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EDITORIAL

Diminishing restrictive practices in psychiatric wards *via* virtual reality training: Old wine in a new bottle?

Yan Zeng, Jun-Wen Zhang, Jian Yang

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Abstract

This editorial examines the application of virtual reality (VR) training to mitigate restrictive practices (RPs) within psychiatric facilities. RPs include physical restraints, seclusion, and chemical restraints, used to ensure patient safety but with varying usage rates across regions. In recent years, there has been a growing focus on the adverse effects of RPs on both healthcare workers and patients, leading to calls for its reduction. Previous research has shown the efficiency of VR training in RP reduction. This editorial will analyze the limitations of VR training in prior research aimed at reducing RP, emphasizing that the essence of RPs is a medical safety issue, calling for careful differentiation of the causes of RPs, and avoiding the use of AR technology as a "new bottle" for "old wine" to improve the quality and reproducibility of future research in this field.

Key Words: Virtual reality; Virtual reality training; Restrictive practices; Questions; Inpatient; Psychiatric wards

Core Tip: There has been an increasing clamor for reducing restrictive practices (RPs), alongside a surge in practical explorations to address this issue. This editorial comments on an article published in the *World Journal of Psychiatry*, which explored the application of virtual reality (VR) training as a strategy to reduce RPs within psychiatric wards. This editorial emphasizes the need to focus on the underlying issues of medical safety associated with RPs, discusses the strengths and limitations of VR training, and advocates for the differentiation of RPs based on their causes while also cautioning against overcorrection in the clinical practices of reducing RPs.

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INTRODUCTION

Restrictive practices (RPs) encompass a range of medical interventions intended to ensure medical safety and prevent self-harm or the potential for harm to others by patients, which include physical restraints, seclusion, and chemical restraints[1]. The utilization of RP exhibits substantial variations across different regions and healthcare institutions, with reported usage rates differing by more than a hundredfold among various countries[2-4]. Such variations are attributed to disparities in the definitions and subjective interpretations of RPs and individual healthcare providers' values, professional levels, experience, cultural nuances, and the specific health policies of different regions[5]. In recent years, there has been a growing focus on RP's adverse physical and psychological impacts on healthcare staff and patients[6,7]. Consequently, there has been an increasing clamor for the reduction of RP, along with a surge in practical explorations within the field to address this challenge.

We are interested in an article published in the *World Journal of Psychiatry*, which explored the application of virtual reality (VR) training as a strategy to reduce RPs within psychiatric wards, offering a fresh approach to bolstering patient care and staff training[8]. Drawing on the valuable insights from the study in question, we are committed to delving deeper into the challenges and doubts associated with applying VR training to reduce RPs in psychiatric wards. This editorial aims to provide a nuanced perspective on this topic, contributing to the ongoing discourse on diminishing RPs.

REASSESSING THE UNDERLYING CAUSES

Reference citation analysis (RCA, https://www.referencecitationanalysis.com/) is a unique artificial intelligence (AI) system for evaluating citations in biomedical literature. RCA was used to analyze previous studies on RPs up to August 2024.

Before exploring the current challenges and potential solutions for reducing RPs, it is imperative to comprehend the rationale behind their clinical implementation. RPs are pervasive across medical practices due to their effectiveness in safeguarding patients from self-harm or harm to others, ensuring ward security, and mitigating conflicts and acts of violence within medical institutions[1]. At their essence, RPs are about safeguarding medical safety. However, it is evident that the factors influencing medical safety are intricate and cannot be resolved solely by training healthcare professionals[9,10]. Furthermore, it is a misconception to view the safety of healthcare workers as being in direct conflict with patient safety. From this perspective, any strategy that seeks to reduce the safety requirements of healthcare providers or patients to decrease RPs is misguided and counterproductive[11].

Concurrently, we cannot overlook that, despite calls from various nations and scholars to reduce RPs, their frequent use in real-world scenarios remains a cause for concern[12]. This situation necessitates a reevaluation of the issues within the realm of medical safety, encompassing the safety of both healthcare providers and patients. Taking the quality of medical care in psychiatric wards as an example, concerns about reduced medical quality and safety stem from human resources, technical expertise, ethical dilemmas, management levels, healthcare systems, or economic support[13,14]. Furthermore, there is a lack of viable alternatives to RPs and research and consensus on determining the least restrictive options that patients perceive[15-17]. Without addressing these fundamental issues, innovations in training methods may provide only temporary solutions or potentially lead to further complications in the future, including the widespread investment of already strained healthcare funds in areas with low cost-effectiveness. Such complications may exacerbate the economic burden in the public health sector and further diminish the quality of care, leading to increased medical inequities and safety concerns[18].

POTENTIAL AND LIMITATIONS OF VR TRAINING

As an engaging and immersive educational tool, VR training has received acknowledgment for its potential to facilitate learning without actual safety risks. VR technology can potentially enhance patient safety by allowing staff to practice crisis intervention techniques, communication strategies, and de-escalation methods in a safe and repeatable setting[19]. A recent study compared the incidence of violent incidents and the use of restrictive measures on the wards in the 12 wk preceding the introduction of VR with the first 12 wk following its adoption. It revealed that during the VR relaxation training phase, the frequency of violent incidents and the application of RPs were halved[20]. Meanwhile, some studies have also found that VR training may not outperform traditional face-to-face methods in specific complex medical procedure training, and there are issues with low knowledge retention rates among employees after 4 wk of training in non-medical fields[21,22]. Other limitations of VR training include its inapplicability to individuals with motion sickness or those unaccustomed to VR environments, the necessity for additional training on VR technology, the inability to fully replicate the complexity and unpredictability of real-world medical issues, and ethical concerns, such as the simulation of

distressing scenarios or the potential for desensitization to certain aspects of care[23,24].

The effectiveness of VR training depends on the quality of the simulated environments and the system's ability to provide realistic and engaging training experiences[25,26]. However, previous studies' lack of detailed information regarding VR training content, specific training programs, and quality control raises concerns about its efficacy and replicability in reducing RPs[8]. Moreover, the VR training simulations are relatively short, as indicated in the previous study, with each simulation lasting approximately 5 min[8]. Meanwhile, the long-term efficacy of VR training in reducing RPs remains unestablished. Consequently, it is also essential to investigate whether extended VR training sessions differ significantly from the current shorter duration regarding their long-term impact. Furthermore, ensuring a sustained effect of VR training requires its seamless integration into standard psychiatric care protocols. It involves developing standardized VR training programs, establishing best practices, and continuously evaluating VR training's effectiveness in real-world clinical scenarios. In addition, VR training requires expensive hardware, such as VR headsets, and continually updated software, which may increase the cost and complexity of training and exacerbate the financial strain on the healthcare industry, especially in the current poor economic environment worldwide.

More importantly, future research should concentrate more on the content and design of personalized training programs rather than just adopting an expensive new technology to repackage existing training content. After all, VR is just a medium, and the medium itself cannot guarantee that the costly VR procedure is suitable for all kinds of training and produces more optimal results than the existing training methods[27]. From this angle, for the previous study aiming to improve "self-efficacy, anxiety, burnout, discrimination, and empathy" through VR training to reduce RPs[8], we are concerned that VR may only be an expensive new bottle for old wine, as the effectiveness of VR training may not so much depend on the VR "bottle" itself, but on the quality of the "wine" inside, where VR training plays a role in enhancing the experience. This understanding is easily overlooked in the constant flow of new technologies. Taking the interactivity of VR as an example, while VR's interactivity enables immediate feedback and strategic adjustments, which are crucial for the complexity and dynamism of psychiatric care, the effectiveness of VR training ultimately depends on the pre-designed quality and diversity of the training modules. Therefore, merely transferring conventional, video-based training content into a VR shell should be avoided.

DIMINISHING RPs IN PSYCHIATRIC WARDS

The reduction of RPs can be broadly achieved by reducing their incidence and shortening the duration of its employment. Effective methods encompass staff training, risk evaluation, management enhancement, and alterations to laws and regulations[28,29]. Additionally, digitalized mental health services and training initiatives have more recently been acknowledged as promising approaches[8,14]. VR technology significantly improves the customization of psychiatric staff training programs. A notable study has demonstrated that interactive VR (IVR)-based training in psychiatry represents an enticing and practical alternative to traditional face-to-face instruction, showcasing considerable promise for the field. IVR enables trainees to become fully immersed in simulations while maintaining control over their learning experience, including the ability to dictate the direction of their inquiries[30]. In the intricate clinical milieu of psychiatric units, a critical yet often overlooked aspect before addressing the reduction of RPs is the necessity to examine the specific causes of which RPs occur within a particular healthcare setting during a given period. These causes may include subjective decisions by inadequately trained staff, urgent interventions following an acute violent act after thorough risk assessments, or the resort to RPs due to a lack of de-escalation or alternative approaches. Blending RPs stemming from various sources for intervention effectiveness statistics may lack scientific rigor and the ability to be replicated in real-world scenarios. Moreover, a secure treatment environment is an essential need for every patient in a psychiatric ward, and it is imperative to avoid a swing from an extreme over-reliance on RPs to the opposite extreme of diminishing RPs altogether, which could result in an overcorrection.

This understanding can guide the development of targeted interventions that are more likely to be effective and replicable across different settings. For example, if RPs result from healthcare providers' overreaction to certain behaviors, interventions could concentrate on improving alternative techniques and communication skills through training. If RPs stem from inadequate staffing or resource allocation, strategies could be designed to enhance staffing levels and resource management[31].

When integrating new technological approaches, such as digital mental health care and VR technology, into training methods, it is essential to consider how they will complement and integrate with traditional training modalities and other emerging technologies. A potential limitation of psychiatric VR training, its focus on short-term outcomes, underscores the need for ongoing observation of the long-term effectiveness and sustainability of VR training programs[8,32]. Incorporating AI for adaptive learning and collecting longitudinal data can be particularly beneficial[33]. By leveraging AI for adaptive learning, VR training can become more personalized and responsive to individual trainees' needs, potentially enhancing its long-term impact[34]. Moreover, collecting longitudinal data allows for monitoring and evaluating VR training's sustained effects over time. This data-driven approach not only aids in refining training modules but also provides a mechanism for ensuring VR technology's ongoing relevance and efficacy in psychiatric care. By integrating VR training with AI and longitudinal data collection, healthcare managers and staff can better understand and enhance the long-term impact of VR training in reducing RPs, thereby improving the overall quality of care in psychiatric settings.

CONCLUSION

Given ethical considerations, patient needs, and the ongoing refinement of healthcare management, reducing unnecessary RPs is an inevitable trend in psychiatry. Implementing VR training in psychiatric institutions to diminish RPs represents an innovative strategy with promising potential; however, it must be accompanied by ongoing evaluation and monitoring to ensure its real-world outcomes. Although the previous study has limitations, it provides valuable insights into the feasibility and potential benefits of VR training in this context. To avoid VR training merely being a "new bottle for old wine", strategies including focusing on individual patient needs, further optimizing the quality of module design within VR, and continuously exploring integrating AI for adaptive learning to enhance the long-term effectiveness of the training may all be beneficial.

FOOTNOTES

Author contributions: Zhang JW and Yang J conceptualized and designed the research; Zeng Y performed the literature search, analyzed the data, and wrote the original manuscript; Zhang JW and Yang J edited the final manuscript; all authors have read and approved the final manuscript.

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EDITORIAL

Optimizing anesthesia depth to enhance seizure quality during electroconvulsive therapy in major depressive disorder

Haewon Byeon

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Abstract

This editorial evaluated the findings of a comprehensive study focused on the effects of anesthesia depth on seizure parameters during electroconvulsive therapy (ECT) in patients with major depressive disorder. The study utilized quantitative consciousness and quantitative nociceptive indices for monitoring sedation, hypnosis, and nociceptive responses. The analysis included 193 ECT sessions across 24 patients, revealing significant impacts of anesthesia depth on electroencephalography (EEG) seizure parameters. Key findings include that lighter anesthesia resulted in longer EEG seizure duration and higher post-ictal suppression index, without increasing complications. These insights emphasize the importance of optimal anesthesia management to improve therapeutic outcomes in ECT.

Key Words: Electroconvulsive therapy; Anesthesia depth; Major depressive disorder; Electroencephalography seizure parameters; Quantitative consciousness index; Quantitative nociceptive index; Seizure quality; Editorial

Core Tip: This editorial comments on the study by Zhao *et al* which evaluates the impact of anesthesia depth on electroencephalography (EEG) seizure parameters during electroconvulsive therapy (ECT) in patients with major depressive disorder. Utilizing quantitative consciousness and quantitative nociceptive indices, the study reveals that lighter anesthesia results in longer EEG seizure durations and higher post-ictal suppression index without increasing complications. These findings underscore the importance of optimal anesthesia management to improve therapeutic outcomes in ECT, providing valuable insights for refining clinical practices and enhancing patient care.

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INTRODUCTION

Electroconvulsive therapy (ECT) continues to be an essential therapeutic modality for addressing treatment-resistant major depressive disorder (MDD), particularly in clinical scenarios characterized by an elevated risk of suicide and pronounced psychiatric manifestations. The clinical utility of ECT stems from its efficacy in precipitating rapid symptom resolution, thereby significantly impacting the treatment trajectory for individuals grappling with severe forms of depression that have proven recalcitrant to conventional pharmacological interventions. However, notwithstanding its effectiveness, ECT is not devoid of adverse effects, which predominantly arise as a consequence of the patient's status under anesthesia. The depth of anesthesia, in this context, emerges as a critical determinant not only influencing the therapeutic efficacy of ECT but also bearing significant implications for patient safety and the overall tolerability of the procedure.

Anesthesia management within the ambits of ECT, therefore, assumes a pivotal place in optimizing therapeutic outcomes while concurrently endeavoring to mitigate the untoward effects associated with the procedure. In a recent endeavor to elucidate the effects of varying anesthesia depths on ECT-induced seizure parameters, a novel approach was employed through the utilization of the quantitative consciousness (qCON) and quantitative nociceptive (qNOX) indices. These indices serve as sophisticated measures for monitoring the depth of anesthesia and the nociceptive response, respectively, thus providing a granular understanding of the interplay between anesthesia depth and the electrophysiological underpinnings of seizures induced through ECT.

A noteworthy study in this domain explored the correlation between the pre-ECT BIS and seizure durations during ECT under propofol anesthesia. Intriguingly, the findings revealed a positive correlation between pre-ECT BIS values-a parameter indicative of anesthetic depth-and the duration of seizure activity[1]. This relationship underscores the nuanced dynamics between anesthesia depth and seizure characteristics, lending support to the hypothesis that more profound insights into anesthetic management strategies may pave the way for enhancing the efficacy and safety profile of ECT.

The exploration of anesthesia depths, particularly as monitored through advanced indices like qCON and qNOX, represents a significant frontier in refining ECT protocols. This approach not only holds promise for tailoring anesthesia to individual patient needs but also for elucidating the mechanisms through which anesthesia modulates seizure activity and, by extension, therapeutic outcomes in ECT. This editorial study sought to explore the implications for future research by examining Zhao *et al*'s study on the impact of anesthesia depth on seizure parameters during ECT in patients with MDD, utilizing the qCON and qNOX indices[2].

VALUE OF MONITORING ANESTHESIA DEPTH IN ECT

In the realm of ECT, the precision in monitoring anesthesia depth is paramount to achieving the dual goal of ensuring therapeutic efficacy while mitigating the potential for patient discomfort and adverse ououtcomes[3,4]. This is particularly true given that ECT involves the deliberate induction of a brief seizure, the quality of which is closely tied to both immediate therapeutic outcomes and longer-term patient well-being[5]. In addressing this need for precision, the study in question has underscored the utility of employing quantitative indices, specifically the qCON and qNOX indices, as instrumental tools in the nuanced monitoring of anesthesia depth during ECT procedures.

The qCON index serves as a window into the patient's levels of sedation and hypnosis, reflecting the depth of unconsciousness and thereby guiding the administration of hypnotic agents to reach a desired state of sedation without oversedation or undersedation[6]. On the other hand, the qNOX index provides insights into the patient's response to nociceptive stimuli, offering an objective measure of pain perception and nociception during the procedure[7]. Together, these indices embody a holistic approach to anesthesia management that prioritizes both the avoidance of unnecessary patient distress and the optimization of seizure quality-a determinant critically linked to the therapeutic success of ECT [8].

By intricately balancing the depth of anesthesia, as gauged by the qCON and qNOX indices, this approach ensures that seizures induced during ECT achieve requisite therapeutic parameters without subjecting patients to the potential harms of excessive nociception or inadequate sedation. It is this judicious management of anesthesia depth that minimizes the likelihood of adverse outcomes, thus enhancing the safety and tolerability of ECT as a treatment modality for MDD and other psychiatric conditions resistant to conventional treatment modalities.

Given the complex interplay between effective seizure induction, patient comfort, and the prevention of adverse effects-elements central to the optimization of ECT outcomes-the utilization of qCON and qNOX indices represents a significant advancement in the field. Such advancements facilitate a more refined and patient-centered application of ECT, ensuring that therapeutic goals are achieved within an optimized framework of patient care.

SIGNIFICANT FINDINGS AND CLINICAL IMPLICATIONS

This study involved 193 ECT sessions across 24 patients, organized into groups based on qCON indices (qCON60-70, qCON50-60, and qCON40-50). The analysis revealed that lighter anesthesia, reflected by higher qCON scores, was linked to longer electroencephalography (EEG) seizure durations, greater mid-ictal amplitudes, and elevated maximum heart rates, as shown in Table 1. Conversely, deeper anesthesia, indicated by lower qCON scores, resulted in reduced values for these parameters.

Moreover, the qNOX index played a significant role in affecting the post-ictal suppression index (PSI), with higher qNOX scores associated with increased suppression, pointing to a stronger nociceptive response under lighter anesthesia conditions. Other factors such as patient age, number of ECT sessions, and the interval between anesthesia and ECT significantly influenced EEG seizure metrics, highlighting the complexity of anesthesia management in ECT.

These results highlight the importance of using qCON and qNOX indices to fine-tune anesthesia depth, thereby optimizing seizure characteristics and treatment outcomes in ECT. Adjusting anesthesia to maintain a qCON index within 60-70 can improve EEG seizure quality without raising complication rates, thus enhancing the effectiveness and safety of ECT for patients with MDD (Table 1).

CLINICAL RECOMMENDATIONS AND FUTURE DIRECTIONS

The findings of the study underscore the critical importance of adopting tailored anesthesia management protocols during ECT to optimize seizure quality and therapeutic efficacy. Specifically, the utilization of anesthesia protocols aiming for a qCON index of 60-70 has been shown to achieve desirable seizure parameters, such as prolonged EEG seizure duration and enhanced PSI, without escalating the risk of complications[2,3]. This evidence advocates for a nuanced approach to anesthesia depth management, balancing the need for effective seizure induction with patient safety.

Anesthesia depth monitoring, particularly using indices like qCON and qNOX, represents a significant advancement in the field of ECT. Traditional monitoring methods such as the BIS and Narcotrend focus primarily on sedation and hypnosis, lacking the ability to adequately assess nociceptive responses[3,4]. The qCON index offers a dynamic measure of sedation, while the qNOX index provides valuable insights into the nociceptive stimulus response, thus offering a more comprehensive monitoring framework during ECT. The integration of these indices facilitates precise adjustments in anesthesia depth, optimizing seizure quality while minimizing adverse effects such as awareness and nociceptive discomfort[2,5].

Future research should prioritize refining these anesthesia protocols to further enhance therapeutic outcomes and explore the long-term effects of ECT administered under varying depths of anesthesia. This includes investigating the longitudinal impact on cognitive and psychiatric outcomes, as well as examining potential benefits in diverse patient populations and different clinical settings[4-6]. Such studies are essential for developing robust, evidence-based guidelines that can be universally applied, ensuring that all patients receive the highest standard of care during ECT.

Moreover, expanding the scope of research to include diverse patient demographics and varying ECT settings will provide a more comprehensive understanding of the dynamics involved. This will help in identifying any differential effects of anesthesia depth on seizure quality and patient outcomes across different populations, thus allowing for more personalized and effective treatment strategies[9-14]. By addressing these research gaps, future studies can contribute significantly to the optimization of ECT protocols, ultimately improving the therapeutic efficacy and safety of this vital treatment modality.

Future research should prioritize refining these anesthesia protocols to further enhance therapeutic outcomes and explore the long-term effects of ECT administered under varying depths of anesthesia. Longitudinal studies are essential to monitor cognitive and psychiatric outcomes over time, providing a more comprehensive understanding of the impact of anesthesia depth on ECT efficacy. Additionally, expanding the scope of research to include diverse patient populations and different clinical settings will help identify any differential effects of anesthesia depth on seizure quality and therapeutic outcomes, allowing for more personalized and effective treatment strategies.

Furthermore, the study underscores the importance of addressing potential limitations such as study heterogeneity, potential publication bias, and variations in diagnostic criteria. Standardizing research protocols and establishing uniform diagnostic criteria across studies will enhance the reliability and reproducibility of findings, ultimately contributing to the development of robust, evidence-based guidelines for anesthesia management during ECT. By addressing these research gaps, future studies can significantly improve the therapeutic efficacy and safety of ECT, leading to better outcomes for

Table 1 Effects of anesthesia depth on electroencephalography seizure parameters

Parameter	qCON 60-70	qCON 50-60	qCON 40-50	*P* value
EEG seizure duration	Longer	Moderate	Shorter	< 0.05
Mid-ictal amplitude	Higher	Moderate	Lower	< 0.05
Maximum heart rate	Higher	Moderate	Lower	< 0.05
Post-ictal suppression	Higher (qNOX > 60)	Moderate	Lower (qNOX < 40)	< 0.05
Complication rates	No significant change	No significant change	No significant change	> 0.05

EEG: Electroencephalography; qCON: Quantitative consciousness; qNOX: Quantitative nociceptive.

patients with MDD.

CONCLUSION

The insights gained from this study are pivotal in refining clinical practices and improving the management of anesthesia during ECT for patients with MDD. By identifying optimal anesthesia depths and utilizing advanced monitoring techniques, clinicians can enhance seizure quality and therapeutic outcomes, ultimately improving patient care and recovery in this vulnerable population.

FOOTNOTES

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EDITORIAL

Embracing the complexity of lived experiences in psychiatry research: Reflexivity, cultural sensitivity, and emergent design

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Abstract

This article examines the critical integration of reflexivity, cultural sensitivity, and emergent design in qualitative psychiatry research focused on lived experiences. While quantitative methods offer essential clinical insights, qualitative approaches provide a deeper understanding of the emotional, psychological, and social dimensions of mental health. Reflexivity enables researchers to remain aware of how their personal biases and professional backgrounds shape data interpretation. Cultural sensitivity ensures that mental health conditions are understood within their broader cultural contexts, helping avoid misrepresentation and promoting authentic participant expression. Emergent design offers flexibility in adapting the research process to evolving themes, particularly in the dynamic and multifaceted realm of psychiatric conditions. Together, these principles promote ethically sound, participant-centered research that captures the full complexity of lived experiences. The article also highlighted the practical implications of these principles for enhancing both academic knowledge and clinical practice in psychiatry.

Key Words: Reflexivity; Cultural sensitivity; Emergent design; Qualitative research; Psychiatry; Lived experiences; Mental health; Patient-centered research

Core Tip: The core message of this article was that the integration of reflexivity, cultural sensitivity, and an emergent design approach is crucial to capturing the full complexity of lived experiences in qualitative psychiatry research. Reflexivity ensures that researchers maintain awareness of how their own biases and professional identities shape the research process. Cultural sensitivity facilitates a more comprehensive understanding of how mental health is influenced by cultural norms and beliefs. Emergent design introduces flexibility, enabling the research to adapt to unforeseen themes and the participants' evolving narratives. Collectively, these principles foster ethically responsible and deeply insightful research in psychiatry.

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INTRODUCTION

We carefully reviewed the recently published study, "Nurse anesthetists' perceptions and experiences of managing emergence delirium: A qualitative study" in the *World Journal of Psychiatry*[1]. The study employed a descriptive phenomenological approach to effectively investigate the real-world challenges faced by anesthesia nurses in managing emergence delirium. Through semi-structured interviews, analyzed using Colaizzi's method, the research offered critical insights into cognitive gaps, work-related pressures, and systemic challenges in the management of emergence delirium. This study also stimulated reflection on the broader application of qualitative research in psychiatry.

In psychiatry, qualitative research plays an indispensable role in capturing the complex, subjective experiences of both patients and healthcare providers, which is essential for understanding individuals in their full, multifaceted dimensions [2]. While quantitative methods contribute essential data on clinical outcomes, they often overlook the emotional, psychological, and social dimensions of mental health. Lived experiences (personal narratives of individuals dealing with psychiatric conditions) offer crucial insights that are vital to improving both clinical practice and patient care[3]. However, to conduct qualitative research effectively, it is critical to integrate three key principles: Reflexivity; cultural sensitivity; and emergent design[4,5]. These principles ensure that qualitative research remains flexible, contextually relevant, and ethically sound. This article explores the significance of these elements in psychiatric research, provides practical recommendations, and emphasizes their essential role in generating meaningful and impactful findings.

REFLEXIVITY: CRITICAL PRACTICE FOR MITIGATING BIAS IN PSYCHIATRY RESEARCH

Reflexivity, or the practice of critically reflecting on one's own biases, assumptions, and professional identity, is a fundamental component of qualitative research[6,7]. In psychiatry, where researcher-participant dynamics can be deeply influenced by power imbalances, reflexivity is especially critical[8]. Researchers should consistently evaluate how their professional background, personal experiences, and mental health paradigms influence their interpretation of data and interactions with participants. Notably, clinician-researchers may adopt different stances during reflexivity, depending on whether they are functioning in their role as a researcher or a clinician.

For instance, a psychiatrist conducting research on the experiences of patients with depression may interpret patient narratives through a clinical lens, focusing on symptoms and treatment adherence while potentially overlooking the emotional burden of living with depression, such as feelings of isolation, hopelessness, or stigma. By engaging in reflexive practices, such as maintaining a reflexive journal, the researcher can identify and mitigate these biases, ensuring a more comprehensive understanding of the patient's lived experience[7].

Moreover, reflexivity encompasses the researcher-participant relationship[9]. In psychiatric contexts where participants may feel vulnerable or deferential to the authority of the researcher reflexivity encourages mindfulness regarding how these dynamics shape the dialogue. For example, a participant may provide responses they believe the researcher wants to hear, particularly if the researcher also serves as their clinician. Through reflexive practice, the researcher can create a more open and authentic environment for participants to express themselves freely, thus safeguarding the integrity of the data collected[5,7].

CULTURAL SENSITIVITY: KEY TO UNDERSTANDING LIVED EXPERIENCES ACROSS CONTEXTS

Mental health is deeply embedded in cultural contexts, and cultural sensitivity is crucial to capturing the lived experiences of psychiatric patients[10,11]. Psychiatric conditions are understood, treated, and stigmatized differently across cultures, making it essential for researchers to approach their studies with cultural awareness of these variations.

For instance, in some cultures, mental illness may be framed as a spiritual issue or moral failure, while in others, it is regarded as a medical condition requiring treatment[12]. A researcher conducting interviews in a culture where mental illness is stigmatized may find that participants underreport or conceal their symptoms out of fear of social repercussions

[13]. In such cases, researchers must design their interview guides to be culturally sensitive, enabling participants to express their experiences in culturally congruent ways.

To enhance cultural sensitivity, researchers should collaborate with cultural intermediaries, such as community leaders, cultural experts, or local mental health advocates[5,15]. These intermediaries can offer valuable insights into culturally appropriate language, communication styles, and thematic elements for interviews. For example, when studying post-traumatic stress disorder among immigrant populations, cultural intermediaries can provide critical guidance in understanding the trauma of migration, acculturation stress, and discrimination. These experiences often differ across cultural groups, and the involvement of intermediaries ensures that the research approach is tailored to the unique context of each population.

Additionally, researchers should recognize that mental health conditions are often stigmatized differently in collectivist *vs* individualist societies[14]. In collectivist cultures, mental illness may be regarded as a family issue rather than an individual problem, influencing how participants discuss their experiences. Culturally sensitive research enables the researcher to navigate these nuances, ensuring a more authentic representation of participants' mental health journeys.

EMERGENT DESIGN: NAVIGATING THE COMPLEXITIES OF LIVED EXPERIENCES

Psychiatric conditions are dynamic and multifaceted, rendering a rigid research design unsuitable for qualitative studies on lived experiences. An emergent design approach allows researchers to maintain flexibility and responsiveness to evolving data, adapting their methods to capture the full complexity of participants' experiences[5].

For example, a researcher studying patients with bipolar disorder may initially focus on manic and depressive episodes[16]. However, during interviews, participants may repeatedly raise concerns about the social isolation they experience between episodes or their difficulties with medication side effects. An emergent design would enable the researcher to adjust the interview questions or analysis framework to delve deeper into these unforeseen yet significant themes. This adaptability is especially crucial in psychiatric research, where individual variations in illness experiences are pronounced.

Moreover, emergent design strengthens ethical accountability[5]. In psychiatry, participants may experience distress while discussing their mental health, and an emergent approach allows the researcher to adjust the pace or direction of the interview to prioritize the participant's emotional well-being[17,18]. For instance, if a participant becomes visibly uncomfortable when recounting traumatic experiences, the researcher can pause or redirect the conversation to less distressing topics. This flexibility guarantees that the research remains both participant-centered and ethically sound.

Emergent design also enhances the richness of data collection, with semi-structured or unstructured interview guides being particularly useful in providing the necessary flexibility for such adaptations[5]. As new themes arise, the researcher can adjust the scope of the study to further explore these areas, allowing for a more comprehensive understanding of lived experiences. For instance, a study on schizophrenia may uncover participants' greater concern for the social stigma of their condition than for the symptoms themselves. An emergent design permits the researcher to pivot and investigate this issue in greater depth, thereby capturing a more nuanced view of the patient's experience.

CONCLUSION

Qualitative research on lived experiences in psychiatry necessitates a focused approach to reflexivity, cultural sensitivity, and emergent design to ensure meaningful, participant-centered results. Reflexivity enables researchers to maintain awareness of how their positionality influences the research process, cultural sensitivity ensures that mental health experiences are understood within their broader cultural contexts, and emergent design allows the study to adapt to the dynamic nature of psychiatric conditions. Together, these elements cultivate a deeper and more nuanced comprehension of mental health and offer valuable insights that can inform both academic knowledge and clinical practice. By embracing these principles, researchers are positioned to contribute to more compassionate, contextually grounded, and ethically sound psychiatry research.

FOOTNOTES

Author contributions: Jiang YL wrote the original draft; Xiao ZS and Samah NA contributed to conceptualization, writing, reviewing, and editing; Xiao ZS, Zhou H and Jiang YL participated in drafting the manuscript. All authors read and approved the final version of the manuscript. All authors participated in critical discussions regarding the paper's structure, focus, and theoretical alignment. Designating Jiang YL and Samah NA as co-corresponding authors is appropriate due to their complementary roles and leadership in the study. Samah NA, as the primary supervisor, provided foundational guidance and inspiration for the research, especially in shaping its focus on cultural sensitivity and addressing complex lived experiences in psychiatry. Jiang YL offered critical contributions to methodology and data analysis, ensuring the study's adherence to rigorous reflexive practices. Their joint expertise and continuous oversight were vital in fulfilling the research objectives, making their co-corresponding authorship essential. The co-first authors, Xiao ZS and Zhou H, collaboratively conceptualized the research framework and jointly completed the organization and refinement of the manuscript.

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Depression and anxiety disorders in chronic obstructive pulmonary disease patients: Prevalence, disease impact, treatment

Chang-Jian Qiu, Shuang Wu

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Abstract

Chronic obstructive pulmonary disease (COPD) is a common respiratory disorder that often co-occurs with depression and anxiety, worsening disease progression and reducing quality of life. A thorough review of the existing literature was conducted, including searches in PubMed, Embase, PsycINFO, and Cochrane Library databases up to 2024. This review encompasses a critical analysis of studies reporting on the prevalence, impact, and management of depression and anxiety in COPD patients. We found a high prevalence of psychological comorbidities in COPD patients, which were associated with worse disease outcomes, including increased exacerbations, hospitalizations, and reduced health-related quality of life. Diagnosing and managing these conditions is complex due to overlapping symptoms, necessitating a comprehensive patient care approach. While there has been progress in understanding COPD comorbidities, there is a need for more personalized and integrated treatments. This review emphasizes the need for increased awareness, tailored treatment plans, and further research for effective interventions.

Key Words: Chronic obstructive pulmonary disease; Depression; Anxiety; Comorbidities; Treatment strategies; Narrative review

Core Tip: Chronic obstructive pulmonary disease (COPD) is a global respiratory condition that affects public health. Depression and anxiety often accompany COPD, which can worsen the disease and lower patient quality of life. This narrative review examines COPD patients' depression and anxiety rates, their effects on disease progression, and current treatment options.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a prevalent respiratory disorder characterized by airflow obstruction, often stemming from chronic bronchitis or emphysema[1]. It poses a significant threat to public health, with a high prevalence rate of 9% to 10% among individuals over the age of 40 worldwide[2-4]. COPD diminishes patient quality of life and imposes a substantial economic burden on families and healthcare systems[5].

The etiology of COPD is not fully understood but is generally associated with chronic bronchitis and emphysema[5]. Risk factors include environmental exposures such as smoking, dust, chemicals, respiratory infections, air pollution, and lower socioeconomic status, as well as individual factors like genetic predispositions and developmental issues during critical periods. Patients exhibit a range of symptoms including chronic cough, sputum production, shortness of breath, chest tightness, wheezing, fatigue, and weight loss[6]. COPD is a complex disease primarily caused by exposure to toxic particles or gases, leading to abnormalities in the airways and/or alveoli. It affects the lungs, the cardiovascular, nervous, endocrine, and mental health systems, resulting in complications such as asthma, lung cancer, diffuse pulmonary fibrosis, pulmonary hypertension, right-sided heart failure, diabetes, gastroesophageal reflux disease, depression, and anxiety[7,8]. Among these, depression and anxiety are the most common comorbidities, often underdiagnosed due to overlapping symptoms[9]. The overlap between physical and mental symptoms complicates the diagnostic process and necessitates a comprehensive approach to patient care[10].

This review aims to delve into the prevalence of anxiety disorders in COPD patients and scrutinize the profound impact of depression and anxiety on disease progression. By synthesizing current research and treatment strategies, we aim to shed light on the importance of addressing these psychological comorbidities in clinical practice, thereby enhancing patient care and improving outcomes.

CURRENT STATUS OF DEPRESSION AND ANXIETY DISORDERS IN COPD PATIENTS

Prevalence and symptoms of depression and anxiety

Depression is a debilitating disorder that affects both the physiological and psychological well-being of individuals, often leading to a sense of helplessness and an increased risk of suicidal tendencies. Individuals with depression exhibit a loss of interest in activities they once enjoyed, impaired social relationships, and a range of other symptoms including sleep disturbances, fatigue, difficulty concentrating, and disordered eating patterns. The World Health Organization (WHO) recognizes major depressive disorder as one of the leading contributors to the global burden of disease[11]. In the context of comorbid physical illnesses, particularly chronic and severe conditions, the prevalence of major depressive disorder ranges from 10% to 20%[12-15]. Anxiety disorders, characterized by feelings of fear, avoidance, and restlessness, often co-occur with depression, exacerbating the complexity of the conditions[16,17]. The coexistence of depression and anxiety is more common than either disorder in isolation, and individuals with chronic illnesses such as COPD are 2 to 3 times more likely to experience depression compared to the general population matched for age and sex[12,18,19].

Prevalence of depression and anxiety in COPD patients

Depression is a common comorbidity in adult COPD patients, with an estimated prevalence of 24.6%[20]. The incidence of anxiety and depressive disorders in COPD patients is significantly higher, primarily associated with damage to the central nervous system and the chronic experience of negative emotions in COPD[21]. The likelihood of a COPD patient developing comorbid depression is four times higher than that of an individual without COPD[21]. Furthermore, patients with other chronic conditions such as arthritis, cancer, diabetes, hypertension, and stroke are twice as likely to develop depression compared to those without these conditions[22]. Among many chronic diseases, the incidence of depression is significantly higher in women than in men[23], and this disparity is also observed in COPD patients, where the proportion of women with comorbid depression is notably higher than that of men[24].

Analysis of anxiety factors in patients with COPD

COPD causes organ damage but also inflicts psychological harm on patients, who can often exhibit various psychological abnormalities, predominantly characterized by anxiety, irritability, and depression[25]. Studies have indicated that the incidence of comorbid anxiety in COPD patients ranges from 50% to 75%[26]. Psychological disorders significantly impair patient recovery and quality of life and are one of the major factors leading to patient mortality[27]. Consequently, numerous clinical researchers are dedicated to analyzing the causes of anxiety in COPD patients. Through the analysis and summary of patient onset factors, effective measures can be taken to intervene, thereby improving the psychological state of patients and promoting faster recovery to health. For instance, Song *et al*[28] conducted a study on elderly patients with COPD to explore the best psychological nursing plan using anxiety and depression scales to identify the main factors affecting patient anxiety and depressive emotions. The study found that factors influencing anxiety in COPD

patients include occupation, education level, economic status, family relationships, and disease severity. Effective psychological nursing interventions based on these factors have been developed to improve patient psychological conditions, leading to a significant improvement in anxiety and depressive symptoms and promoting faster patient recovery.

Lokesh *et al*[29] selected 100 patients with COPD for anxiety and depression scale assessment and found that the incidence of anxiety and depression in COPD patients was 65% and 54%, respectively. Patients who were more aware of their condition had poorer quality of life and more severe anxiety and depression. Living alone was identified as a significant factor contributing to patient anxiety, with males being more prone to anxiety than females. Therefore, if patients are diagnosed with symptoms of anxiety or depression, timely diagnosis and effective treatment measures should be taken to improve patient quality of life and prognosis.

Wu *et al*[30] studied related factors of patients with COPD and comorbid anxiety and depression disorders and found that the higher the quality of life assessment test score, the higher the probability of comorbid anxiety and depression. Patients without medical insurance and with longer disease courses had a higher probability of anxiety, more hospital admissions, and lower quality of life. Therefore, the clinical treatment of COPD patients with comorbid anxiety should be emphasized.

Cao *et al*[31] found that due to the chronic and protracted nature of COPD, patients experience a continuous decline in lung function and activity tolerance, reduced labor capacity, and decreased quality of life. The long-term medical treatment places a heavy economic burden on patients, often leading to negative psychological states such as hopelessness, apathy, inferiority, self-blame, and anxiety. Psychological counseling is an effective measure in treating anxiety and depression, and pharmacological treatment (*e.g.*, with Dailixin) is also noteworthy for its ability to alleviate anxiety and depressive emotions and control the disease.

IMPACT OF DEPRESSION AND ANXIETY ON COPD

Influence on disease course

A comprehensive meta-analysis by Atlantis *et al*[32] examined 22 studies, substantiating the bidirectional relationship between depression, anxiety, and COPD. Sixteen of these studies, encompassing 28759 patients followed for 1 year to 8 years, were utilized to predict the impact of depression and anxiety on COPD outcomes. Conversely, six studies, including 7439159 patients, investigated the influence of COPD on the incidence of depression and anxiety. The findings indicate that depression and anxiety significantly increase the risk of adverse COPD outcomes [relative risk (RR) = 1.43; 95%CI: 1.22-1.68], with a pronounced effect in patients under the age of 66. Comorbid depression augments the risk of mortality in COPD (RR = 1.83; 95%CI: 1.00-3.36), particularly among males. In the majority of studies, anxiety (or psychological stress) raised the risk of COPD exacerbation or death (RR = 1.27; 95%CI: 1.02-1.58). Furthermore, COPD elevated the risk of developing depression (RR = 1.83; 95%CI: 1.00-3.36).

Pooler *et al*[33] conducted a systematic review and meta-analysis of 24 studies, revealing that 17 studies (70.9%) provided evidence linking comorbid depression and anxiety with higher hospitalization and readmission rates due to COPD exacerbations. The analysis demonstrates that patients with comorbid depression and anxiety, once hospitalized, have longer hospital stays and a higher risk of mortality post-discharge[34].

Mathew *et al*[35] performed a single laboratory assessment of 37 COPD patients, including 17 current daily smokers and 20 former smokers. Participants completed self-report measures of psychological factors, impact of COPD symptoms, symptom response, and symptoms of anxiety and depression. Three psychological factors were evaluated: Anxiety sensitivity (AS), distress intolerance (DI), and anhedonia (Anh). In univariate regression models, AS, DI, and Anh were all correlated with severe COPD dyspnea symptoms. After adjusting for symptoms of generalized depression and anxiety, AS remained a significant predictor of dyspnea symptoms in COPD[36].

Impact on health-related quality of life

Enhancing health-related quality of life (HRQL) is a critical goal in the treatment of patients with chronic respiratory failure (CRF) undergoing long-term oxygen therapy and/or home non-invasive ventilation. A systematic review and meta-analysis included six studies to examine the association between comorbid depression and anxiety in COPD and HRQL[37]. The results indicate that comorbid depression at the 1-year follow-up is significantly correlated with HRQL (pooled $r = 0.48$, 95%CI: 0.37-0.57, $P < 0.001$). Similarly, comorbid anxiety at the 1-year follow-up was also significantly related to HRQL (pooled $r = 0.36$, 95%CI: 0.23-0.48, $P < 0.001$). A multicenter prospective cross-sectional study involving 80 severe COPD patients with an average age of 66 years and 93% male participants selected depression status, dyspnea, exacerbation frequency, and exercise capacity as predictors for the total St. George's Respiratory Questionnaire score. The findings suggest that the presence of comorbid depression is the strongest predictor of disease-specific and general HRQL. Screening and early intervention for depression in severe COPD patients can improve HRQL[38].

Recent evidence underscores the importance of comprehensive care in addressing the psychological comorbidities in COPD[16,19,31]. The use of remote patient monitoring (RPM) technologies has shown promise in helping patients self-manage and reducing COPD-related hospital readmissions[28]. These technologies, which include devices like pulse oximeters and spirometers, can aid in the early recognition of COPD exacerbations, potentially leading to better disease management and improved HRQL[30]. Pulmonary rehabilitation, a key non-pharmacological intervention, has been shown to improve not only physical capacity but also mood symptoms in COPD patients. This holistic approach can be particularly beneficial in enhancing HRQL by reducing symptoms, optimizing functional status, and increasing patient participation. The integration of psychological support with medical management is crucial in enhancing HRQL for COPD patients. The adoption of RPM technologies and participation in pulmonary rehabilitation programs can provide

additional benefits beyond traditional pharmacological treatments, offering a more comprehensive approach to care. The impact of depression and anxiety on COPD are summarized in Table 1.

TREATMENT STRATEGIES

When comorbid with COPD, depression and anxiety significantly impact patients' quality of life and functional outcomes. The WHO advocates for chronic disease patients, such as those with COPD, to receive patient-centered, comprehensive care plans that extend beyond disease-specific treatments[39]. Therapeutic approaches for psychological symptoms in COPD patients typically include cognitive-behavioral therapy, pharmacological interventions, pulmonary rehabilitation, relaxation techniques, and palliative care.

Pharmacological interventions

The National Institute for Health and Care Excellence (NICE) guidelines for the treatment of depression in older adults recommend the use of antidepressant medications for moderate to severe depression, including in patients with COPD. Selective serotonin reuptake inhibitors (SSRIs) are suggested as the first-line treatment for depression and should be accompanied by appropriate depression rating scales, such as the Patient Health Questionnaire-9 or the Hospital Anxiety and Depression Scale[40]. A subset of randomized clinical trials has confirmed the benefits of antidepressant treatment for patients with COPD and comorbid depression, not only reducing depressive symptoms but also decreasing tobacco dependence, improving subjective breathlessness, enhancing appetite, preventing weight loss, and alleviating anxiety symptoms[41]. Current pharmacological research for depression and anxiety in COPD patients primarily focuses on SSRIs and tricyclic antidepressants (TCAs). An evaluation of antidepressants, mainly SSRIs and TCAs, has shown significant improvement for patients with depression or depressive symptoms comorbid with physical illnesses. This assessment also demonstrated that SSRIs have a higher degree of long-term improvement compared to TCAs[42]. Therefore, SSRIs are the preferred treatment for depression and anxiety[43].

In a randomized controlled trial[44] involving 120 patients with stable COPD and moderate to severe depression, there was no statistically significant difference in lung function test parameters between the placebo and intervention groups treated with sertraline ($P > 0.05$). However, patients in the sertraline group showed a greater change in the Hamilton Depression Scale scores and the COPD Assessment Test after treatment ($P < 0.05$), and they also walked a longer distance in the 6-minute walk test compared to the placebo group ($P < 0.05$). A single-blind study[45] followed 14 COPD patients with comorbid depression who took fluoxetine 20 mg daily for 6 months, with 7 completing the study. Among those who completed the study, 4 responded to fluoxetine (a 50% reduction in the Geriatric Mental State Schedule scores). After 6 months of fluoxetine treatment, there were no significant improvements in forced expiratory volume in 1 second or physical activity scores. A study[46] compared the efficacy of paroxetine (20 mg/day) with placebo in 28 COPD patients over 6 weeks. There were no statistically significant differences in exercise capacity, lung function, and quality of life between the two groups. After the 6-week open-label phase with paroxetine, both groups continued to take 20 mg paroxetine for an additional 3 months, resulting in significant improvements in depression scores, walking distance, and quality of life.

Potential drug interactions

In the management of COPD, β2-agonists and anticholinergic medications are frequently utilized. Notably, β2-agonists such as salbutamol, indacaterol, and salmeterol can lead to dose-dependent prolongation of the QT interval and potassium loss. The co-administration of these medications with certain SSRIs known to prolong the QT interval, such as escitalopram, citalopram, and fluoxetine, and TCAs like nortriptyline and dothiepin, may result in additive effects and an increased risk of ventricular arrhythmias[47]. Furthermore, TCAs have the potential to exacerbate cardiovascular adverse effects associated with β2-agonists, including hypertension, tachycardia, and chest pain. Additionally, the anticholinergic properties of TCAs can intensify the effects of anticholinergic bronchodilators used in COPD, such as tiotropium and ipratropium, leading to side effects like dry mouth, urinary retention, constipation, mydriasis, blurred vision, and fever, and potentially worsening glaucoma.

Non-pharmacological interventions

The NICE guidelines for depression in adults highlight the importance of psychosocial interventions for patients with chronic health conditions, including those with clinical or subthreshold depression. These interventions can range from low to high intensity, tailored to the severity of mood symptoms[48]. A systematic review of randomized controlled trials involving psychological and/or lifestyle interventions for adult COPD patients indicates that complex interventions, including an exercise component, significantly improve depressive and anxiety symptoms. Importantly, multi-component exercise training can effectively alleviate anxiety and depressive symptoms in all COPD patients, irrespective of the severity of these conditions[49].

CONCLUSION

Current studies on treating depression and anxiety in COPD patients face limitations such as small sample sizes, diverse patient populations, and inconsistent assessment tools. These issues necessitate more rigorous validation through larger

Table 1 Impact of depression and anxiety on chronic obstructive pulmonary disease

Disease impact	Details
Bidirectional relationship	A significant bidirectional relationship between depression, anxiety, and COPD[32]
Impact on COPD outcomes	Depression and anxiety significantly increase the risk of adverse COPD outcomes and mortality in COPD. Anxiety raises the risk of COPD exacerbation or death[32]
Hospitalization and readmission rates	Higher hospitalization and readmission rates due to COPD exacerbations in patients with comorbid depression and anxiety[33]
Psychological factors and dyspnea	Anxiety sensitivity to be a significant predictor of dyspnea symptoms in COPD, even after adjusting for generalized depression and anxiety[35]
HRQL	Comorbid depression and anxiety at the 1-year follow-up are significantly correlated with HRQL in COPD[35]
Predictors of HRQL	Comorbid depression as the strongest predictor of disease-specific and general HRQL in severe COPD patients[38]

COPD: Chronic obstructive pulmonary disease; HRQL: Health-related quality of life.

randomized controlled trials to confirm treatment effectiveness. For patients with mild to moderate depression, non-pharmacological interventions like psychological therapy and lifestyle changes are recommended. These methods have shown efficacy in managing symptoms without medication-related risks. In severe cases where non-pharmacological approaches are inadequate, cautious use of antidepressants like SSRIs may be necessary. Regular ECG assessments are recommended to monitor for potential QT interval prolongation[30]. Patients should be informed about the importance of immediate medical attention for symptoms like palpitations or syncope, which could signal cardiac side effects. Regular monitoring of electrolyte levels is also crucial to prevent arrhythmias. The use of antidepressants requires careful consideration of potential drug interactions. Balancing the benefits of symptom relief against treatment risks is key, emphasizing the need for personalized treatment strategies tailored to each patient's specific needs. The findings highlight the importance of a multifaceted approach to managing depression and anxiety in COPD patients. This includes the development of more robust research methodologies, the promotion of non-pharmacological interventions, and the cautious application of pharmacological treatments with comprehensive patient education and monitoring.

FOOTNOTES

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ORIGINAL ARTICLE

Case Control Study

Interaction between serum inflammatory cytokines and brain-derived neurotrophic factor in cognitive function among first-episode schizophrenia patients

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Abstract

BACKGROUND

The pathogenesis of cognitive impairment in schizophrenia (SCZ) remains unclear. Accumulating studies showed that inflammatory-immune dysregulation and altered brain derived neurotrophic factor (BDNF) levels play a crucial role in the psychopathology of SCZ. However, their association with cognitive dysfunction in first-episode SCZ patients has not been thoroughly investigated.

AIM

To explore the interaction effects between cognitive function and inflammatory cytokines and BDNF in first-episode SCZ.

METHODS

The current study is a cross-sectional case-control investigation that recruited 84 patients with first-episode SCZ (SCZ group) and 80 healthy controls (HCs group) at the Huzhou Third Municipal Hospital between August 2021 and September 2023. ELISA was employed to measure the serum levels of interleukin (IL)-1β, IL-4, IL-6, IL-10, and BDNF. The Chinese brief cognitive test (C-BCT) and the positive and negative syndrome scales were measured the severity of cognitive impairment and psychiatric symptoms.

RESULTS

Compared to the HC group, the SCZ group exhibited elevated IL-1β and IL-6 levels, decreased BDNF levels, and reduced C-BCT scores (all $P < 0.001$). In SCZ, BDNF was negatively correlated with IL-6 ($r = -0.324$, $P < 0.05$). Information processing speed was negatively correlated with IL-6 ($r = -0.315$, $P < 0.05$) and positively with BDNF ($r = 0.290$, $P < 0.05$); attention, working memory, comprehensive ability, and executive function were negatively correlated with IL-1β and IL-6 (all $P < 0.05$) and positively with BDNF (all $P < 0.05$). Multiple regression analysis showed IL-6 influenced C-BCT dimensions ($\beta = -0.218$ to -0.327, all $P < 0.05$); attention and executive ability were influenced by IL-1β ($\beta = -0.199$ to -0.261, all $P < 0.05$); comprehensive executive ability was influenced by BDNF ($\beta = 0.209$, $P < 0.05$).

CONCLUSION

Our findings suggested that interrelationships between immune dysfunction and neurotrophic deficiency might underlie the pathological mechanisms of cognitive impairments in first-episode SCZ patients.

Key Words: Brain-derived neurotrophic factor; Inflammatory cytokines; First-episode schizophrenia; Cognitive function; Pro-inflammatory cytokines; Neuroinflammation; Serum biomarkers

Core Tip: The previous literature has demonstrated that dysregulation of the inflammatory immune and alterations in brain derived neurotrophic factor (BDNF) levels play a pivotal role in the pathophysiology of schizophrenia (SCZ). In this study, 84 patients with first-episode SCZ and 80 healthy volunteers were recruited. We assessed the cognitive function and psychiatric symptoms of the subjects, measured their serum inflammatory cytokines and BDNF levels, and explored the interaction between cognitive impairment and serum inflammatory cytokines and BDNF in first-episode SCZ. The findings of this study suggest that cognitive impairment in first-episode SCZ was related to immune inflammation imbalance and neurotrophic deficiency.

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INTRODUCTION

Schizophrenia (SCZ) is a prevalent severe mental disorder with an incidence rate of approximately 1%[1]. The exact etiology remains unclear, believed to arise from the complex interplay of biological, psychological, social, and other factors[2]. Cognitive impairment stands out as a fundamental symptom of SCZ, significantly impacting patients' quality of life, social function, and imposing a substantial burden on family and society[3]. In clinical practice, nearly 90% of first-episode schizophrenic patients have cognitive impairment, primarily characterized by executive dysfunction and working memory deficits which display a broad and continuous progression[4]. Moreover, the cognitive function of most patients was much different than predicted based on pre-onset intelligence and education level[5]. Despite recent research has made progress, the pathogenesis is still unclear for cognitive impairment in patients with first-episode SCZ.

Inflammation, or the inflammatory response, is a consequence of immune system activation. Substantial evidence suggests that immune inflammation plays a crucial role in the onset and progression of SCZ[6-8]. The central inflammatory reaction includes pro-inflammatory and anti-inflammatory responses[9]. Pro-inflammatory cytokines that are generated as part of the pro-inflammatory response have the ability to activate microglia and hinder the formation of nerve cells in the hippocampus[10]. This leads to the impairment of synaptic plasticity, which in turn hinders the repair of neurological dysfunction and ultimately results in cognitive decline. The anti-inflammatory reaction can produce anti-inflammatory cytokines, which have a certain protective effect on neural cells related to cognitive function[11]. Maes and Anderson[12] and Maes *et al*[13] found that patients with first-episode SCZ have increased levels of pro-inflammatory cytokines, including interleukin (IL)-1, IL-6, IL-17, tumor necrosis factor (TNF-α), and eotaxin (CCL11). These cytokines trigger tryptophan catabolism through the TRYCAT pathway, increase IgA levels, and ultimately lead to the accumulation of neurotoxic substances such as pyridinic acid, xanthine aci, quinolinic acid, and 3-oh-kynurenin. This accumulation may disrupt functional connectivity in brain regions associated with cognitive functions[14]. Studies have also reported unaltered levels of IL-6 and IL-8 in the cerebrospinal fluid of newly diagnosed SCZ patients[15].

A study of multicenter longitudinal found that lower levels of anti-inflammatory cytokines (IL-2 and IL-10) in patients with SCZ were associated with higher suicide risk scores[16]. At the same time, other studies have reported unchanged in anti-inflammatory cytokines levels (IL-4 and IL-10) in patients with acute SCZ. The above studies have reflected that the abnormalities of immune regulation in SCZ are the result of the joint action of pro-inflammatory and anti-inflammatory

cytokines to antagonize each other. The current literature lacks research investigating the collaborative involvement of pro-inflammatory cytokines and anti-inflammatory cytokines in the cognitive impairment process among first-episode SCZ patients.

It is important to study the potential neurochemical basis associated with cognitive impairment in first-episode patients with SCZ. Abnormalities in neurotrophic molecules are one of the important candidate factors for explaining cognitive impairment in first-episode patients with SCZ[17,18]. The brain derived neurotrophic factor (BDNF) plays an important role in maintaining neuronal survival, differentiation migration, neurogenesis, and synaptic plasticity[19,20]. Most studies have found a decrease in serum BDNF levels in patients with SCZ, which is closely related to cognitive function[21,22]. The abnormal BDNF-mediated pathways, including the extracellular regulatory protein kinase (MEK-ERK), phosphatidylinositol kinase (PI3K), and phospholipase CPC-γ pathway, are considered to serve as mediators between neuroinflammation and neuronal dysfunction[23]. This suggests that the cognitive impairment observed in SCZ may involve a reciprocal regulation between various inflammatory cytokines and BDNF. However, there are currently few studies on the interaction between cognitive impairment in first-episode SCZ and inflammatory cytokines and neurotrophic factors[24]. Therefore, it is necessary to further understand the role of the regulatory mechanisms of inflammatory cytokines and neurotrophic factors in cognitive impairment in first-episode SCZ. It may have some enlightening effects on early clinical intervention and treatment. Therefore, this study aims to explore by analyzing 84 patients with first-episode SCZ and 80 healthy controls (HCs) to address two questions: (1) The disparity in serum levels of IL-1β, IL-4, IL-6, IL-10, and BDNF between first-episode SCZ patients and HCs; and (2) The correlation between serum inflammatory cytokines, BDNF, and the severity of cognitive impairment in first-episode SCZ patients.

MATERIALS AND METHODS

Research participants

SCZ group was admitted to the Third People's Hospital of Huzhou City from August 2021 to September 2023.

Inclusion criteria: (1) Meeting the diagnostic criteria for SCZ in The American Psychiatric Association's Diagnostic and Statistical Manual, Fifth Edition; (2) Aged between from 18 to 65 years old; (3) Having a positive and negative symptom scale (PANSS) score of ≥ 60; (4) Experiencing the first onset of illness without prior use of any antipsychotic medication; (5) Possessing a junior high school or above education level and being able to cooperate in completing tests; and (6) Obtaining informed consent from the patient's parents or legal guardians.

Exclusion criteria: (1) Mental disorders caused by organic brain diseases, mental retardation, *etc.*; (2) Patients with severe physical illnesses, especially those with a history of immune system related diseases or recent use of nonsteroidal anti-inflammatory drugs or immune modulators; (3) Patients receiving physical intervention for mental symptoms, such as repeated transcranial magnetic stimulation or modified electroconvulsive therapy; and (4) Pregnant/lactating women. HCs group were recruited from healthy volunteers who came to the hospital for physical examination at the same time, as well as medical staff in our hospital. Exclusion criteria are the same as those for the SCZ group. Fully inform all participants and their guardians of the content of this study and sign an informed consent form before enrollment. This study was approved by the Ethics Committee of Huzhou Third Municipal Hospital (Ethical Approval No. 2021-018). According to the sample size calculation formula of correlation analysis, $\alpha = 0.05$, $\beta = 0.20$, 85 patients with SCZ need to be included, and HCs will be matched 1:1. Finally, 80 healthy volunteers will be recruited.

Method

Clinical data collection: The present study is a cross-sectional case-control investigation that recruited 84 patients with first-episode SCZ (SCZ group) and 80 HCs (HCs group) at the Huzhou Third Municipal Hospital between August 2021 and September 2023. To minimize potential confounding factors, control group participants were matched for age, sex, and educational level. Additionally, a family history of psychiatric disorders was considered during selection to further refine matching.

Clinical assessment: Two psychiatrists evaluated the psychiatric symptoms of the SCZ group using the PANSS scale and evaluated the cognitive function of all subjects using Chinese brief cognitive test (C-BCT)[25], and the consistency test kappa value ≥ 0.90.

The PANSS consists of positive symptoms, negative symptoms, and general pathology. Positive symptoms include delusions, hallucinations, excitement, confusion, arrogance, suspicion or persecution, and hostility. Negative symptoms include emotional passivation, affective disturbance, emotional withdrawal, passivity or apathy, lack of spontaneity in conversation, abstract thinking, and rigid thinking. General pathology includes 16 items, such as worry about physical health, anxiety, guilt, tension, affectation, depression, and slowness. The above three sub-items are scored on a scale of 1-7 points. Scores 1-7 represent no symptoms, very mild symptoms, mild symptoms, moderate symptoms, mild symptoms, severe symptoms, and very severe symptoms, respectively. The higher the PANSS score, the more severe the symptoms.

BCT operates electronically and has a duration of approximately 15 minutes. It includes four dimensions: Connectivity test, continuous operation, digital breadth, and symbol encoding. These dimensions include information processing speed, attention, working memory and comprehensive + executive ability, respectively. During the test, information such as age, gender, and education level of the subjects are entered, and scores for each dimension are generated. Each dimension is evaluated based on its T score, deficit score, level of impairment, and percentile ranking in the Chinese test population. The relationship between the T score, deficit score, and damage degree is defined as follows: A T score of 40

or above indicates no deficits and normal functioning; a T score of 35-39 indicates a deficit score of 1 and mild impairment; a T score of 30-34 corresponds to a deficit score of 2 and mild to moderate impairment; a T score of 25-29 corresponds to a deficit score of 3 and moderate impairment; a T score of 20-24 indicates a deficit score of 4 and moderate to severe impairment; finally, a T score below 19 indicates a deficit score of 5 and severe impairment.

Blood sample collection and indicator testing: The 5 mL of fasting venous blood was collected from all subjects on the day of enrollment or the next morning from 6: 30 to 7: 30 to avoid the influence of changes in the biological rhythm of the measured factors. After collection, the blood was centrifuged at 3000 r/min at 4 °C for 10 minutes after stewing for 30 minutes. The isolated serum was stored in a refrigerator at -80 °C before testing. The using reagent kits were provided by Jiangsu Jingmei Biotechnology Co., Ltd. The ELISA was used to detect IL-1β, IL-4, IL-6, IL-10, and BDNF in serum levels.

Statistical analysis

Statistical analysis was performed using SPSS 19.0. Quantitative data that conform to a normal distribution are represented by (mean ± SD, and independent sample *t*-tests are used for inter group comparisons. Count data is represented as [*n* (%)], and inter group comparison is used χ^2 inspection. Using Pearson correlation analysis test the correlation between serum biomarkers and cognitive function, and screen for independent variables with statistical differences. Multiple linear regression analysis was employed to assess the impact on cognitive function, with significance denoted by $P < 0.05$, indicating a statistically significant difference.

RESULTS

Comparison of clinical data and serum inflammatory cytokines and BDNF between two groups

The final study included 84 first-episode SCZ patients (40 males and 44 females), 1 patient who withdrew midway without completing C-BCT, and 80 HCs (51 males and 49 females). There was no statistically significant difference in general information such as sex, age, years of education, and smoking history between the two groups (all $P > 0.05$). The scores of all dimensions of C-BCT in the SCZ group were lower than those in the HCs group, and the differences were statistically significant (all $P < 0.001$). The serum BDNF levels in the SCZ group were significantly lower than those in the HCs group, and the difference was statistically significant (all $P < 0.001$). The levels of IL-1β and IL-6 of the SCZ group were higher than the HCs group, and the difference was statistically significant (all $P < 0.001$; Table 1).

Individuals with first-episode SCZ exhibit extensive cognitive impairments in cognitive function assessments, particularly evident in significant reductions in information processing speed, attention, working memory, and overall executive functions. Simultaneously, these patients show elevated levels of inflammatory cytokines IL-1β and IL-6 in their serum, while the levels of BDNF are decreased. The alterations in these biomarkers are closely associated with cognitive dysfunction.

Correlation analysis between serum BDNF and inflammatory cytokines in the SCZ group

The serum BDNF level in the SCZ group had a negative correlation with IL-6 ($r = -0.324$, $P < 0.05$), and there was no correlation between the levels of IL-1β, IL-4, and IL-10 (all $P > 0.05$; Table 2).

As a vital neurotrophic factor, the decrease in BDNF levels may be attributed to neuroinflammatory damage mediated by elevated inflammatory cytokines such as IL-6. This interaction suggests that inflammatory factors may further lead to cognitive impairment by influencing the expression of BDNF.

Correlation analysis between the scores of various dimensions of C-BCT in the SCZ group and serum BDNF and inflammatory cytokines

Correlation analysis was conducted between the scores of various dimensions of C-BCT in the SCZ group and serum inflammatory cytokines and BDNF. Wherein the information processing speed score was a negative correlation with IL-6 ($r = -0.315$, $P < 0.05$) and a positive correlation with BDNF ($r = 0.290$, $P < 0.05$); attention was a negative correlation with IL-1β and IL-6 ($r = -0.226$, -0.412, all $P < 0.05$); working memory was a negative correlation with IL-1β and IL-6 ($r = -0.324$, -0.236, all $P < 0.05$) and positive correlation with BDNF ($r = 0.296$, $P < 0.05$); comprehensive + execution ability was a negative correlation with IL-1β and IL-6 ($r = -0.284$, -0.386, all $P < 0.05$) and a positive correlation with BDNF ($r = 0.357$, $P < 0.05$; Table 3).

The above results indicate that the elevation of IL-6 levels, in conjunction with the reduction of BDNF levels, collectively impacts various dimensions of cognitive function, such as information processing speed, attention, working memory, and executive function. Elevated concentrations of IL-1β and IL-6 may potentially impair cognitive function by disrupting signaling between neurons, while the decrease in BDNF levels further exacerbates this impairment.

Multiple linear regression analysis of factors affecting the degree of cognitive impairment in first-episode SCZ patients

The T score of each dimension of C-BCT was used as the dependent variable. The biological markers, such as inflammatory cytokines with statistical differences obtained from Pearson correlation analysis, were included as independent variables in the multiple linear regression equation. The results showed that IL-6 had an impact on the scores of each dimension of C-BCT in the SCZ group ($\beta = -0.218$, -0.426, -0.321, -0.327, $t = -2.039$, -4.219, -3.039, -3.242, all $P < 0.05$); IL-1β has an impact on attention, comprehensive + execution ability ($\beta = 0.209$, $t = 2.041$, $P < 0.05$, all $P < 0.05$). BDNF only has an impact on comprehensive + execution ability ($\beta = 0.209$, $t = 2.041$, $P < 0.05$; Table 4).

Table 1 Comparison of clinical data and serum inflammatory cytokines and brain derived neurotrophic factor between the schizophrenia and healthy controls groups

Variable	SCZ group (84 cases)	HCs group (80 cases)	χ^2/t value	*P* value
Sex, *n* (%)			0.216	0.642
Male	40 (48)	41 (51)		
Female	44 (52)	49 (49)		
Age (years, mean ± SD)	39.09 ± 10.24	40.35 ± 11.11	0.224	0.815
Education years (years, mean ± SD)	13.41 ± 3.35	14.54 ± 4.02	1.121	0.262
Smoking history, *n* (%)			0.081	0.776
Yes	28 (30)	25 (31)		
No	56 (70)	55 (69)		
Duration of illness (months, mean ± SD)	9.75 ± 3.42	NA	NA	NA
PANSS score (points, mean ± SD)				
Positive symptom score	24.63 ± 1.71	NA	NA	NA
Negative symptom score	20.05 ± 2.09	NA	NA	NA
General pathology score	41.77 ± 2.06	NA	NA	NA
Total score	80.05 ± 4.28	NA	NA	NA
C-BCT cognitive function assessment scores for various dimensions (points, mean ± SD)				
Information processing speed	32.95 ± 5.12[a]	47.58 ± 5.69	17.313	< 0.001
Attention	31.17 ± 7.47[a]	41.55 ± 7.76	12.073	< 0.001
Working memory	35.01 ± 7.18[a]	47.071 ± 1.16	8.271	< 0.001
Comprehensive + execution ability	32.31 ± 9.89[a]	47.30 ± 7.48	12.395	< 0.001
Levels of serum inflammatory factors and BDNF (pg/mL, mean ± SD)				
IL-1β	37.08 ± 5.11[a]	26.95 ± 3.54	14.579	< 0.001
IL-4	30.85 ± 7.59	29.35 ± 4.13	1.558	0.121
IL-6	41.15 ± 5.92[a]	29.37 ± 7.58	11.104	< 0.001
IL-10	28.76 ± 9.51	26.43 ± 6.58	1.690	0.093
BDNF	1383.98 ± 315.33[a]	2692.42 ± 301.03	17.711	< 0.001

[a]$P < 0.001$.

SCZ: Schizophrenia; HC: Healthy control; C-BCT: Chinese brief cognitive test; PNASS: Positive and negative symptom scale; BDNF: Brain derived neurotrophic factor; IL: Interleukin; NA: Not available.

Through multiple linear regression analysis, it is evident that IL-1β and IL-6 serve as risk factors for cognitive impairment, while BDNF acts as a protective factor for cognitive function. This indicates the significant roles of inflammatory cytokines and neurotrophic factors in the cognitive impairment of first-episode SCZ patients.

DISCUSSION

This research focuses on cognitive impairment in first episode of SCZ and investigates the correlation between serum inflammatory cytokines, including IL-1β and IL-6, and BDNF. The findings revealed a notable presence of cognitive deficits in first-episode SCZ individuals accompanied by elevated levels of inflammatory cytokines, specifically IL-1β and IL-6, and a reduction in BDNF levels. Further analysis negative association between IL-6 levels and BDNF. The study also established a connection among IL-1β, IL-6, BDNF, and the severity of cognitive impairment in these patients, suggesting that abnormal neuroimmune activity and nutritional deficiencies may converge in contributing to cognitive impairment during the initial stages of SCZ.

This study employs C-BCT to assess the cognitive functions of all participants, focusing on information processing speed, working memory, attention, and executive function. The analysis revealed that the T scores of individuals with first-episode SCZ patients were notably lower than those of the HCs group. The result indicates that the SCZ patients had

Table 2 Correlation analysis between serum brain derived neurotrophic factor levels and inflammatory cytokines and brain derived neurotrophic factor in the schizophrenia group (*n* = 84)

Serum inflammatory factors	BDNF	
	r value	*P* value
IL-1β	-0.160	0.145
IL-4	0.196	0.073
IL-6	-0.324[a]	0.003
IL-10	0.080	0.470

[a]*P* < 0.05.
BDNF: Brain derived neurotrophic factor; IL: Interleukin.

Table 3 Correlation analysis between Chinese brief cognitive test scores of various dimensions in the schizophrenia group and serum brain derived neurotrophic factor and inflammatory cytokines (*n* = 84)

Variable	Information processing speed		Attention		Working memory		Comprehensive + execution ability	
	r value	*P* value	*r* value	*P* value	*r* value	*P* value	*r* value	*P* value
IL-1β	-0.198	0.071	-0.226[a]	0.039	-0.324[a]	0.003	-0.284[a]	0.009
IL-4	0.123	0.266	0.025	0.823	0.089	0.421	0.116	0.294
IL-6	-0.315[a]	0.004	-0.412[b]	< 0.001	-0.236[a]	0.030	-0.386[b]	< 0.001
IL-10	0.122	0.270	0.161	0.143	-0.025	0.822	0.105	0.343
BDNF	0.290[a]	0.008	0.189	0.085	0.296[a]	0.006	0.357[b]	< 0.001

[a]*P* < 0.05.
[b]*P* < 0.001.
BDNF: Brain derived neurotrophic factor; IL: Interleukin.

comprehensive cognitive impairment.

The findings align with previous research[26,27] supporting the assertion that cognitive impairment significantly contributes to the social deterioration observed in individuals with SCZ[28]. This impairment is believed to stem from a multifaceted pathological mechanism that may involve genetic predisposition, neuroimmunity, and environmental influences. Increasingly, research suggests that dysregulated neurobiochemical processes and immune-inflammatory responses may underlie the cognitive deficits seen in SCZ patients[29-31]. Our study found that the serum levels of IL-1β and IL-6 in first-episode SCZ patients were higher than those in HCs, while the concentration of BDNF was lower than that of the HCs group. The results are consistent with those of most previous groups[3,32]. Pro-inflammatory cytokines are secreted by persistently stimulated macrophages and T lymphocytes. Formerly recognized as indicative markers for SCZ, cytokines like IL-1β and IL-6 are known for their pro-inflammatory properties within the immune system[33]. That is, they increase during the exacerbation of mental illness and gradually recover after drug treatment[34]. The central nervous system's immune abnormalities further stimulate the active activity of microglia. Then, cytokine secretion disorders are promoted, which lead to abnormal brain neuron and synaptic function, cell apoptosis, decreased neuronal production, and secretion of BDNF levels[35]. The negative effects of reduced BDNF levels on cortical integrity (that is, inner temporal lobe and other temporal lobe regions) and white matter microstructure (that is, frontotemporal connectivity disorder) may eventually manifest the cognitive functional damage of patients with SCZ[31]. At the same time, studies have also found that there is no significant change in the levels of anti-inflammatory cytokines IL-4 and IL-10 in patients with first-episode SCZ, and our study also issued the same results[36]. Parksepp *et al*[37] have also reported a 5-year follow-up study on inflammation and metabolic indicators in first-time SCZ patients, and there was no significant change in IL-4 and IL-10 Levels before treatment with antipsychotic drugs. However, Borovcanin *et al*[38] found that the serum levels of IL-4 increased and IL-10 decreased in patients with first-episode SCZ and recurrent SCZ. After treatment with antipsychotic drugs, the expression levels were reversed of these two inflammatory cytokines[39]. The different results may be related to factors such as the race, age, and duration of illness of the patients in their study. This inconsistent manifestation precisely reflects the imbalance between anti-inflammatory and pro-inflammatory immune regulation in first-episode SCZ patients, which plays an important role in the pathological process of SCZ.

In this study, we found that serum IL-6 Level was negatively correlated with BDNF in patients with first-episode SCZ, suggesting that the expression of pro-inflammatory cytokines IL-6 mediated neuroinflammatory damage, resulting in decreased expression of synaptic plasticity related proteins, which was manifested as decreased level of neurogenic factor

Table 4 Multiple linear regression analysis of factors affecting the degree of cognitive impairment in first-episode schizophrenia patients

Dependent variable		Non standardized coefficient		Standard coefficient	*t* value	*P* value	95%CI of *B*	
		B	Standard error	*β*			Lower limit	Upper limit
Information processing speed	Constant	35.834	5.378		6.663	0.000	25.134	46.535
	BDNF	0.002	0.002	0.156	1.396	0.167	-0.001	0.005
	IL-6	-0.173	0.088	-0.218	-2.039	0.046	-0.349	0.003
Attention	Constant	61.450	7.025		8.747	0.000	47.473	75.428
	IL-6	-0.492	0.114	-0.426	-4.329	0.000	-0.718	-0.266
	IL-1β	-0.312	0.155	-0.199	-2.019	0.047	-0.619	-0.005
Working memory	Constant	48.866	9.263		5.276	0.000	30.433	67.300
	IL-1β	-0.230	0.150	-0.155	-1.532	0.129	-0.529	0.069
	BDNF	0.004	0.002	0.192	1.793	0.077	0.000	0.008
	IL-6	-0.350	0.115	-0.321	-3.039	0.003	-0.580	-0.121
Comprehensive + execution ability	Constant	52.628	8.983		5.858	0.000	34.751	70.505
	IL-1β	-0.394	0.146	-0.261	-2.699	0.008	-0.684	-0.103
	BDNF	0.004	0.002	0.209	2.041	0.045	0.000	0.008
	IL-6	-0.362	0.112	-0.327	-3.242	0.002	-0.585	-0.140

BDNF: Brain derived neurotrophic factor; IL: Interleukin.

BDNF. Williams *et al*[40], in their investigations on inflammation and brain structure in SCZ, also discovered that the elevation of serum IL-6 could potentially impact the volume of the hippocampus and the thickness of the cortex while concurrently reducing BDNF expression. Further analysis revealed significant correlations between cognitive function scores and levels of serum inflammatory cytokines as well as BDNF.

Elevated IL-6 levels are linked to lower BDNF levels, indicative of a more significant impairment in information processing speed[41]. Increased IL-1β and IL-6 Levels are associated with reduced attention. Elevated IL-1β and IL-6 levels, along with decreased BDNF levels, are connected to impairments in working memory and declining comprehensive executive function. Notably, there was no observed correlation between serum IL-4, IL-10 levels, and cognitive function. The study findings suggest that heightened levels of pro-inflammatory cytokines disrupt signal transmission among neuronal synapses in the brain, contributing to cognitive dysfunction. Previous research has also established a relationship between elevated IL-6 Levels, decreased BDNF levels, and impaired information processing in the cognitive function of individuals with SCZ[30,42]. Furthermore, the overexpression of IL-1β can trigger localized and persistent inflammation in the hippocampus, hindering hippocampal-mediated memory formation[43].

Şimşek *et al*[44] found that the severity of negative symptoms in patients with first-episode SCZ was positively correlated with serum IL-4 level and negatively correlated with IL-10, while the changes in cognitive function were not correlated with the two anti-inflammatory cytokines. Our study carefully selected relevant independent variables for conducting multiple linear regression analysis. The findings revealed that IL-1β and IL-6 are significant risk factors for cognitive impairment among patients with first-episode SCZ, while BDNF emerged as a protective factor for cognitive function in the same population. Hakeim *et al*. also found[45] that IL-6 levels increase during the acute phase of SCZ. After controlling for variables such as body mass inde, smoking history, and duration of illness using multiple regression analysis, elevated levels of IL-6 persist as a significant risk factor for cognitive impairment.

Immunoinflammation and neurotrophic deficiencies do not exist in isolation in SCZ, but were part of a tight neural network composed of protein-protein interactions[46]. Elevated IL-1β, IL-6 and other related pro-inflammatory cytokines had a variety of neuroimmunotoxic effects, including activation of autoimmune response, maintenance of persistent peripheral inflammation and neuroinflammation, reduction of hippocampal neurogenesis, activation of microglia, tissue damage in the central nervous system, and induction of MAPK pathway[47-49], these mechanisms are associated with neuroplasticity, synaptic assembly, axonogenesis, and abnormalities in presynaptic and postsynaptic neural connections, leading to impairment of neuronal function[13,46]. The impact of this phenomenon may be more pronounced in cases of neuronutrition deficiency, particularly when there is a reduction in BDNF levels[46]. The activation of immunoinflammatory pathways and the decrease in BDNF could potentially play a pivotal role in cognitive impairment observed in individuals with SCZ[50].

This study focuses on the first episode of SCZ and explores the correlation between cognitive impairment and serum inflammatory cytokines and BDNF. Our findings are consistent with previous research that shows elevated levels of IL-1β

and IL-6 and decreased BDNF levels in SCZ patients. However, we specifically highlight the interaction between these cytokines and BDNF in relation to cognitive impairment, which has been less explored in existing literature. Additionally, our study uses the C-BCT for a comprehensive evaluation of cognitive functions, including information processing speed, working memory, attention, and executive function, providing a multidimensional perspective. The study's innovation lies in its focus on the first-episode SCZ patients, which offers insights into early intervention and treatment strategies.

Longitudinal studies are needed to observe the dynamic changes in BDNF levels and cognitive function throughout the progression of SCZ. Such studies would enable a deeper understanding of how these factors interact over time and in response to treatment, potentially guiding more effective intervention strategies. Moreover, the current study utilized specific cognitive assessment tools, but future research should incorporate more comprehensive neuropsychological test batteries. This approach would provide a fuller picture of cognitive impairments, covering a wider range of cognitive domains and offering more detailed insights into the nature of these impairments in SCZ. Additionally, it is important to consider the impact of various confounding factors on the relationship between BDNF levels and cognitive function. Future research should include genetic predispositions, environmental influences, and medication use as covariates or through stratified analyses. This would help in isolating the specific contributions of inflammatory cytokines and neurotrophic factors to cognitive impairments, thereby refining our understanding of the underlying mechanisms.

This study has several limitations that warrant consideration. Firstly, inflammatory cytokines and BDNF levels were measured in peripheral blood, raising uncertainty about whether changes observed reflect similar alterations in the central nervous system. Furthermore, the origin of IL-1β, IL-6, and BDNF in serum from the brain is unclear, necessitating further investigation. Secondly, the cross-sectional design employed does not establish causality between biomarkers like inflammatory cytokines and cognitive impairment in first-episode SCZ patients. Thirdly, the study focused on patients with first-episode SCZ characterized by more severe clinical symptoms, particularly positive symptoms, potentially limiting the generalizability of these findings to outpatient populations.

CONCLUSION

In summary, our study revealed aberrant immune function and neurotrophic deficiency in patients with first-episode SCZ, while also establishing a correlation between elevated serum levels of IL-1β and IL-6 and reduced levels of BDNF as well as cognitive impairment. Further longitudinal studies with larger sample sizes were warranted to validate these findings. The underlying mechanisms or pathways linking peripheral immune cytokines to cognitive function in first-episode SCZ still require elucidation.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Trends and prevalence of eating disorders in children and adolescents

Qi Chen, Shu Huang, Jie-Yu Peng, Huan Xu, Ping Wang, Xiao-Min Shi, Shi-Qi Li, Rui Luo, Wei Zhang, Lei Shi, Yan Peng, Xiao-Hong Wang, Xiao-Wei Tang

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Abstract

BACKGROUND

Eating disorders (EDs) have increasingly become a public health problem globally, especially among children and adolescents.

AIM

To estimate the burden of EDs in children and adolescents (ages 5-19 years) at the global, regional, and national levels.

METHODS

Retrieved from Global Burden of Disease Study 2019 for EDs, including anorexia nervosa and bulimia nervosa, we extracted the disability-adjusted life years (DALYs) and prevalence rates with 95% uncertainty intervals between 1990-2019. The temporal trends of the DALYs and prevalence rates of EDs were assessed according to the estimated annual percentage changes.

RESULTS

In our study, we found that the burden of EDs continuously increased globally

from 1990 to 2019. Although females accounted for more EDs cases, the burden of EDs in males had a greater increment. Meanwhile, the burden of EDs was associated with the high sociodemographic index (SDI) over the past 30 years and the human development indexes in 2019.

CONCLUSION

EDs, predominantly in high-income countries, are rising globally, especially in Asia, highlighting the need for resource planning and medical policy prioritization across all SDI quintiles.

Key Words: Eating disorders; Global Burden of Disease Study 2019; Children and adolescents; Epidemiology; Prevalence

Core Tip: This study offered a comprehensive assessment of the global burden of eating disorders (EDs) among children and adolescents over three decades using data from the Global Burden of Disease Study 2019. We observed a continuous increase in the disability-adjusted life years and prevalence rates of anorexia nervosa and bulimia nervosa worldwide. Notably, while EDs predominantly affected females, the relative increase in burden was more significant among males. The study highlighted an association between higher sociodemographic index regions and increased EDs burden, underscoring the need for targeted healthcare strategies across varying socioeconomic landscapes.

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INTRODUCTION

Eating disorders (EDs), which are characterized by abnormal eating habits, overconcern with body image and weight-control behaviors, are severe psychiatric illnesses that include anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED). With the highest mortality rate among all psychiatric disease, AN is a serious mental disorder typified by starvation and malnutrition[1]. BN is characterized by repetitive episodes of binge eating followed by compensatory actions to avoid weight gain[2]. In addition to the impairment in psychosocial functioning and physical health, compared with those without these disorders, people with EDs have higher health care costs, and for those who die prematurely, lost lifetime income[3].

EDs can affect people of all ages, genders, ethnicities, sexual orientations, and geographic locations. There is evidence of sex differences, as females have an 8 times greater likelihood of having AN or BN than males, and periods of elevated risk of onset, including childhood and adolescence. These disorders can lead to significant impairments in cognitive development, physical health, and psychosocial function, which can go undetected for months or even years. At the same time, there has been a 25% increase in the prevalence of EDs globally[4,5]. Thus, focusing on children and adolescents is essential for implementing early intervention strategies and improving long-term outcomes.

The Global Burden of Disease (GBD) Study 2019, a comprehensive global effort, involves the measurement of the burden of mental disorders using disability-adjusted life years (DALYs) to assess the disparity between the current health status and an ideal situation where the entire population is disease free to an advanced age.

In this study, we used GBD 2019 data to estimate the trends and annual changes in DALYs and the prevalence of EDs in children and adolescents at the regional, national, and global levels. Furthermore, we determined the association between the burden of EDs and level of development as quantified by human development indices (HDIs).

MATERIALS AND METHODS

Data sources

Covering 204 countries and regions, GBD 2019 offered a comprehensive assessment of the global health burden of 369 diseases and injuries from 1990 to 2019. Details on the general methods used are available on the official website (GBD, Institute for Health Metrics and Evaluation; healthdata.org). The GBD 2019 divided 204 countries into 21 regions, and these countries or territories were stratified into five regions based on the sociodemographic index (SDI): Low, low-middle, middle, high-middle, and high. Furthermore, the HDIs of all countries were obtained from the official website (Human Development Index, Human Development Reports; undp.org)[6].

The burden of EDs was quantified by the rates of DALYs and prevalence rates retrieved from the Global Health Data Exchange query tool (VizHub, GBD Results; healthdata.org), with 95% uncertainty intervals (95%UIs) calculated according to the GBD 2019 global age-standard population. We also described the burden of EDs subdivided type: AN

and BN.

Definition of EDs

EDs were defined based on the criteria from the International Classification of Diseases (ICD) and the diagnostic and statistical manual of mental disorders (DSM), including different versions of the ICD (ICD-9 and ICD-10) and DSM (DSM-5, DSM-III, DSM-III-R, DSM-IV, and DSM-IV-TR). There were no EDs cases before the age of 5 years, as assumed by the GBD 2019, which was in accordance with the corresponding cause in the EDs death model. Considering that the GBD 2019 has no precisely designated age categories (*i.e.*, age < 10 is considered a child, age 10-19 is considered an adolescent), we divided the children and adolescents into three groups by age: 5-9 years, 10-14 years, and 15-19 years[7,8].

Statistical analysis

The estimated annual percentage change (EAPC) was evaluated to clarify the secular trends in the burden of EDs more fully. When calculating the EAPC, the calendar year used as the variable X and ln (rate) used as the variable Y were fitted to a regression line: $Y = \alpha + \beta x + \varepsilon$, where the EAPC was calculated $[100 \times (\exp(\beta) - 1)]$ with its 95%UI obtained from the fitted regression model. An upward trend could be considered if the EAPC > 0 and 95%UI > 0. Conversely, a downward trend could be considered if the EAPC > 0 and 95%UI > 0. Otherwise, the rates were regarded as stable.

Along with the EAPCs and HDIs in 2019, the associations between the EAPCs and rates in 1990 were assessed at the national level using Pearson's correlation analysis and scatterplots. The HDIs indicate the availability and quality of medical services in each country.

R (version 4.1.3, R core team) was used to perform all the statistical procedures. All *P* values < 0.05 were considered statistically significant.

RESULTS

Burden of EDs at the global level

As shown in Table 1, the DALY rate of EDs at the global level gradually increased from 11.03 (95%UI: 6.12-17.72) per 100000 people in 1990 to 12.92 (95%UI: 7.12-20.97) per 100000 people in 2019, with an EAPC of 0.68 (95%UI: 0.62-0.73; Figure 1). Moreover, an increasing trend was also observed in the prevalence rate from 116.66 (95%UI: 79.78-172.01) in 1990 per 100000 people to 137.36 (95%UI: 93.24-203.11) in 2019 per 100000 people, with an average rate of 0.68 (95%UI: 0.63-0.73; Figure 1).

As shown in Supplementary Table 1, the DALY rate of AN at the global level gradually increased from 4.99 (95%UI: 2.78-8.35) per 100000 people in 1990 to 5.66 (95%UI: 3.15-9.62) per 100000 people in 2019, indicating an increase of 0.57 (95%UI: 0.51-0.62; Supplementary Figure 1). The global prevalence rate of AN increased from 53.36 (95%UI: 34.86-79.10) per 100000 people in 1990 to 60.67 (95%UI: 39.31-89.93) per 100000 people in 2019, indicating an increase of 0.56 per year (95%UI: 0.52-0.61; Supplementary Figure 1). The DALY rate of BN at the global level gradually increased from 6.03 (95%UI: 2.91-11.14) per 100000 people in 1990 to 7.26 (95%UI: 3.51-13.60) per 100000 people in 2019 (Supplementary Table 2), with an EAPC of 0.76 (95%UI: 0.70-0.82; Supplementary Figure 2). The global prevalence rate of BN increased from 65.29 (95%UI: 35.91-112.75) per 100000 people in 1990 to 78.81 (95%UI: 43.27-136.07) per 100000 people in 2019, indicating an increase of 0.75 per year (95%UI: 0.70-0.81; Supplementary Figure 2).

The rate of DALYs [17.60 (95%UI: 9.89-28.34) *vs* 8.51 (95%UI: 4.71-14.12) per 100000 people], and prevalence [187.84 (95%UI: 128.69-278.59) *vs* 89.82 (95%UI: 60.03-134.94) per 100000 people] of EDs in 2019 among females was higher than that among males. However, men had greater increases than women did in terms of DALYs and the prevalences of EDs (Table 1), AN (Supplementary Table 1), and BN (Supplementary Table 2). We also analyzed these indices in different age groups in terms of EDs (Figure 2), AN (Supplementary Figure 3), and BN (Supplementary Figure 4). The highest DALY and prevalence rates concerning EDs and its subtypes were reported among those aged 15-19 years.

The highest DALY and prevalence rates concerning EDs and its subtypes in 2019 were found in the high-SDI region. All the SDI regions in the observed period showed an increasing trend in these indices, with the greatest increases observed in the middle-SDI and low-middle-SDI regions in terms of EDs (Figure 1), AN (Supplementary Figure 1), and BN (Supplementary Figure 2).

Burden of EDs at the regional level

As shown in Table 1, at the regional level, Australasia recorded the highest DALY (59.45, 95%UI: 34.84-95.13 per 100000 people) and prevalence (642.40, 95%UI: 458.62-902.39 per 100000 people) rates of EDs. There was an increasing trend in all geographic regions in the past 30 years in the DALY and prevalence rates, except for Eastern Europe and Central Sub-Saharan Africa. The greatest increase in these indices was observed in East Asia (EAPC for DALYs = 1.98, 95%UI: 1.72-2.25; EAPC for prevalence = 1.97, 95%UI: 1.73-2.22), followed by South Asia (EAPC for DALYs = 1.42, 95%UI: 1.34-1.5; EAPC for prevalence = 1.44, 95%UI: 1.36-1.52).

In 2019, Australasia had the highest DALY and prevalence rates for AN (DALYs = 22.55, 95%UI: 13.12-36.74; prevalence = 243.99, 95%UI: 168.36-341.27 per 100000 people; Supplementary Table 1) and BN (DALYs = 36.90, 95%UI: 19.96-64.25; prevalence = 402.81, 95%UI: 258.27-632.07, per 100000 people; Supplementary Table 2). Similar to EDs, there was an increasing trend in all geographic regions in the past 30 years in the DALY and prevalence rates for AN and BN, except for Eastern Europe and Central Sub-Saharan Africa. The most significant increase in these indices was detected in East Asia in terms of AN (EAPC for DALYs = 1.77, 95%UI: 1.54-2.00; EAPC for prevalence = 1.73, 95%UI: 1.52-1.94) and

Table 1 Rates of prevalence and disability-adjusted life-years of eating disorders in 2019 and their temporal trend from 1990 to 2019 at global and regional levels

	Prevalence (95%UI)			DALYs (95%UI)		
	Rate in 1990 (per 100000 population)	Rate in 2019 (per 100000 population)	EAPC (1990-2019)	Rate in 1990 (per 100000 population)	Rate in 2019 (per 100000 population)	EAPC (1990-2019)
Global	116.66 (79.78-172.01)	137.36 (93.24-203.11)	0.68 (0.63-0.73)	11.03 (6.12-17.72)	12.92 (7.12-20.97)	0.68 (0.62-0.73)
Sex						
Male	74.37 (50.29-110.67)	89.82 (60.03-134.94)	0.78 (0.73-0.84)	7.09 (3.91-11.72)	8.51 (4.71-14.12)	0.78 (0.72-0.85)
Female	160.91 (111.16-237.28)	187.84 (128.69-278.59)	0.64 (0.59-0.69)	15.15 (8.57-24.17)	17.60 (9.89-28.34)	0.64 (0.58-0.69)
Aetiology						
Anorexia nervosa	53.63 (34.86-79.10)	60.67 (39.31-89.93)	0.56 (0.52-0.61)	4.99 (2.78-8.35)	5.66 (3.15-9.62)	0.57 (0.51-0.62)
Bulimia nervosa	65.29 (35.91-112.75)	78.81 (43.27-136.07)	0.75 (0.70-0.81)	6.03 (2.91-11.14)	7.26 (3.51-13.60)	0.76 (0.70-0.82)
Socio-demographic index						
High SDI	299.36 (207.55-448.68)	348.17 (239.80-519.36)	0.57 (0.46-0.68)	28.11 (16.03-45.81)	32.45 (18.25-53.04)	0.56 (0.45-0.66)
High-middle SDI	140.06 (96.78-208.68)	180.32 (122.09-268.88)	1.12 (1.03-1.21)	13.25 (7.35-21.47)	17.02 (9.44-27.79)	1.14 (1.03-1.25)
Middle SDI	92.70 (62.71-137.46)	127.24 (85.94-190.46)	1.30 (1.22-1.38)	8.82 (4.90-14.31)	12.03 (6.59-19.62)	1.30 (1.21-1.39)
Low-middle SDI	76.24 (51.53-112.46)	106.44 (72.15-158.41)	1.24 (1.16-1.31)	7.22 (4.02-11.58)	10.02 (5.54-16.18)	1.22 (1.14-1.30)
Low SDI	68.49 (46.47-100.95)	80.38 (53.89-118.39)	0.54 (0.42-0.66)	6.47 (3.58-10.44)	7.58 (4.20-12.28)	0.55 (0.43-0.67)
Region						
High-income Asia Pacific	285.39 (196.42-419.28)	320.41 (220.92-478.15)	0.37 (0.30-0.44)	27.11 (15.26-43.7)	30.48 (17.14-49.63)	0.35 (0.28-0.43)
Central Asia	92.37 (63.29-136.71)	98.59 (66.23-145.22)	0.83 (0.58-1.08)	8.79 (4.82-14.56)	9.41 (5.24-15.38)	0.85 (0.60-1.11)
East Asia	68.76 (45.77-102.21)	102.83 (68.86-153.09)	1.97 (1.73-2.22)	6.67 (3.63-10.73)	9.93 (5.55-16.12)	1.98 (1.72-2.25)
South Asia	70.42 (47.56-103.77)	105.56 (71.36-156.29)	1.44 (1.36-1.52)	6.68 (3.7-10.85)	9.93 (5.51-16.06)	1.42 (1.34-1.50)
Southeast Asia	68.95 (46.53-101.56)	94.80 (63.78-137.60)	1.07 (1.02-1.12)	6.56 (3.69-10.67)	9.01 (5.00-14.43)	1.07 (1.02-1.12)
Australasia	532.55 (358.55-822.91)	642.40 (458.62-902.39)	1.15 (0.93-1.37)	49.69 (27.35-84.76)	59.45 (34.84-95.13)	1.14 (0.93-1.36)
Caribbean	144.60 (96.82-219.61)	149.19 (102.06-223.98)	0.41 (0.3-0.53)	13.61 (7.61-21.96)	14.00 (7.67-23.33)	0.40 (0.28-0.52)
Central Europe	116.32 (78.80-175.62)	139.85 (94.41-210.18)	0.77 (0.63-0.90)	10.90 (5.94-17.80)	13.2 (7.22-21.69)	0.82 (0.68-0.96)
Eastern Europe	117.66 (79.92-175.80)	117.20 (80.21-172.70)	0.22 (-0.03-0.48)	11.29 (6.31-18.24)	11.26 (6.33-17.97)	0.28 (0.02-0.54)
Western Europe	381.80 (269.38-568.79)	400.24 (273.13-603.52)	0.19 (0.12-0.26)	35.72 (20.50-58.66)	37.28 (20.88-61.76)	0.18 (0.12-0.25)
Andean Latin America	153.87 (100.49-239.82)	190.08 (125.35-297.51)	0.82 (0.76-0.87)	14.43 (7.79-24.44)	17.91 (9.79-30.26)	0.83 (0.78-0.88)
Central Latin America	147.26 (99.41-222.31)	170.20 (116.58-255.62)	0.53 (0.46-0.61)	13.88 (7.60-22.96)	16.02 (8.79-26.23)	0.52 (0.45-0.60)

Southern Latin America	218.40 (147.13-331.21)	275.00 (181.83-418.71)	0.90 (0.85-0.94)	20.48 (11.20-34.32)	25.85 (14.07-42.95)	0.88 (0.84-0.93)
Tropical Latin America	151.49 (103.53-219.35)	188.20 (129.48-277.01)	0.87 (0.80-0.93)	14.08 (7.92-23.05)	17.48 (9.84-28.51)	0.88 (0.81-0.95)
North Africa and Middle East	148.28 (99.21-228.58)	179.56 (118.89-275.01)	0.81 (0.71-0.92)	13.88 (7.53-23.43)	16.79 (9.08-27.91)	0.82 (0.72-0.93)
High-income North America	315.82 (214.28-474.18)	356.89 (242.46-543.67)	0.29 (0.08-0.49)	29.44 (16.23-48.98)	32.87 (18.07-54.22)	0.27 (0.06-0.47)
Oceania	68.28 (44.42-100.92)	72.02 (46.08-107.19)	0.22 (0.16-0.28)	6.46 (3.58-10.67)	6.84 (3.73-11.23)	0.23 (0.17-0.30)
Central Sub-Saharan Africa	74.02 (48.53-108.66)	74.26 (49.07-111.50)	0.07 (-0.12-0.26)	6.96 (3.91-11.22)	7.01 (3.79-11.42)	0.10 (-0.09-0.29)
Eastern Sub-Saharan Africa	64.43 (43.29-95.11)	75.92 (51.59-110.99)	0.52 (0.40-0.64)	6.08 (3.40-9.80)	7.19 (4.02-11.52)	0.54 (0.43-0.65)
Southern Sub-Saharan Africa	109.01 (73.73-164.18)	114.62 (77.31-168.01)	0.25 (0.16-0.33)	10.29 (5.70-16.77)	10.84 (6.00-17.6)	0.27 (0.19-0.35)
Western Sub-Saharan Africa	75.83 (51.77-111.61)	88.52 (59.61-131.32)	0.57 (0.47-0.68)	7.18 (4.02-11.52)	8.34 (4.59-13.39)	0.57 (0.47-0.67)

EAPC: Estimated annual percentage change; DALYs: Disability-adjusted life years; 95%UI: 95% uncertainty intervals; SDI: Sociodemographic index.

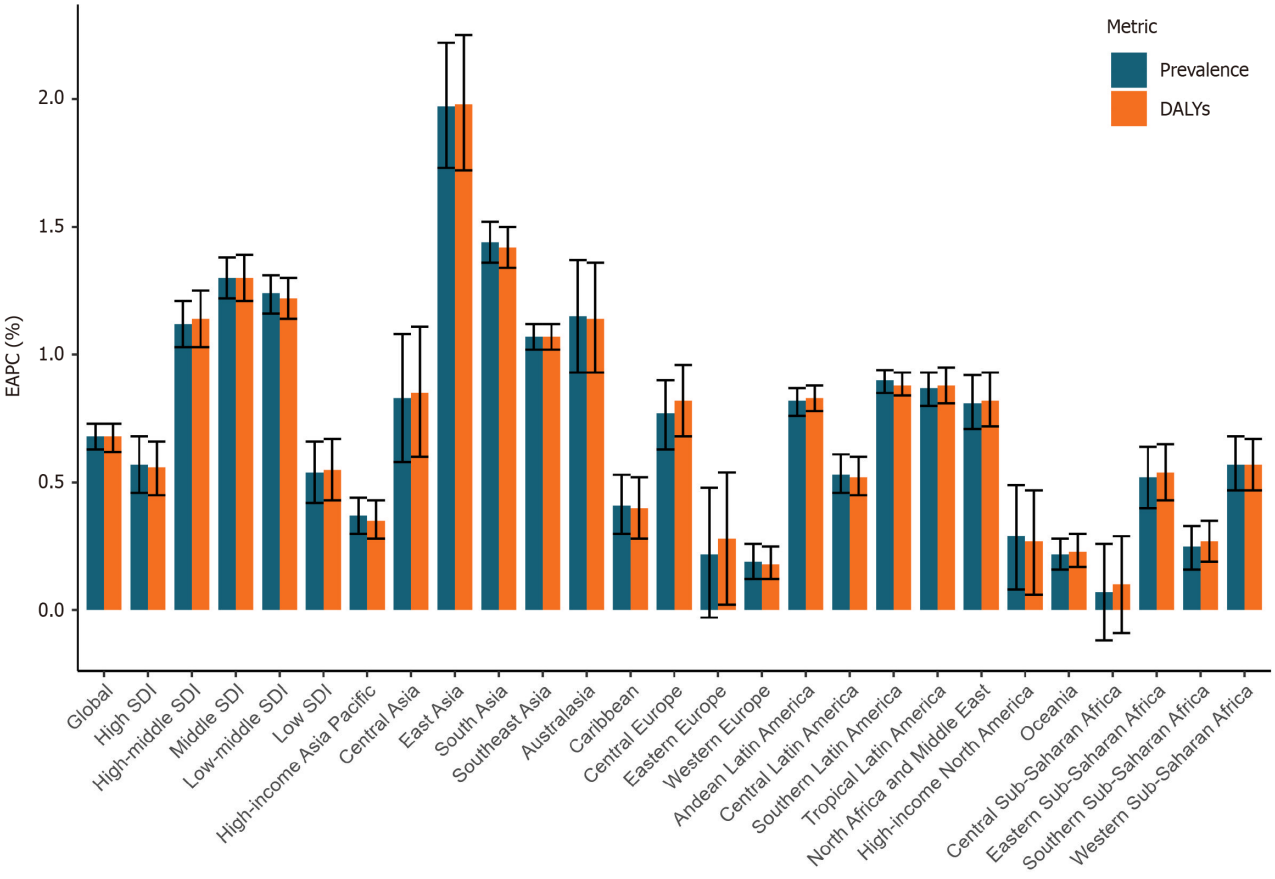

Figure 1 Estimated annual percentage change of prevalence and disability-adjusted life years for eating disorders at the global and regional levels. EAPC: Estimated annual percentage change; DALYs: Disability-adjusted life years; SDI: Sociodemographic index.

BN (EAPC for DALYs = 2.21, 95%UI: 1.92-2.51; EAPC for prevalence = 2.19, 95%UI: 1.92-2.46), followed by South Asia.

Burden of EDs at the national level

At the national level, as listed in Supplementary Table 3, the highest DALY and prevalence rates of EDs in 2019 were reported in Monaco, followed by Australia and Spain (Figure 3A and C). An increasing trend was detected in the DALY

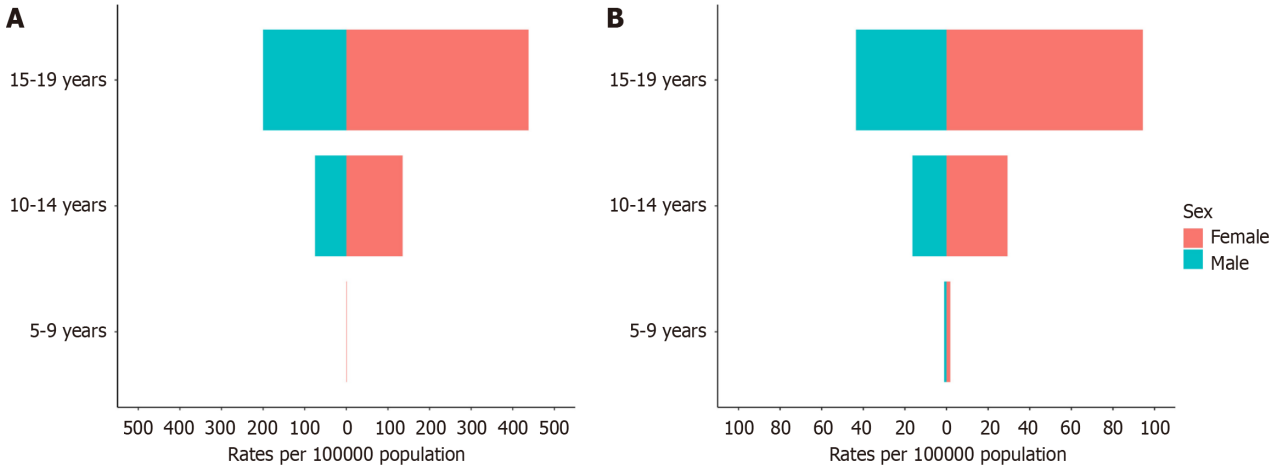

Figure 2 Prevalence rates and disability-adjusted life years rates of eating disorders in different age groups globally. A: Prevalence rates; B: Disability-adjusted life years rates.

and prevalence rates of EDs in 204 countries and territories. The three countries with the greatest increase from 1990 to 2019 were Equatorial Guinea, Turkey, and China (Figure 3B and D).

As presented in Supplementary Table 4, the highest DALY and prevalence rates of AN in 2019 were found in Australia, followed by Monaco and Spain (Supplementary Figure 5A and Supplementary Figure 6A). As presented in Supplementary Table 5, Monaco, Australia, and Spain were the three countries with the highest DALY and prevalence rates of BN in 2019 (Supplementary Figure 7A and Supplementary Figure 8A). During the observed period, increasing trends were detected in the DALY and prevalence rates of AN and BN in 204 countries and territories. The three countries with the greatest increase due to AN were Equatorial Guinea, the Netherlands, and China (Supplementary Figure 5B and Supplementary Figure 6B), whereas Equatorial Guinea, Turkey, and China had the highest EAPCs in DALYs and prevalence of BN (Supplementary Figure 7B and Supplementary Figure 8B).

Relationship between SDI levels and burden estimates of EDs

The associations between SDI levels and burden estimates of EDs for each geographic region during the observation period are presented in Figure 4; positive associations are shown. In the past 30 years, the number of SDIs has increased in all geographic regions. There was a slight increase in the burden estimates, as the SDIs increased when the SDIs were less than 0.67. Conversely, a more rapid increase with increasing SDIs was detected in burden estimates when the SDIs were above 0.67.

Influencing factors of the EAPC

As shown in Figure 5, there was a negative association between the rates and the EAPCs in the DALY (ρ = -0.141, P = 0.045) and prevalence (ρ = -0.133, P = 0.057) rates. A positive correlation was detected between the human development indices in 2019 and the EAPCs in the DALY (ρ = 0.199, P = 0.012) and prevalence (ρ = 0.200, P = 0.012) rates of EDs when HDIs < 0.7, whereas a negative association was detected when HDIs > 0.7.

DISCUSSION

To our knowledge, the present study is the first to explore trends in and the prevalence of EDs in children and adolescents in the past three decades based on the GBD 2019. We examined the burden of EDs in terms of DALY and prevalence rates at the regional, national, and global levels. In our study, an increasing trend was observed in the burden of EDs globally, but the rate of increase varied by gender, location, and age. Moreover, regardless of the SDI, there was an increasing trend in the burden of EDs in almost all regions, and it increased with increasing SDI. Among 204 countries and territories, an increasing trend was also detected, and the three countries with the greatest increase were Equatorial Guinea, Turkey, and China.

The burden of EDs has increased globally and peaks at 15-19 years among children and adolescents[9,10]. This trend is consistent with the change in the DSM-5, which includes broadened diagnostic criteria to promote inclusion[11]. Ornstein revealed that the proposed DSM-5 criteria substantially increased the prevalences of AN and BN among young patients [12]. In accordance with this increasing trend in EDs, there was a rapid increase in the overall burden of mental illness.

Economic growth may be another important factor. For example, China's rapidly developing economy and urbanization could be significant contributing factors in the development of EDs[13]. During the psychosocial developmental phase of adolescence, the incidence of EDs reaches its highest point. Several studies have demonstrated that the highest incidence rates are found in individuals aged 15-19 years, and there has been an increase in this age group over the past decades[1,14]; this may be attributed to puberty, a time of increased vulnerability to developing an EDs due to normal weight gain, which is associated with sexual maturation[15].

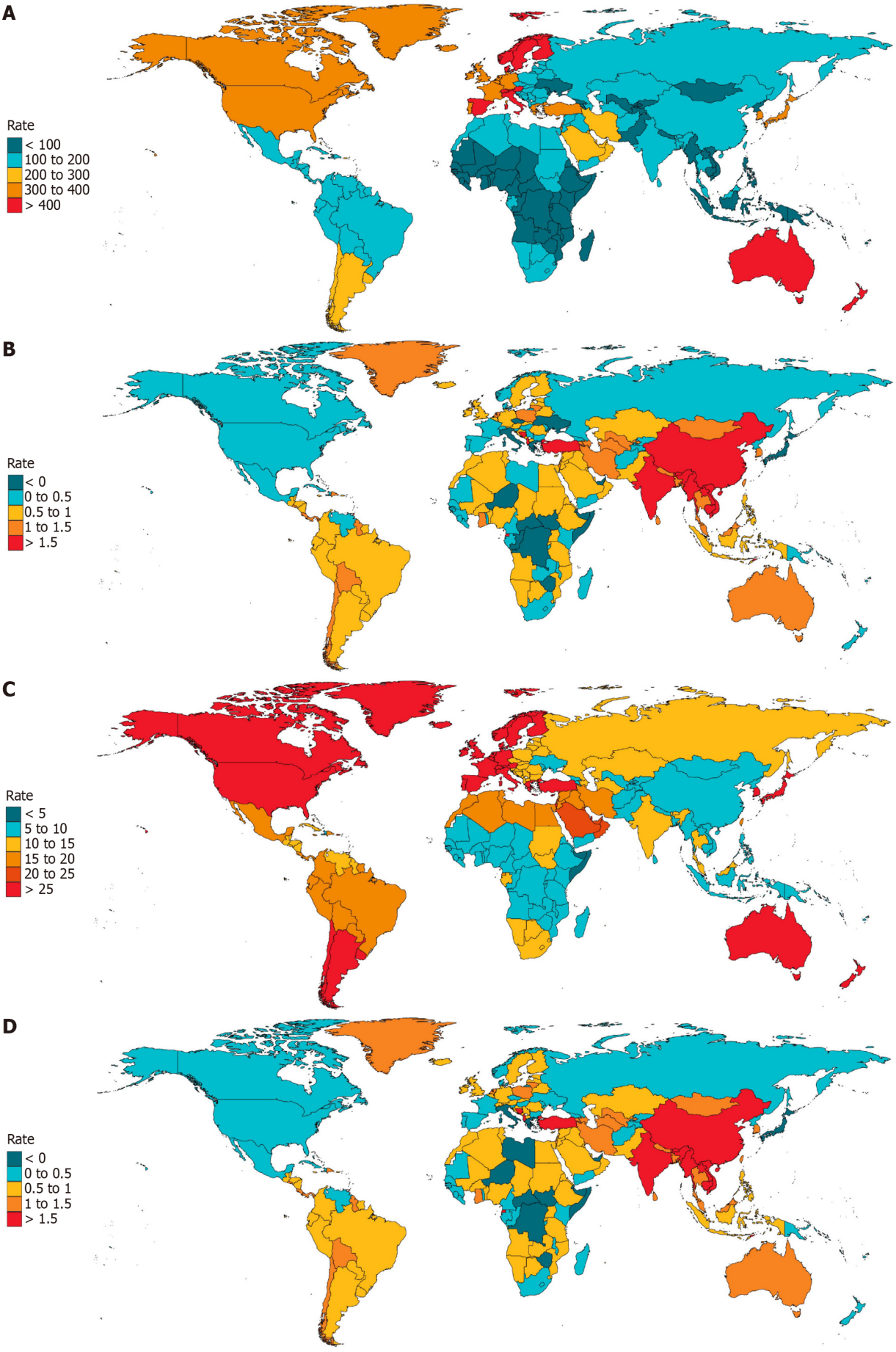

Figure 3 Burden of eating disorders at the national level. A and B: Prevalence rates in 2019 (A) and the estimated annual percentage change of

prevalence rates from 1990 to 2019 (B) of eating disorders in 204 countries or territories; C and D: Disability-adjusted life years (DALY) rates in 2019 (C) and the estimated annual percentage change of DALY rates from 1990 to 2019 (D) of eating disorders in 204 countries or territories.

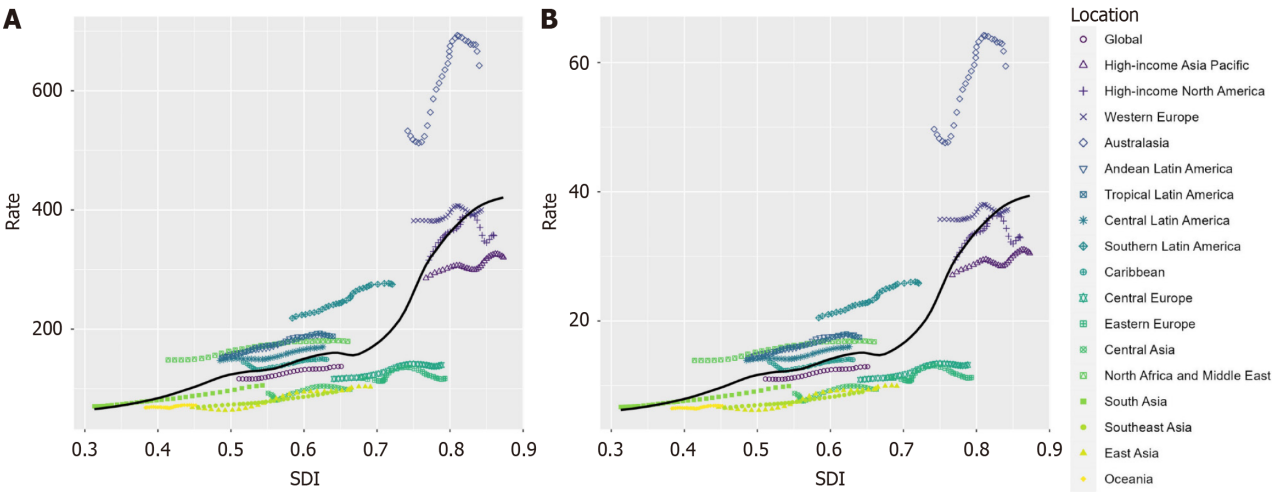

Figure 4 Rates of prevalence A and disability-adjusted life years B of eating disorders by sociodemographic index from 1990 to 2019, and expected value-based sociodemographic index. A and B: The black line represents the average expected relationship between sociodemographic index and prevalence (A) or disability-adjusted life years (B) of eating disorders based on values from all regions from 1990 to 2019. SDI: Sociodemographic index.

In line with previous consensus, we found that the burden of EDs was gender-related and that the DALY and prevalence rates of EDs were greater for women than men in all age groups[16-18]. Given the emphasis on attractiveness in female gender role stereotypes and the correlations between thinness, femininity, and beauty, girls may be particularly susceptible to engaging in unhealthy weight-control behaviors. Moreover, as semiclosed environments, campuses can exacerbate sociocultural pressures to maintain a thin body shape, and females are more significantly affected by these conditions[19]. Furthermore, there is ongoing debate regarding whether there is a correlation with Western culture or the contemporary influence of the media[18]. EDs were historically considered the most common gender-related mental illnesses, with females experiencing the majority of cases. However, according to recent evidence, approximately 25% of individuals with AN and BN are male, which indicates that this disease burden in male patients is a health problem that warrants attention[20].

In fact, although females still accounted for more ED cases, males had a greater increase in DALY and prevalence rates than females did. Gorrell explained why the burden of EDs has been underestimated among males[20]. First, EDs have been regarded as female phenomena, leading to the neglect of males over the past several decades of research efforts. Second, a lack of insight, denial, secrecy, and shame related to having a "female disorder" could contribute to male patients' refusal to seek treatment. Third, the diagnostic criteria are biased toward females, resulting in low diagnostic efficiency in males. To address this gap, it is important to eliminate amenorrhea as a diagnostic criterion for AN in the DSM-5, improving the accuracy of the prevalence estimates among males[11]. Early research findings demonstrated that up to 42% of men who were diagnosed with an ED were identified as homosexual or bisexual[21,22]. Notably, given that adolescence is a crucial period in the development of gender identity and sexual orientation as well as body image disturbances, EDs may disproportionately impact vulnerable youth. Lesbian, gay, bisexual, and transgender (LGBT) youth, as indicated by the extant literature, are especially vulnerable to body dissatisfaction and EDs[23,24]. Therefore, more concern and support should be provided to male patients and LGBT youth.

The highest burdens of EDs and its subtypes were observed in the high-SDI region. This result was consistent with those of Castaldelli-Maia, who demonstrated that countries with higher SDI levels had a greater prevalence of mental and substance use disorders, indicating a greater recognition of mental disorders in developed countries as a sign of relatively greater allocation of resources toward mental health and higher education levels[25]. Another reason for the higher prevalence of these disorders in high-income Western countries, such as America, could be the development of psychiatric diagnostic criteria, which are largely impacted by local schools of psychiatry. Moreover, the validity of these psychiatric diagnostic manuals (*e.g.*, DSM-5 and ICD-10) is weak in some areas, leading to systematic differences.

Although more ED cases can be found in the industrialized Western world, a greater increase in the burden of EDs was observed in Asian countries, including China and India. Moreover, the greatest increasing trend among the five SDI regions was observed in middle-SDI regions. With almost one-fifth of the world's population, China, which is classified as part of the middle-SDI region, is the third fastest-growing country in terms of the burden of EDs. According to Huang, China has undergone economic development and social changes at an unprecedented rate in the past 30 years, leading to tremendous changes in its urbanization, education, population structure, culture, social concept, and so on[13]. These changes may increase psychological pressure, resulting in mood, cognitive, and behavioral disorders, along with related problems[13,26]. In addition to the economic growth and urbanization in these areas, globalization could also increase the risk of exposure to risk factors. For example, another study conducted in India showed that increasing exposure to global

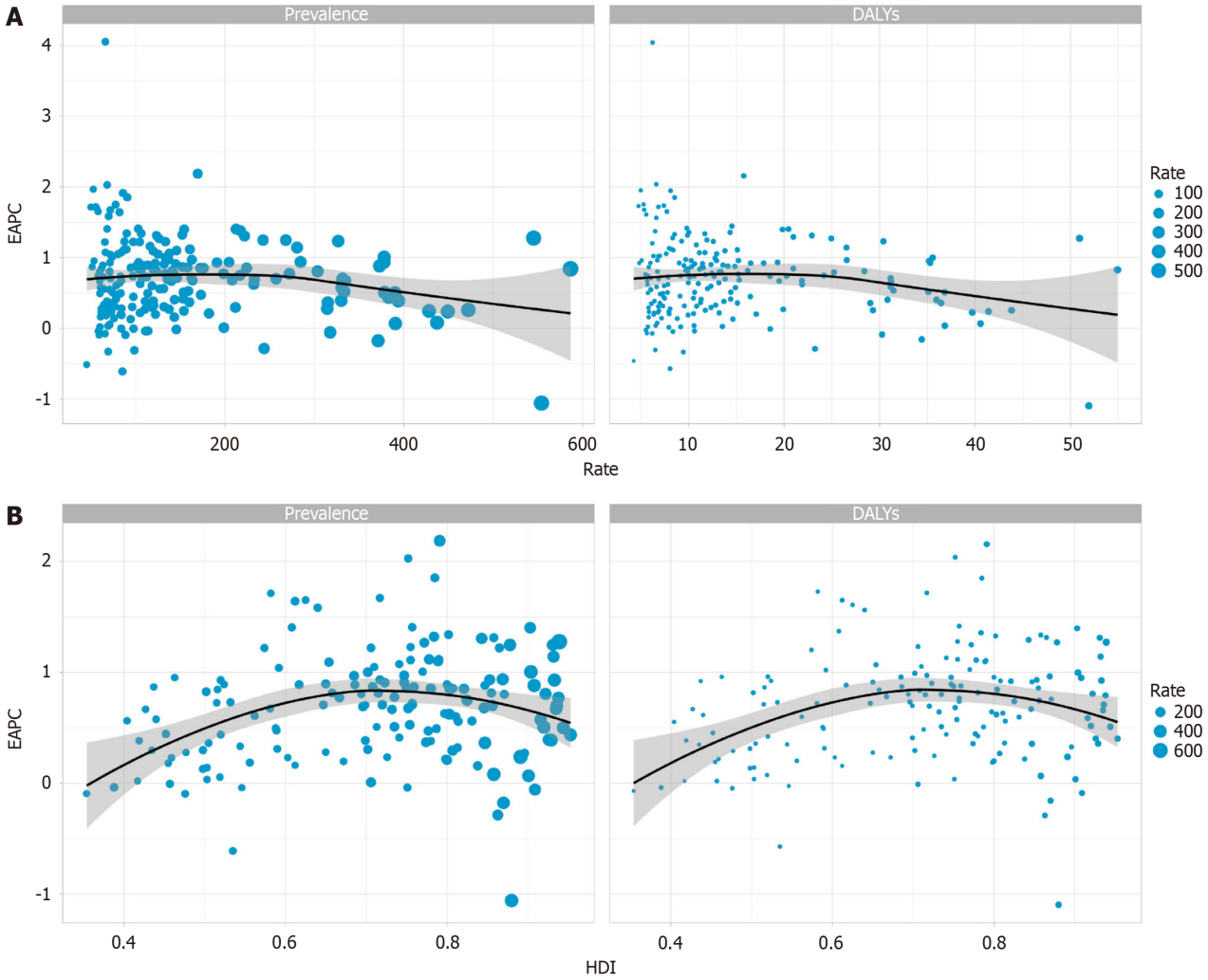

Figure 5 Correlation. A: Correlation between the estimated annual percentage change (EAPC) of prevalence rates and the prevalence rates in 1990, and the EAPC of disability-adjusted life year rates and the disability-adjusted life year rates in 1990; B: Correlation between the EAPC of prevalence rates and the human development indexes (HDIs) in 2019, the EAPC of disability-adjusted life year rates and the HDIs in 2019. EAPC: Estimated annual percentage change; HDIs: Human development indexes.

body image trends may contribute to an increase in EDs[27]. Furthermore, the lack of awareness, insufficient coverage of mental health services, and stigma attached to these disorders in these areas could pose great challenges to the diagnosis, prevention, and treatment of EDs.

The burden of EDs varies across regions and countries. Although AN has historically been regarded as a possible "culture-bound syndrome" rooted in Western culture, which emphasizes body dissatisfaction and EDs, they are widespread and associated with the specific culture in which they develop. There is significant heterogeneity concerning attitudes toward body image and food across countries and ethnic groups. Traditional cultures in these countries can act as protective factors against the increasing prevalence of EDs. However, increased utilization of mass media and peer exposure can be a catalyst for the dissemination of Western-oriented values, resulting in the ineffectiveness of the protective factors mentioned above[28,29]. On the other hand, the emergence of EDs in certain regions of Asia predated Western influences, challenging such theories and underscoring the distinct phenotypic expressions of EDs that may develop without societal factors emphasizing concerns about shape and weight. For example, a study in Japan revealed that restrictive EDs were observed as early as the 18th century and that EDs symptoms can persist independently of Western influence, with sociocultural factors, such as family dynamics and gender-specific stressors, contributing to the prevalence of EDs in Japanese people[30]. In addition to culture, environmental factors can differ across countries.

It was found that the burden of EDs increases with increasing SDI, and a positive correlation was detected between HDIs and the burden of EDs. This may be due to more social pressure and greater use of electronic media in these high socioeconomic countries[25]; it could also be due to the insufficient coverage of mental health services in developing countries, leading to a relatively lower diagnosis rate[27].

This study investigated the trends and prevalences of EDs in children and adolescents and the associations with SDI over the past 30 years and HDIs in 2019. Our study revealed the increasing burden of EDs among males and LGBT youth. However, there are several limitations of our study. First, this research shared the limitations of the GBD 2019 database that which have been detailed in previous studies[31]. Whereas GBD 2019 employed several techniques to mitigate bias and inaccuracy, completely eliminating bias remains a challenge[32]. Second, only AN and BN were included in GBD

2019, whereas BED, which is one of the most prevalent EDs, was not included. The potential inclusion of BED when quantifying the burden of EDs, as the GBD is designed for continual updates, offers an opportunity to increase the accuracy of estimating the burden. Third, considering the diversity of cultures, different results may be obtained when the same diagnostic tools are used across cultures. Therefore, the development of diagnostic criteria needs to consider cultural factors[33].

CONCLUSION

Although the greatest burden of EDs remains in high-income Western countries, a global increase was observed across all SDI regions, particularly in Asia. These results are helpful for resource planning and medical policy prioritization.

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FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Correlation between self-efficacy, parental parenting patterns, and severe depression in adolescents

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Abstract

BACKGROUND

Adolescence is a critical period marked by significant psychological changes. This study explores how self-efficacy and parental parenting styles may influence the risk of severe depression among teens. The hypothesis is that higher self-efficacy and authoritative parenting patterns will be negatively correlated with severe depression in adolescents.

AIM

To investigate the correlation between self-efficacy, parenting patterns and major depression in adolescents, and to provide guidance for mental intervention.

METHODS

Using a cross-sectional survey design, the data were collected through a questionnaire survey. Patients with major depression and healthy adolescents in the hospital control group were selected as the study objects. The General Self-Efficacy Scale, the Parenting Style Evaluation Scale, and the Beck Depression Inventory were used as research instruments. Data input and statistical analysis were performed, including descriptive statistics, correlation analysis, through SPSS software.

RESULTS

The study found that depressed patients had significantly lower self-efficacy than healthy controls, and parenting style was significantly associated with depressive symptoms in terms of emotional warmth and understanding, punishment severity, and denial. Specifically, parental emotional warmth and understanding were significantly negatively associated with depressive symptoms, while parental punishment severity and denial were significantly positively associated with

depressive symptoms. Self-efficacy showed a significant negative correlation with depressive symptoms, indicating that higher self-efficacy had lower depressive symptoms.

CONCLUSION
Adolescent major depressive disorder patient was significantly associated with their parenting style and self-efficacy. Higher self-efficacy is associated with decreased depressive symptoms, so improving adolescent self-efficacy and improving parenting style are important.

Key Words: Adolescent depression; Self-efficacy; Parental parenting patterns; Correlation analysis; Psychological interventions

Core Tip: This investigation delineates a significant correlation between adolescent major depressive disorder and parental rearing practices, emphasizing the beneficial impact of parental warmth and understanding, in contrast to the adverse consequences of punitive parenting. The study accentuates the mitigating influence of self-efficacy on depressive symptoms, thereby advocating for targeted interventions to enhance these protective factors and promote psychological well-being. Consequently, the research advances a dual-pronged approach, which simultaneously addresses the amelioration of depressive symptoms and cultivates a resilient, supportive milieu for adolescents, thereby fostering enduring psychological health.

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INTRODUCTION

Adolescent depression refers to a kind of mental diseases characterized by continuous and significant emotional loss and loss of interest[1]. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition[2] specifically mentions that children and adolescents depression may have special symptoms, in terms of physical fitness, it may not meet the corresponding physical standards; in terms of emotion, adolescents can be manifested as emotional instability and irritability, rather than sadness. Mullen[3] pointed out children and adolescents depressive symptoms can show symptoms different from adults, such as they will show palpitation, chest tightness, numbness of hands and feet and other physical discomfort symptoms, but with the growth of age, its symptoms will gradually close to adult depressive symptoms[4]. Because the psychological development of adolescence is not mature, their clinical manifestations often appear with atypical characteristics[5], such as academic failure, social disorders, *etc.*, their performance is often mistaken for the normal phenomenon[6,7] in adolescence. Other studies show that adolescent depressive symptoms include four symptom dimensions: Physical symptoms, irritability, cognitive symptoms and anhedonia, which are significantly different from adults[8]. Therefore, often lead to early adolescent depression is difficult to identify, treatment effect is bad, poor prognosis, and prone to serious behavior such as suicide, incidence increased year by year, serious harm to adolescent physical and mental health, in recent years some scholars research application of adolescent autism depression symptoms assessment scale can be used as screening adolescent depression symptoms[9], but the etiology and pathogenesis is unknown. The relationship between general self-efficacy and depression (self-efficacy) refers to the subjective judgment of their ability, that is, the degree of confidence, that is, when an individual has a goal, the individual determines whether he has the ability to complete the goal. It is a very important variable that influences its individual self-regulation. This concept was first proposed by Bandura[10], a famous American psychologist, and it is the most core concept in Bandura's social cognitive theory. General self-efficacy plays a very important role in the dynamic psychological process of individuals performing target activities. Wood and Bandura[11] have suggested that general self-efficacy is based on cognitive process, behavioral choice, emotional process, and motivational effort to influence individual mental activities. In 1986, Bandura, in his book social foundation of thought and behavior: Theory of social cognition, summarized the three functions of general self-efficacy, as follows: Influencing people's emotional response patterns and thinking patterns; influencing individuals' behavioral choices; and determining the durability of people's implementation of tasks[12]. It is believed that general self-efficacy plays a role in depression[10], which is the ineffective of individuals in the face of their own goals beyond their own ability. That is, the individual set a goal for himself, but the individual judgment 10 cannot be achieved by their own ability, that is, when the general self-efficacy is low, the individual will produce frustration and depression[10,13]. Studies believe that this way is related to the theory of self-difference, the self-difference theory namely adolescent reality-ideal self-difference, when reality and ideal, patients on their set goals can be complete, on the contrary, when the adolescent individual reality and ideal gap is larger, patients in the ideal is ineffective, there will be emotions such as depression, depression level with the rise of reality-ideal self-difference rise, but the speed with the increase of general self-efficacy and slow[14]. Adolescent general self-efficacy level

regulates the relationship between reality-ideal self-differences and depression. Some foreign scholars have concluded that the general level of self-efficacy of depression is low[15-17]. Some scholars have examined depression and general self-efficacy and concluded that self-efficacy may be one of the important influences on depression[18]. Wang *et al*[19] showed that general self-efficacy mediated the role between depression and other factors; therefore, improving the general self-efficacy of patients has very positive significance to alleviate depressive symptoms. On the relationship between general self-efficacy and depression, the results of domestic and foreign studies are more consistent. In general self-efficacy, the general self-efficacy is emotional regulation, which refers to the ability or confidence that individuals can well regulate their emotional state. It will act on behaviors by affecting motivation, cognition, emotion and decision-making, and then affect the mental health level of individuals. Therefore, the general self-efficacy of emotional regulation plays a very important role in regulating individual behavior and personality[20]. Conversely, negative emotions gradually increase when individuals feel powerless to get rid of repeatedly thinking about negative events. In recent years, studies have confirmed that people's confidence in doing something is higher, the stronger the efficiency of they do something, therefore, improve the depression emotional regulation of general self-efficacy, strengthen the confidence of the treatment, alleviate negative emotions has positive significance[21], emotional regulation of depression, the higher level of general self-efficacy, depression symptoms are lighter, and emotional regulation level of lower depression symptoms will be more serious, the two are closely related. Improving the general self-efficacy of emotion regulation is important for reducing depressive symptoms[22,23]. Parenting style is a combination of parents 'parenting concepts, parenting behavior and their emotional expression of their children. It is a relatively stable behavior style and behavior tendency, which centrally reflects parents' attitude towards their children and their educational concepts[24,25]. Parenting has different classification, is commonly used to distinguish the parenting into two dimensions: Parents (control) and reaction (warm), in turn into four types of breeding: Authority (high response), excessive doting (low demand high reaction), autocratic (high demand low reaction), neglect (low request low reaction). Psychologists at home and abroad used empirical research to explore the influence of parenting style on personality perfection, cognitive development and value formation of teenagers, as well as the characteristics and characteristics of parenting style and its influencing factors. Research shows that family education has a profound effect on children's personal psychological development, and whether the correct parenting style adopted by parents largely determines whether children can grow up healthily[26]. Parents adopt an autocratic and neglect parenting style, their children are most prone to depression, they often lack competition, fear of authority, and often show low self-esteem, academic difficulties, behavioral problems, and internalizing symptoms[27]. The parents of teenagers with depression disorder lack due care, understanding and protection, and have more punishment, refusal and denial. In fact, such negative parenting style is easy to weaken the children's confidence, so that excessive self-restraint, gradually initiation of helplessness, and then develop a sense of despair, negative attribution, leading to depression[28]. In conclusion, mental health during adolescence is crucial for their growth and development. Through in-depth research on the correlation between self-efficacy, parenting patterns and major depression in adolescents, we can better understand the causes of depression and provide more effective support and help for adolescents. This will not only help promote the mental health of teenagers, but also foster a healthier and more capable next generation for the society. The association of self-efficacy, parenting patterns and these factors with adolescent major depressive disorder (MDD), which was explored in this study and reported below.

MATERIALS AND METHODS

General information about research objective

In this study, 120 adolescents with multiple depressive disorders diagnosed between January 2023 and January 2024 were recruited from multiple secondary schools and community mental health centers as an observation group using stratified random sampling, and 120 adolescents with healthy physical examination results during the same period were selected as a control group. The sample size for this study was selected based on expected effect size, significance level, statistical efficacy, and resource constraints. Through the pre-experiment and literature review, we expected an effect size of medium, with the significance level set at 0.05 and statistical efficacy at 0.80. Calculations using the G*Power software yielded a minimum of 100 participants for each group. To increase the robustness of the study, we finalized a sample size of 120 participants per group. This sample size was considered statistically sufficient to detect a medium effect size effect. In the depression group, 54 males and 66 females, aged 15 to 18, mean: 16.08 ± 0.66; in the control group, 51 males and 69 females, aged 14 to 17, mean: 15.95 ± 0.70. Education level: The participants of education from junior high school to high school, including depression group junior middle school education level of 50, high school education level of 70, control group of junior high school education level of 65, high school education level of 55, the two groups of basic data difference without statistical significance ($P > 0.05$), is comparable. All participants participated in the study with informed consent from their parents or legal guardians. Through the detailed description of the general data described above, this study establishes a comprehensive research foundation, which provides a solid foundation for further data analysis and interpretation of the results.

Inclusion and exclusion criteria

Inclusion criteria include: (1) Age between 13 and 18 years old; (2) Patients diagnosed with MDD (according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition or International Classification of Diseases, 10th Revision criteria); (3) The healthy controls had no history of mental illness; and (4) Was able to understand and agree to participate in the study. Exclusion criteria include: (1) Adolescents with serious physical illness or mental disorders; (2) Adolescents with intellectual disabilities or other developmental disabilities; and (3) Adolescents who declined

participation in the study or were unable to obtain parental consent.

Methods

Data collection was conducted through questionnaires and clinical assessments, including: (1) The General Self-Efficacy Scale (GSES) is a psychometric tool used to assess individual self-efficacy. Self-efficacy refers to an individual's confidence and judgment that he can effectively perform the necessary actions to achieve the desired outcome in a given situation. This concept was first proposed by the psychologist Albert Bandura in 1977, and was widely studied and applied in the subsequent decades. GSES typically contains 10 to 20 items that assess individual general self-efficacy by means of self-report, and usually in the Likert scale format, where participants need to choose within a predetermined response range, such as a four-comment subscale from "completely incorrect" to "completely correct". After adding the scores of each item, the total score was obtained, the higher the total score, the stronger the individual; (2) Parenting style evaluation Scale. The Parenting style evaluation Scale was used to evaluate the parenting style of the two groups of tested subjects, a total of 66 entries in the scale, using the 1- to 4-point scoring method, a total of 11 factors were included, father had 6 factors (58 items): Emotional warmth and understanding (FF1), severe punishment (FF2), excessive interference (FF3), preferred subjects (FF4), refused denial (FF5), and excessive protection (FF6); mothers had 5 factors (56 items): Emotional warmth and understanding (MF1), excessive interference protection (MF2), denial (MF3), severe punishment (MF4), and preferred subjects (MF5); (3) The Beck Depression Inventory (BDI) was administered by American psychologist Aaron Baker (Aaron T Beck) was developed in 1961 as a psychometric tool to assess the degree of depression. It is a self-rating scale designed to measure individual severity of depressive symptoms at a given time. Each entry was scored on a scale of 0 to 3, with 0 indicating the absence of the symptom and 3 indicating very severe symptoms. Individuals choose the options that best fit their current state according to their feelings. The scores of all entries were then summed up to obtain the total score; and (4) Using SPSS26.0 statistical software, the collected data was anonymized to ensure that the privacy of the participants was protected, and professional data management software was used for data entry to ensure the accuracy of the data.

Statistical analysis

SPSS26.0 software package was used for statistical analysis. Measurement information was expressed as mean ± SD, and independent sample *t*-test was used for comparison between groups; count information was expressed as rate, and χ^2 test was used for comparison between groups. Correlation analysis was done by calculating Pearson's correlation coefficient. $P < 0.05$ indicated that the difference was statistically significant.

RESULTS

This study aimed to investigate the correlation between MDD and self-efficacy, parenting patterns in adolescents. The following are the results of the statistical analysis based on the hypothetical data: Basic information of the samples. Data were collected from 240 adolescents, 120 in the depression group and 120 in healthy controls. The two groups were well matched for gender, age and literacy, and specific data are shown in Table 1.

Self-efficacy

The self-efficacy scores were significantly lower in the depressed patient group than in the healthy controls. Scores on the GSES scale ranged from 1-4, with higher scores indicating greater self-efficacy. The results showed that GSES scores were significantly lower in depressed patients than in healthy controls. The mean GSES score in the depressed group was 19.82 (standard deviation = 6.01), while the mean score for healthy controls was 24.78 (standard deviation = 5.71). The independent sample *t*-test of scores between the two groups was statistically significant ($t = -6.554$, $P < 0.001$), indicating a significant decrease in self-efficacy in depressed patients compared to healthy adolescents. Specific data are given in Table 2. This difference may reflect poor confidence in their abilities and the possible lack of necessary intrinsic motivation and positive coping strategies in the face of challenges and adversity. The reduced self-efficacy may be related to the severity of depressive symptoms and may affect the overall mental health and quality of life.

Parenting style

The results of the depressed subjects were statistically significant in FF1, FF2, FF4, FF5, MF6, MF1, MF2, MF3 and MF4 factors, $P < 0.05$; no significant difference between the two groups on FF3 and MF5 factors, $P > 0.05$. Specific data are given in Table 3.

Depressive symptoms

The mean score on the BDI was 26.4 (SD = 8.2) in the depressed group and 5.5 (SD = 3.0) for healthy controls. The difference in the BDI scores between the two groups was statistically significant ($t = 26.22$, $P < 0.001$). Specific data are given in Table 4.

Correlation analysis

Correlation between parenting style and depressive symptoms among adolescents (specific data are given in Table 5 and Figure 1): (1) Fanal emotional warmth and comprehension (FF1) were significantly negatively associated with depressive symptoms (Pearson's correlation coefficient = -0.499, $P < 0.01$); (2) Fanal punishment severity (FF2) was significantly

Table 1 Basic information of the samples

Variable	Observation group (*n* = 120)	Control group (*n* = 120)
Age (mean ± SD)	16.53 ± 0.59	15.42 ± 0.66
Gender (male/female)	54/66	51/69
Degree of education	Junior high school: 50	Junior high school: 65
	High school: 70	High school: 55

Table 2 The score for self-efficacy

Group	GSES score (mean ± SD)
Observation group	19. 82 ± 6. 01
Control group	24. 78 ± 5. 71
t	-6.554
P value	< 0.001

GSES: General Self-Efficacy Scale.

Table 3 Parenting Style Evaluation Scale score

Group	Observation group	Control group	*t*	*P* value
FF1	44.7 ± 5.7	52.1 ± 5.5	-10.234	< 0.001
FF2	20.1 ± 3.5	14.0 ± 2.5	15.536	< 0.001
FF3	21.4 ± 4.2	21.3 ± 4.4	0.180	0.857
FF4	9.2 ± 1.0	9.6 ± 1.3	-2.672	0.008
FF5	11.1 ± 1.7	7.1 ± 1.1	21.640	< 0.001
FF6	10.7 ± 1.2	8.0 ± 1.0	18.935	< 0.001
MF1	46.7 ± 5.9	51.3 ± 6.5	-5.740	< 0.001
MF2	36.9 ± 3.6	0.331 ± 3.0	13.091	< 0.001
MF3	0.113 ± 1.6	10.4 ± 1.1	15.233	< 0.001
MF4	13.8 ± 1.4	10.6 ± 1.2	19.011	< 0.001
MF5	9.0 ± 0.6	9.1 ± 0.9	-1.013	0.312

Table 4 Score for depressive symptoms

Group	BDI score (mean ± SD)
Observation group	26.4 ± 8.2
Control group	5.5 ± 3.0
t	26.221
P value	< 0.001

BDI: Beck Depression Inventory.

positively associated with depressive symptoms (Pearson's correlation coefficient = 0.600, $P < 0.01$); (3) Fanal denial (FF5) showed a significant positive association with depressive symptoms (Pearson's correlation coefficient = 0.702, $P < 0.01$); (4) Maternal excessive interference protection (MF2) was significantly positive associated with depressive symptoms (Pearson's correlation coefficient = 0.620, $P < 0.01$); (5) Maternal refusal denial (MF3) was significantly positively associated with depressive symptoms (Pearson's correlation coefficient = 0.610, $P < 0.01$); and (6) Maternal severity of

Table 5 Correlation between parenting style and depressive symptoms among adolescents

		FF1	FF2	FF3	FF4	FF5	FF6	MF1	MF2	MF3	MF4	MF5	BDI
FF1	Pearson correlation	1											
FF2	Pearson correlation	-0.378[a]	1										
FF3	Pearson correlation	0.027	-0.077	1									
FF4	Pearson correlation	0.123	-0.141[b]	-0.044	1								
FF5	Pearson correlation	-0.428[a]	0.548[a]	-0.016	-0.029	1							
FF6	Pearson correlation	-0.477[a]	0.546[a]	0.017	-0.106	0.667[a]	1						
MF1	Pearson correlation	0.074	-0.340[a]	0.012	-0.036	-0.319[a]	-0.315[a]	1					
MF2	Pearson correlation	-0.369[a]	0.476[a]	0.046	-0.047	0.556[a]	0.508[a]	-0.289[a]	1				
MF3	Pearson correlation	-0.344[a]	0.521[a]	0.025	-0.156[b]	0.562[a]	0.551[a]	-0.215[a]	0.418[a]	1			
MF4	Pearson correlation	-0.459[a]	0.597[a]	-0.008	-0.057	0.630[a]	0.588[a]	-0.316[a]	0.487[a]	0.530[a]	1		
MF5	Pearson correlation	0.063	-0.032	-0.039	-0.019	-0.088	-0.077	0.035	-0.054	-0.044	-0.082	1	
BDI	Pearson correlation	-0.499[a]	0.600[a]	0.04	-0.133[b]	0.702[a]	0.705[a]	-0.264[a]	0.620[a]	0.610[a]	0.662[a]	-0.082	1

[a]Significant correlation at the 0.01 level (two-tailed).
[b]Significant correlation at the 0.05 level (two-tailed).

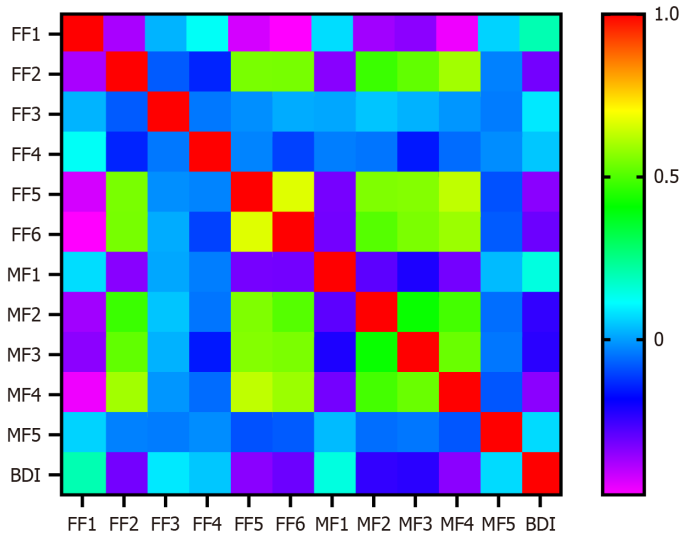

Figure 1 Correlation between parenting style and depressive symptoms among adolescents. BDI: Beck Depression Inventory.

punishment (MF4) was significantly positively associated with depressive symptoms (Pearson's correlation coefficient = 0.662, $P < 0.01$). Correlation between self-efficacy and depressive symptoms in adolescents (specific data are given in Table 6): Self-efficacy (GSES) showed a significant negative correlation with depressive symptoms (BDI) (Pearson's correlation coefficient = -0.287, $P < 0.01$), indicating that higher self-efficacy means lower depressive symptoms.

DISCUSSION

This study aimed to investigate the correlation between MDD and self-efficacy, parenting patterns in adolescents. Through survey analysis of 120 depressed patients and 120 healthy control adolescents, this study yielded a series of meaningful results. The self-efficacy and depression study found significantly lower self-efficacy in depressed patients than in healthy controls, consistent with Bandura *et al*'s social cognitive theory that self-efficacy is an important predictor of individual mental health[13]. Low self-efficacy may lead to adolescent lack of confidence in the face of challenges and difficulty with effective coping strategies, thus increasing the risk of depressive symptoms[29]. Furthermore, increased self-efficacy may contribute to enhanced individual coping and psychological resilience, subsequently reducing the occurrence of depressive symptoms.

Table 6 Correlation between self-efficacy and depressive symptoms in adolescents

		GSES	BDI
GSES	Pearson correlation	1	
BDI	Pearson correlation	-0.287[a]	1

[a]Significant correlation at the 0.01 level (two-tailed).
GSES: General Self-Efficacy Scale; BDI: Beck Depression Inventory.

Parenting and depression

This study also found that parents of depressed patients scored lower on emotional warmth and understanding, and higher on severe punishment and denial. This is consistent with findings from previous studies suggesting that poor parenting practices may negatively affect the mental health of adolescents[30]. Parental emotional warmth and understanding are recognized as important protective factors for positive adolescent development, while severe punishment and refusal denial may lead to adolescents feeling excluded and not understood, thus increasing the risk of depressive symptoms. Based on the results of the correlation analysis, we could further confirm that there was a significant correlation between parenting style and adolescent depressive symptoms. In particular, parental punishment severity and denial had a significant positive association with increased depressive symptoms, whereas parental emotional warmth and understanding showed a significant negative association with reductions in depressive symptoms. Furthermore, increased self-efficacy was significantly associated with decreased depressive symptoms, underscoring the potential role of self-efficacy in preventing and alleviating depressive symptoms in adolescents. These findings provide us with a deeper understanding that parenting style and adolescent self-efficacy are important factors affecting adolescent mental health. Therefore, improving parenting practices and enhancing adolescent self-efficacy should be considered when designing prevention and interventions. The results of this study have important theoretical and practical implications for the prevention and intervention of adolescent depression. Theoretically, this study provides new perspectives for understanding the complex causes of depressive disorder in adolescents, highlighting the role of self-efficacy and parenting style in the development of depression. The results of the study are consistent with the existing literature and support Bandura's self-efficacy theory and attachment theory, which emphasize the importance of a positive parent-child relationship for adolescent mental health[13]. In addition, the results of this study are also relevant to psychological resilience theory, which suggests that an individual's adaptive capacity is not only influenced by risk factors but also by protective factors. Self-efficacy and positive parenting patterns can be considered as protective factors that can help adolescents resist the risk of depression. These findings provide theoretical support for the design of preventive measures aimed at enhancing adolescents' self-efficacy and optimizing the family environment, which can help promote adolescents' mental health. Practice, this study suggests that educators and mental health professionals should consider improving adolescent self-efficacy and improving parenting style when designing interventions for adolescent depression. Specifically speaking, it can be achieved in the following aspects: Family education guidance: To provide parents with guidance and training on how to establish a positive parenting style, to help them understand the importance of emotional warmth and understanding to adolescent mental health. Mental health education: Popularize mental health knowledge in schools and communities, let teenagers understand the symptoms and prevention methods of depression, and improve their self-awareness and awareness for help. Psychological intervention services: Professional psychological intervention services, such as cognitive behavioral therapy, are provided for adolescents in need to help them establish positive coping strategies and improve self-efficacy. Social support networks: Establish and strengthen social support networks, including schools, communities and professional institutions, to provide the necessary support and resources for teenagers. Policy advocacy: Through policy advocacy, improve the social awareness and attention to the mental health problems of teenagers, and create a more healthy and supportive environment for teenagers to grow up.

CONCLUSION

This study provides valuable insight into the relationship between self-efficacy, parenting style and depression, but at the same time has some limitations. First, since this study used a cross-sectional design, we were unable to determine the causal relationships between the variables. To compensate for this deficiency, future studies could employ a longitudinal design to explore in depth the developmental trajectories and potential causal links between these variables. Given the limitations of the current study, future work can be improved in the following ways: (1) Improve the geographical diversity of the sample: The case-control group in this study was mainly drawn from the hospital, while the control group was limited to middle school students in a certain area, which may lead to geographical differences. Future studies should expand the sample sources to ensure the geographic diversity and homogeneity of the case and control groups; (2) Expanding sample size and coverage: The relatively small sample size of this study and the limited coverage area may limit the generality of the findings. Future studies should expand the sample size and cover a wider range of areas to improve study representativeness and applicability; (3) Reducing the impact of subjective evaluation: The self-filled scales used in this study may have introduced some degree of subjective bias. To improve the objectivity of the data,

future studies could employ multi-source data collection methods, such as family interviews and focus groups, to reduce single-source bias. Combining qualitative and quantitative methods provides a richer understanding of adolescents' experiences and perceptions of self-efficacy and parenting; (4) Expanding variable statistics: Researchers should also consider other variables that may affect parenting styles and mental health outcomes, such as socioeconomic status, academic performance, cultural background, family structure, and parents' mental health status. By taking these factors into account, we can gain a more comprehensive understanding of the complex relationship between parenting styles and adolescent mental health, and provide more targeted recommendations for promoting adolescent mental health; and (5) Longitudinal approach: This study mainly analyzed the relationship between general self-efficacy, parenting, coping style and depressive mood from a static perspective, but did not address the dynamic evolution of these relationships over time. Future research could adopt a longitudinal study design to more fully reveal the interactions between these variables and their trends over time, in order to gain a deeper understanding of how these factors change over time and to assess their impact on mental health outcomes over time. Through these improvements, future research will be able to provide a deeper and more comprehensive understanding, thus providing a more solid foundation for theory and practice in related fields.

FOOTNOTES

Author contributions: Zhang BF and Zhang XY contributed to the research design and data analysis; Zhang BF participated in the data collection and paper writing; Zhang XY took part in the funding application, reviewing and editing, communication coordination, ethical review, copyright and licensing, and follow-up.

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ORIGINAL ARTICLE

Retrospective Study

Depression and anxiety, peripheral blood inflammatory factors, and stress levels on therapeutic outcomes in patients with chronic wounds

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Abstract

BACKGROUND

The incidence of chronic wounds is rising due to an aging population and lifestyle changes in our country. In addition, as the disease spectrum evolves, chronic wounds have become common clinical issues that seriously threaten health and impose significant social and economic burdens.

AIM

To investigate how depression, anxiety, peripheral blood inflammatory factors, and stress levels affect therapeutic outcomes in patients with chronic wounds.

METHODS

Retrospectively collected clinical data from 110 patients with chronic wounds treated at Changde Hospital, Xiangya School of Medicine, Central South University (The First People's Hospital of Changde City) between January 2021 and December 2023, categorizing them into effective and ineffective groups based on treatment effects. Differences between both groups were analyzed using univariate analysis, independent risk factors identified *via* logistic regression, and their predictive value assessed through receiver operating characteristic analysis.

RESULTS

Following treatment, 95 cases were classified as the effective group (cured or improved), while 15 cases with improvement formed the ineffective group. Significant differences between both groups were noted in wound area, infection status, daily bed time, Hamilton Anxiety Rating Scale (HAMA) scores, Hamilton Depression Rating Scale (HAMD) scores, and levels of interleukin-6, tumor necrosis factor-alpha, and superoxide dismutase ($P < 0.05$). Logistic regression analysis identified a wound area ≥ 7 cm^2, HAMA ≥ 9 scores, and HAMD ≥ 8 scores were independent risk factors for ineffective treatment in patients with chronic wounds ($P < 0.05$). The receiver operating characteristic curve analysis revealed that the area under the curve for ineffective treatment based on wound area, HAMA, and HAMD was 0.767, 0.805, and 0.768 respectively.

CONCLUSION

Wound size, anxiety, and depression are significant factors influencing the therapeutic outcomes in patients with chronic wounds that require careful attention, alongside the development of appropriate strategies.

Key Words: Chronic wound; Depression; Anxiety; Inflammatory factors; Stress level; Clinical effect

Core Tip: This study retrospectively analyzed clinical data from 110 patients with chronic wounds to assess the effects of depressive and anxious moods, peripheral blood inflammatory markers, and stress levels on treatment outcomes. The results showed an overall efficacy rate of 86.36%, with independent risk factors identified as wound size and depression/anxiety levels. Additionally, peripheral blood inflammatory markers and stress levels were lower in the effective group than in the ineffective group. Therefore, for patients with chronic wound, it is crucial to address not only the wounds but also their psychological well-being and inflammatory stress status to improve treatment effectiveness.

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INTRODUCTION

Chronic wounds are defined as skin tissue damage resulting from various etiologies that fail to heal within a typical timeframe, generally beyond four weeks. These include pressure injury, venous ulcers of the lower extremities, diabetic foot ulcers, radiation ulcers, and postoperative wound complications[1]. Chronic wounds are characterized by high incidence rates, prolonged treatment durations, and substantial healthcare costs. They not only cause physical pain in patients but also interfere with their normal life, increase the economic and psychological burden, and seriously affect the quality of life[2,3]. Therefore, it is of great significance to explore the factors affecting the clinical outcomes of patients with chronic wounds to optimize treatment plans, improve the quality of life of patients, and reduce medical costs. Recently, with the continuous increase in medical research and progress in medical technology, treatment methods for chronic wounds have become increasingly diversified, mainly including drug, physical, surgical, and biological therapies [4]. However, due to the complexity and heterogeneity of chronic wounds, the effectiveness of identical treatments can vary significantly among different patients. Relevant studies have indicated that the onset and progression of chronic wounds are associated with inflammatory response, suggesting that their clinical effectiveness may be influenced by inflammatory factors and stress levels[5,6]. Additionally, other studies have demonstrated that some patients with chronic wounds experience mobility challenges and may require assistance from others for activities such as attending medical appointments or changing dressings[7]. This reliance can lead to emotional burdens characterized by feelings of guilt towards caregivers[7]. Therefore, this study investigates the effects of depression, anxiety, peripheral blood inflammatory factors, and stress levels on the therapeutic outcomes in patients with chronic wounds to provide a theoretical foundation for clinical diagnosis and treatment.

MATERIALS AND METHODS

General information

The clinical data of 110 patients with chronic wounds treated at Changde Hospital, Xiangya School of Medicine, Central South University (The First People's Hospital of Changde City) from January 2021 to December 2023 were retrospectively collected. Inclusion criteria were as follows: (1) Skin and subcutaneous tissue injuries; (2) Wounds unhealed for more than 4 weeks; and (3) Wound area ≤ 25 cm^2. Exclusion criteria were: (1) Evident signs of wound infection; (2) Ulcers resulting

from diabetic conditions, venous insufficiency, malignancy, or radiation; (3) Concurrent systemic diseases such as hematological disorders, immune system dysfunctions, infections, or malignancies; (4) Vital organ failure including the heart, liver, or kidneys; (5) Presence of mental health disorders; (6) Severe malnutrition or compromised immunity; (7) Incomplete clinical data; and (8) Participants lost to follow-up. The study was reviewed and approved by the Institutional Review Board of Changde Hospital, Xiangya School of Medicine, Central South University (The First People's Hospital of Changde City), approval No. 2024-148-01.

Efficacy criteria

On the 30th day following the completion of treatment, the patients were asked to review and observe recovery and determine its efficacy. The evaluation criteria for the curative effect were as follows: (1) Cure: Pain disappeared, wound healing, no secretions, and fresh red granulation tissue can be seen; (2) Improvement: The pain is reduced, the area of the wound is reduced, there is a small amount of secretion and fresh red granulation tissue can be seen; and (3) Not healed: The pain is strong, the wound has not healed, and there is a large amount of secretion[8]. The total effective rate = (cured cases + improved cases)/total cases × 100%.

Data collection

General information: Age, sex, education level, wound area, wound type, wound infection, physical exercise, daily bedtime. The Hamilton Anxiety Rating Scale (HAMA) and the Hamilton Depression Rating Scale (HAMD) were employed to assess the level of anxiety and depression in patients within one week of treatment. The HAMA comprises 14 items, with scores interpreted as follows: (1) ≤ 7 reflects no anxiety symptoms; (2) 8-13 suggests possible anxiety; (3) 14-20 indicates definite anxiety; (4) 21-28 denotes marked anxiety; and (5) ≥ 29 indicates severe anxiety[9]. The HAMD consists of 17 items, with scores interpreted as follows: (1) ≤ 7 indicates no depressive symptoms; (2) 8-16 suggests possible depression; (3) 17-24 indicates moderate depression; and (4) ≥ 24 signifies severe depression[10]. Levels of inflammatory factors interleukin (IL)-6 and tumor necrosis factor-alpha (TNF-α) and stress factors [superoxide dismutase (SOD) and malondialdehyde (MDA)] were measured within 24 hours of patient admission. A fasting venous blood sample (5 mL) was collected in the morning, centrifuged at 3000 rpm for 15 minutes to obtain the supernatant, which was stored at -80 °C for subsequent analysis using an enzyme-linked immunosorbent assay.

Statistical analysis

Statistical software (SPSS 27.0) was used to process the data of the 110 patients with chronic wounds. Normally distributed measurement data were expressed as mean ± SD, and comparisons between the two groups were performed using a two-independent sample *t* test. The ratio of counting data (%) is indicated, and the χ^2 test was used for intergroup comparisons. $P < 0.05$ indicated that the difference was statistically significant. Logistic regression analysis was performed on the statistically significant variables identified in the univariate analysis. The enter method was employed to iteratively compute the odds ratio (OR) and 95% confidence interval (95%CI). The receiver operating characteristic (ROC) curve of a single continuous variable was obtained using the MedCalc software, and the area under the curve (AUC) and optimal cut-off value of the continuous variable were calculated.

RESULTS

Clinical efficacy rate in patients with chronic wounds

Following treatment, 53 patients were cured and 42 exhibited an improvement in their condition, classifying them into the effective group. Conversely, 15 patients exhibited no changes and were categorized as the ineffective group. The details of the treatment are presented in Figure 1A.

General data of patients with chronic wounds

Compared with the ineffective group, the effective group had a smaller wound area, a higher incidence of wound infection, and a lower daily bed time ($P < 0.05$). There were no significant differences between the two groups in terms of age, sex, educational level, wound type, or physical exercise participation ($P > 0.05$) (Table 1).

Depression and anxiety scores of patients with chronic wounds

The HAMA and HAMD scores of the effective group were 6.49 ± 2.18 points and 6.24 ± 2.39 points, respectively. In the ineffective group, the HAMA score was 10.60 ± 2.61, and the HAMD score was 8.33 ± 1.92. Compared to the ineffective treatment group, the HAMA and HAMD scores in the effective group were lower ($t = 6.600$, $P < 0.001$ and $t = 3.229$, $P = 0.002$, respectively) (Figure 1B).

Levels of inflammatory factors in the peripheral blood of patients with chronic wounds

The levels of IL-6 and TNF-α in the effective group were 16.19 ± 4.01 pg/mL and 56.49 ± 13.36 pg/mL, respectively. In the ineffective group, the levels of IL-6 were 22.67 ± 5.92 pg/mL, and the level of TNF-α was 65.80 ± 12.87 pg/mL. Levels of IL-6 and TNF-α in the effective group were lower than those in the ineffective group ($t = 4.089$, $P = 0.001$ and $t = 2.520$, $P = 0.013$, respectively) (Figure 1C).

Table 1 General data of patients with chronic wounds, *n* (%)

Index	Effective group (*n* = 95)	Ineffective group (*n* = 15)	χ^2/t	*P* value
Age (year), mean ± SD	56.09 ± 13.89	54.20 ± 18.11	0.470	0.639
Sex	/	/	0.322	0.571
Man	56 (58.95)	10 (66.67)	/	/
Woman	39 (41.05)	5 (33.33)	/	/
Educational level	/	/	0.006	0.938
Junior college or below	58 (61.05)	9 (60.00)	/	/
College degree or above	37 (38.95)	6 (40.00)	/	/
Wound area (cm^2), mean ± SD	5.29 ± 1.54	7.73 ± 1.79	5.586	< 0.001
Wound type	/	/	0.454	0.978
Pressure ulcer	21 (22.11)	4 (26.67)	/	/
Venous blood ulcer	18 (18.95)	3 (20.00)	/	/
Diabetic foot ulcers	16 (16.84)	3 (20.00)	/	/
Traumatic ulcer	23 (24.21)	3 (20.00)	/	/
Other	17 (17.89)	2 (13.33)	/	/
Wound infection	/	/	11.579	< 0.001
Yes	32 (33.68)	12 (80.00)	/	/
No	63 (66.32)	3 (20.00)	/	/
Participates in physical exercise	/	/	0.750	0.387
Yes	71 (74.74)	5 (33.33)	/	/
No	24 (25.26)	10 (66.67)	/	/
Daily bed time (hour), mean ± SD	11.71 ± 2.36	15.93 ± 2.40	6.431	< 0.001

Stress levels of patients with chronic wounds

The SOD and MDA levels in the effective group were 103.72 ± 14.77 nmol/L and 37.23 ± 8.61 nmol/L, respectively. The SOD and MDA levels in the ineffective group were 107.80 ± 12.28 nmol/L and 47.20 ± 9.41 nmol/L, respectively. There was no significant difference in the SOD levels between the two groups (t = 1.016, P = 0.312). The MDA levels in the effective treatment group were lower than those in the ineffective treatment group (t = 4.117, P < 0.001) (Figure 1D).

Multivariate logistic regression analysis

Using clinical efficacy as the dependent variable, wound area, presence of wound infection, daily bed rest duration, HAMA, HAMD, IL-6, TNF-α, and MDA were incorporated as independent variables in the logistic regression model. Continuous variables were assigned using their optimal cut-off values as detailed in Table 2. Logistic analysis showed that wound area ≥ 7 cm^2 (OR = 16.374, 95%CI: 1.037-258.609), HAMA scores ≥ 9 (OR = 100.709, 95%CI: 2.587-3927.125), and HAMD scores ≥ 8 (OR = 90.937, 95%CI: 2.231-3707.301) were independent risk factors for treatment inefficacy in patients with chronic wounds (P < 0.05) (Table 3).

ROC curve analysis of relevant variables

The ROC analysis results showed that the AUC of the wound area, HAMA, and HAMD, were 0.767, 0.805, 0.768, respectively, and the integrated AUC for the three methods is 0.940 (Table 4 and Figure 1E).

DISCUSSION

Chronic wounds represent significant clinical and public health challenges due to their high incidence, complex pathogenesis, and treatment difficulties[11]. Statistics indicate that among patients with diabetes aged > 50 years, the incidence of diabetic foot is as high as 8.1%, the annual mortality rate of diabetic foot ulcers is as high as 11%, and the mortality rate of amputation patients is as high as 22%, with a high overall incidence[12,13]. In addition, patients with chronic wounds often face huge psychological pressure due to long-term disease failure, long treatment cycles, and possible complications, resulting in emotional problems, such as anxiety and depression, which affect clinical efficacy and are not conducive to postoperative recovery. Therefore, it is essential to investigate the factors influencing clinical efficacy

Table 2 Logistic regression model assignment situation

Variables	Assignments
Clinical efficacy	1: Ineffective, 0: Effective
Wound area	1: ≥ 7 cm^2, 0: < 7 cm^2
Wound infection	1: Yes, 0: No
Daily bed time	1: ≥ 14 hours, 0: < 14 hours
HAMA	1: ≥ 9 scores, 0: < 9 scores
HAMD	1: ≥ 8 scores, 0: < 8 scores
IL-6	1: ≥ 19 pg/mL, 0: < 19 pg/mL
TNF-α	1: ≥ 63.88 pg/mL, 0: < 63.88 pg/mL
MDA	1: ≥ 41 nmol/L, 0: < 41 nmol/L

HAMD: Hamilton Depression Rating Scale; HAMA: Hamilton Anxiety Rating Scale; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-alpha; MDA: Malondialdehyde.

Table 3 Multivariate logistic analysis of factors influencing clinical efficacy in patients with chronic wounds

Variable	B	SE	Wald χ^2	*P* value	OR	95%CI
Wound area	2.796	1.408	3.943	0.047	16.374	1.037-258.609
Wound infection	0.062	1.343	0.002	0.963	1.064	0.077-14.787
Daily bed time	2.170	1.695	1.640	0.200	8.761	0.316-242.699
HAMA	4.613	1.869	6.094	0.014	100.790	2.587-3927.125
HAMD	4.510	1.892	5.684	0.017	90.937	2.231-3707.301
IL-6	0.917	1.323	0.480	0.488	2.501	0.187-33.450
TNF-α	0.164	1.323	0.015	0.902	1.178	0.088-15.752
MDA	2.934	1.716	2.923	0.087	18.797	0.651-542.754

OR: Odds ratio; CI: Confidence interval; HAMD: Hamilton Depression Rating Scale; HAMA: Hamilton Anxiety Rating Scale; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-alpha; MDA: Malondialdehyde.

Table 4 Receiver operating characteristic curve analysis of the related variables

Variable	AUC	SE	95%CI	*P* value
Wound area	0.767	0.063	0.676-0.842	< 0.001
HAMA	0.805	0.057	0.719-0.875	< 0.001
HAMD	0.768	0.058	0.678-0.844	< 0.001
United	0.940	0.0297	0.878-0.976	< 0.001

CI: Confidence interval; HAMD: Hamilton Depression Rating Scale; HAMA: Hamilton Anxiety Rating Scale; AUC: Area under the curve.

in patients with chronic wounds. This study included 110 patients with chronic wounds to evaluate clinical efficacy. The results showed that 95 patients were cured or showed improvement, and the total efficacy rate was 86.36%. Further analysis of the clinical data of 110 patients with chronic wounds showed that the single-factor results such as wound area, wound infection, HAMA, HAMD, IL-6, TNF-α, and MDA influenced poor treatment outcomes in patients with chronic wounds. Multifactor logistic analysis showed that a wound area ≥ 7 cm^2, HAMA scores ≥ 9, and HAMD scores ≥ 8 are independent risk factors for poor treatment efficacy in patients with chronic wounds.

Oliveira *et al*[14] pointed out that the wound area is related to growth factors, whereby a larger wound area necessitates an increased supply of nutrients and growth factors to facilitate the healing process. However, patients' nutritional status and self-repair capabilities are often limited, making it challenging to meet the healing demands of

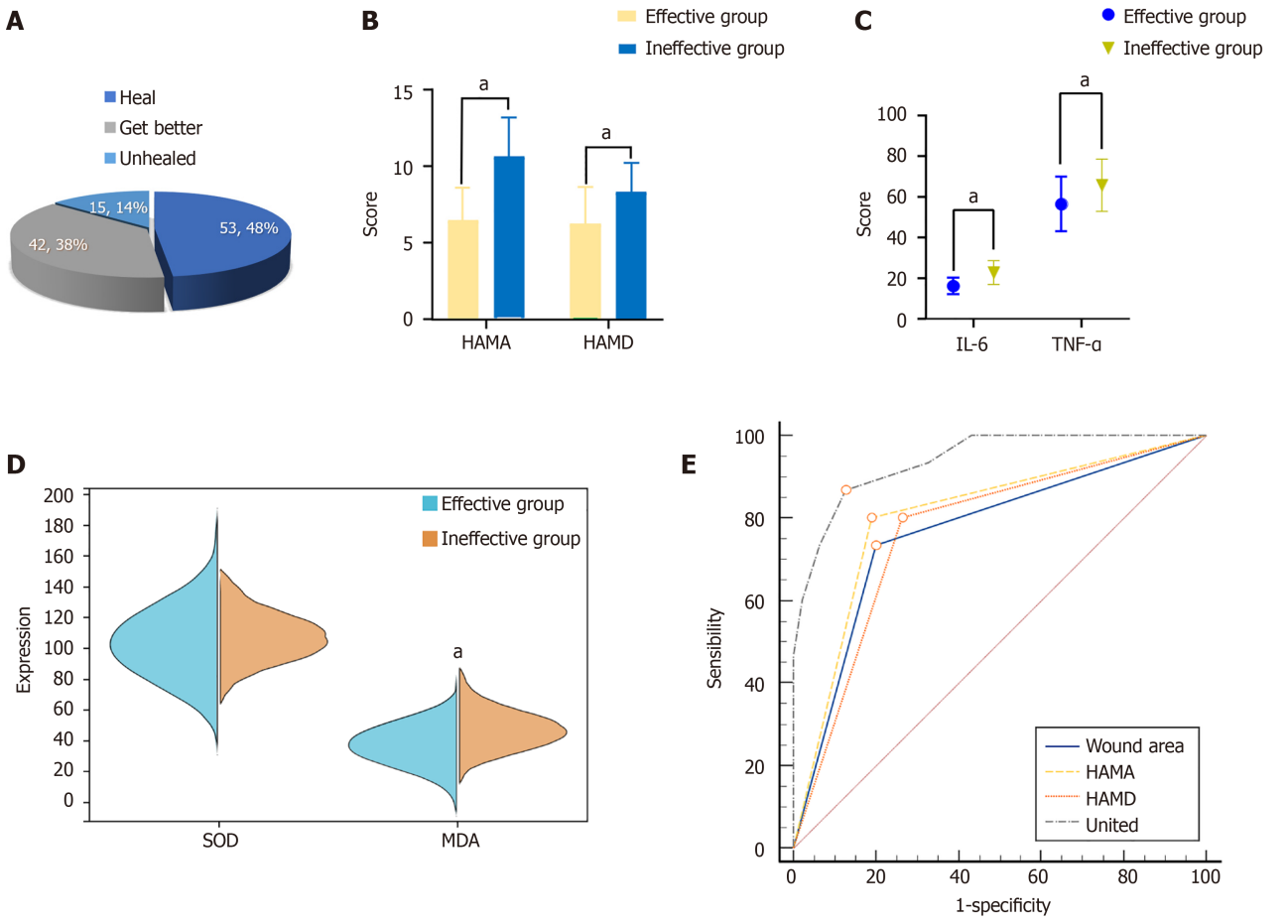

Figure 1 Patients with chronic wounds. A: Clinical effective rate in patients with chronic wounds; B: Depression and anxiety scores in patients with chronic wounds; C: Level of inflammatory factors in the peripheral blood of patients with chronic wound surfaces; D: Stress levels in patients with chronic wounds; E: The receiver operating characteristic curves of the related variables. $^{a}P < 0.05$ *vs* ineffective group. HAMD: Hamilton Depression Rating Scale; HAMA: Hamilton Anxiety Rating Scale; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-alpha; SOD: Superoxide dismutase; MDA: Malondialdehyde.

extensive wounds. In addition, large wounds often take longer to heal, and a longer healing process may lead to more complications, such as scarring and dysfunction. Liu *et al*[15] pointed out that when inflammation occurs in the body, it further damages the wounded tissue and may also affect the normal function of the surrounding healthy tissue, which is not conducive to patient recovery. Pomponio *et al*[16] found that during wound infection, bacteria, and bacterial metabolites would remain in the patient's wound, which affects the normal growth of the wound tissue and leads to difficult wound healing. Currently, the main treatment for acute wound infections is antibiotics, however, their inappropriate and excessive use in chronic wound infections not only increases treatment costs but may also prolong recovery time. Moreover, long-term use of antibiotics may lead to an increase in bacterial resistance, making infections more difficult to control[17]. In addition, prolonged bed rest can result in decreased physical activity, compromised blood circulation, and impaired nutrient delivery and waste removal from the wound, all of which are detrimental to the healing process. Alinia-Najjar *et al*[18] demonstrated that anxiety and depression can reduce patients' treatment compliance and negatively impact their diet and sleep, indirectly hindering wound healing. Physiologically, these conditions may influence the endocrine and immune systems, further affecting wound repair[19]. For instance, negative emotions can elevate stress hormone levels in patients, impacting inflammatory responses and cellular proliferation in wounds. Additionally, anxiety and depression may also reduce the patient's immune function, making them more susceptible to infection and delaying wound healing. Schlosser *et al*[20] found a correlation between anxiety and preoperative comorbidities as well as poor postoperative outcomes. Depression in patients with preoperative wounds is often difficult to heal, which may be related to a reduction in patient self-assessment, self-denial, and psychological factors such as giving up.

IL-6 is an important cytokine produced by the innate immune system during the initial response to injury and infection, promoting the production of acute-phase reactants such as C-reactive protein[21]. In chronic wounds, IL-6 levels may remain persistently elevated due to ongoing inflammation. A study indicated that IL-6 plays a central role in the acute inflammatory response; after infection and inflammation, IL-6 is first generated, and levels rise rapidly, peaking within 2 hours. The higher level is consistent with the severity of inflammation[22]. Excessive IL-6 may lead to an excessive inflammatory response and increase the risk of wound infection, thereby inhibiting wound healing. TNF-α is a key proinflammatory cytokine in skin trauma, which can activate immune cells and promote inflammatory response[23]. Xi *et al*[24] pointed out that TNF-α can lead to excessive inflammation and poor prognosis, which is consistent with the

results of this study. TNF-α can affect the balance of cell proliferation and apoptosis, which may hinder wound healing by promoting cell apoptosis and inhibiting cell proliferation, leading to slow wound tissue repair and poor wound healing. Additionally, TNF-α may negatively affect angiogenesis. Overexpression of TNF-α in chronic wounds may inhibit the proliferation and migration of vascular endothelial cells and reduce the production of vasoactive factors, resulting in impaired wound angiogenesis and further hindering wound healing. Huang *et al*[25] found that the over-expression of TNF-α and the lack of anti-inflammatory cytokines such as IL-10 and transforming growth factor-beta in diabetic wounds lead to poor wound healing. This observation further supports the negative role of TNF-α in chronic wounds.

MDA is commonly used as an indicator of oxidative damage in the medical field, and increased levels usually indicate that the level of free radicals in the body exceeds the normal range, which may lead to cell damage and an inflammatory response[26]. However, direct studies on the effect of excess MDA on clinical efficacy in patients with chronic wounds are uncommon. The possible mechanisms are as follows. First, chronic wounds are often accompanied by increased oxidative stress. That is, the balance between the antioxidant system and free radicals in the body is destroyed. Increased levels of MDA, a marker of oxidative stress, may reflect the exacerbation of this imbalance[27]. Second, while inflammation is crucial for healing in chronic wounds, excessive inflammatory responses can impede normal healing. Increased MDA levels are generally linked to heightened inflammatory responses[28]. In addition, rising MDA may directly or indirectly affect cellular functions such as proliferation, migration, and differentiation, all of which play important roles in the healing process of chronic wounds[29].

The ROC analysis revealed that wound area, HAMA, and HAMD exhibited high AUC values for predicting poor outcomes in patients with chronic wounds, underscoring their clinical significance. Consequently, for patients with extensive chronic wounds, active debridement should be undertaken to control infection. Negative pressure wound therapy and other advanced techniques should be employed to facilitate healing. Additionally, the patient's overall nutritional status must be optimized, along with effective management of underlying conditions. For patients experiencing depression and anxiety, psychological evaluation and therapeutic interventions are crucial. Approaches such as psychological counseling, pharmacotherapy, or physical therapy can alleviate emotional distress while enhancing psychological well-being and immune function. However, this study is not without limitations. Firstly, as a retrospective analysis, data collection relies on existing medical records, which may be incomplete or inaccurate, thereby impacting the reliability of the results. Secondly, the sample size is relatively small at 110 patients, which may restrict the generalizability and applicability of the findings; thus, larger prospective studies are warranted for further validation.

CONCLUSION

This study explored the effects of anxiety and depression, inflammatory factors in peripheral blood, and stress levels on clinical efficacy in patients with chronic wounds. The results indicated that patients with larger wound areas and elevated anxiety and depression scores experienced poorer outcomes, identifying these factors as independent risk factors for adverse outcomes in chronic wounds. ROC analysis further corroborated the significance of these factors in predicting unfavorable outcomes. Consequently, healthcare professionals should closely monitor both the wound status and psychological well-being of patients, implementing timely and effective interventions for high-risk individuals to enhance treatment efficacy for chronic wounds.

FOOTNOTES

Author contributions: Li B and Xu XR designed the study; Li B and Li C performed data extraction and wrote the manuscript; Zhong XJ provided professional support; and all authors read and approved the final version.

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ORIGINAL ARTICLE

Retrospective Study

Influence of preoperative comprehensive education on anxiety, depression, pain, and sleep in elderly patients operated under general anesthesia

Li Qu, Rui Ma, Yan-Kai Ma, Xuan Zhao, Jing Jin, Qian-Qian Zhu, Xue-Ying Chen, Gui-Ping Xu

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Abstract

BACKGROUND

Owing to the particularities of their physical characteristics, older patients undergoing surgery under general anesthesia experience great surgical traumas. Thus, exploring more refined and individualized nursing approaches is an urgent need to mitigate the negative effects of surgery on such patients.

AIM

To analyze the influence of preoperative comprehensive education on anxiety, depression, pain, and sleep in older patients who underwent surgery under general anesthesia.

METHODS

In total, 163 older adults who underwent surgery under general anesthesia between June 2022 and November 2023 were selected, 77 of them received routine nursing care (control group), and 86 received preoperative comprehensive education (research group). Subsequently, comparative analyses were performed from the following perspectives: Surgical indicators (operation time, time to complete regain of consciousness, and temperature immediately after the procedure and upon recovery from anesthesia) before and after nursing care; negative emotions [self-rating anxiety scale (SAS)/self-rating depression scale (SDS)]; pain severity [visual analog scale (VAS)]; sleep quality [Pittsburgh sleep quality index (PSQI)]; incidence of sleep disturbances (difficulties in falling asleep for the first

time, falling asleep again after waking up frequently at night, falling asleep again after waking up early, and falling asleep all night); and incidence of adverse events (airway obstruction, catheter detachment, aspiration, and asphyxia).

RESULTS

The research group had significantly lower operation time and time to complete regain of consciousness than the control group after nursing care and markedly better recovery of postoperative body temperature and body temperature at awakening. In addition, more notable decreases in SAS, SDS, VAS, and PSQI scores were observed in the research group than in the control group. Furthermore, the incidence rate of sleep disturbance (8.14% *vs* 29.87%) and adverse events (4.65% *vs* 19.48%) were lower in the research group than in the control group.

CONCLUSION

Preoperative comprehensive education in older patients who underwent surgery under general anesthesia can improve postoperative indicators, effectively reduce the occurrence of anxiety and depression, alleviate postoperative pain, and improve sleep quality.

Key Words: Preoperative comprehensive education; Surgery under general anesthesia; Elderly patients; Anxiety and depression; Pain; Sleep

Core Tip: This study primarily analyzed the influence of preoperative comprehensive education on anxiety, depression, pain, and sleep in older patients who underwent surgery under general anesthesia to address the relatively greater surgical traumas endured by older patients owing to their particular physical characteristics. We conducted a comprehensive analysis from multiple dimensions, including surgical indicators, negative emotions, pain levels, sleep quality, incidence of sleep disturbances, and the incidence of adverse events. Providing comprehensive preoperative education to older patients undergoing surgery under general anesthesia can improve postoperative indicators, significantly reduce anxiety and depression, alleviate postoperative pain, and enhance patients' sleep quality. Our findings can provide more optimized management options for older patients undergoing general anesthesia surgery.

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INTRODUCTION

Anesthesia plays a crucial role in the surgical process because it can inhibit the function of the central and peripheral nervous systems, thereby temporarily depriving the patient of pain sensation and providing a guarantee for smooth surgical progress[1]. General anesthesia is a frequently employed form of anesthesia in surgical procedures[2]. However, for patients who underwent surgery under general anesthesia, particularly older adults who require higher doses of drugs to achieve anesthesia and analgesia, their health is compromised to a certain extent[3]. Considering the particular physical characteristics of older patients and surgical trauma, appropriate preventive measures must be taken when performing surgery under general anesthesia[4].

As the number of patients receiving general anesthesia continues to increase, optimizing and improving the overall quality of care have become core issues in surgical care[5]. However, surgery as a strong external stimulus often causes both physical and mental stress to patients, which may trigger adverse stress reactions and adversely affect patients' recovery[6]. Therefore, more sophisticated and individualized care methods must be explored to reduce the negative effects of surgery on patients[7]. Routine nursing care for patients who underwent surgery under general anesthesia can help them quickly respond to complications and take timely measures to ensure patient safety. However, this nursing model is ineffective in promoting rapid recovery and reducing complications, which limits its clinical application[8]. On the contrary, one-on-one preoperative physiotherapy education sessions were found to effectively shorten the postoperative hospital stay and reduce the number of postoperative visits in patients who underwent total arthroplasty [9]. Moreover, preoperative comprehensive education, as a form of preoperative physical therapy education, is essentially a cognitive orientation that elaborates on the anesthesia methods to be used in the operation and informs patients in advance of physical reactions they may encounter during their postoperative regain of consciousness[10]. This education intervention aims to prepare the patient psychologically and adjust the patient's perception of the procedure, thereby relieving tension and eliminating the effects of negative emotions[11]. Another study showed that for colorectal surgery requiring catheterization (using tetracaine mucus), patients who received preoperative simulated education experienced significantly mild catheter-induced bladder discomfort and postoperative pain within 6 hours after the operation

compared with those who did not receive such education[12].

This study included 163 older patients who underwent surgery under general anesthesia to comparatively analyze the effects of preoperative comprehensive education on anxiety, depression, pain, and sleep in these patients.

MATERIALS AND METHODS

Patient selection and grouping

This retrospective study included 163 patients who underwent surgery under general anesthesia between June 2022 and November 2023. Seventy-seven participants (control group) received routine nursing care, whereas 86 (research group) received comprehensive preoperative education.

Eligibility and exclusion criteria

Inclusion criteria: Patients who received surgical treatment and could tolerate general anesthesia, had normal temperature measured before surgery, and were > 65 years old.

Exclusion criteria: Preoperative fever and infection; abnormal function of vital organs, such as the heart, liver, kidneys, and lungs; cognitive dysfunction; recovery affected by other drug interventions; failure to effectively control diabetes and hypertension; and coagulation dysfunction.

Nursing models

The control group was cared for by routine nursing interventions: Patients received daily health education and psychological support to enhance their understanding of the surgery process under general anesthesia and help them lessen their psychological stress and negative emotions. In addition, they were guided to perform preoperative preparations such as fasting and water prohibition. The operating room temperature was adjusted to an appropriate level, and all instruments needed for the operation were comprehensively inspected to ensure that everything was in good condition. To manage possible emergencies, corresponding emergency items were also prepared. During the procedure, nurses worked closely with the anesthesiologists and surgeons and monitored the patient's vital signs in real time to ensure the safety and smooth progress of the procedure.

The research group received comprehensive education interventions: (1) Admission evaluation: The patient underwent a comprehensive physical examination upon admission, and based on the results of the examination and questionnaire, a detailed admission evaluation form, particularly the assessment of anesthesia risk, was developed. For high-risk patients identified during anesthesia evaluation, specialized clinical coping strategies and nursing plans were formulated in advance to provide better medical services. Patients who undergo surgery under general anesthesia often bear a heavy psychological burden because of their severe and complex condition and aggravated anxiety because of upcoming major surgical procedures. Therefore, since admission to the hospital, the nursing staff explained the importance of surgical treatment and previous successful cases to appease their emotions and encourage them to wait for the surgery with peace of mind. The nursing staff also explained the necessity of general anesthesia to patients to dispel their concerns;

(2) Psychological nursing: Through active communication, medical staff helped family members to face patients' condition with a more optimistic attitude, thereby providing necessary family support for patients, inspiring their yearning for a new postoperative life, and helping them face surgery and illness more bravely. To allow patients and their families have a deeper understanding of the disease, surgery, and general anesthesia, nurses provided relevant knowledge, particularly possible adverse reactions caused by anesthesia, prepared patients for minor postoperative discomfort and reduced psychological and physiological stress reactions;

(3) Intraoperative thermal insulation: During the operation, nursing staff paid special attention to the patient's thermal insulation and closely monitored vital signs. To ensure the stability of the patient's body temperature, the fluids used for fluid replacement were preheated and kept at approximately 37 °C to prevent a sudden drop in the body temperature and local blood circulation caused by a large volume of low-temperature fluids entering the body quickly;

And (4) Postoperative care: After the operation, the patients were transferred to the postanesthesia care unit, where the nursing staff would choose a comfortable posture for them and regularly assisted them in adjusting their posture to ensure a smooth respiratory tract. Once changes in the patient's vital signs were noted, the nursing staff immediately notified the doctor and took appropriate measures promptly. When patients gradually regained consciousness, nurses inquired about their feelings in time, and analgesic drugs were administered as prescribed for those with unbearable pain.

Analysis indexes

Surgical indicators: The surgical indicators of the two groups were recorded in detail and compared. These parameters include the operation time (OT), time to complete regain consciousness, and temperature (measured using an infrared tympanic thermometer) immediately after the procedure and upon recovery from anesthesia.

Negative emotions: Before and after nursing care, a comprehensive assessment of the patient's psychological state was conducted using the specialized self-rating anxiety scale (SAS) and self-rating depression scale (SDS). An SAS score > 50 points and an SDS score > 53 points indicate anxiety and depression symptoms, respectively. Higher scores indicate greater anxiety or depression.

Pain severity: Pain levels before and after nursing were evaluated using the visual analog scale (VAS). The score is capped at a score of 10, and the resulting score is proportional to the level of pain felt, *i.e.*, higher scores indicate more intense pain experienced by the patient.

Sleep quality: The Pittsburgh sleep quality index (PSQI) was used to evaluate the sleep quality of patients before and after receiving nursing care. The total scale score is 21 points, and the score is inversely proportional to sleep quality; that is, the higher the score, the less satisfactory the patient's sleep quality.

Incidence of sleep disturbances: The incidence of sleep disorders in the two groups, such as difficulties in falling asleep for the first time, falling asleep after waking up frequently at night, falling asleep again after waking up early, and falling asleep all night, were observed and recorded.

Adverse events: The incidences of respiratory tract obstruction, catheter detachment, aspiration, and asphyxia were recorded.

Statistical analysis

The normality test for quantitative data was conducted using the Kolmogorov–Smirnov test. The quantitative data are expressed by as means ± SE. The independent sample *t*-test was used for intergroup comparisons, whereas paired *t*-tests were used for intragroup comparisons before and after treatment. Categorical data are presented as the number of cases (percentages), and χ^2 tests were used for intergroup comparisons. All data analyses were performed using IBM SPSS Statistics for Windows version 22.0 (Armonk, NY, United States). Significance was indicated by a P value < 0.05.

RESULTS

Comparative analysis of general data

The research and control groups did not differ significantly in terms of age, body mass index, sex, American Society of Anesthesiologists grading, surgical grading, and anesthesia mode ($P > 0.05$; Table 1).

Comparison of surgical indexes

In the two groups, the surgical indicators observed were the OT, time to complete regain of consciousness, temperature immediately after the procedure, and temperature upon recovery from anesthesia before and after nursing. After nursing, the OT and time to complete regain of consciousness were significantly lower in the research group than in the control group, whereas the temperatures immediately after the procedure and upon recovery from anesthesia were significantly better ($P < 0.05$; Table 2).

Comparison of psychological states

The psychological states of the patients in the two groups were evaluated by SAS and SDS. No significant intergroup differences were found in SAS and SDS scores before nursing care ($P > 0.05$). After nursing care, the SAS and SDS scores of both groups were significantly reduced, with a more notable decrease in the research group than in the control group ($P < 0.05$; Figure 1A and B).

Intergroup comparison of pain assessed by the VAS

A light difference in the VAS scores was noted between the two groups before nursing care ($P > 0.05$). An obvious decrease in VAS scores was observed in both groups after nursing care. Moreover, the research group had a more significant decrease in VAS scores than the control group ($P < 0.05$; Figure 1C).

Intergroup comparison of sleep quality evaluated by the PSQI

The two groups had similar PSQI scores before nursing care ($P > 0.05$). PSQI scores were markedly reduced in both groups after nursing care. Moreover, the research group exhibited a more significant decrease in the PSQI score than the control group ($P < 0.05$; Figure 1D).

Intergroup comparison of the incidence of sleep disturbances

The number and percentage of difficulties in falling asleep for the first time, falling asleep again after waking up frequently at night, falling asleep again after waking up early, and falling asleep all night in the two groups were counted. The incidence of sleep disturbances was 8.14% in the research group, which was significantly lower than the 29.87% in the control group ($P < 0.05$; Table 3).

Intergroup comparison of the incidence of adverse events

By counting the number and percentage of cases of respiratory tract obstruction, catheter detachment, aspiration, and asphyxia, the adverse event rate in the research group (4.65%) was significantly lower than that in the control group (19.48%) ($P < 0.05$; Table 4).

Table 1 Comparative analysis of general data, *n* (%)

Indicators	Research group (*n* = 86)	Control group (*n* = 77)	χ^2/t	*P* value
Age (years old)	57.63 ± 7.39	58.44 ± 6.81	0.725	0.469
Body mass index (kg/m^2)	21.31 ± 2.37	21.55 ± 2.24	0.662	0.509
Sex			1.086	0.297
Male	45 (52.33)	34 (44.16)		
Female	41 (47.67)	43 (55.84)		
ASA grading			0.034	0.983
Grade I	34 (39.53)	30 (38.96)		
Grade II	29 (33.72)	27 (35.06)		
Grade III	23 (26.74)	20 (25.97)		
Surgical grading			0.237	0.972
Grade I	21 (24.42)	18 (23.38)		
Grade II	25 (29.07)	22 (28.57)		
Grade III	24 (27.91)	24 (31.17)		
Grade IV	16 (18.60)	13 (16.88)		
Anesthesia mode			0.547	0.908
Epidural anesthesia	27 (31.40)	23 (29.87)		
Subarachnoid block	15 (17.44)	11 (14.29)		
Block anesthesia	18 (20.93)	19 (24.68)		
Combined spinal-epidural anesthesia	26 (30.23)	24 (31.17)		

The inter-group comparison of quantitative data and categorical data employed the χ^2 test and the independent sample *t*-test, respectively. ASA: American Society of Anesthesiologists.

Table 2 Inter-group comparison of surgical indicators

Groups	*n*	Operation time (minute)	Time to complete regain of consciousness (minute)	Temperature immediately after the procedure (°C)	Temperature upon recovery from anesthesia (°C)
Research group	86	143.17 ± 13.31	27.90 ± 2.66	36.38 ± 1.04	36.85 ± 0.49
Control group	77	188.12 ± 19.26	43.09 ± 3.17	35.62 ± 0.82	36.09 ± 0.64
t	-	17.480	33.250	5.139	8.562
P value	-	< 0.001	< 0.001	< 0.001	< 0.001

Independent sample *t*-tests were used for inter-group comparisons of quantitative data.

DISCUSSION

Surgery is undoubtedly a significant psychological and physiological stressor for older patients[13]. Typically, anxiety is evident in patients who are entering the operating room for major or minor surgeries, particularly those who are entering the operating room for the first time because they are often concerned about the possible detrimental effects of surgery on their health[14]. This intense sense of anxiety will not only affect the surgical process but may also adversely influence postoperative rehabilitation[15]. Many factors can cause perioperative anxiety in older patients, including the surgical procedure, anesthesia process, postoperative recovery, postoperative pain, and effect of surgery on physical function[16]. Therefore, to ensure a smooth recovery for patients after surgery, it is necessary to attach importance to and strengthen preoperative and postoperative nursing work[17].

In traditional preoperative visits, health education is often unilateral explanation by nurses without knowing whether patients understand and need these contents[18]. To improve this, a new comprehensive preoperative health education

Table 3 Inter-group comparison of sleep disturbances, *n* (%)

Indicators	Research group (*n* = 86)	Control group (*n* = 77)	χ^2	*P* value
Difficulty in falling asleep for the first time	3 (3.49)	7 (9.09)	-	-
Difficulty in falling asleep again after waking up frequently at night	2 (2.33)	8 (10.39)	-	-
Difficulty in falling asleep again after waking up early	2 (2.33)	5 (6.49)	-	-
Difficulty in falling asleep all night	0 (0.00)	3 (3.90)	-	-
Total	7 (8.14)	23 (29.87)	12.771	< 0.001

The inter-group comparison of categorical data was conducted using the χ^2 test.

Table 4 Inter-group comparison of the incidence of adverse events, *n* (%)

Indicators	Research group (*n* = 86)	Control group (*n* = 77)	χ^2	*P* value
Respiratory tract obstruction	1 (1.16)	4 (5.19)	-	-
Catheter detachment	2 (2.33)	4 (5.19)	-	-
Aspiration	1 (1.16)	5 (6.49)	-	-
Asphyxia	0 (0.00)	2 (2.60)	-	-
Total	4 (4.65)	15 (19.48)	8.676	0.003

The χ^2 test was used for the inter-group comparison of categorical data.

model was adopted[19]. The patient's dedicated ward nurse will provide comprehensive and systematic preoperative education, including basic knowledge of surgery and anesthesia, and key points of perioperative care and postoperative recovery[20]. Unlike traditional methods, the current education approach encourages patients to take the initiative to raise questions, and professional health educators then provide detailed answers to ensure that the information is relevant to the actual needs of patients[21]. Preoperative patient education has been indicated to be the basic responsibility of any healthcare provider, and patients who receive detailed preoperative education have better extubation quality and improved quality of recovery from general anesthesia[22]. In the present study, the OT and time to complete regain of consciousness were significantly lower in the research group than in the control group after nursing, and the temperatures immediately after the procedure and upon recovery from anesthesia were significantly better. Thus, through comprehensive preoperative education, patients' OT can be significantly shortened, they can regain postoperative consciousness faster, the intraoperative body temperature can be better stabilized, and the postoperative body temperature can be also quickly returned to normal. A study showed that patients' deep fear, severe anxiety, and great concerns about surgery may have adverse effects on the perioperative progress. These findings highlight the importance of paying attention to the preoperative psychological state of patients undergoing surgery and propose strengthening patient education regarding anesthesia to alleviate their fear and enhance their understanding of the anesthesia process [23]. Peng *et al*[24] reported that successful preoperative anesthesia education effectively prevented anxiety in female patients before laparoscopic cholecystectomy, improved their overall health level, and shortened their hospital stays[24], which is similar to the results of this study. The results of the analysis of negative emotions showed that compared with the control group, the SAS and SDS scores of the research group decreased more significantly, proposing that preoperative comprehensive education can help patients maintain a stable mindset and emotional state during the perioperative period. Proactive communication before and after surgery, establishment of a trusting relationship, and provision of personalized comfort according to the patient's situation are conducive to improving physical and mental comfort and preventing safety risks caused by negative emotions. Furthermore, surgery may induce physical and psychological stress to patients, whereas preoperative education can reduce anxiety, relieve pain, and improve postoperative outcomes[25]. The pain severity results showed that VAS score reduction was more significant in the research group than in the control group. Preoperative comprehensive education was suggested to help patients fully understand the relevant knowledge during the perioperative period, thereby reducing uncertainties and worries about the disease, helping them to be psychologically prepared, and reducing surgical pain. Surgery and general anesthesia have deleterious effects on sleep, and interference with perioperative sleep health is a risk factor for poor surgical outcomes[26]. The results of the analysis of sleep quality revealed that the PSQI score decreased more significantly and the incidence of sleep disturbances was significantly lower in the research group than in the control group. The results indicated that preoperative comprehensive education can help older patients stabilize their mental health by providing them with detailed surgical information, thus creating more favorable conditions for anesthesia and implementation of surgery, and indirectly promoting their emotional stability and relaxation. Therefore, the sleep quality of older patients was significantly improved, laying a good foundation for postoperative recovery. Finally, a significantly lower incidence of adverse events

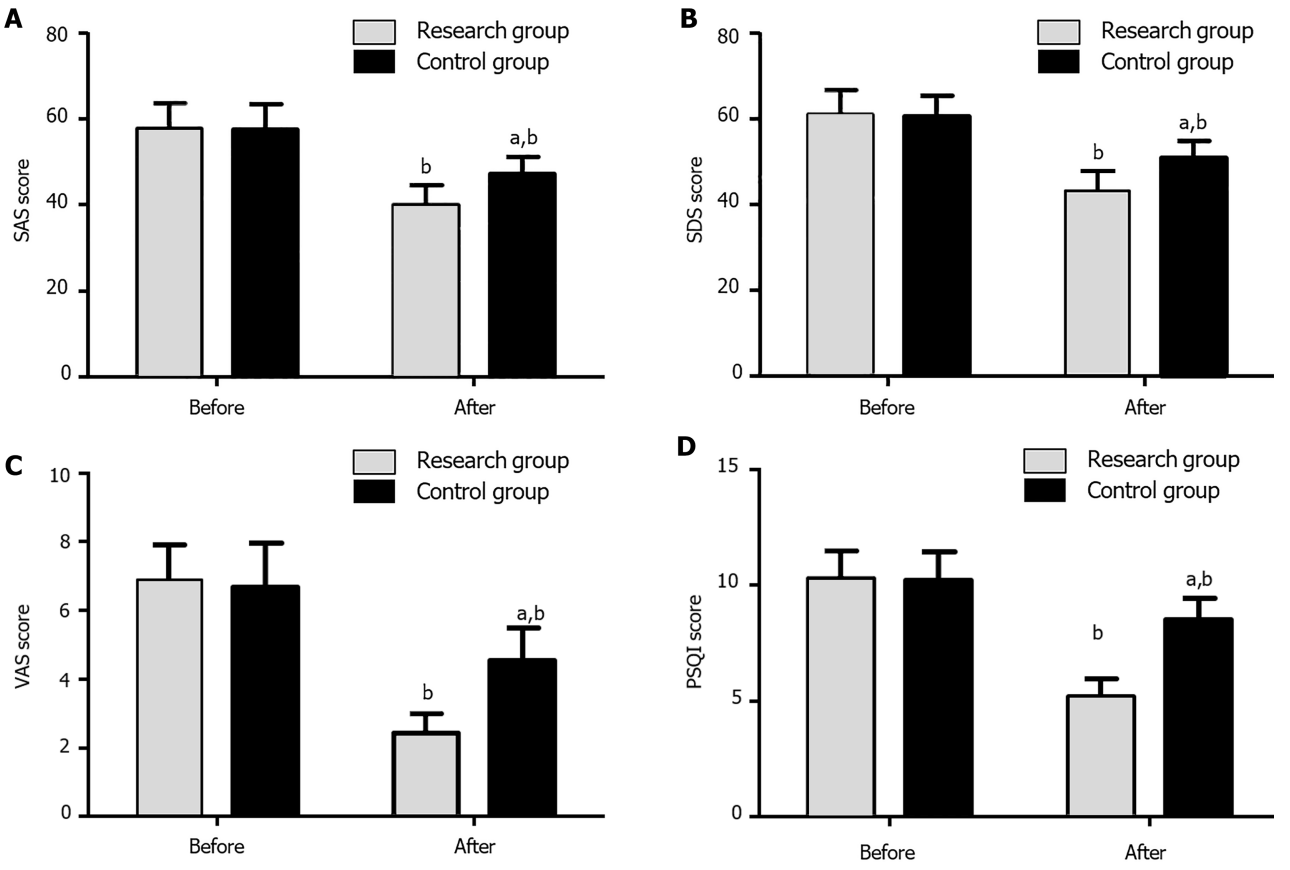

Figure 1 Detection of scores before and after nursing. A: Self-rating anxiety scale scores before and after nursing in the two groups; B: Self-rating depression scale scores of the two groups before and after nursing; The paired *t*-test was employed to compare the data before and after treatment. For the inter-group comparison, the independent sample *t*-test was utilized (A and B); C: The visual analogue scale scores of two groups before and after nursing. We used the paired *t*-test to compare the data before and after treatment and the independent sample *t*-test to compare the data between the two groups; D: The Pittsburgh sleep quality index scores before and after nursing in the two groups; The paired *t*-test was employed to compare the data before and after treatment, while the independent sample *t*-test was used to compare the data between the two groups. $^{a}P < 0.05$ *vs* Control, $^{b}P < 0.01$ *vs* before nursing; SAS: Self-rating anxiety scale; SDS: Self-rating depression scale; VAS: Visual analog scale; PSQI: Pittsburgh sleep quality index.

was noted in the research group than in the control group, indicating that preoperative comprehensive education not only focuses on preoperative preparation but extends to postoperative care. This education system prompts medical staff to closely monitor patients' vital signs in the postoperative stage, deeply analyze the risk factors that may lead to vital signs fluctuations, proactively identify and prevent various potential hazards, and provide meticulous comfort, thus lowering the probability of adverse events[27].

CONCLUSION

The application of preoperative comprehensive education for older patients who underwent surgery under general anesthesia can improve postoperative indicators, significantly reduce the occurrence of anxiety and depression, reduce postoperative pain, and improve the sleep quality of the patients.

FOOTNOTES

Author contributions: Qu L, Ma R and Xu GP designed the study, collected and analyzed data, and wrote the manuscript; Qu L, Ma R, Ma YK, Zhao X, Jin J, Zhu QQ, Chen XY and Xu GP participated in the study's conception and data collection; Qu L, Ma R and Xu GP participated in study design and provided guidance; All authors read and approved the final version.

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ORIGINAL ARTICLE

Retrospective Study

Impact of solution-focused brief therapy and vacuum sealing drainage on mental health of wound care patients

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Abstract

BACKGROUND

Improving mental health is crucial for patients who require wound treatment.

AIM

To analyze the effects of solution-focused brief therapy (SFBT) combined with vacuum sealing drainage on the psychological health of patients undergoing wound treatment, providing a basis for selecting wound treatment protocols.

METHODS

A total of 102 patients undergoing wound treatment were included, with the study period from March 2020 to March 2024. Sex was not a factor, and patients were randomly assigned to two groups of 51 cases each. The control group received negative pressure wound therapy (NPWT), while the experimental group received NPWT plus SFBT. The recovery of wounds, granulation tissue scores, and psychological health levels were compared between the two groups. Statistical analysis was conducted using SPSS Windows software version 26.0 and GraphPad Prism 8.0.

RESULTS

Post-treatment, the levels of high-sensitivity C-reactive protein, white blood cell count, and lactate dehydrogenase in the experimental group were significantly lower than those in the control group ($P < 0.05$). The two groups had no significant difference in granulation tissue scores ($P < 0.05$). The psychological health level in the experimental group was significantly higher than in the control group ($P < 0.05$).

CONCLUSION

The combination of SFBT and NPWT accelerates wound healing, promotes granulation tissue growth, and improves psychological well-being, making it a valuable approach for clinical application.

Key Words: Solution-focused brief therapy; Negative pressure wound therapy; Psychological health; Wound healing; Clinical treatment

Core Tip: Combining solution-focused brief therapy with negative pressure wound therapy can significantly enhance the healing process of wounds, improve psychological well-being, and help patients regain confidence. Solution-focused brief therapy is a brief psychotherapy approach that focuses on the client's strengths and resources, emphasizing the present and future rather than past problems, to help individuals create positive changes and achieve their goals. Negative pressure wound therapy, on the other hand, is a physical therapy method that applies subatmospheric pressure to wounds to promote blood circulation, reduce infection, and accelerate the healing process.

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INTRODUCTION

In recent years, the prevalence of acute and chronic non-healing wounds caused by trauma, burns, and various chronic diseases has been increasing annually. The incidence rate of pressure ulcers is approximately 3%, and approximately 8 million patients have traumatic ulcers yearly. Additionally, the incidence rate of common diabetic foot ulcers in China is about 2%. Promoting wound healing remains one of the most challenging areas in clinical practice[1-3]. Clinical surveys have found that in social interactions, work, and romantic relationships, a healthy and attractive appearance often brings confidence and advantages[4,5]. Wounds affect the patient's appearance and impose a heavy burden on psychological health and quality of life, leading to severe mental health issues over time. At present, negative pressure wound therapy (NPWT) is the primary method for treating wounds, ensuring blood flow to the wound, promoting healing, and efficiently draining, with comprehensive, zero-accumulation effects, which are favored by many patients and physicians [6,7]. However, physical therapy alone does not address the psychological aspect. Therefore, to improve the psychological health of patients further, psychological therapy is needed as an adjunct. Solution-focused brief therapy (SFBT) is a short-term psychological treatment technique centered on goal achievement methods, helping patients solve problems, change adverse behaviors and thinking patterns, adjust negative emotions, and achieve ideal goals[8,9]. However, there are few reports on the impact of SFBT combined with NPWT on the psychological health of patients undergoing wound treatment. Against this background, this study focuses on patients receiving wound treatment as the research participants. SFBT is applied alongside NPWT in the observation group, aiming to provide a basis for comprehensive wound care.

MATERIALS AND METHODS

General data

A total of 102 patients admitted to our hospital for wound treatment from March 2020 to March 2024 were selected. They were grouped using a simple random sampling method, with 51 cases in the control group, comprising 31 men and 20 women; age ranging from 22 to 60 years old (41.25 ± 6.82); and wound area accounting for body surface area (2.22 ± 0.22 cm^2). The observation group also included 51 cases, with 30 men and 21 women aged 21 to 65 years old (42.56 ± 7.02) and wound area accounting for body surface area (2.19 ± 0.11 cm^2). The baseline data of the two groups were compared ($P > 0.05$), indicating statistically significant differences.

Inclusion and exclusion criteria

Inclusion criteria: (1) Wound area ≤ 3% of body surface area; (2) Presence of varying degrees of psychological health issues due to the wound; (3) No contraindications to the treatment plan of this study; and (4) Informed consent obtained from patients and their families.

Exclusion criteria: (1) Actively bleeding wounds; (2) Patients with malignant tumors; (3) Pregnant or lactating women; (4) Patients with immunological diseases or in an immunosuppressed state; (5) Patients from other regions or unable to follow up after discharge; (6) Patients with important organ diseases such as heart, liver, or kidney; (7) Patients who have undergone other treatment methods; and (8) Wounds with eschar necrotic or malignant tissues.

Methods

Both groups underwent bacterial culture of wound secretions and treatment of primary diseases, with local debridement to ensure blood supply to the fresh wound. The control group received vacuum sealing drainage (VSD) treatment. A trauma-negative pressure drainage kit [SAC-A2-D2, SAGE (Xiamen) Medical Technology Co., Ltd.] was used. A disposable VSD negative pressure wound dressing (15 cm × 10 cm) was selected and cut to fit the size and shape of the wound. This ensured complete contact with the entire wound surface after placement. The edges were then sutured and secured to the surrounding healthy skin. A semi-permeable membrane was applied to cover and seal the VSD system and the surrounding healthy skin. The membrane was cut and attached to a drainage suction cup. When an external fixation device was used, the "mesentery method" was applied. This involved wrapping the film around the Steinmann pin sufficiently long before securing it around the wound. Subsequently, the central negative pressure device was connected and adjusted between 0.017 MPa and 0.06 MPa. Continuous, strict monitoring of the negative pressure drainage was conducted, and the drainage tube was flushed with 0.9% sodium chloride solution (Otsuka Pharmaceutical Co., Ltd.). The VSD dressing was replaced after 7 days and removed after 14 days if no abnormalities were observed. If there was still a large amount of necrotic tissue in the wound, pulse flushing was performed. This was followed by negative pressure suction until the condition improved, and then free grafting could be performed - continuous treatment for 14 days.

The observation group applied SFBT therapy to the VSD treatment plan: (1) Team formation: A "SFBT team" was established consisting of one deputy chief physician, three attending physicians, and three nursing staff from the department, with the department head serving as the team leader, and the hospital's psychological counselors were involved in providing special training on "SFBT therapy" to the team members; (2) Plan formulation: This includes describing the problem, constructing goals, exploring exceptions, providing feedback, and evaluating progress; (3) Describing the problem: Preliminary communication with the patient was established to ask about their current most distressing issues, guiding them to describe the problem correctly, and assess the patient's current psychological state through listening, understanding, respect, and acceptance, identifying the critical psychological focus issues; (4) Constructing goals: A positive emotional atmosphere was actively created. The patient's inner needs were understood through "miracle questions" and "scale questions", and stage goals were jointly formulated with the patient. These encompassed "how to adjust adverse emotions", guiding the patient to explore their current efforts, and analyzing the benefits of goal achievement. When patients perform well, timely affirmation and encouragement prompt them to discover their strengths and continue their efforts according to the set goals; (5) Exploring exceptions: Narrative and recalling past positive life experiences. This included their most memorable music, videos, or photos, cherished relationships, memorable work experiences, pleasant travels, and loved ones. The goal was to help patients reflect on past successes in overcoming difficulties, build confidence for the future, and cultivate a sense of responsibility. These methods encouraged patients to actively adapt to role changes and manage negative emotions more effectively; (6) Providing feedback: After the patient completes the stage goal, their psychological health status was asked, such as "After VSD treatment, do you feel your wound has improved?". If the patient answers "improved", continue asking, "How is your current mood? Is it better than before?". This helps patients understand the importance of maintaining a good mood during wound treatment and better tap into their potential, prompting them to cooperate with treatment; and (7) Evaluating progress: Affirm every patient's progress, and when they are in a low mood, encourage them to adjust their emotions by themselves, guiding patients to complete the expected goals. This cycle continues for 14 days.

Observation indicators

Laboratory parameters: Granulation tissue from the center of the wound was harvested from liquid nitrogen and stored in an environment maintained at 2-8 °C. The tissue was then treated with phosphate-buffered saline, followed by homogenization and centrifugation. Enzyme-linked immunosorbent assay was employed to measure the levels of high-sensitivity C-reactive protein (hs-CRP; GILED Biotechnology, China, ID: J21212), white blood cell (WBC) count, and lactate dehydrogenase (LDH; GILED Biotechnology, China, ID: J20956).

Wound granulation score: The attending physician of our department and the director designed the wound granulation scoring method based on relevant authoritative literature. The reliability and validity were tested to be 0.836 and 0.821, respectively. The scoring criteria are: (1) 1 point: The wound surface is dull, the base is concave, granulation tissue grows, and the coverage of the wound is less than 25%; (2) 2 points: The wound surface is light red, the base is relatively flat, and the granulation tissue covers 25%-50%; (3) 3 points: The wound surface is bright red, the base has granular protrusions, granulation tissue grows vigorously, and coