating their social support status (23). Furthermore, sleep quality affects women's ability to cope with motherhood and future expectations, both practically and emotionally (24, 25). Goyal et al. found that prolonged nighttime wakefulness (>2 h) is associated with more severe depressive symptoms (26).

When investigating sleep quality in the perinatal period, many studies focus on changes in the average sleep quality over time in the perinatal period (27, 28), ignoring the fact that not all pregnant women experience the same pattern of sleep changes during the perinatal period. Although sleep disorders are correlated with the appearance of new depressive symptoms during pregnancy (17), it seems inappropriate to use a fixed sleep pattern to explain perinatal depression due to individual differences. Therefore, it is of great significance to study the sleep quality trajectory, which is used to distinguish different subgroups of sleep quality. Some previous studies explore the correlation between sleep quality trajectories and postpartum depression. Because of differences in grouping standards and statistical methods, the trajectories of sleep vary in different previous studies. For example, Tomfohr et al. chose four-time nodes to measure sleep quality and found that subgroups having a considerable decline in sleep quality from early to late pregnancy as well as poor sleep quality throughout pregnancy were more likely to experience depression in the postpartum period (29). This study ignores the time note of 6 weeks following delivery because it is a time when postpartum depression was of high incidence (30). Wang et al. chose more time nodes to evaluate sleep quality and found that poor sleep quality increased mood disorders at 36 months postpartum (31), but it ignored some psychosocial stressors. Because psychosocial stressors are risk factors that can affect sleep and perinatal depression, they should not be ignored when studying sleep quality trajectories and depressive symptoms.

In Asia, there are currently just a few studies on monitoring sleep trajectories during the perinatal period. Exploring sleep trajectories will help in better understanding the relationship between sleep and perinatal depression and provide timely and targeted interventions for more personalized treatment. Therefore, the objectives of this study are to (1) investigate the sleep trajectory of the Asian population during the perinatal period, (2) explore the differences in social and psychological factors among the trajectory groups, and (3) study the relationship between sleep trajectory and maternal depressive symptoms. Women with the greatest increase in sleep problems were assumed to be the most likely to experience high-level depressive symptoms during the postpartum period.

METHODS

This study is a longitudinal investigation of all pregnant women who underwent an obstetric examination and will give birth in the First Affiliated Hospital of Wenzhou Medical University. Participants will be enrolled in the third trimester of pregnancy, and the investigator will only further screen women for eligibility after obtaining oral consent. We employed a structured neuropsychiatric interview, the Mini International Neuropsychiatric Interview, to evaluate the presence of psychiatric disorders (32). The inclusion criteria are (1) 18–40 years old, (2) 28 weeks of pregnancy or more, (3) regular check-ups in the research hospital, (4) elementary school and higher education, (5) no sleep problems before pregnancy, and (6) voluntarily signed informed consent. Women with severe pregnancy complications or any mental/cognitive

problems, including pregnant women with a history of prenatal depression, other mental illnesses, and intellectual disability, that would prevent them from completing the survey were excluded from this study.

Procedure

The pregnant women who agreed to participate in the study underwent obstetric examination and data collection at three time points: T1 (gestational week 36), T2 (within 1 week postpartum) and T3 (6 weeks postpartum). Two psychiatrists trained three graduate students who major in psychiatry before the research. The graduate students were taught to fully comprehend the specific meaning of each item in each scale and know how to respond to the issues raised by participants and guide them in completing the whole experiment. Once the participant fills out the informed consent form, the researchers will help the participant complete the survey. This study was approved by the Ethics Committee of Wenzhou Medical University.

This study is part of a larger longitudinal study of maternal mental health being conducted at the First Affiliated Hospital of Wenzhou Medical University. From December 2017 to January 2019, a total of 988 people completed enrollment with 667 completing the first follow-up and 412 people completing the second follow-up, hence making the final sample of this study to 412 women. There was a 42% completion rate among the 988 initially enrolled participants.

Measures

Participants completed the Pittsburgh Sleep Quality Index (PSQI) and Edinburgh Postpartum Depression Scale (EPDS) at three time points (T1, T2, and T3). Furthermore, a self-edited demographic questionnaire survey was conducted at T1, and the Social Support Rating Scale (SSRS) and postpartum data update were completed at T2. The initial follow-up was conducted in the ward. The researchers contacted the participants before the second follow-up to confirm the review date, and the participants completed the second follow-up in the obstetric clinic.

Self-Edited Census Form

Under the supervision of a well-trained evaluator, pregnant women filled out a social demographic survey, including age, gestational age, BMI, years of education, race, place of residence, marital status, family monthly income, currently smoking and drinking, long-term exercise habits, and the number of existing children. In addition, following delivery, updated obstetric data, such as planned pregnancy, postpartum complications, delivery methods, etc., were also incorporated in the survey.

Evaluation of Sleep Quality

The PSQI (33) was used to evaluate the preceding month's sleep quality, and it has a maximum total score of 21 points. In total, 19 individual items generate seven component scores (range 0–3 with higher scores indicating worse sleep): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. This scale has good internal consistency, test–retest reliability, and validity (34). A score of >5 indicates clinically significant sleep disruption (35).

Evaluation of Depressive Symptoms

The EPDS (36) is a frequently used depression assessment scale in Western countries. It is believed to be effective during pregnancy and postpartum in multiple countries (37–40). The EPDS investigates 10 items: mood, pleasure, guilt, anxiety, fear, insomnia, ability to cope, sadness, crying, and self-injury. Each item is divided into 0–3 points in accordance with the severity of the relevant symptom, and the total score ranges from 0 to 30 points. The scale has good reliability and validity among populations in Mainland China (41). A total score of >9 was classified as depression in this experiment (42).

Social Support Assessment

The SSRS is used to evaluate the social support of pregnant women. The Chinese version of SSRS was first developed by Xiao in 1986 (43). It comprises objective support, subjective support, and availability. The total score ranges from 12 to 66 points. The higher the score, the higher the level of social support. The scale has been developed and widely used in China and has high reliability and validity.

Statistical Analysis

GBTM (44) was used to identify sleep quality trajectories from late pregnancy to 6 weeks postpartum. Such models use a semiparametric approach to identify a set of curves (the trajectories) that capture the main features of the data with each curve representing a different trajectory group. Unlike traditional growth curve models that assume a single average population growth trajectory, GBMT does not assume a unique potential growth trajectory and considers within-population heterogeneity. The polynomial equation modeling was used to model the relationship between time (perinatal) and outcome (sleep quality) to best define the trajectory. To obtain information that maximizes relevant heterogeneity while maintaining parsimony, the number of subgroups was selected by the following criteria: (1) the absolute value of Bayesian information criterion (BIC) was minimal, (2) the number of people in each group was not <5% of the sample, (3) it was clinically interpretable, and (4) the increased trajectory showed essential features in the data.

Continuous variables were expressed as mean ± standard deviation (SD), whereas categorical data were described by numbers (percentages). The normally distributed data were analyzed by one-way analysis of variance, whereas non-parametric data are analyzed by Kruskal–Wallis test statistics. Categorical data were evaluated by the chi-square test. Multiple comparisons among the four groups were performed after the significance test to better understand the difference between the baseline variables. After establishing the meaningfulness of the Kruskal–Wallis test, the least significant difference (LSD) method is used for pairwise comparison. After making corrections, the chi-square segmentation method is used for pairwise comparison after establishing the meaningfulness of the chi-square test. Finally, multivariate logistic regression was used to determine

TABLE 1 | Socio-demographics and clinical characteristics between the groups of responders and non-responders.

Variables	Responders (*N* = 412)	Non-responders (*N* = 576)	*P*
Age, years	28.5 (4.09)	29.1 (4.26)	0.021*
BMI, kg/m^2	25.3 (2.89)	25.3 (3.05)	0.763
Education, years	13.5 (2.59)	13.2 (2.97)	0.493
Gestational week	36.10 (34.50, 37.20)	36.00 (34.50, 37.10)	0.484
Currently married, %	409 (99.3)	565 (98.1)	0.121
Currently drinking, %	18 (4.4)	32 (5.6)	0.401
Currently smoking, %	3 (0.7)	12 (2.1)	0.086
Residence, %			0.108
Town	141 (34.2)	226 (39.2)	
Countryside	271 (65.8)	350 (60.8)	
Monthly household income, %			0.001**
<5,000 (RMB)	81 (19.7)	143 (24.8)	
5,000–10,000 (RMB)	201 (48.8)	213 (37.0)	
>10,000 (RMB)	130 (31.6)	220 (38.2)	
Long-term exercise habits			0.199
No	355 (86.2)	479 (83.2)	
Yes	57 (13.8)	97 (16.8)	
Have children			0.060
0	231 (56.1)	297 (51.6)	
1	171 (41.5)	213 (47.4)	
≥2	10 (2.4)	6 (1.0)	
EPDS (T1)	7.6 (3.74)	7.9 (3.96)	0.204
PSQI (T1)	6.4 (3.28)	6.6 (3.42)	0.222

EPDS, Edinburgh Postpartum Depression Scale; PSQI, Pittsburgh Sleep Quality Index.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.*

the independent effects of the sleep quality trajectory group on depression. All results were analyzed using IBM SPSS Statistics 22.0 and Stata 14.1, and $p < 0.05$ on both sides was considered statistically significant.

RESULTS

Characteristics of the Study Population

The study included 988 pregnant women, of whom 412 completed all assessments. Those who completed all assessments were regarded as responders ($n = 412$), and those who did not complete all assessments were regarded as non-responders ($n = 576$). **Table 1** shows that there is no significant difference in T1 sleep status and depression between pregnant women who withdrew from follow-up during the T2 and T3 time periods and those who completed all three evaluations (both *p*s > 0.05).

Identification of Perinatal Sleep Quality Trajectories

The main objective of the trajectory analysis model is to determine the appropriate number of subgroups and the shape of each subgroup. To determine the best one, the model was first determined based on only one trajectory. It was found that obtaining the trajectory twice was more appropriate (BIC = −3,258.14). Then, models of two (BIC = −3,163.27), three (BIC = −3,147.67), four (BIC = −3,144.12), and five trajectories (BIC = −3,139.26) were estimated. Although the BIC is the smallest in a model of five trajectories, one of the groups has nine people (2.18% < 5%). Finally, four groups are selected as the best fit model.

Characteristics of the Trajectory Groups

Figure 1 shows the identified four trajectories to reflect the changes in sleep quality. The first group is the "stable-good" group. The sleep quality of patients in this group fluctuates a little, and the PSQI scores are all below six points. The second group was defined as the "worsening" group. The PSQI value of women in this group continued to rise, reaching a peak at 6 weeks postpartum. The third group is the "improving" group. Women in this group suffer from poor sleep during the third trimester, which continues to deteriorate, but the score drops 1 week after delivery and is close to normal at 6 weeks after delivery. The fourth group is defined as the "stable-poor" group, and the PSQI score has always been at a high level.

Table 2 and **Supplementary Table 1** show the differences in baseline characteristics of the sleep trajectory groups. Other demographic data did not differ across sleep trajectory groups ($P > 0.05$) except for years of education ($P = 0.003$). After pairwise comparison and correction (LSD method), the number of years of education in the "stable-poor" group was lower than in the "stable-good" group ($P = 0.006$). Compared with the "stable-good" group, the EPDS scores of the other three trajectory groups were higher with statistically significant differences ($P < 0.001$), but there was no difference among the other three trajectory groups after pairwise comparison.

Table 3 shows the updated obstetric data following delivery. SSRS, EEPDS, planned pregnancy, delivery method, feeding method, and expectations of the baby's gender were statistically different among the four sleep trajectory groups (all $p < 0.05$). After pairwise comparison (**Supplementary Table 2**), the social support scores of the "improving" and the "stable-poor" groups were lower than that of the "stable-good" group ($p < 0.05$). The degree of compliance with the baby's gender expectations was lower in the "worsening" group ($p < 0.0071$). The incidence of cesarean section was higher in the "improving" group ($p < 0.0071$).

Predictors of Membership in Postpartum Depression

Finally, multivariate logistic regression was used to check whether sleep trajectories are associated with an increased risk of postpartum depression symptoms (**Table 4**). At the same time, variables including age, BMI, years of education, monthly family income, currently drinking, parenting experience, and social support (SSRS) that may cause postpartum depression were added into the model. The results show that the "stable-good" group was the reference group in the comparison of the sleep track group. Compared with the "stable-good" group, there was no significant difference in the "improving" group.

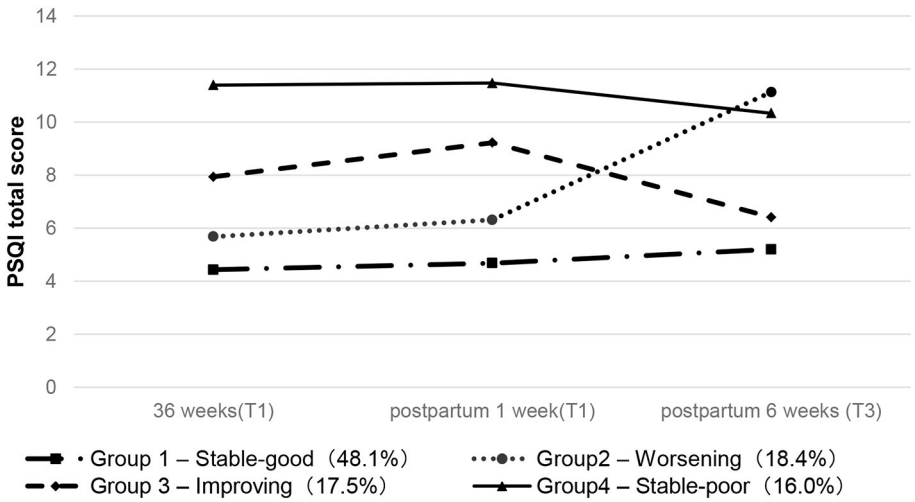

FIGURE 1 | Latent trajectories of four groups about sleep quality.

The "worsening" and "stable-poor" groups had higher incidence of postpartum depression symptoms (AOR is 2.56 and 3.57, respectively). For every one-point increase in the social support scale score, the probability of postpartum depression decreased by 12% ($P < 0.001$). Besides this, pregnant women with childcare experience had a lower risk of depression than those without childcare experience (AOR = 0.49).

DISCUSSION

This longitudinal study of sleep quality trajectory during the perinatal period among Chinese women demonstrated four distinct trajectories based on the GBTM. From the third trimester to 6 weeks postpartum, four different sleep trajectories were found: "stable-good" (group 1), "worsening" (group 2), "improving" (group 3), and "stable-poor" (group 4). Importantly, trajectories of sleep quality were also found to be associated with depressive symptoms. Even after controlling for relevant demographic factors and childbirth-related covariates, the track group with the worst sleep quality in the third trimester was most likely to have high-level depressive symptoms in the postpartum period. Besides this, the time points of detection we chose were reasonable, and this study highlights the role of social and psychological factors among different sleep quality trajectory groups on depressive symptoms in the postpartum period.

Most of the previous studies on sleep quality and perinatal depression are based on cross-sectional sleep quality to predict depression. However, this study found that the trajectory of perinatal sleep is not static, meaning that certain limitations are present in predicting postpartum depression based on sleep quality at a time point. A significant correlation was found between sleep trajectory groups (the "worsening" and "stable-poor" group) and postpartum depression in this study. It is believed that longitudinal sleep trajectories may be a better predictor of postpartum depression. Although there are relatively few studies on the perinatal sleep trajectory group, this study's findings are consistent with the previous ones (29, 31, 45–47). In the past, there was also some longitudinal evidence of an association between pregnant women's sleep quality during pregnancy and postpartum depression (48, 49), but there were fewer studies in the perinatal trajectory group and poor sleep quality/shortened sleep time/insomnia during the perinatal period. Women with poor sleep trajectories are more likely to suffer from depression (29, 31, 45, 50), and this is also reflected in the women with cesarean section (47).

At present, the relationship between sleep and perinatal depression is not very clear. As we all know, the perinatal period is a special stage marked by great physical and mental changes. Therefore, it is believed that the relationship between them may be attributed to a combination of social, psychological, and physiological factors. Most previous sociodemographic studies find that multiple factors, such as age, income, education, and social support, were involved in the relationship between sleep and postpartum depression (51). In addition, the related neurotransmitters (estrogen, progesterone) that regulate sleep quality were also involved in the regulation of emotions. Therefore, the sharp drop in estrogen and progesterone levels after childbirth aggravate sleep disturbances in women, leading to postpartum depression (52, 53). Sustained sleep time shortening/sleep deprivation in postpartum women was related to the increase of systemic inflammation. Severe systemic inflammation itself was associated with postpartum depression (54).

This study's results show that, except for years of education and prenatal EPDS scores, there were no significant differences among the sleep trajectory groups in other sociodemographic factors during the baseline period. The number of years of education in the "stable-good" group was found to be significantly higher than that of the "stable-poor" group. It is well-documented that people with low years of education have more frequent sleep problems (55, 56). The "stable-good" group were found to have the lowest depressive symptoms at baseline,

TABLE 2 | Differences in baseline characteristics among sleep trajectory groups.

Variable	Group 1 *N* = 198	Group 2 *N* = 76	Group 3 *N* = 72	Group 4 *N* = 66	*P*
Age, years	28.04 (3.96)	28.62 (3.99)	29.31 (4.13)	28.85 (4.46)	0.114
BMI, kg/m^2	24.96 (3.18)	25.49 (3.08)	25.60 (3.26)	25.09 (2.98)	0.738
Education, years	13.84 (2.50)	13.18 (2.46)	13.08 (3.21)	12.85 (2.45)	0.003**
Currently married, %	197 (99.5)	75 (98.7)	72 (100.0)	65 (98.5)	0.587
Currently drinking, %	6 (3.0)	2 (2.6)	4 (5.6)	6 (9.1)	0.160
Currently smoking, %	1 (0.5)	1 (1.3)	1 (1.4)	0 (0.0)	0.529
Residence, %					0.877
Town	66 (33.3)	27 (35.5)	23 (31.9)	25 (37.9)	
Countryside	132 (66.7)	49 (64.5)	49 (68.1)	41 (62.1)	
Monthly household income, %					0.426
<5,000 (RMB)	39 (19.7)	15 (19.7)	15 (20.8)	13 (19.7)	
5,000–10,000 (RMB)	97 (49.0)	42 (55.3)	36 (50.0)	25 (37.9)	
>10,000 (RMB)	62 (31.3)	19 (25.0)	21 (29.2)	28 (42.4)	
Long-term exercise habits					0.717
No	172 (86.9)	66 (86.8)	59 (81.9)	58 (87.9)	
Yes	26 (13.1)	10 (13.2)	13 (18.1)	8 (12.1)	
Have children now					0.739
0	109 (35.1)	45 (59.2)	45 (62.5)	31 (47.0)	
1	84 (42.4)	28 (36.8)	27 (37.5)	33 (50.0)	
≥2	5 (2.5)	3 (3.9)	1 (0.0)	2 (3.0)	
EPDS (T1)	6.22 (3.01)	7.84 (3.67)	9.07 (3.45)	9.85 (4.40)	<0.001***
PSQI (T1)	4.34 (1.79)	5.63 (1.90)	8.13 (1.92)	11.39 (2.76)	<0.001***

Group 1, the stable-good group; Group 2, the worsening group; Group 3, the improving group; Group 4, the stable-poor group. EPDS, Edinburgh Postpartum Depression Scale; PSQI, Pittsburgh Sleep Quality Index.
$^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

the "stable-poor" group had the highest level of depression, and the other two groups were in the middle. This result is consistent with previous results stating that the trajectory of poor sleep quality was associated with higher depressive symptoms at baseline (29, 31).

In terms of postpartum, there are also significant differences among the trajectory groups. Among them, the "stable-good" group has the best social support, whereas the "stable-poor" group has the worst social support, meaning that pregnant women with low social support are more likely to face sleep problems (29). At the same time, this research also concludes that social support is negatively correlated with postpartum depression, further confirming that social support may be a sociological factor related to perinatal sleep and postpartum depression. Compared with the "stable-good" group, the "worsening" group has lower expectations for the baby's gender. This trajectory group is one of the important factors for the continuous worsening of sleep of pregnant and lying-in women. Finally, the incidence of cesarean section in the "improving" group is higher, and it is believed that its possible mechanism is that there are more cesarean sections in this trajectory group within 1 week after delivery, and wound pain has a certain impact on sleep. As the wound improves, the impact of cesarean section decreases and sleep improves gradually. It is worth mentioning that there is a negative correlation between parenting experience and postpartum depression, which may be related to the important life event of childbirth. The transition from a woman to being a "mother" is a complex process that may lead to psychological disorders or psychopathological conditions, such as postpartum depression. Previous studies show that the risk of postpartum depression for primiparous women is greater than multiparas women (57, 58), which indicates that women with parenting experience may have a lower risk of postpartum depression than those without parenting experience. Providing parenting support for new mothers may help reduce their suffering, and some studies also support our view (59, 60). In the future, parenting-related education for primipara should be valued, which may reduce the incidence of postpartum depression.

This study has some limitations. First, it has a small sample size for all assessments and a higher rate of loss to follow-up. Second, the assessment of sleep quality comes from a subjective scale. Although PSQI is an effective measurement method, objective (such as activity recording) sleep measurement methods are more important. In addition, the measurement and evaluation points are too few, and future research should focus on the entire perinatal period and the period even before pregnancy. It should also be noted that significant differences are present between responders (completed three assessments) and non-responders. Respondents were younger and had a lower family monthly income ratio, but there was no statistically significant difference in the evaluation scores of prenatal sleep and childbirth

TABLE 3 | Comparison among the sleep trajectory groups after delivery.

Variable	Group 1 *N* = 198	Group 2 *N* = 76	Group 3 *N* = 72	Group 4 *N* = 66	*P*
EPDS (T2)	5.45 (2.85)	7.17 (3.49)	7.32 (3.43)	8.30 (4.55)	<0.001***
SSRS (T2)	30.52 (3.79)	29.00 (4.41)	28.38 (4.18)	28.02 (4.80)	<0.001***
Planned pregnancy					0.038*
Yes	133 (67.2)	40 (52.6)	37 (51.4)	42 (63.6)	
No	65 (32.8)	36 (47.4)	35 (48.6)	24 (36.4)	
Postpartum complications					0.489
No	184 (92.9)	71 (93.4)	63 (87.5)	60 (90.9)	
Yes	14 (7.1)	5 (6.6)	9 (12.5)	6 (9.1)	
Full-term birth					0.840
No	3 (1.5)	2 (2.6)	2 (2.8)	2 (3.0)	
Yes	195 (98.5)	74 (97.4)	70 (97.2)	64 (97.0)	
Delivery method					0.011*
Vaginal delivery	156 (78.8)	52 (68.4)	43 (59.7)	44 (66.7)	
Cesarean section	42 (21.2)	24 (31.6)	29 (40.3)	22 (33.3)	
Dystocia					0.597
No	192 (97.0)	73 (96.1)	68 (94.4)	65 (98.5)	
Yes	6 (3.0)	3 (3.9)	4 (5.6)	1 (01.5)	
Fetal sex habits					0.172
Boy	107 (54.0)	39 (51.3)	37 (52.1)	26 (39.4)	
Girl	91 (46.0)	36 (47.4)	34 (47.9)	40 (60.6)	
Boy and girl	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	
Gender expectations					0.020*
Satisfaction	187 (94.4)	63 (82.9)	63 (87.5)	57 (86.4)	
Dissatisfied	11 (5.6)	13 (17.1)	9 (12.5)	9 (13.6)	
Feeding method					0.823
Breastfeeding	184 (92.9)	72 (94.7)	66 (91.7)	60 (90.9)	
Non-breastfeeding	14 (7.1)	4 (5.3)	6 (8.3)	6 (9.1)	
Parenting experience					0.505
Yes	92 (46.5)	32 (42.1)	30 (41.7)	35 (53.0)	
No	106 (53.5)	44 (57.9)	42 (58.3)	31 (47.0)	

Group 1, the stable-good group; Group 2, the worsening group; Group 3, the improving group; Group 4, the stable-poor group; EPDS, Edinburgh Postpartum Depression Scale; SSRS, The Social Support Rating Scale.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.*

TABLE 4 | Multivariate logistic regression for risks of postpartum depression symptoms.

Variables	Unadjusted model		Adjusted model	
	OR (95%CI)	*P*-value	AOR (95%CI)	*P*-value
Group				
Stable-good	1 (Reference)		1 (Reference)	
Worsening	2.88 (1.40–5.95)	0.004**	2.56 (1.20–5.48)	0.015*
Improving	2.00 (0.91–4.39)	0.084	1.54 (0.67–3.54)	0.311
Stable-poor	4.35 (2.13–8.88)	<0.001***	3.57 (1.64–7.76)	0.001**
SSRS	0.86 (0.81–0.92)	<0.001***	0.88 (0.82–0.94)	<0.001***
Parenting experience				
No	1 (Reference)		1 (Reference)	
Yes	0.52 (0.30–0.91)	0.021*	0.49 (0.25–0.96)	0.038*

AOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio; SSRS, Social Support Rating Scale; Group, perinatal sleep quality trajectory groups.
Adjusted for age, BMI, education, currently drinking, Monthly household income, SSRS, parenting experience.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.*

depression symptoms between the two groups. Finally, future efforts will focus on expanding the sample size and reducing the loss to follow-up rate.

CONCLUSION

This study clarified the four trajectories of perinatal sleep and the correlation between sleep trajectories and postpartum depression. The results demonstrate that the "stable-poor" sleep trajectory group had a higher incidence of postpartum depression. Higher social support and parenting experience are protective factors for postpartum depression. As an extension of this research, it is possible to detect perinatal sleep disturbances as early as possible. In future studies, multiple sleep assessments during the perinatal period can be used as a screening and early intervention tool for stopping the occurrence of postpartum depression and adverse pregnancy outcomes.

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

AUTHOR CONTRIBUTIONS

KZ, XY, and SZ conceived and designed the study. CB developed it in discussion with SS, LX, WT, and CW. DJ, CW, WZ, YB, and DX were involved in the acquisition and analysis of the data. CB wrote the first draft of the article. All authors contributed to critically revising the paper, participated in the interpretation of the data, read, and approved the final manuscript.

FUNDING

This work was supported by the Zhejiang Provincial Natural Science Foundation (LY19H090015 and LY22H090022) and the Wenzhou Science and Technology Bureau project (Y20210763 and S20180012). The preparation of material scales is part of the fund's funding.

ACKNOWLEDGMENTS

We wish to thank all the participants and medical staff of the First Affiliated Hospital of Wenzhou Medical University who supported our research. We thank all of the volunteers for their study participation and the support of the First Affiliated Hospital of Wenzhou Medical University.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.762719/full#supplementary-material

REFERENCES

1. Virgara R, Maher C, Van Kessel G. The comorbidity of low back pelvic pain and risk of depression and anxiety in pregnancy in primiparous women. *BMC Pregnancy Childbirth.* (2018) 18:288. doi: 10.1186/s12884-018-1929-4
2. Okun ML. Disturbed sleep and postpartum depression. *Curr Psychiatry Rep.* (2016) 18:66. doi: 10.1007/s11920-016-0705-2
3. Brugha TS, Sharp HM, Cooper SA, Weisender C, Britto D, Shinkwin R, et al. The Leicester 500 Project. Social support and the development of postnatal depressive symptoms, a prospective cohort survey. *Psychol Med.* (1998) 28:63–79. doi: 10.1017/S0033291797005655
4. Milgrom J, Gemmill AW, Bilszta JL, Hayes B, Barnett B, Brooks J, et al. Antenatal risk factors for postnatal depression: a large prospective study. *J Affect Disord.* (2008) 108:147–57. doi: 10.1016/j.jad.2007.10.014
5. Schweiger MS. Sleep disturbance in pregnancy. A subjective survey. *Am J Obstet Gynecol.* (1972) 114:879–82. doi: 10.1016/0002-9378(72)90091-9
6. Suzuki S, Dennerstein L, Greenwood KM, Armstrong SM, Satohisa E. Sleeping patterns during pregnancy in Japanese women. *J Psychosom Obstet Gynaecol.* (1994) 15:19–26. doi: 10.3109/01674829409025625
7. Hedman C, Pohjasvaara T, Tolonen U, Suhonen-Malm AS, Myllyla VV. Effects of pregnancy on mothers' sleep. *Sleep Med.* (2002) 3:37–42. doi: 10.1016/S1389-9457(01)00130-7
8. Pien GW, Schwab RJ. Sleep disorders during pregnancy. *Sleep.* (2004) 27:1405–17. doi: 10.1093/sleep/27.7.1405
9. Hutchison BL, Stone PR, McCowan LM, Stewart AW, Thompson JM, Mitchell EA, et al. postal survey of maternal sleep in late pregnancy. *BMC Pregnancy Childbirth.* (2012) 12:144. doi: 10.1186/1471-2393-12-144
10. Baratte-Beebe KR, Lee K. Sources of midsleep awakenings in childbearing women. *Clin Nurs Res.* (1999) 8:386–97. doi: 10.1177/10547739922158377
11. Facco FL, Kramer J, Ho KH, Zee PC, Grobman WA. Sleep disturbances in pregnancy. *Obstet Gynecol.* (2010) 115:77–83. doi: 10.1097/AOG.0b013e3181c4f8ec
12. Driver HS, Shapiro CM, A. longitudinal study of sleep stages in young women during pregnancy and postpartum. *Sleep.* (1992) 15:449–53. doi: 10.1093/sleep/15.5.449
13. Coble PA, Reynolds CF III, Kupfer DJ, Houck PR, Day NL, Giles DE. Childbearing in women with and without a history of affective disorder II Electroencephalographic sleep. *Compr Psychiatry.* (1994) 35:215–24. doi: 10.1016/0010-440X(94)90194-5
14. Montgomery-Downs HE, Insana SP, Clegg-Kraynok MM, Mancini LM. Normative longitudinal maternal sleep: the first 4 postpartum months. *Am J Obstet Gynecol.* (2010) 203:465 e1–7. doi: 10.1016/j.ajog.2010.06.057
15. Bei B, Milgrom J, Ericksen J, Trinder J. Subjective perception of sleep, but not its objective quality, is associated with immediate postpartum mood disturbances in healthy women. *Sleep.* (2010) 33:531–8. doi: 10.1093/sleep/33.4.531
16. Dørheim SK, Bjorvatn B, Eberhard-Gran M. Insomnia and depressive symptoms in late pregnancy: a population-based study. *Behav Sleep Med.* (2012) 10:152–66. doi: 10.1080/15402002.2012.660588
17. Skouteris H, Wertheim EH, Germano C, Paxton SJ, Milgrom J. Assessing sleep during pregnancy: a study across two time points examining the Pittsburgh Sleep Quality Index and associations with depressive symptoms. *Womens Health Issues.* (2009) 19:45–51. doi: 10.1016/j.whi.2008.10.004

18. Park EM, Meltzer-Brody S, Stickgold R. Poor sleep maintenance and subjective sleep quality are associated with postpartum maternal depression symptom severity. *Arch Womens Mental Health.* (2013) 16:539–47. doi: 10.1007/s00737-013-0356-9
19. Nicolaides NC, Charmandari E, Chrousos GP, Kino T. Circadian endocrine rhythms: the hypothalamic-pituitary-adrenal axis and its actions. *Ann N Y Acad Sci.* (2014) 1318:71–80. doi: 10.1111/nyas.12464
20. Wohleb ES, Franklin T, Iwata M, Duman RS. Integrating neuroimmune systems in the neurobiology of depression. *Nat Rev Neurosci.* (2016) 17:497–511. doi: 10.1038/nrn.2016.69
21. Gong S, Miao YL, Jiao GZ, Sun MJ Li H, Lin J, et al. Dynamics and correlation of serum cortisol and corticosterone under different physiological or stressful conditions in mice. *PLoS ONE.* (2015) 10:e0117503. doi: 10.1371/journal.pone.0117503
22. Cutrona CE, Troutman BR. Social support, infant temperament, and parenting self-efficacy: a mediational model of postpartum depression. *Child Dev.* (1986) 57:1507–18. doi: 10.2307/1130428
23. Gan Y, Xiong R, Song J, Xiong X, Yu F, Gao W, et al. The effect of perceived social support during early pregnancy on depressive symptoms at 6 weeks postpartum: a prospective study. *BMC Psychiatry.* (2019) 19:232. doi: 10.1186/s12888-019-2188-2
24. Coo S, Milgrom J, Trinder J. Mood and objective and subjective measures of sleep during late pregnancy and the postpartum period. *Behav Sleep Med.* (2014) 12:317–30. doi: 10.1080/15402002.2013.801348
25. Posmontier B. Sleep quality in women with and without postpartum depression. *J Obstet Gynecol Neonatal Nurs.* (2008) 37:722–35; quiz 35-7. doi: 10.1111/j.1552-6909.2008.00298.x
26. Goyal D, Gay C, Lee K. Fragmented maternal sleep is more strongly correlated with depressive symptoms than infant temperament at three months postpartum. *Arch Womens Ment Health.* (2009) 12:229–37. doi: 10.1007/s00737-009-0070-9
27. Kang MJ, Matsumoto K, Shinkoda H, Mishima M, Seo YJ. Longitudinal study for sleep-wake behaviours of mothers from pre-partum to post-partum using actigraph and sleep logs. *Psychiatry Clin Neurosci.* (2002) 56:251–2. doi: 10.1046/j.1440-1819.2002.00992.x
28. Signal TL, Gander PH, Sangalli MR, Travier N, Firestone RT, Tuohy JF. Sleep duration and quality in healthy nulliparous and multiparous women across pregnancy and post-partum. *Aust N Z J Obstet Gynaecol.* (2007) 47:16–22. doi: 10.1111/j.1479-828X.2006.00672.x
29. Tomfohr LM, Buliga E, Letourneau NL, Campbell TS, Giesbrecht GF. Trajectories of sleep quality and associations with mood during the perinatal period. *Sleep.* (2015) 38:1237–45. doi: 10.5665/sleep.4900
30. Desai ND, Mehta RY, Jaishree G. Study of prevalence and risk factors of postpartum depression. *Natl J Med Res.* (2012) 29:198–202. doi: 10.5001/omj.2014.49
31. Wang G, Deng Y, Jiang Y, Lin Q, Dong S, Song Y, et al. Trajectories of sleep quality from late pregnancy to 36 months postpartum and association with maternal mood disturbances: a longitudinal and prospective cohort study. *Sleep.* (2018) 41:zsy179. doi: 10.1093/sleep/zsy179
32. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry.* (1998) 59 (Suppl. 20):22–33;quiz 4-57.
33. Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* (1989) 28:193–213. doi: 10.1016/0165-1781(89)90047-4
34. Tsai PS, Wang SY, Wang MY, Su CT, Yang TT, Huang CJ, et al. Psychometric evaluation of the Chinese version of the Pittsburgh Sleep Quality Index (CPSQI) in primary insomnia and control subjects. *Qual Life Res.* (2005) 14:1943–52. 16155782. doi: 10.1007/s11136-005-4346-x
35. Dietch JR, Taylor DJ, Sethi K, Kelly K, Bramoweth AD, Roane BM. Psychometric evaluation of the PSQI in US college students. *J Clin Sleep Med.* (2016) 12:1121–9. doi: 10.5664/jcsm.6050
36. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. *Br J Psychiatry.* (1987) 150:782–6. doi: 10.1192/bjp.150.6.782
37. Joshi U, Lyngdoh T, Shidhaye R. Validation of hindi version of Edinburgh postnatal depression scale as a screening tool for antenatal depression. *Asian J Psychiatr.* (2020) 48:101919. doi: 10.1016/j.ajp.2019.101919
38. Kozinszky Z, Dudas RB. Validation studies of the Edinburgh Postnatal Depression Scale for the antenatal period. *J Affect Disord.* (2015) 176:95–105. doi: 10.1016/j.jad.2015.01.044
39. Stewart RC, Umar E, Tomenson B, Creed F. Validation of screening tools for antenatal depression in Malawi–a comparison of the Edinburgh Postnatal Depression Scale and Self Reporting Questionnaire. *J Affect Disord.* (2013) 150:1041–7. doi: 10.1016/j.jad.2013.05.036
40. Zhao Y, Kane I, Wang J, Shen B, Luo J, Shi S. Combined use of the postpartum depression screening scale (PDSS) and Edinburgh postnatal depression scale (EPDS) to identify antenatal depression among Chinese pregnant women with obstetric complications. *Psychiatry Res.* (2015) 226:113–9. doi: 10.1016/j.psychres.2014.12.016
41. Wang Y, Guo X, Lau Y, Chan KS, Yin L, Chen J. Psychometric evaluation of the Mainland Chinese version of the Edinburgh Postnatal Depression Scale. *Int J Nurs Stud.* (2009) 46:813–23. doi: 10.1016/j.ijnurstu.2009.01.010
42. Gaynes BN, Gavin N, Meltzer-Brody S, Lohr KN, Swinson T, Gartlehner G, et al. Perinatal depression: prevalence, screening accuracy, and screening outcomes. *Evid Rep Technol Assess.* (2005) 119:1–8. doi: 10.1037/e439372005-001
43. Xiao. Theoretical foundation and research application about the social support rating scale. *J Clin Psychiatry.* (1994) 4:98–100.
44. Nagin DS. Group-based trajectory modeling: an overview. *Ann Nutr Metab.* (2014) 65:205–10. doi: 10.1159/000360229
45. Plancoulaine S, Flori S, Bat-Pitault F, Patural H, Lin JS, Franco P. Sleep Trajectories among pregnant women and the impact on outcomes: a population-based cohort study. *Matern Child Health J.* (2017) 21:1139–46. doi: 10.1007/s10995-016-2212-9
46. Sivertsen B, Hysing M, Dorheim SK, Eberhard-Gran M. Trajectories of maternal sleep problems before and after childbirth: a longitudinal population-based study. *BMC Pregnancy Childbirth.* (2015) 15:129. doi: 10.1186/s12884-015-0577-1
47. Tzeng YL, Chen SL, Chen CF, Wang FC, Kuo SY. Sleep trajectories of women undergoing elective cesarean section: effects on body weight and psychological well-being. *PLoS ONE.* (2015) 10:e0129094. doi: 10.1371/journal.pone.0129094
48. Tham EK, Tan J, Chong YS, Kwek K, Saw SM, Teoh OH, et al. Associations between poor subjective prenatal sleep quality and postnatal depression and anxiety symptoms. *J Affect Disord.* (2016) 202:91–4. doi: 10.1016/j.jad.2016.05.028
49. Dorheim SK, Bjorvatn B, Eberhard-Gran M. Can insomnia in pregnancy predict postpartum depression? A longitudinal, population-based study. *PLoS ONE.* (2014) 9:e94674. doi: 10.1371/journal.pone.0094674
50. Sedov ID, Tomfohr-Madsen LM. Trajectories of insomnia symptoms and associations with mood and anxiety from early pregnancy to the postpartum. *Behav Sleep Med.* (2021) 19:395–406. doi: 10.1080/15402002.2020.1771339
51. Okun ML. Sleep and postpartum depression. *Curr Opin Psychiatry.* (2015) 28:490–6. doi: 10.1097/YCO.0000000000000206
52. Ross LE, Murray BJ, Steiner M. Sleep and perinatal mood disorders: a critical review. *J Psychiatry Neurosci.* (2005) 30:247–56.
53. Ross LE, Sellers EM, Gilbert Evans SE, Romach MK. Mood changes during pregnancy and the postpartum period: development of a biopsychosocial model. *Acta Psychiatr Scand.* (2004) 109:457–66. doi: 10.1111/j.1600-0047.2004.00296.x
54. Paul S, Corwin EJ. Identifying clusters from multidimensional symptom trajectories in postpartum women. *Res Nurs Health.* (2019) 42:119–27. doi: 10.1002/nur.21935
55. Grandner MA, Patel NP, Gehrman PR, Xie D, Sha D, Weaver T, et al. Who gets the best sleep? Ethnic and socioeconomic factors related to sleep complaints. *Sleep Med.* (2010) 11:470–8. doi: 10.1016/j.sleep.2009.10.006
56. Lallukka T, Sares-Jaske L, Kronholm E, Saaksjarvi K, Lundqvist A, Partonen T, et al. Sociodemographic and socioeconomic differences in sleep duration and insomnia-related symptoms in Finnish adults. *BMC Public Health.* (2012) 12:565. doi: 10.1186/1471-2458-12-565

57. Gillespie SL, Mitchell AM, Kowalsky JM, Christian LM. Maternal parity and perinatal cortisol adaptation: the role of pregnancy-specific distress and implications for postpartum mood. *Psychoneuroendocrinology*. (2018) 97:86–93. doi: 10.1016/j.psyneuen.2018.07.008
58. Nakamura Y, Okada T, Morikawa M, Yamauchi A, Sato M, Ando M, et al. Perinatal depression and anxiety of primipara is higher than that of multipara in Japanese women. *Sci Rep*. (2020) 10:17060. doi: 10.1038/s41598-020-74088-8
59. Shimpuku Y, Iida M, Hirose N, Tada K, Tsuji T, Kubota A, et al. Prenatal education program decreases postpartum depression and increases maternal confidence: a longitudinal quasi-experimental study in urban Japan. *Women Birth*. (2021). doi: 10.1016/j.wombi.2021.11.004
60. Tsuchida A, Hamazaki K, Matsumura K, Miura K, Kasamatsu H, Inadera H. Changes in the association between postpartum depression and mother-infant bonding by parity: longitudinal results from the Japan Environment and Children's Study. *J Psychiatr Res*. (2019) 110:110–6. doi: 10.1016/j.jpsychires.2018.11.022

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

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Psychiatry

ORIGINAL RESEARCH
published: 29 April 2022
doi: 10.3389/fpsyt.2022.838825

Sleep Difficulties Among COVID-19 Frontline Healthcare Workers

*Rony Cleper[1], Nimrod Hertz-Palmor[2,3], Mariela Mosheva[1,2], Ilanit Hasson-Ohayon[4], Rachel Kaplan[2], Yitshak Kreiss[1,2], Arnon Afek[1,2], Itai M. Pessach[1,2], Doron Gothelf[1,2] and Raz Gross[1,2]**

[1] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, [2] The Chaim Sheba Medical Center, Ramat Gan, Israel, [3] School of Psychological Sciences, Tel Aviv University, Tel Aviv, Israel, [4] Department of Psychology, Bar-Ilan University, Ramat Gan, Israel

Objective: To identify COVID-19 work-related stressors and experiences associated with sleep difficulties in HCW, and to assess the role of depression and traumatic stress in this association.

Methods: A cross-sectional study of HCW using self-report questionnaires, during the first peak of the pandemic in Israel (April 2020), conducted in a large tertiary medical center in Israel. Study population included 189 physicians and nurses working in designated COVID-19 wards and a comparison group of 643 HCW. Mean age of the total sample was 41.7 ± 11.1, 67% were female, 42.1% physicians, with overall mean number of years of professional experience 14.2 ± 20. The exposure was working in COVID-19 wards and related specific stressors and negative experiences. Primary outcome measurement was the Insomnia Severity Index (ISI). Secondary outcomes included the Primary Care-Post Traumatic Stress Disorder Screen (PC-PTSD-5); the Patient Health Questionnaire-9 (PHQ-9) for depression; the anxiety module of the Patient-Reported Outcomes Measurement Information System (PROMIS); Pandemic-Related Stress Factors (PRSF) and witnessing patient suffering and death.

Results: Compared with non-COVID-19 HCW, COVID-19 HCW were more likely to be male (41.3% vs. 30.7%) and younger (36.91 ± 8.81 vs. 43.14 ± 11.35 years). COVID-19 HCW reported higher prevalence of sleep difficulties: 63% vs. 50.7% in the non-COVID group (OR 1.62, 95% CI 1.15–2.29, $p = 0.006$), mostly difficulty maintaining sleep: 26.5% vs. 18.5% (OR 1.65, 95% CI 1.11–2.44, $p = 0.012$). Negative COVID-19 work-related experiences, specifically witnessing patient physical suffering and death, partially explained the association. Although past psychological problems and current depression and PTSD were associated with difficulty maintaining sleep, the main association remained robust also after controlling for those conditions in the full model.

Conclusion and Relevance: COVID-19 frontline HCW were more likely to report sleep difficulties, mainly difficulty maintaining sleep, as compared with non-COVID-19 HCW working at the same hospital. Negative patient-care related experiences likely mediated the increased probability for those difficulties. Future research is needed to elucidate the long-term trajectories of sleep difficulties among HCW during large scale outbreaks, and to identify risk factors for their persistence.

Keywords: sleep, sleep difficulties, COVID-19, health care workers (HCW), COVID-19 outbreak, sleep disorders, health care staff, stress

OPEN ACCESS

Edited by:
Heon-Jeong Lee, Korea University, South Korea

Reviewed by:
Francesco Chirico, Catholic University of the Sacred Heart, Rome, Italy
Athanasia Pataka, Aristotle University of Thessaloniki, Greece

****Correspondence:***
Raz Gross
Raz.Gross@sheba.health.gov.il

Specialty section:
This article was submitted to Sleep Disorders, a section of the journal Frontiers in Psychiatry

Received: *18 December 2021*
Accepted: *28 March 2022*
Published: *29 April 2022*

Citation:
Cleper R, Hertz-Palmor N, Mosheva M, Hasson-Ohayon I, Kaplan R, Kreiss Y, Afek A, Pessach IM, Gothelf D and Gross R (2022) Sleep Difficulties Among COVID-19 Frontline Healthcare Workers. Front. Psychiatry 13:838825. doi: 10.3389/fpsyt.2022.838825

INTRODUCTION

The COVID-19 pandemic continues to challenge health care workers, as a new COVID variants keep emerging. Working at the frontline of this global pandemic is highly stressful and can significantly impact various aspects of daily life, including sleep quality and quantity (1). Recently, studies from several countries have shown high prevalence of insomnia and of sleep difficulties among hospital medical staff involved in the pandemic, especially among female staff and those with psychological symptoms and with lower educational attainment (2–6).

The association between stressful workplace experiences and poor sleep quality, independent of home-related stress, was previously reported (7). Sleep difficulties were found to be associated with poorer cognitive performance (8, 9), increased numbers of occupational accidents and injuries (10, 11) and car crashes (12, 13). Impaired cognitive and motor skills were found among hospital residents, even with acute, short-standing sleep loss (14). Sleep deprivation was found to negatively impacts surgeons' technical skills, with obvious implications for patient safety (15), and in the longer term, it was associated with neurological dysfunction and even death (16). In addition, sleep deprivation was found to predict a wide variety of mental disorders (17), including increased risk for stress (18), depression (19), suicidality (20, 21), and also psychotic experiences (22). Furthermore, during stressful events, short sleep was associated with diminished coping with stress (23), increased susceptibility for posttraumatic stress disorder (PTSD) (24–27), as well as for anxiety and hypomania (28).

Although previous research on frontline COVID-19 health care workers (HCW) found high prevalence of sleep difficulties, detailed data on the nature of those difficulties and on associated risk factors are still limited. Furthermore, it is unclear whether sleep difficulties are an independent outcome among COVID-19 HCW or merely a manifestation of other mental health outcomes, such as depression and PTSD. We set to compare the frequency of sleep difficulties among COVID-19 and non-COVID-19 HCW during the first peak of the pandemic in Israel, to identify factors associated with those difficulties, and to investigate whether they occur independent of PTSD and depression. We aim to explore the association between factors related to work at COVID-19 wards and reported sleep difficulties. More specifically, we ask whether negative experiences that are more prevalent among COVID-19 HCW play a role as intermediates in that association.

MATERIALS AND METHODS

We conducted a single-center, cross-sectional study among physicians and nurses working at the Sheba Medical Center, a large tertiary medical center in central Israel. The study was conducted between April 19–23, 2020. During this period the total number of confirmed COVID-19 cases in Israel peaked from 13,319 (April 19) to 14,511 (April 23).

This study followed the standards and ethics of the American Association for Public Opinion Research reporting guidelines (29) and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines (30). The protocol was approved by the Institutional Review Board of the Sheba Medical Center. Participation in the study was solely voluntary. All participants signed an electronic consent form. The data collected did not include personal identifiers (e.g., name, home address, phone number or email).

Participants

As part of the preparation for the surge in COVID-19 confirmed cases in Israel, specialized COVID-19 care wards were set up and isolated from other care areas in the hospital. Designated teams were allocated for COVID-19 containment wards, as well as two intensive care units, a designated emergency department, five inpatient wards and a psychiatry ward were assembled for the expected COVID-19 patients, totaling almost 400 specialized beds. We aimed at oversampling HCW working in COVID-19 wards (31). A total of 189 HCW from designated COVID-19 departments and 643 non-designated COVID-19 ward HCW (comparison group) responded to the survey, a total of 828 HCW. Sample flow across COVID-19 and non-COVID-19 teams is presented in **Supplementary Figure 1**.

Study Measures

The participants completed a self-administered anonymous questionnaire digitally through a secured digital platform (Qualtrics). The questionnaire included information on current ward (COVID-19 containment wards or regular wards), sociodemographic characteristics, general and mental health items, and a question about having to go into quarantine (yes/no).

Sleep difficulties were measured with the validated Hebrew version of the Insomnia Severity Index (ISI) (32, 33). Response options of the ISI questions were collapsed into dichotomous values (yes/no) for each of the three ISI items.

The prevalence of having at least one form of sleep difficulty was significantly higher among COVID-19 vs. non-COVID-19 HCW (63% and 50.7%, respectively, $p = 0.004$). Specifically, COVID-19 HCW were more likely to experience difficulty maintaining sleep (26.5% and 18.5%, respectively, $p = 0.02$) as presented in **Figure 1**.

Traumatic stress during the past month was assessed with the validated Hebrew version of the Primary Care PTSD Screen for DSM-5 (PC-PTSD-5) (34). The PC-PTSD-5 has a score range of 0-5, and we set a cutoff of 3 to define traumatic stress symptoms (35). Participants were asked to respond about their traumatic symptoms specifically in relation to the COVID-19 pandemic.

Depression was assessed with the Hebrew version of the well-validated Patient Health Questionnaire-9 (PHQ-9) (36). The PHQ-9 has a score range of 0–27, and a score of $\geq$10 was used to identify probable depression in the current study (37).

Anxiety among HCW was assessed by means of the 8-item Hebrew version of the National institution of Mental Health (NIMH) Patient-Reported Outcomes Measurement Information System (PROMIS) anxiety module (38–41). PROMIS has an established coding system validated by the NIMH, with standardized "T" scores ranging between 36.3–82.7 ("PROMIS® Scoring Manuals.," n.d.). The cutoff point for probable anxiety

TABLE 1 | Sociodemographic and clinical characteristics of the sample.

Characteristic	Total sample (*n* = 828)	COVID-19 team (*n* = 189)	non-COVID-19 team (*n* = 639)	*P*-value†
Age, Mean (SD), y	41.7 (11.1)	36.9 (8.8)	43.1 (11.3)	<0.0001
	n(%)	n (%)	n (%)	
Sex, female	557 (67.0%)	111 (58.7%)	443 (69.3%)	0.006
Physician/nurse	349/479 (42.1/57.9)	73/116 (38.6/61.4)	276/363 (43.2/56.8)	0.264
Quarantined	139 (16.7)	41 (21.7)	78 (15.3)	0.038
Having medical conditions	225 (26.7)	47 (25.0)	178 (27.9)	0.439
Past psychological problems	297 (35.2)	82 (43.6)	215 (33.6)	0.012
Marital status				<0.0001
Single	157 (18.9)	59 (31.2)	98 (15.3)	
Married	584 (70.6)	114 (60.3)	470 (73.5)	
Divorced	61 (7.3)	11 (5.8)	50 (7.8)	
Other	26 (3.1)	5 (2.6)	21 (3.2)	
Living alone	122 (14.8)	44 (23.7)	78 (12.8)	<0.0001
Religion				<0.0001
Jewish	687 (82.7)	131 (69.7)	556 (86.5)	
Muslim	69 (8.3)	36 (19.1)	33 (5.1)	
Christian	6 (0.7)	2 (1.1)	4 (0.6)	
Atheist	56 (6.7)	17 (9.0)	39 (6.1)	
Other	13 (1.6)	2 (1.1)	11 (1.7)	
Professional experience, mean (SD), years	14.2 (20)	9.9 (9.4)	15.4 (12.3)	<0.0001
ISI items				
- Any sleep difficulties	445 (52.8)	119 (63.0)	326 (50.7)	0.004
-Difficulties falling asleep	280 (33.2)	73 (38.6)	207 (32.2)	0.11
-Maintaining sleep	169 (20.0)	50 (26.5)	119 (18.5)	0.02
-Early morning awakening	149 (17.7)	40 (21.2)	109 (17.0)	0.19
PC-PTSD-5, No. of symptoms, median (IQR)		1 (0–2)	0 (0–1)	
-0 symptoms	459 (55.4)	88 (46.6)	371 (57.7)	0.004
-1–2 symptoms	253 (30.5)	67 (35.5)	186 (28.9)	
-3–5 symptoms	115 (13.8)	32 (16.9)	83 (12.9)	
PHQ-9, mean (SD)		6.6 (4.9)	5.4 (5.0)	0.079
-PHQ-9 ≥10	169 (20.4)	47 (25.0)	113 (17.7)	0.025
PROMIS Anxiety, mean (SD)		58.2 (7.8)	57.9 (7.8)	0.427
-PROMIS ≥62.3	277 (33.4)	70 (37.0)	207 (32.2)	0.234
Pandemic-related stress factors (endorsing "often" or "always")				
Anxiety about being infected	165 (19.9)	34 (18.1)	131 (20.4)	0.350
Anxiety about infecting family	403 (48.6)	102 (53.9)	301 (47.1)	0.014
Lack of knowledge about infectiveness and virulence	149 (17.3)	37 (19.6)	112 (17.5)	0.700
Lack of knowledge about prevention and protection	120 (14.4)	28 (14.8)	92 (14.4)	0.126
Financial concerns	267 (32.2)	59 (31.7)	208 (32.6)	0.387
Negative experiences				
High exposure to physical suffering of patients (often\always)	637 (76.9)	154 (81.5)	483 (75.6)	0.004
High exposure to mental suffering of patients (often\always)	650 (78.5)	140 (74.9)	510 (80.0)	0.442
Negative self-perceived health (fair\poor)	79 (9.5)	17 (9.0)	62 (9.8)	0.191
Witnessing patient death	274 (33.0)	95 (50.2)	179 (24.7)	<0.001
-None	572 (69.0)	92 (48.7)	480 (74.7)	<0.001
-1	123 (14.8)	34 (18.0)	89 (13.8)	
-≥2	131 (15.8)	61 (32.2)	70 (10.9)	

COVID-19, coronavirus disease 2019; ISI, Insomnia Severity Index; PC-PTSD-5, Primary Care-Post Traumatic Stress Disorder Screen for DSM-5; PHQ-9, Patient Health Questionnaire-9; PROMIS, the anxiety module of the Patient-Reported Outcomes Measurement Information System.

†PC-PTSD-5, Pandemic-related stress factors and negative experiences were tested with Mann–Whitney U test for independent samples. PHQ-9 and PROMIS Anxiety were tested with ANCOVA adjusted for age, sex and physician\nurse. Above\below cutoff proportions of PHQ-9 and PROMIS Anxiety were tested with Z-test for 2-populations proportions.

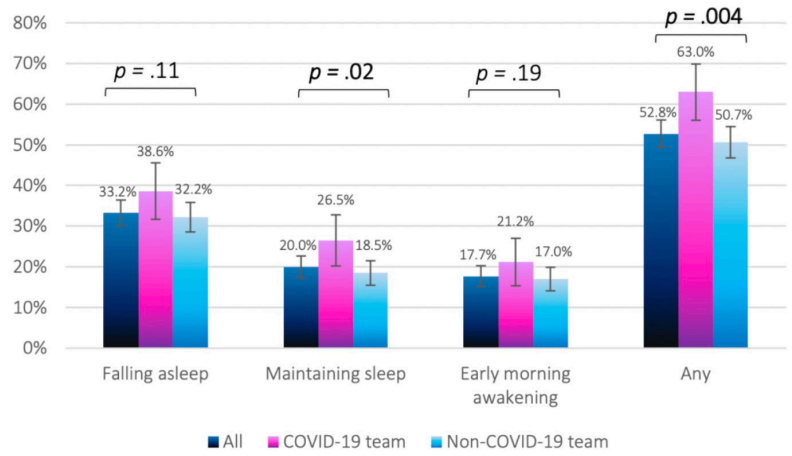

FIGURE 1 | Distribution of sleep difficulties by study group.

was set at T ≥62.3, considered as equivalent to the GAD-7 standard cutoff score for moderate anxiety (=10) (40).

Pandemic-related stress factors (PRSF) were measured with an inventory compiled from questions which were proved to be pertinent in research carried out during the SARS and N1H1 pandemics (42–44). A 4-point Likert-type scale was used for scoring the items (from 0 = never to 3 = always). Questions concerning negative experiences included exposure to patients' physical and mental suffering, the number of patient deaths witnessed over the past month (none, one, more than one) (45), and the self-perceived physical health question from the 12-item Medical Outcomes Study (MOS) Short-Form Health Status Survey (SF-12) (Hebrew version) (poor, fair, good, very good, excellent) (46).

Statistical Analysis

Descriptive statistics were used to describe the sample. We used chi-square tests to compare sociodemographic characteristics, sleep difficulties, prevalence of specific traumatic stress symptoms, probable depression (PHQ-9 score ≥10), probable PTSD (PC-PTSD-5 score ≥3) and probable anxiety (PROMIS score ≥62.3) between COVID-19 and non-COVID-19 HCW. *T*-tests were used to compare PHQ-9 and PROMIS anxiety module mean scores between study teams. We recoded ordinal variables with multiple categories (e.g., PRSF items, exposure to patient suffering) as categorical, with 1 and 0 representing high and low categories, respectively. Missing values in the PROMIS Anxiety module and the PHQ-9 questionnaire were imputed by the group mean score (47). Logistic regression was used to compare the likelihood of sleep difficulties among COVID-19 and non-COVID-19 wards. Multiple logistic models were used to assess potential mediators and confounders. Adjusted ORs and 95% *CIs* were computed, with non-COVID-19 team as the reference group.

Next, we conducted a three-step hierarchical logistic regression, to explore the role of potential confounders and mediators in the association between working at COVID-19 wards and sleep difficulties. Covariates were included based on the following criteria: (1) basic sociodemographic characteristics (age, sex, profession and professional experience); (2) theoretical and empirical framework developed based on research carried out during previous and current pandemics (witnessing patient suffering and death, and past psychological problems); and (3) variables that did not have considerable effect on the association between study group and sleep difficulties (PRSF and financial concerns) were not included in the hierarchical model. As model fitting *via* logistic regression is sensitive to collinearities among independent variables, we decontaminated the strongly correlated witnessing patient physical suffering and witnessing patient death variables from common variance by regressing them out of each other and including their standardized residuals in the final model (48). This method does not affect model's predictability, and therefore R2 remains unchanged compared with the non-residualized model but reduces multicollinearity and extracts the unique variance explained by each predictor, resulting in purified more powerful coefficients.

A three-step hierarchical logistic regression was used to test whether probable depression and PTSD, either alone or combined, accounted for the increased likelihood of sleep difficulties among COVID-19 HCW. Alpha was set at 0.05, and all tests were 2-tailed. Statistical analyses were conducted with IBM SPSS V25 software.

RESULTS

The analytic sample included a total of 828 HCW (42.1% physician, 57.9% nurses), of whom 189 worked in the COVID-19 wards (42.3% of total COVID-19 team members in the hospital) and 639 in the non-COVID-19 wards (20.1% of total non-COVID-19 teams). Detailed description of the study sample are reported elsewhere (49). The main characteristics and work-related experiences of the study groups are presented in **Table 1**.

COVID-19 HCW were more likely to experience any sleep difficulties (OR 1.62, 95% CI 1.15–2.29, p = 0.006). Difficulty

TABLE 2 | Crude and adjusted odds ratios for sleep difficulties among COVID-19 vs. non- COVID-19 teams.

		Difficulty falling asleep		Difficulty maintaining sleep		Early morning awakening		Any sleep difficulties	
		COVID 19 team	Non-COVID-19 team	COVID 19 team	Non-COVID-19 team	COVID 19 team	Non-COVID-19 team	COVID 19 team	Non-COVID-19 team
Unadjusted									
	OR (CI 95%)	1.35 (0.95–1.92)	1.00	1.65 (1.11–2.44)	1.00	1.28 (0.84–1.96)	1.00	1.62 (1.15–2.29)	1.00
	P	0.089		0.012		0.249		0.006	
Adjusted models									
Model 1	aOR (CI 95%)	1.17 (0.81–1.70)	1.00	1.56 (1.04–2.35)	1.00	1.20 (0.77–1.87)	1.00	1.52 (1.06–2.19)	1.00
	P	0.378		0.030		0.410		0.022	
Model 2	aOR (CI 95%)	1.16 (0.80–1.68)	1.00	1.59 (1.05–2.40)	1.00	1.25 (0.80–1.96)	1.00	1.56 (1.08–2.26)	1.00
	P	0.419		0.026		0.322		0.017	
Model 3	aOR (CI 95%)	1.21 (0.84–1.75)	1.00	1.59 (1.06–2.40)	1.00	1.21 (0.77–1.89)	1.00	1.58 (1.10–2.27)	1.00
	P	0.289		0.024		0.391		0.013	
Model 4	aOR (CI 95%)	1.17 (0.80–1.72)	1.00	1.46 (0.96–2.23)	1.00	1.16 (0.73–1.85)	1.00	1.54 (1.05–2.25)	1.00
	P	0.398		0.075		0.504		0.025	
Model 5	aOR (CI 95%)	1.15 (0.78–1.70)	1.00	1.49 (0.97–2.29)	1.00	1.21 (0.75–1.93)	1.00	1.56 (1.06–2.29)	1.00
	P	0.786		0.067		0.422		0.024	

Model 1: Adjusted for age, sex, profession and years in profession.
Model 2: Adjusted for age, sex, profession, years in profession and PRSF.*
Model 3: Adjusted for age, sex, profession, years in profession and financial concerns.
Model 4: Adjusted for age, sex, profession, years in profession and negative experiences.
Model 5: Adjusted for age, sex, profession, years in profession, PRSF, financial concerns and negative experiences.*
**PRSF items include: anxiety about being infected; anxiety about infecting family; lack of knowledge about infectiveness and virulence; lack of knowledge about prevention and protection.*
CI, confidence interval; OR, odds ratio; COVID-19, coronavirus disease 2019; aOR, adjusted odds ratio; PRSF, Pandemic-Related Stress Factors.

TABLE 3 | Factors associated with likelihood of difficulty maintaining sleep in COVID-19 and non-COVID-19 teams.

	Step I		Step II		Step III	
Variable	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
COVID-19 team	1.59 (1.06, 2.38)	**0.024**	1.43 (0.94, 2.19)	0.093	1.35 (0.89, 2.06)	0.162
Age (older)	0.86 (0.56, 1.31)	0.477	0.91 (0.59, 1.41)	0.678	0.89 (0.58, 1.39)	0.627
Sex (female)	0.93 (0.62, 1.39)	0.711	0.98 (0.65, 1.48)	0.925	0.91 (0.60, 1.39)	0.678
Physician/nurse (physician)	0.67 (0.45, 1.00)	**0.050**	0.69 (0.46, 1.03)	0.066	0.66 (0.44, 0.99)	**0.049**
Professional experience (longer)	0.89 (0.58, 1.36)	0.578	0.95 (0.62, 1.46)	0.824	0.96 (0.62, 1.48)	0.841
Witnessing patient physical suffering	–		1.40 (1.15, 1.71)	**0.001**	1.37 (1.12, 1.67)	**0.002**
Witnessing patient death	–		1.24 (1.04, 1.48)	**0.017**	1.23 (1.03, 1.47)	**0.022**
Past psychological problems	–		–	–	1.68 (1.17, 2.43)	**0.005**

Non-COVID-19 is the reference group (OR = 1.00).
Age and professional experience were computed as standardized residualized from each other, due to co-linearity.
CI, confidence interval; COVID-19, coronavirus disease 2019; OR, odds ratio.
The bold figures are highlighted for significant p-values (< 0.05).

maintaining sleep emerged as the strongest and most significant finding (OR 1.65, 95% CI 1.11–2.44, p = 0.012). These associations persisted in the multivariate models that adjusted for age, sex, and profession (model 1), and for PRSF items (anxiety about being infected, anxiety about infecting family, lack of knowledge about infectiveness and virulence, and lack of knowledge about prevention and protection) (model 2). The effect of financial concerns on the associations was negligible. The association between working in COVID-19 wards and difficulty maintaining sleep was attenuated when negative experiences were added to the model as shown in **Table 2**.

Next, we focused on exploring the association between difficulty maintaining sleep and variables selected according to the aforementioned criteria, using three-step hierarchical logistic

TABLE 4 | The association between difficulty maintaining sleep and PTSD and depression in COVID-19 and non-COVID- 19 healthcare workers.

	Difficulty maintaining sleep							
	Step I		Step IIa depression		Step IIb PTSD		Step III depression and PTSD	
Variable	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
COVID-19 team	1.57 (1.05, 2.36)	**0.027**	1.53 (1.01, 2.32)	0.044	1.61 (1.07, 2.43)	0.023	1.57 (1.03, 2.39)	**0.035**
Age (older)	0.86 (0.56, 1.32)	0.496	1.09 (0.70, 1.71)	0.700	1.02 (0.66, 1.58)	0.928	1.18 (0.75, 1.85)	0.480
Sex (female)	0.93 (0.62, 1.39)	0.726	0.87 (0.57, 1.31)	0.502	0.88 (0.58, 1.33)	0.556	0.85 (0.56, 1.30)	0.457
Physician/nurse (physician)	0.66 (0.44, 0.98)	**0.042**	0.73 (0.48, 1.11)	0.137	0.71 (0.47, 1.07)	0.099	0.75 (0.49, 1.13)	0.169
Professional experience (longer)	0.89 (0.58, 1.37)	0.606	1.10 (0.70, 1.71)	0.684	1.05 (0.68, 1.62)	0.833	1.17 (0.75, 1.84)	0.480
Depression	–	–	3.36 (2.23, 5.04)	**<0.001**	–	–	2.68 (1.72, 4.19)	**<0.001**
PTSD	–	–	–	–	3.12 (1.98, 4.91)	**<0.001**	2.03 (1.23, 3.35)	**0.006**

Non-COVID-19 is the reference group (OR = 1.00).
Age and professional experience were computed as standardized residualized from each other, due to collinearity.
CI, confidence interval; COVID-19, coronavirus disease 2019; OR, odds ratio.
The bold figures are highlighted for significant p-values (< 0.05).

regression model, presented in **Table 3**. We found that the main effect of work in COVID-19 ward on difficulty maintaining sleep was considerably attenuated after adjusting for witnessing patient physical suffering and death were added to the model. Adding self-reported past psychological problems to the model, which was found to be associated with difficulty maintaining sleep, further attenuated the association in the full model (OR 1.35, 95% CI 0.89–2.06, $p = 0.162$).

Lastly, although difficulty maintaining sleep was associated with both probable depression and PTSD (OR 3.36 and 3.12, respectively), those conditions did not account for the increased likelihood of difficulty maintaining sleep among COVID-19 HCW as shown in **Table 4**.

DISCUSSION

The main finding that emerged from our data was that COVID-19 HCW experienced higher prevalence of sleep difficulties, specifically difficulty maintaining sleep, compared with non-COVID-19 HCW in a large tertiary medical center in central Israel, during the first peak of COVID-19 pandemic. Although sleep difficulties among frontline HCW were previously reported in the current and previous pandemics (2, 3, 50–57), there are no published data on the role of mediating factors that might explain the association between work in COVID-19 wards and sleep difficulties.

We found that negative experiences, most notably witnessing physical suffering by the patient and patient death, accounted partially for the association between working in COVID-19 ward and difficulty maintaining sleep. The role of those two negative experiences as intermediates persisted also after adjusting for the potential confounding effect of past psychological problems. The mediation effect was unique for those negative experiences and was not found for other variables related to the pandemic, such as PRSF and financial concerns. It is plausible that witnessing patient suffering and death induced distressing dreams (nightmares), which interrupted REM sleep (58). Interestingly, the association between working in COVID-19 ward and difficulty maintaining sleep in our sample could not be attributed to current probable depression or PTSD, despite the fact that sleep difficulties are common symptoms in both disorders.

A plausible contributor to the increase in sleep difficulties among frontline HCW during the pandemic is workplace violence, shown in other studies to have increased during the pandemic (59–61).

The main strength of our study is that both study group and comparison group (COVID-19 team and non-COVID-19 team, respectably) were sampled from the same underlying cohort of physicians and nurses, sharing occupational, organizational and hospital leadership features. Additional strengths of our study include: (1) the 'real-time' nature of our data, as it were collected during the first peak of the pandemic in Israel, and not retrospectively, thus reducing the likelihood of recall bias; (2) availability of objective information on study group allocation; (3) study outcomes were measured by means of well-validated instruments; and (4) a very low proportion of missing data.

Our findings have several potential implications for the frontline workforce during a pandemic. First, screening for sleep difficulties among COVID-19 HCW, especially those exposed to negative experiences, could prompt targeted early intervention, especially in light of reported beneficial impact of fatigue training for improving personnel and patient safety, and reducing stress and burnout among HCW (62). Second, achieving trauma-induced sleep disorder normalization was shown to reduced risk of PTSD (63, 64), frequently reported among COVID-19 HCW (41, 65, 66). Additionally, integrating occupational mental health programs at healthcare settings, was shown to help alleviating pandemic-related sleep difficulties (67).

Limitations

Our study has several limitations. First, conclusion about directionality is limited by the cross-sectional study design. However, it is unlikely that assignment of HCW to COVID-19 wards was conditioned on history of sleep difficulties. Second, the higher prevalence of sleep difficulties among the COVID-19 HCW might be partially explained by the higher workload in COVID-19 wards, especially considering the reduced work volume in the non-COVID-19 wards during that time. Third, the

study was conducted in a single medical center in Israel during the first wave of the pandemic, and therefore the generalizability of our findings might be limited. Fourth, non-responders had slightly different sociodemographic characteristics. Fifth, data were collected by means of self-report questionnaires rather than clinical interviews.

CONCLUSION

We found that COVID-19 frontline HCW were more likely to report sleep difficulties, mainly difficulty maintaining sleep, as compared with HCW working in regular wards at the same hospital, and that negative patient-care related experiences likely mediated the increased likelihood for those difficulties. Future research is needed to elucidate the long-term trajectories of sleep difficulties among HCW caring for COVID-19 patients, and to identify antecedents and risk factors for persistence of those difficulties.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

RC, MM, RG, NH-P, DG, IP: conceiving and designing the study. MM, NH-P, and IP: data collection. NH-P: statistical analyses. RC, RG, NH-P, IH-O, RK, RC, YK, DG, and IP: data interpretation. RC and RG: writing the final manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

Supported by grants from Foundation Dora and the Binational Science Foundation (Grant No. 2017369).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.838825/full#supplementary-material

Supplementary Figure 1 | Flow diagram for study participants.

REFERENCES

1. Chirico F, Ferrari G, Nucera G, Szarpak Ł, Ilesanmi O. Prevalence of anxiety, depression, burnout syndrome, and mental health disorders among healthcare workers during the COVID-19 pandemic: a rapid umbrella review of systematic reviews. *J Health Soc Sci.* (2021) 6:209–20.
2. Zhang C, Yang L, Liu S, Ma S, Wang Y, Cai Z, et al. Survey of insomnia and related social psychological factors among medical staff involved in the 2019 novel coronavirus disease outbreak. *Front Psychiatry.* (2020) 11:306. doi: 10.3389/fpsyt.2020.00306
3. Wu K, Wei X. Analysis of psychological and sleep status and exercise rehabilitation of front-line clinical staff in the fight against COVID-19 in China. *Med Sci Monit Basic Res.* (2020) 26:e924085. doi: 10.12659/MSMBR.924085
4. Salari N, Khazaie H, Hosseinian-Far A, Ghasemi H, Mohammadi M, Shohaimi S, et al. The prevalence of sleep disturbances among physicians and nurses facing the COVID-19 patients: a systematic review and meta-analysis. *Global Health.* (2020) 16:92. doi: 10.1186/s12992-020-00620-0
5. Stewart NH, Koza A, Dhaon S, Shoushtari C, Martinez M, Arora VM. Sleep disturbances in frontline health care workers during the COVID-19 pandemic: social media survey study. *J Med Internet Res.* (2021) 23:e27331. doi: 10.2196/27331
6. Jahrami H, BaHammam AS, Bragazzi NL, Saif Z, Faris M, Vitiello MV. Sleep problems during the COVID-19 pandemic by population: a systematic review and meta-analysis. *J Clin Sleep Med.* (2021) 17:299–313. doi: 10.5664/jcsm.8930
7. Burgard SA, Ailshire JA. Putting work to bed: stressful experiences on the job and sleep quality. *J Health Soc Behav.* (2009) 50:476–92. doi: 10.1177/002214650905000407
8. Wardle-Pinkston S, Slavish DC, Taylor DJ. Insomnia and cognitive performance: a systematic review and meta-analysis. *Sleep Med Rev.* (2019) 48:101205. doi: 10.1016/j.smrv.2019.07.008
9. Lee H-J, Kim L, Suh K-Y. Cognitive deterioration and changes of P300 during total sleep deprivation. *Psychiatry Clin Neurosci.* (2003) 57:490–6. doi: 10.1046/j.1440-1819.2003.01153.x
10. Uehli K, Mehta AJ, Miedinger D, Hug K, Schindler C, Holsboer-Trachsler E, et al. Sleep problems and work injuries: a systematic review and meta-analysis. *Sleep Med Rev.* (2014) 18:61–73. doi: 10.1016/j.smrv.2013.01.004
11. Swanson LM, Arnedt JT, Rosekind MR, Belenky G, Balkin TJ, Drake C. Sleep disorders and work performance: findings from the 2008 National sleep foundation sleep in America poll. *J Sleep Res.* (2011) 20:487–94. doi: 10.1111/j.1365-2869.2010.00890.x
12. Terán-Santos J, Jiménez-Gómez A, Cordero-Guevara J. The association between sleep apnea and the risk of traffic accidents. cooperative group burgos-santander. *N Engl J Med.* (1999) 340:847–51. doi: 10.1056/NEJM199903183401104
13. Connor J, Whitlock G, Norton R, Jackson R. The role of driver sleepiness in car crashes: a systematic review of epidemiological studies. *Accid Anal Prev.* (2001) 33:31–41. doi: 10.1016/s0001-4575(00)00013-0
14. Mansukhani MP, Kolla BP, Surani S, Varon J, Ramar K. Sleep deprivation in resident physicians, work hour limitations, and related outcomes: a systematic review of the literature. *Postgrad Med.* (2012) 124:241–9. doi: 10.3810/pgm.2012.07.2583
15. Whelehan DF, McCarrick CA, Ridgway PF. A systematic review of sleep deprivation and technical skill in surgery. *Surgeon.* (2020) 18:375–84. doi: 10.1016/j.surge.2020.01.004
16. Lewis LD. The interconnected causes and consequences of sleep in the brain. *Science.* (2021) 374:564–8. doi: 10.1126/science.abi8375
17. Hertenstein E, Feige B, Gmeiner T, Kienzler C, Spiegelhalder K, Johann A, et al. Insomnia as a predictor of mental disorders: a systematic review and meta-analysis. *Sleep Med Rev.* (2019) 43:96–105. doi: 10.1016/j.smrv.2018.10.006
18. Grandner MA, Patel NP, Gehrman PR, Perlis ML, Pack AI. Problems associated with short sleep: bridging the gap between laboratory and epidemiological studies. *Sleep Med Rev.* (2010) 14:239–47. doi: 10.1016/j.smrv.2009.08.001
19. Zhai L, Zhang H, Zhang D. Sleep duration and depression among adults: a meta-analysis of prospective studies. *Depress Anxiety.* (2015) 32:664–70. doi: 10.1002/da.22386
20. Pigeon WR, Pinquart M, Conner K. Meta-analysis of sleep disturbance and suicidal thoughts and behaviors. *J Clin Psychiatry.* (2012) 73:e1160–7. doi: 10.4088/JCP.11r07586

21. Bernert RA, Kim JS, Iwata NG, Perlis ML. Sleep disturbances as an evidence-based suicide risk factor. *Curr Psychiatry Rep.* (2015) 17:554. doi: 10.1007/s11920-015-0554-4
22. Freeman D, Sheaves B, Goodwin GM, Yu LM, Nickless A, Harrison PJ, et al. The effects of improving sleep on mental health (OASIS): a randomised controlled trial with mediation analysis. *Lancet Psychiatry.* (2017) 4:749–58. doi: 10.1016/S2215-0366(17)30328-0
23. Sexton-Radek K. Stress triggers of long, short, and variable sleep patterns. *Percept Mot Skills.* (1998) 87:225–6. doi: 10.2466/pms.1998.87.1.225
24. Colvonen PJ, Straus LD, Acheson D, Gehrman P. A review of the relationship between emotional learning and memory, sleep, and PTSD. *Curr Psychiatry Rep.* (2019) 21:2. doi: 10.1007/s11920-019-0987-2
25. Thormar SB, Gersons BPR, Juen B, Djakababa MN, Karlsson T, Olff M. The impact of disaster work on community volunteers: The role of peri-traumatic distress, level of personal affectedness, sleep quality and resource loss, on post-traumatic stress disorder symptoms and subjective health. *J Anxiety Disord.* (2014) 28:971–7. doi: 10.1016/j.janxdis.2014.10.006
26. Gehrman P, Seelig AD, Jacobson IG, Boyko EJ, Hooper TI, Gackstetter GD, et al. Predeployment sleep duration and insomnia symptoms as risk factors for new-onset mental health disorders following military deployment. *Sleep.* (2013) 36:1009–18. doi: 10.5665/sleep.2798
27. Miller KE, Brownlow JA, Gehrman PR. Sleep in PTSD: treatment approaches and outcomes. *Curr Opin Psychol.* (2020) 34:12–7. doi: 10.1016/j.copsyc.2019.08.017
28. Monk TH, Buysse DJ, Welsh DK, Kennedy KS, Rose LR. A sleep diary and questionnaire study of naturally short sleepers. *J Sleep Res.* (2001) 10:173–9. doi: 10.1046/j.1365-2869.2001.00254.x
29. The American Association for Public Opinion Research[AAPOR]. *Standard Definitions: Final Dispositions of Case Codes and Outcome Rates for Surveys*. 9th ed. (2016).
30. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ.* (2007) 335:806–8.
31. Leshem E, Klein Y, Haviv Y, Berkenstadt H, Pessach IM. Enhancing intensive care capacity: COVID-19 experience from a tertiary center in Israel. *Intensive Care Med.* (2020) 46:1640–1. doi: 10.1007/s00134-020-06097-0
32. Bastien CH, Vallières A, Morin CM. Validation of the insomnia severity index as an outcome measure for insomnia research. *Sleep Med.* (2001) 2:297–307. doi: 10.1016/s1389-9457(00)00065-4
33. Morin CM, Belleville G, Bélanger L, Ivers H. The insomnia severity index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep.* (2011) 34:601–8. doi: 10.1093/sleep/34.5.601
34. Spoont MR, Williams JW, Kehle-Forbes S, Nieuwsma JA, Mann-Wrobel MC, Gross R. Does this patient have posttraumatic stress disorder?: rational clinical examination systematic review. *JAMA.* (2015) 314:501–10. doi: 10.1001/jama.2015.7877
35. Prins A, Bovin MJ, Smolenski DJ, Marx BP, Kimerling R, Jenkins-Guarnieri MA, et al. The primary care PTSD Screen for DSM-5 (PC-PTSD-5): development and evaluation within a veteran primary care sample. *J Gen Intern Med.* (2016) 31:1206–11. doi: 10.1007/s11606-016-3703-5
36. Geulayov G, Jungerman T, Moses S, Friedman N, Miron R, Gross R. Validation of the hebrew version of the PHQ-9, a screening instrument for depression in primary care. *Isr J Psychiatry.* (2009) 46:45.
37. Levis B, Benedetti A, Thombs BD. DEPRESsion screening data (DEPRESSD) collaboration. accuracy of patient health questionnaire-9 (PHQ-9) for screening to detect major depression: individual participant data meta-analysis. *BMJ.* (2019) 365:l1476. doi: 10.1136/bmj.l1476
38. Yardeni MAM, Abebe Campino G, Bursztyn B, Shamir A, Mekori-Domachevsky E, Toren A, et al. A three-tier process for screening depression and anxiety among children and adolescents with cancer. *Psychooncology.* (2020) 29:2019–27. doi: 10.1002/pon.5494
39. National Institutes of Health. *PROMIS: Dynamic Tools to Measure Health Outcomes from the Patient Perspective*. Maryland: National Institutes of Health (2017).
40. Bevans M, Ross A, Cella D. Patient-reported outcomes measurement information system (PROMIS): Efficient, standardized tools to measure self-reported health and quality of life. *Nurs Outlook.* (2014) 62:339–45. doi: 10.1016/j.outlook.2014.05.009
41. Mosheva M, Hertz-Palmor N, Dorman Ilan S, Matalon N, Pessach IM, Afek A, et al. Anxiety, pandemic-related stress and resilience among physicians during the COVID-19 pandemic. *Depress Anxiety.* (2020) 37:965–71. doi: 10.1002/da.23085
42. Leung GM, Lam TH, Ho LM, Ho SY, Chan BH, Wong IO, et al. The impact of community psychological responses on outbreak control for severe acute respiratory syndrome in Hong Kong. *J Epidemiol Community Health.* (2003) 57:857–63. doi: 10.1136/jech.57.11.857
43. Imai H, Matsuishi K, Ito A, Mouri K, Kitamura N, Akimoto K, et al. Factors associated with motivation and hesitation to work among health professionals during a public crisis: a cross sectional study of hospital workers in Japan during the pandemic (H1N1) 2009. *BMC Public Health.* (2010) 10:672. doi: 10.1186/1471-2458-10-672
44. Tan BYQ, Chew NWS, Lee GKH, Jing M, Goh Y, Yeo LLL, et al. Psychological impact of the COVID-19 pandemic on health care workers in Singapore. *Ann Intern Med* (2020) 173:317–20.
45. Laor-Maayany R, Goldzweig G, Hasson-Ohayon I, Bar-Sela G, Engler-Gross A, Braun M. Compassion fatigue among oncologists: the role of grief, sense of failure, and exposure to suffering and death. *Support Care Cancer.* (2020) 28:2025–31. doi: 10.1007/s00520-019-05009-3
46. Amir M, Lewin-Epstein N, Becker G, Buskila D. Psychometric properties of the SF-12 (Hebrew version) in a primary care population in Israel. *Med Care.* (2002) 40:918–28. doi: 10.1097/00005650-200210000-00009
47. Altman DG, Bland JM. Missing data. *BMJ.* (2007) 334:424.
48. Garson GD. *Multilevel Modeling: Applications in STATA®, IBM® SPSS®, SAS®, R, & HLMTM*. Thousand Oaks, CA: SAGE (2020).
49. Mosheva M, Gross R, Hertz-Palmor N, Hasson-Ohayon I, Kaplan R, Cleper R, et al. The association between witnessing patient death and mental health outcomes in frontline COVID-19 healthcare workers. *Depress Anxiety.* (2021) 38:468–79. doi: 10.1002/da.23140
50. Jahrami H, BaHammam AS, AlGahtani H, Ebrahim A, Faris M, AlEid K, et al. The examination of sleep quality for frontline healthcare workers during the outbreak of COVID-19. *Sleep Breath.* (2020): 25, 503–511. doi: 10.1007/s11325-020-02135-9
51. Qi J, Xu J, Li B-Z, Huang JS, Yang Y, Zhang ZT, et al. The evaluation of sleep disturbances for Chinese frontline medical workers under the outbreak of COVID-19. *Sleep Med.* (2020) 72:1–4. doi: 10.1016/j.sleep.2020.05.023
52. Wang S, Xie L, Xu Y, Yu S, Yao B, Xiang D. Sleep disturbances among medical workers during the outbreak of COVID-2019. *Occup Med.* (2020) 70:364–9. doi: 10.1093/occmed/kqaa074
53. Li X, Yu H, Bian G, Hu Z, Liu X, Zhou Q, et al. Prevalence, risk factors, and clinical correlates of insomnia in volunteer and at home medical staff during the COVID-19. *Brain Behav Immun.* (2020) 87:140–1. doi: 10.1016/j.bbi.2020.05.008
54. Lai J, Ma S, Wang Y, Cai Z, Hu J, Wei N, et al. Factors associated with mental health outcomes among health care workers exposed to coronavirus disease 2019. *JAMA Netw Open.* (2020) 3:e203976. doi: 10.1001/jamanetworkopen.2020.3976
55. Preti E, Di Mattei V, Perego G, Ferrari F, Mazzetti M, Taranto P, et al. The psychological impact of epidemic and pandemic outbreaks on healthcare workers: rapid review of the evidence. *Curr Psychiatry Rep.* (2020) 22:43. doi: 10.1007/s11920-020-01166-z
56. Shi L, Lu Z-A, Que J-Y, Huang XL, Liu L, Ran MS, et al. Prevalence of and risk factors associated with mental health symptoms among the general population in china during the coronavirus disease 2019 pandemic. *JAMA Netw Open.* (2020) 3:e2014053. doi: 10.1001/jamanetworkopen.2020.14053
57. Su T-P, Lien T-C, Yang C-Y, Su YL, Wang JH, Tsai SL, et al. Prevalence of psychiatric morbidity and psychological adaptation of the nurses in a structured SARS caring unit during outbreak: a prospective and periodic assessment study in Taiwan. *J Psychiatr Res.* (2007) 41:119–30. doi: 10.1016/j.jpsychires.2005.12.006
58. Tang W, Lu Y, Yang Y, Xu J. An epidemiologic study of self-reported sleep problems in a large sample of adolescent earthquake survivors: the effects of

age, gender, exposure, and psychopathology. *J Psychosom Res.* (2018) 113:22–9. doi: 10.1016/j.jpsychores.2018.07.006
59. Devi S. COVID-19 exacerbates violence against health workers. *Lancet.* (2020) 396:658. doi: 10.1016/S0140-6736(20)31858-4
60. Dye TD, Alcantara L, Siddiqi S, Barbosu M, Sharma S, Panko T, et al. Risk of COVID-19-related bullying, harassment and stigma among healthcare workers: an analytical cross-sectional global study. *BMJ Open.* (2020) 10:e046620. doi: 10.1136/bmjopen-2020-046620
61. Magnavita N, Di Stasio E, Capitanelli I, Lops EA, Chirico F, Garbarino S. Sleep problems and workplace violence: a systematic review and meta-analysis. *Front Neurosci.* (2019) 13:997. doi: 10.3389/fnins.2019.00997
62. Barger LK, Runyon MS, Renn ML, Moore CG, Weiss PM, Condle JP, et al. Effect of fatigue training on safety, fatigue, and sleep in emergency medical services personnel and other shift workers: a systematic review and meta-analysis. *Prehosp Emerg Care.* (2018) 22:58–68. doi: 10.1080/10903127.2017.1362087
63. Germain A, McKeon AB, Campbell RL. Sleep in PTSD: Conceptual model and novel directions in brain-based research and interventions. *Curr Opin Psychol.* (2017) 14:84–9. doi: 10.1016/j.copsyc.2016.12.004
64. Germain A. Sleep disturbances as the hallmark of PTSD: where are we now? *Am J Psychiatry.* (2013) 170:372–82. doi: 10.1176/appi.ajp.2012.12040432
65. Carmassi C, Foghi C, Dell'Oste V, Cordone A, Bertelloni CA, Bui E, et al. PTSD symptoms in healthcare workers facing the three coronavirus outbreaks: what can we expect after the COVID-19 pandemic. *Psychiatry Res.* (2020) 292:113312. doi: 10.1016/j.psychres.2020.113312
66. Johnson SU, Ebrahimi OV, Hoffart A. PTSD symptoms among health workers and public service providers during the COVID-19 outbreak. *PLoS One.* (2020) 15:e0241032. doi: 10.1371/journal.pone.0241032
67. Chirico F, Ferrari G. Role of the workplace in implementing mental health interventions for high-risk groups among the working age population after the COVID-19 pandemic. *J Health Soc Sci.* (2021) 6:145–50.

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

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Psychiatry

ORIGINAL RESEARCH
published: 30 May 2022
doi: 10.3389/fpsyt.2022.816893

Intranasal Dexmedetomidine for the Treatment of Pre-operative Anxiety and Insomnia: A Prospective, Randomized, Controlled, and Clinical Trial

Wen Zeng[1], *Li Chen*[2]*, *Xin Liu*[1], *Xujiang Deng*[1], *Kuan Huang*[2], *Maolin Zhong*[2], *Shubao Zhou*[2], *Lifang Zhan*[2], *Yulu Jiang*[3] *and Weidong Liang*[2]

[1] *The First School of Clinical Medicine, Gannan Medical University, Ganzhou, China,* [2] *Department of Anaesthesiology, First Affiliated Hospital of Gannan Medical University, Ganzhou, China,* [3] *Department of Obstetrics and Gynecology, Luhe Hospital, Yingkou, China*

OPEN ACCESS

Edited by:
Heon-Jeong Lee,
Korea University, South Korea

Reviewed by:
Egidio Barbi,
University of Trieste, Italy
Heguo He Luo,
Third Affiliated Hospital of Nanchang University, China

***Correspondence:**
Li Chen
zgx8778@163.com

Specialty section:
This article was submitted to Sleep Disorders, a section of the journal Frontiers in Psychiatry

Received: *17 November 2021*
Accepted: *21 April 2022*
Published: *30 May 2022*

Citation:
Zeng W, Chen L, Liu X, Deng X, Huang K, Zhong M, Zhou S, Zhan L, Jiang Y and Liang W (2022) Intranasal Dexmedetomidine for the Treatment of Pre-operative Anxiety and Insomnia: A Prospective, Randomized, Controlled, and Clinical Trial. Front. Psychiatry 13:816893. doi: 10.3389/fpsyt.2022.816893

Background and Objective: Several patients with pre-operative anxiety and insomnia refuse to take sleeping pills because of the side effects of sleeping pills. This study aimed to evaluate the applicability of intranasal dexmedetomidine (DEX) in the treatment of pre-operative anxiety and insomnia.

Methods: A total of 72 patients with insomnia and anxiety were randomly divided into two groups of intranasal DEX (n = 36) and intranasal normal saline (NS, n = 36). The primary outcomes included patients' time to fall asleep, total sleep time, insomnia severity index (ISI) after treatment, and satisfaction with the treatment effect. The secondary outcomes were mean arterial pressure (MAP), oxygen saturation (SPO_2), heart rate (HR), Narcotrend index (NI) in the first 2 h of treatment, and the incidence of adverse events within 12 h after treatment.

Results: The time to fall asleep (22.08 ± 3.95 min) and total sleep time (400.06 ± 28.84 min) in the DEX group were significantly different from those in the NS group [time to fall asleep, 89.31 ± 54.56 min; total sleep time (295.19 ± 73.51 min; $P < 0.001$)]. ISI after treatment in the DEX group was lower than that in the NS group ($P < 0.001$). Satisfaction with the treatment effect was better in the DEX group than that in the NS group ($P < 0.001$). The general vital signs in the two groups were stable during the treatment. The drowsiness rate in the NS group was higher than that in the DEX group ($P < 0.001$).

Conclusion: Intranasal DEX can significantly improve pre-operative anxiety and insomnia.

Clinical Trial Registration: This study was registered on Chinese Clinical Trial Registry (http://www.chictr.org.cn/searchproj.aspx, ChiCTR2100044747).

Keywords: intranasal dexmedetomidine, pre-operative anxiety and insomnia, Narcotrend index, insomnia severity index, dexmedetomidine

INTRODUCTION

Insomnia refers to a subjective experience of patients who are not satisfied with the time or quality of sleep, influencing their social functions. It is mainly characterized by dissatisfaction with sleep quantity or quality, associated with difficulty falling asleep, frequent nighttime awakenings with difficulty returning to sleep, and/or awakening earlier in the morning than desired (1–3). A recent study showed that the incidence of insomnia among the general population in China is 12.1–18.5% (4). Multiple factors are associated with sleep disorders in hospitalized patients, including ambient environmental noise, the underlying acute illness, pain, anxiety, depression, delirium, etc. (5). The incidence of pre-operative insomnia is 37–38.2% (6, 7). Such a high incidence requires clinicians' additional attention to provide more efficacious treatments for patients with insomnia.

A growing body of evidence demonstrated that there is an association between pre-operative insomnia and short-term and long-term adverse post-operative consequences. Insomnia can damage immune function (8), and it is related to a high blood pressure (BP) and other cardiovascular risk factors (9, 10), a poor blood sugar control (11, 12), cognitive impairment (13, 14), and mental health (15). In addition, pre-operative insomnia causes patients' poor medical experience, while increases the incidence of disease complications (16, 17).

Improving patients' pre-operative sleep quality may accompany by positive consequences and improve safety in the perioperative period. To date, benzodiazepine and non-benzodiazepine hypnotics were commonly used to improve patients' pre-operative sleep quality, which were mainly administered orally and intravenously. Oral administration of sleeping pills may improve short-term sleep outcomes in adults with insomnia, whereas sleeping pills may cause cognitive and behavioral abnormalities (18). Intravenous injection is often accompanied by pain, and the drug dose is difficult to titrate (19). Additionally, some patients were worried about the addiction and side effects of sleeping pills, and resisted taking sleeping pills may assist them to sleep easier. Different from other sedatives acting on GABA, dexmedetomidine (DEX) is a highly selective α2-adrenergic receptor (α2-AR) agonist that is associated with sedative and analgesic sparing effects, as well as reduced delirium and agitation. Intranasal DEX eliminates patients' need to an open vein on the night before surgery. DEX is absorbed by the central nervous system through the capillaries of the nasal cavity and promotion of endogenous sleep pathways, leading to produce sedative and hypnotic effects. Although no previous study has investigated the effectiveness of intranasal DEX for adult patients with insomnia, there is a report of a case of successful long-term home use of intranasal DEX for insomnia in pediatric palliative care of a 10-year-old women with dystrophic epidermolysis bullosa and severe sleep disorders, where treatment resulted in an increase in sleep duration from 2 to 3 consecutive hours to 6–8 consecutive hours (20). Studies suggested that DEX-induced deep sedation mimics stages 2 and 3 of non-rapid eye movement (NREM) sleep (21, 22). In particular, it does not cause respiratory depression (23).

Hence, the present study aimed to evaluate the feasibility of administration of intranasal DEX in the treatment of pre-operative anxiety and insomnia.

MATERIALS AND METHODS

Ethics Approval

The present study was approved by the Scientific Research Ethics Committee of the First Affiliated Hospital of Gannan Medical University (LLSC-2020102701), and registered on Chinese Clinical Trial Registry (ChiCTR2100044747). The study protocol was conducted in accordance with the Declaration of Helsinki. All participants were informed about the objectives of the study by investigators. All participants provided written informed consent before enrollment.

Participants

The research was conducted in the First Affiliated Hospital of Gannan Medical University (Ganzhou, China) between April and October 2021. The following inclusion criteria were used: 1. Patients with American Association of Anesthesiologists (ASA) grade I II; 2. Patients with Hamilton Anxiety Rating Scale (HAMA) score $\geq$ 7 points; 3. Patients with insomnia severity index (ISI) score $\leq$7 points (one week before hospitalization), and ISI >7 points (after hospitalization); 4. Patients with blood oxygen saturation > 95%; 5. Patients who aged 18-60 years old, regardless of gender; 6. Patients with body mass index (BMI) <30 kg/m^2; 7. Patients who participated in completing the questionnaire; 8. Patients with insomnia and were unwilling to use benzodiazepines.

The exclusion criteria were as follows: 1. Patients who were diagnosed or suspected of having sleep apnea syndrome; 2. Patients with alcohol or drug addiction; 3. Patients who have used antidepressants or psychiatric drugs 1 week before enrollment; 4. Patients who were allergic to DEX or other drugs used in this study; 5. Patients with abnormal liver or kidney function; 6. Pregnant or breastfeeding women.

Assessment of Insomnia and Anxiety

Insomnia is defined as chronic dissatisfaction with sleep quantity or quality. Therefore, self-assessment of insomnia severity is important for more effective treatment of insomnia. In insomnia studies, the ISI and the Pittsburgh Sleep Quality Index (PSQI) are recommended measures for overall sleep and insomnia symptoms (24). The majority of ISI-related studies concentrated directly on patients' subjective feelings in association with insomnia symptoms. The PSQI was originally designed to assess general sleep quality over a period of 1 month (25). The Chinese version of ISI successfully distinguished insomnia patients from healthy participants with sensitivity and specificity >0.9 (26). A study conducted in Canada, Hong Kong, and Taiwan further supported the structural validity and cross-cultural comparability of ISI (27). Chen et al. (26) evaluated whether ISI and PSQI were effective outcome indicators of cognitive behavioral therapy for insomnia, suggesting that ISI might be a more reliable scoring scale. Therefore, ISI was used to evaluate the severity of insomnia in the present study. There were 7 items, and each item scored

0–4 points, with a total score of 28 points. A score of more than 8 points was considered as a sleep disorder.

The HAMA includes 14 interview items, with a 5-point scale ranging from 0 (non-existent) to 4 (very severe). Higher scores of HAMA indicate more severe symptoms of anxiety. An overall score of 8 points or higher indicates anxiety.

Narcotrend Index (NI)

The gold standard for sleep stage detection is the sleep multi-channel monitor, however, patients need to be transferred from an adapted ward to a new environment for evaluation. The Observer's Assessment of Alertness/Sedation Scale (OAA/S) can be used to assess patients' sleep status that may interrupt patients' sleep. Narcotrend is an electroencephalogram (EEG) monitor designed to measure the depth of anesthesia. The NI is dimensionless, ranging from 0 to 100. The NI could be divided into six stages [A (awakening) to F (anesthesia with outbreak suppression)] (**Supplementary Table S1**). The NI has a strong correlation with OAA/S, which was supported by Bauerle et al.'s results (28). The selected index of the experiment is the C-F stage which means that the patient was asleep. If the depth of anesthesia does not reach the target state for more than 30 min, the treatment fails.

Methods

Patients were randomly allocated to two groups by a computer-generated sequence. Sleep assessment was performed in the participant's ward on the night before surgery. Bedtime was adjusted according to the patient's sleep habits. Normal bedtime was controlled from 21:00 to 23:00. The NI was used to monitor the patient's EEG and depth of sedation at bedtime, and to simultaneously control the patient's mean arterial pressure (MAP), heart rate (HR), and oxygen saturation (SPO_2). Patients were enrolled in the present study without receiving oxygen through a nasal catheter. Patients administered by the same unsuspecting anesthesiologist through the nasal cavity with a preconfigured drug. At present, there is no relevant study on 95% effective dose of intranasal DEX in adults. According to Li et al.'s study (23), 95% effective dose of intranasal DEX in children was 2.64 μg/kg. Referring to this dose, we carried out a pre-experiment *via* setting up three experimental groups (2.0, 2.5, and 3.0 μg/kg). According to the pre-experiment results, the experimental dose was determined to be 2.5 μg/kg. The dosage was divided evenly between the two sides of the nostrils, in which 0.1 ml was given to each side of the nostrils, and the two sides were alternately given. After each round of administration, gently press on the client's nose and administer the required dose within 5 min. On the next day, the fuzzy number method was utilized to evaluate the degree of satisfaction with the night's sleep. The total score was 10 points, and the final result was 8 points or more, indicating that the patient was satisfied with the sleep. It is noteworthy that final score of 6–8 points indicated that the patient was generally satisfied, and when the final score was <6 points, the patient was not satisfied. Besides, ISI was applied to evaluate the night's sleep. Patients, nurses, and investigators were blinded to the grouping.

Throughout the research process, we collected the following data: sleep onset latency, total sleep time, ISI and HAMA scores before treatment, ISI and satisfaction scores after treatment, MAP, HR, SPO_2 at 0 min (T_0), SPO_2 at 10 min (T_1), SPO_2 at 20 min (T_2), SPO_2 at 30 min (T_3), SPO_2 at 1 h (T_4), and SPO_2 at 2 h (T_5) after treatment.

Interventional Conditions

Hypotension was defined as a decrease in MAP >30% from baseline (before treatment). BP was controlled within 30% of baseline. If BP is outside the target range, phenylephrine may increase BP, and nitroglycerin may decrease BP. If the HR drops below 40 beats/min, atropine may be used, and isoproterenol may be used when atropine is ineffective. Patients were given nasal cannula when SPO_2 was below 90%. The anesthesiologist determined the necessity of further medical management.

Adverse Reactions

Adverse reactions, such as respiratory depression, hypotension, and sinus bradycardia were recorded throughout the treatment period.

Statistical Analysis

SPSS 21.0 software (IBM, Armonk, NY, USA) and GraphPad Prism 8.0 software (GraphPad Software Inc., San Diego, CA, USA) were used to perform the statistical analysis. The Shapiro–Wilk test was used to assess the distribution of continuous variables that were presented as mean [standard deviation (SD)]; categorical variables were expressed as percentage. Normally distributed data were analyzed by one-way analysis of variance (ANOVA) or paired *t*-test to compare differences between groups; abnormally distributed data were analyzed using the non-parametric test to compare differences between groups (the Mann–White *U* test for two independent samples). Comparison of categorical variables between the groups was carried out using the χ^2 test. A two-sided $P < 0.05$ was considered statistically significant.

Sample Size Calculation

A previous study reported that the incidence of pre-operative insomnia is 37–38.2% (6, 7). They assumed that after intranasal DEX administration, the incidence of pre-operative insomnia decreased from 38.2 to 5%, with the statistical power of 90% and a two-sided significance level of 0.05. Besides, 65 patients were required to detect a statistical significance. They considered a loss to follow-up rate of ∼10%. A total of 72 patients were enrolled in the present study.

RESULTS

Among 86 patients who were enrolled, 11 patients refused participation in the study, and 3 patients were excluded due to inconsistency with the surgical plan. A total of 72 patients were finally included and randomly assigned into the DEX group ($n = 36$) and intranasal normal saline (NS) group ($n = 36$). No patients withdrew from the study. The study flow

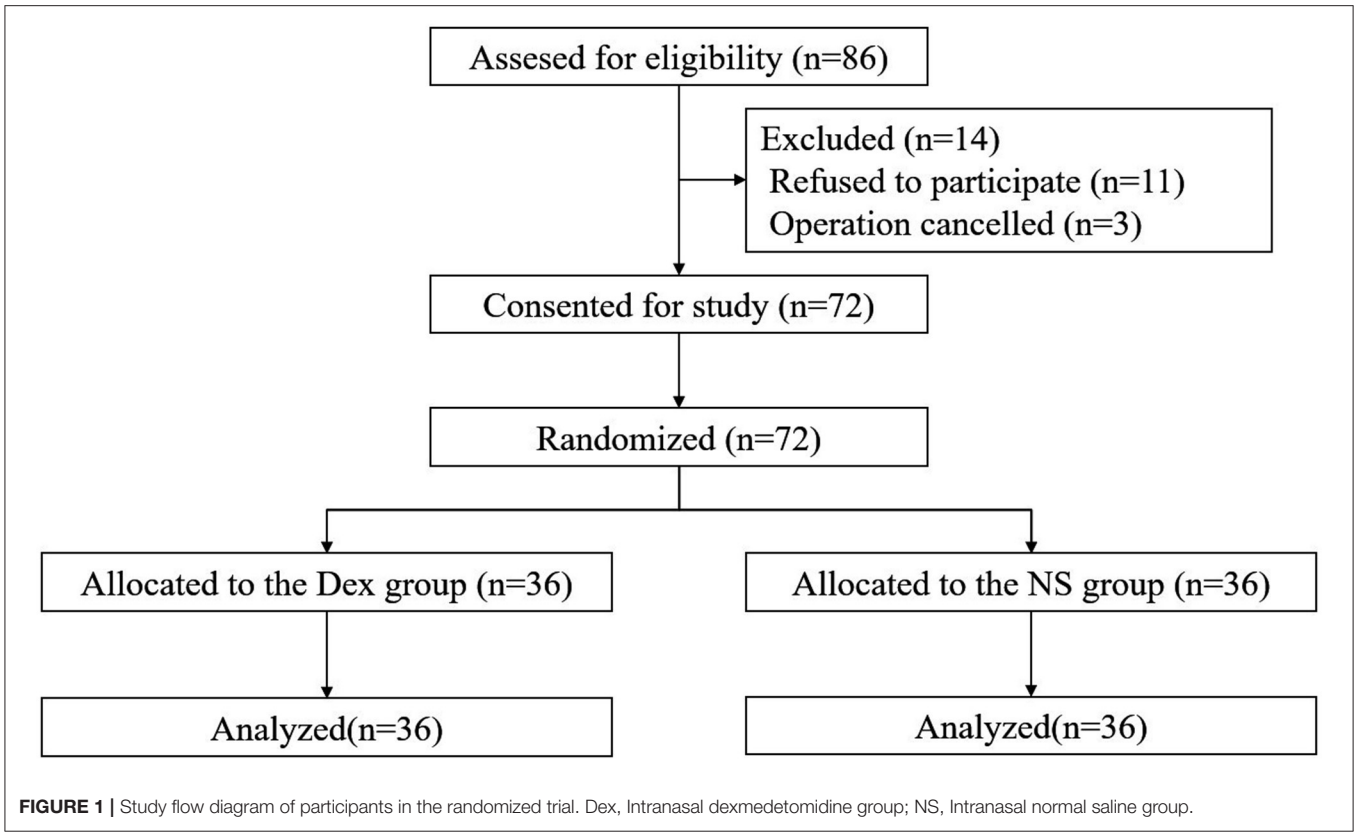

FIGURE 1 | Study flow diagram of participants in the randomized trial. Dex, Intranasal dexmedetomidine group; NS, Intranasal normal saline group.

TABLE 1 | Characteristics of study population.

Characteristic	Dex (n = 36)	NS (n = 36)	P-value
Age (year)	38.11 ± 11.47	40.47 ± 11.17	0.539
Sex (males)	15 (41.7%)	14 (38.9%)	0.810
Height (cm)	164.44 ± 6.87	164.78 ± 7.45	0.648
Standard body weight (Kg/m^2)	57.92 ± 5.46	58.11 ± 5.90	0.866
Body mass index (Kg/m^2)	22.11 ± 2.09	22.23 ± 2.05	0.416
ASA I/II(No)	15/21	13/23	0.515
Baseline heart rate (beats/min)	74.47 ± 8.77	76.58 ± 10.72	0.306
Baseline mean arterlal pressure (mm Hg)	89.17 ± 6.36	87.25 ± 7.86	0.426
Baseline oxygen saturation	97.75 ± 1.08	97.83 ± 0.94	0.687
Narcotrend index	98.17 ± 0.85	98.17 ± 0.74	0.914
Before hospitalization ISI	4.36 ± 1.42	4.22 ± 1.35	0.981
ISI	13.53 ± 4.14	13.50 ± 4.41	0.860
HAMA	14.11 ± 3.23	13.58 ± 2.59	0.637

Values expressed as mean ± standard devlation or number (percentage).
No differences were found ($P < 0.05$).
Dex, Intranasal dexmedetomidine group; NS, Intranasal Normal saline group; ISI, Insomnia severity index; HAMA, Hamilton Anxiety Scale; ASA, American Society of Anesthesiology.

diagram is shown in **Figure 1**. Demographic data, ASA grade, standard bodyweight, NI, ISI (before hospitalization), and ISI and HAMA scores before treatment were similar between the two groups (**Table 1**).

TABLE 2 | Comparison of fall asleep time, total sleep time and satisfaction of patients in two groups ($\bar{x}$± s).

	Dex	NS	P
Fall asleep time	22.08 ± 3.95	89.31 ± 54.56	<0.001
Total sleep time	400.06 ± 28.84	295.19 ± 73.51	<0.001
satisfaction of patients	8.14 ± 0.87	3.50 ± 1.66	<0.001

Dex, Intranasal dexmedetomidine group; NS, Intranasal Normal saline group.

Primary Outcome Measures

(1) The time to fall asleep (22.08 ± 3.95 min) and total sleep time (400.06 ± 28.84 min) in the DEX group were significantly different from those in the NS group (time to fall asleep, 89.31 ± 54.56 min; total sleep time (295.19 ±7 3.51 min; $P < 0.001$). (2) The overall sleep satisfaction rate on the night before surgery was significantly different between the two groups ($P < 0.001$) (**Table 2**). (3) The pre-operative ISI scores were similar in the DEX (13.53 ± 4.14) and NS (13.50 ± 4.41) groups ($P = 0.860$). ISI score after treatment in the DEX group (4.14 ± 1.68) was lower than that in the NS group (13.78 ± 4.80) ($P < 0.001$). The ISI score in the DEX group (4.14 ± 1.68, after treatment) was significantly lower than that in the DEX group (13.53 ± 4.14, before treatment; $P < 0.001$), whereas no significant differences were found between before and after treatment in the NS group ($P = 0.636$) (**Figure 2**).

Secondary Outcome Measures

The MAP, HR, SPO_2, and NI are summarized in **Table 3**. **Figure 3** shows the effects of DEX dose over time on MAP, HR, SPO_2, and NI. 1. MAP and HR in the DEX group were significantly different from those in the NS group from T_2 to T_5 ($P < 0.05$) 0.2. The SPO_2 after treatment did not significantly differ between the two groups at T_0, T_1, T_3, and T_5 ($P > 0.05$); at T_2 and T_4, the SPO_2 in the DEX group (97.17 ± 0.91 at T_4, 97.19 ± 0.95 at T_5) was significantly lower than that in the NS group (97.67 ± 0.86 at T_4, 97.61 ± 0.73 at T_5; $P < 0.05$). However, at T_2 and T_4, the SPO_2 did not fall below 95%, thus, the difference was not clinically significant. 3. At T_2, T_3, T_4, and T_5 after treatment, the NI in the DEX group (77.00 ± 28.77 at T_2, 35.08 ± 11.73 at T_3, 35.31 ± 5.85 at T_4, and 36.08 ± 5.68 at T_5) was significantly lower than that in the NS group (98.31 ± 0.67 at T_2, 94.44 ± 1 3.39 at T_3, 73.19 ± 2 9.61 at T_4, and 51.67 ± 26.12 at T_5; $P < 0.05$).

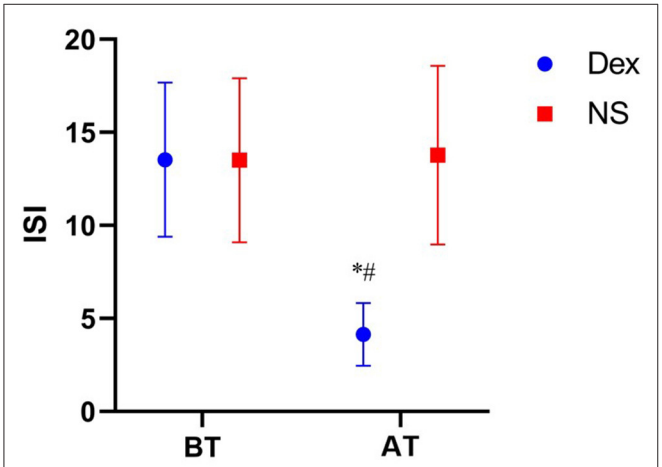

FIGURE 2 | Comparison of ISI scores in two groups at different time points. BT, Before treatment; AT, After treatment; ISI, Insomnia severity index; Dex, Intranasal dexmedetomidine group; NS, Intranasal normal saline group. ISI score comparison of Dex group before and after treatment, $P < 0.01$ vs. *. Comparison of ISI score between Dex group and NS group after treatment, $P < 0.01$ vs. #.

Adverse Reactions

In the present study, 8 (25%) patients in the DEX group and 4 (12.5%) patients in the NS group had a HR lower than 50 beats/min ($P = 0.200$). Besides, 3 (9.38%) patients in the DEX group and 1 (3.13%) patient in the NS group had systolic blood pressure lower than 90 mmHg. The MAP of these 4 patients was not lower than 30% below baseline, therefore, no medication was used. No respiratory depression was recorded. Drowsiness was observed in 18 (56.25%) patients in the NS group, while no drowsiness was found in the DEX group. No patient felt discomfort after intranasal administration of DEX (**Table 4**).

DISCUSSION

It was reported that 38.2% of patients mainly suffered from insomnia due to anxiety on the day before surgery (6). Pre-operative sleep quality has an important influence on post-operative recovery of patients, and poor sleep may increase the incidence of surgical complications (16, 17). Studies have reported the association of insufficient sleep with the increased risk of a variety of human diseases, including heart disease, immune disorders, anxiety, and depression, leading to incurable neurodegenerative diseases (e.g., Alzheimer's disease) (9, 10, 15, 29). Poor pre-operative sleep quality has shown to significantly increase the risk of severe peak pain during exercise after surgery (30). It also increases the incidence of post-operative hyperalgesia (17). Leung et al. (13) revealed the relationship between pre-operative sleep disruption and post-operative delirium. Therefore, improving pre-operative sleep quality may ameliorate a patient's prognosis.

Ellis et al. (31) confirmed that a single session of cognitive behavioral therapy for insomnia (CBT-I) was effective for

TABLE 3 | Comparison at each time point in two groups ($\bar{x}$± s).

	T_0	T_1	T_2	T_3	T_4	T_5
MAP						
Dex	89.17 ± 6.36	83.24 ± 5.98*	78.83 ± 6.22*#	76.59 ± 5.63*#	74.98 ± 5.41*#	76.14 ± 5.05*#
NS	87.29 ± 7.86	85.35 ± 8.67	85.56 ± 9.24	84.31 ± 8.38&	81.82 ± 9.01&	79.95 ± 9.06&
HR						
Dex	74.47 ± 8.77	66.75 ± 8.42*#	60.00 ± 8.52*#	57.28 ± 7.59*#	55.86 ± 6.99*#	56.69 ± 6.24*#
NS	76.58 ± 10.72	73.53 ± 11.91	71.72 ± 12.27&	69.92 ± 13.80&	65.50 ± 11.59&	63.08 ± 9.44&
SPO2						
Dex	97.75 ± 1.08	97.53 ± 1.32	97.11 ± 0.95*	97.39 ± 1.05	97.17 ± 0.91*#	97.19 ± 0.95#
NS	97.83 ± 0.94	97.53 ± 0.84	97.47 ± 0.94	97.67 ± 1.04	97.67 ± 0.86	97.61 ± 0.73
NI						
Dex	98.17 ± 0.85	98.25 ± 0.69	77.00 ± 28.77*#	35.08 ± 11.73*#	35.31 ± 5.85*#	36.08 ± 5.68*#
NS	98.17 ± 0.74	98.28 ± 0.81	98.31 ± 0.67	94.44 ± 13.39	73.19 ± 29.61&	51.67 ± 26.12&

*Dex, Intranasal dexmedetomidine group; NS, Intranasal Normal saline group. Compared with the same group at T_0 time, $P < 0.05$ versus *Dex, &NS, Compared with NS group at the same time point, #$P < 0.05$.*

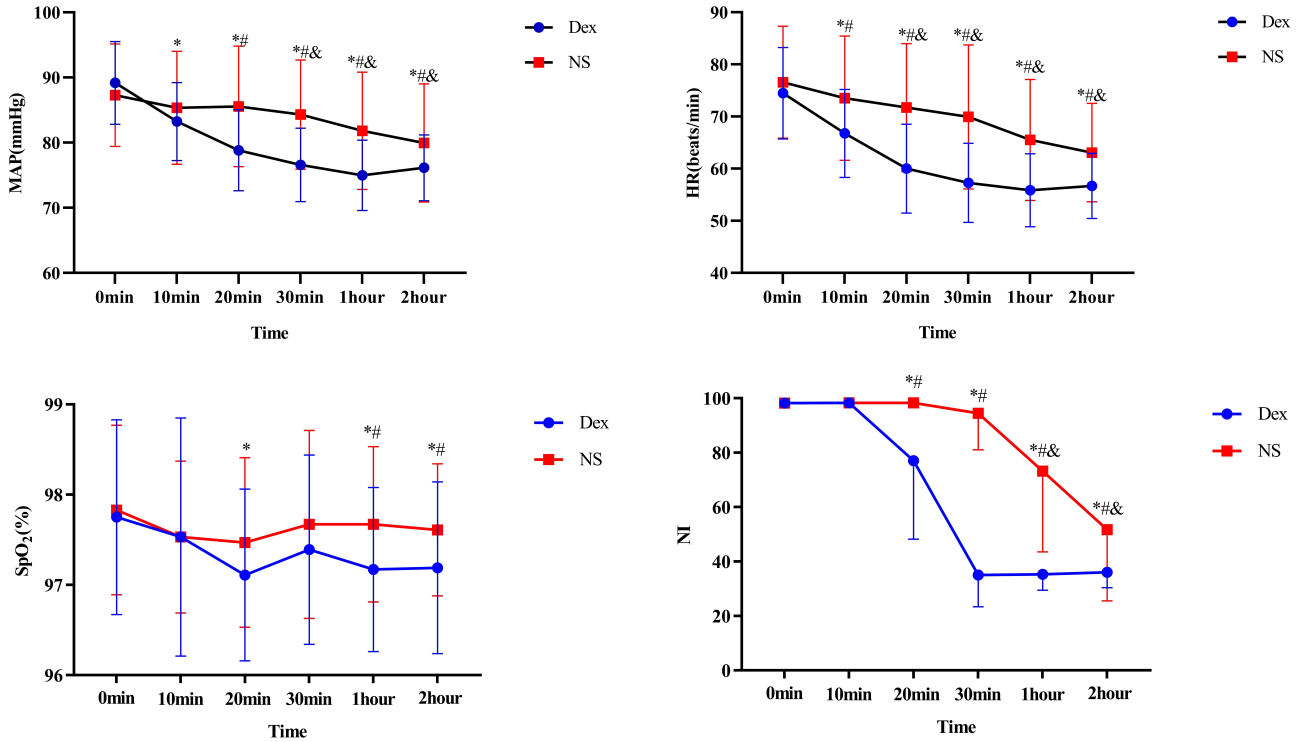

FIGURE 3 | Dex, Intranasal dexmedetomidine group; NS, Intranasal normal saline group. Compared with the same group at T_0 time, $P < 0.05$ vs. *Dex, &NS. Compared with NS group at the same time point, #$P < 0.05$.

TABLE 4 | Comparison of other adverse reactions in two groups (cases, %).

	Respiration depression	Hypotension	Sinus bradycardia	Drowse	Nasal discomfort
Dex	0 (0.00%)	3 (9.38%)	8 (25.00%)	0 (0.00%)	0 (0.00%)
NS	0 (0.00%)	1 (3.13%)	4 (12.50%)	18 (56.25%)	0 (0.00%)
P	1.000	0.302	0.200	<0.001	1.000

Dex, Intranasal dexmedetomidine group; NS, Intranasal Normal saline group.

acute phase. However, patients need to receive treatment for 60–70 min, which limits the use of CBT-I. Benzodiazepine and non-benzodiazepine hypnotics can effectively treat insomnia. However, both have noticeable side effects, including headache, nausea, vomiting, dyspepsia (unpleasant taste), dizziness, drowsiness, migraine, etc. (32). DEX exerts its hypnotic effect by selectively activating presynaptic and postsynaptic central α-2 adrenergic in locus coeruleus. DEX-induced deep sedation mimics stages 2 and 3 of NREM sleep (21, 22).

Intranasal DEX spray may have a better sedative effect than dropping. Xie et al. (33) assessed children's response to peripheral venous intubation after intranasal DEX spray or dropping, and concluded that intranasal DEX spray provided a better sedation. However, there is currently no special dose for DEX atomization in China, and additional atomization devices are required for nasal atomization, causing difficulties in controlling the accuracy of dose, and higher hygienic conditions are therefore required for nasal atomization. The present study aimed to investigate the effects of intranasal DEX administration on sleep quality of patients with pre-operative insomnia, and no spray was herein used. A recent study (34) showed a similar bioavailability (about 40%) for both methods of intranasal delivery (drops or mucosal nebulizer devices). This may be due to the larger mucosal area of the nasal cavity in adults, which has a larger surface area for drug absorption in the nose. The safety and efficacy is not affected by the mode of DEX administration (35). In the future studies, the advantages and disadvantages of these two methods of drug delivery will be further compared.

Expectedly, compared with the NS group, the intranasal DEX improved sleep quality on the night before surgery. Under the standard bodyweight, administration of DEX (2.5 μg per kilogram of bodyweight) could quickly eliminate anxiety and insomnia, and simultaneously improve the total sleep time and sleep quality.

Lirola et al. (36) measured the pharmacokinetics of DEX in adults and found that the onset of clinical sedation was 30–45 min after intranasal administration, in which this onset time was 22.08 ± 3.95 min in the present study, and the difference may be related to the dose of DEX. In Lirola et al.'s study, the dose of intranasal DEX administration was 85 μg, while the dose was based on standard bodyweight in the current study. Miller et al.'s (37) findings also confirmed that the time required for intranasal dextromethorphan administration to reach the lowest effective plasma concentration could be related to the dextromethorphan dose. In Akeju et al.'s (38) study, the total sleep time of patients who received DEX injection was 440.3 min, and the total sleep time of healthy controls was 413.0 min. Compared with our study, the total sleep time of patients who were treated with intravenous DEX was substantially similar to that of patients who were treated with intranasal DEX, while the difference in total sleep time was more significant in the control group. The reason for this difference is that blank control group included patients with pre-operative anxiety and insomnia. The ISI score in the DEX group after treatment was significantly higher than that in the NS group. Besides, no patient in the DEX group felt drowsiness. This is because DEX altered arousal states (38), which is closely related to a natural sleep state, and patients therefore slept with a higher quality.

DEX agonizes α_2-adrenergic receptors in vascular smooth muscle cells at higher concentrations (39, 40), constricts peripheral blood vessels, and increases blood pressure. In the present study, no hypertension requiring treatment was observed in the DEX group. This could be due to the relatively lower absorption rate of DEX in the nose and the lower maximum plasma concentration, which have been previously confirmed by previous studies. Intranasal dexamethasone is different from the rapid intravenous infusion, and it does not increase BP (37).

Bradycardia is a common complication of DEX, while it typically does not cause serious complications (41). In our study, 8 patients developed bradycardia after receiving intranasal dexamethasone, whereas none reached the intervention level with anticholinergic drugs. No patient had a SPO_2 below 95% in the study period. Although the blood oxygen at T_2T_4 in the DEX group was lower than T_0 ($P < 0.05$), no actual clinical significance was found.

We asked patients to record any liquid that had flowed into the oral cavity during the nasal administration. One patient in the DEX group took more than 30 min to fall asleep. This indicated that the liquid had flowed into the mouth during the administration period and it was swallowed. A previous study demonstrated that mean absolute bioavailability after peroral, buccal, and intramuscular administration of DEX was 16, 82, and 104%, respectively (42). The failure of this patient to fall asleep within 30 min could be related to a part of the DEX that was swallowed.

LIMITATIONS

Firstly, the sample size of this study is limited, thus, a large-scale multi-center clinical study is required to provide more reliable data to evaluate safety and efficacy of DEX. Secondly, patients' sleep statuses were not assessed using a polysomnography monitor. Third, the dose of DEX required by adults was noticeable, indicating the necessity of multiple intranasal administrations. Changing to a higher concentration of DEX may solve this problem.

CONCLUSIONS

In summary, this study is the first to introduce the potential treatment of DEX in the treatment of pre-operative anxiety insomnia. Intranasal DEX can safely and effectively improve patients' pre-operative anxiety and insomnia. Intranasal DEX may be used as a complementary therapy for insomnia.

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 Scientific Research Ethics Review Committee of the First Affiliated Hospital of Gannan Medical University (LLSC-2020102701). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LC and WZ: study design. WZ, XL, XD, KH, MZ, SZ, LZ, and YJ: data collection, analysis, and interpretation. WZ, LC, and YJ: drafting of the manuscript. LC and WL: critical revision of the manuscript. All authors: approval of the final version for publication.

FUNDING

This work was supported by the Science and Technology Plan of Health Commission of Jiangxi Province (202130619).

ACKNOWLEDGMENTS

We would like to take this opportunity to thank all the participants for their support and participation, as well as all the medical staff involved in trial design, data collection and analysis, and paper writing.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.816893/full#supplementary-material

REFERENCES

1. Winkelman JW. Clinical practice. *Insomnia Disord*. (2015) 373:1437–44. doi: 10.1056/NEJMcp1412740
2. Buysse DJJ. Insomnia. *JAMA*. (2013) 309:706–16. doi: 10.1001/jama.2013.193
3. Cunnington D, Junge MJB. Chronic insomnia: diagnosis and non-pharmacological management. *BMJ*. (2016) 355:i5819. doi: 10.1136/bmj.i5819
4. Cao X, Wang S, Zhong B, Zhang L, Ungvari G, Ng C, et al. The prevalence of insomnia in the general population in China: a meta-analysis. *PLoS ONE*. (2017). 12:e0170772. doi: 10.1371/journal.pone.0170772
5. Venkateshiah S, Collop NJC. Sleep and sleep disorders in the hospital. *Chest*. (2012) 141:1337–45. doi: 10.1378/chest.11-2591
6. Sun G, Yang Y, Yang X, Wang Y, Cui X, Liu Y, et al. Preoperative insomnia and its association with psychological factors, pain and anxiety in Chinese colorectal cancer patients. *Support Care Cancer*. (2020) 28:2911–9. doi: 10.1007/s00520-019-05151-y
7. Wang Y, Gao F, Yi P, Cao H, Zou H, Zhang SJS, et al. Risk factors for sleep quality disturbances in patients with lumbar spinal stenosis before operation. *Sleep Breath*. (2020) 24:669–74. doi: 10.1007/s11325-020-02055-8
8. Irwin M, Olmstead R, Carroll JE. Sleep disturbance, sleep duration, and inflammation: a systematic review and meta-analysis of cohort studies and experimental sleep deprivation. *Biol Psychiatry*. (2016) 80:40–52. doi: 10.1016/j.biopsych.2015.05.014
9. Sofi F, Cesari F, Casini A, Macchi C, Abbate R, Gensini GF. Insomnia and risk of cardiovascular disease: a meta-analysis. *Eur J Prev Cardiol*. (2014) 21:57–64. doi: 10.1177/2047487312460020
10. Larsson S, Markus HS. Genetic Liability to insomnia and cardiovascular disease risk. *Circulation*. (2019) 140:796–8. doi: 10.1161/CIRCULATIONAHA.119.041830
11. Lee S, Ng K, Chin WK. The impact of sleep amount and sleep quality on glycemic control in type 2 diabetes: a systematic review and meta-analysis. *Sleep Med Rev*. (2017) 31:91–101. doi: 10.1016/j.smrv.2016.02.001
12. DePietro R, Knutson K, Spampinato L, Anderson S, Meltzer D, Van Cauter E, et al. Association between inpatient sleep loss and hyperglycemia of hospitalization. *Diabetes Care*. (2017) 40:188–93. doi: 10.2337/dc16-1683
13. Leung J, Sands L, Newman S, Meckler G, Xie Y, Gay C, et al. Preoperative sleep disruption and post-operative delirium. *J Clin Sleep Med*. (2015) 11:907–13. doi: 10.5664/jcsm.4944
14. Fadayomi A, Ibala R, Bilotta F, Westover M, Akeju O. A systematic review and meta-analysis examining the impact of sleep disturbance on post-operative delirium. (2018) 46:e1204–12. doi: 10.1097/CCM.0000000000003400
15. Dong Y, Yang FM. Insomnia symptoms predict both future hypertension and depression. *Prev Med*. (2019) 123:41–7. doi: 10.1016/j.ypmed.2019.02.001
16. Wang J, Lu S, Guo L, Ren C, Zhang ZW. Poor preoperative sleep quality is a risk factor for severe postoperative pain after breast cancer surgery: a prospective cohort study. *Medicine*. (2019) 98:e17708. doi: 10.1097/MD.0000000000017708
17. Zhang Z, Wang H, Wang Y, Luo Q, Yuan S, Yan F. Risk of postoperative hyperalgesia in adult patients with preoperative poor sleep quality undergoing open-heart valve surgery. *J Pain Res*. (2020) 13:2553–60. doi: 10.2147/JPR.S272667
18. Wilt T, MacDonald R, Brasure M, Olson C, Carlyle M, Fuchs E, et al. Pharmacologic treatment of insomnia disorder: an evidence report for a clinical practice guideline by the American College of Physicians. *Ann Intern Med*. (2016) 165:103–12. doi: 10.7326/M15-1781
19. Lou B, Oks M. Insomnia: pharmacologic treatment. *Clin Geriatr Med*. (2021) 37:401–15. doi: 10.1016/j.cger.2021.04.003
20. De Zen L, Del Rizzo I, Robazza M, Barbieri F, Campagna M, Vaccher S, et al. Home use of intranasal dexmedetomidine in a child with an intractable sleep disorder. *J Pediatr Pharmacol Ther*. (2020) 25:332–5. doi: 10.5863/1551-6776-25.4.332
21. Guldenmund P, Vanhaudenhuyse A, Sanders R, Sleigh J, Bruno M, Demertzi A, et al. Brain functional connectivity differentiates dexmedetomidine from propofol and natural sleep. *Br J Anaesth*. (2017) 119:674–84. doi: 10.1093/bja/aex257
22. Ramaswamy S, Weerink M, Struys M, Nagaraj SB. Dexmedetomidine-induced deep sedation mimics non-rapid eye movement stage 3 sleep: large-scale validation using machine learning. *Sleep*. (2021) 44:zsaa167. doi: 10.1093/sleep/zsaa167
23. Li S, Liu H, Zhang J, Liu Y, Yu Q, Sun M, et al. The 95% effective dose of intranasal dexmedetomidine sedation for pulmonary function testing in children aged 1-3 years: a biased coin design up-and-down sequential method. *J Clin Anesth*. (2020) 63:109746. doi: 10.1016/j.jclinane.2020.109746
24. Buysse D, Ancoli-Israel S, Edinger J, Lichstein K, Morin CM. Recommendations for a standard research assessment of insomnia. *Sleep*. (2006) 29:1155–73. doi: 10.1093/sleep/29.9.1155
25. Buysse D, Reynolds C, Monk T, Berman S, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. (1989) 28:193–213. doi: 10.1016/0165-1781(89)90047-4
26. Chen P, Jan Y, Yang CM. Are the Insomnia Severity Index and Pittsburgh Sleep Quality Index valid outcome measures for Cognitive Behavioral Therapy for Insomnia? Inquiry from the perspective of response shifts and longitudinal measurement invariance in their Chinese versions. *Sleep Med*. (2017) 35:35–40. doi: 10.1016/j.sleep.2017.04.003
27. Chen P, Yang C, Morin CM. Validating the cross-cultural factor structure and invariance property of the Insomnia Severity Index: evidence based on ordinal EFA and CFA. *Sleep Med*. (2015) 16:598–603. doi: 10.1016/j.sleep.2014.11.016
28. Bauerle K, Greim C, Schroth M, Geisselbrecht M, Köbler A, Roewer N. Prediction of depth of sedation and anaesthesia by the Narcotrend EEG monitor. *Br J Anaesth*. (2004) 92:841–5. doi: 10.1093/bja/aeh142
29. Huang Y, Potter R, Sigurdson W, Santacruz A, Shih S, Ju Y, et al. Effects of age and amyloid deposition on Aβ dynamics in the human central nervous system. *Arch Neurol*. (2012) 69:51–8. doi: 10.1001/archneurol.2011.235
30. Orbach-Zinger S, Fireman S, Ben-Haroush A, Karoush T, Klein Z, Mazarib N, et al. Preoperative sleep quality predicts postoperative pain after planned caesarean delivery. *Eur J Pain*. (2017) 21:787–94. doi: 10.1002/ejp.980
31. Ellis J, Cushing T, Germain A. Treating acute insomnia: a randomized controlled trial of a "single-shot" of cognitive behavioral therapy for insomnia. *Sleep*. (2015) 38:971–8. doi: 10.5665/sleep.4752
32. Madari S, Golebiowski R, Mansukhani M, Kolla BP. Pharmacological management of insomnia. *Neurotherapeutics*. (2021) 18:44–52. doi: 10.1007/s13311-021-01010-z
33. Xie Z, Shen W, Lin J, Xiao L, Liao M, Gan X. Sedation effects of intranasal dexmedetomidine delivered as sprays versus drops on pediatric response to venous cannulation. *Am J Emerg Med*. (2017) 35:1126–30. doi: 10.1016/j.ajem.2017.03.021
34. Li A, Yuen V, Goulay-Dufaÿ S, Sheng Y, Standing J, Kwok P, et al. Pharmacokinetic and pharmacodynamic study of intranasal and intravenous dexmedetomidine. *Br J Anaesth*. (2018) 120:960–68. doi: 10.1016/j.bja.2017.11.100
35. Li B, Zhang N, Huang J, Qiu Q, Tian H, Ni J, et al. A comparison of intranasal dexmedetomidine for sedation in children administered either by atomiser or by drops. *Anaesthesia*. (2016) 71:522–8. doi: 10.1111/anae.13407
36. Iirola T, Vilo S, Manner T, Aantaa R, Lahtinen M, Scheinin M, et al. Bioavailability of dexmedetomidine after intranasal administration. *Eur J Clin Pharmacol*. (2011) 67:825–31. doi: 10.1007/s00228-011-1002-y
37. Miller J, Balyan R, Dong M, Mahmoud M, Lam J, Pratap J, et al. Does intranasal dexmedetomidine provide adequate plasma concentrations for sedation in children: a pharmacokinetic study. *Br J Anaesth*. (2018) 120:1056–65. doi: 10.1016/j.bja.2018.01.035
38. Akeju O, Hobbs L, Gao L, Burns S, Pavone K, Plummer G, et al. Dexmedetomidine promotes biomimetic non-rapid eye movement stage 3 sleep in humans: a pilot study. *Clin Neurophysiol*. (2018) 129:69–78. doi: 10.1016/j.clinph.2017.10.005
39. Snapir A, Posti J, Kentala E, Koskenvuo J, Sundell J, Tuunanen H, et al. Effects of low and high plasma concentrations of dexmedetomidine on myocardial perfusion and cardiac function in healthy male subjects. *Anesthesiology*. (2006) 105:902–10. doi: 10.1097/00000542-200611000-00010
40. Colin P, Hannivoort L, Eleveld D, Reyntjens K, Absalom A, Vereecke H, et al. Dexmedetomidine pharmacodynamics in healthy volunteers: 2. haemodynamic profile. *Br J Anaesth*. (2017) 119:211–20. doi: 10.1093/bja/aex086
41. Ebert T, Hall J, Barney J, Uhrich T, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. *Anesthesiology*. (2000) 93:382–94. doi: 10.1097/00000542-200008000-00016

42. Anttila M, Penttilä J, Helminen A, Vuorilehto L, Scheinin H. Bioavailability of dexmedetomidine after extravascular doses in healthy subjects. *Br J Clin Pharmacol.* (2003) 56:691–3. doi: 10.1046/j.1365-2125.2003.01944.x

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

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: frontiersin.org/about/contact

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership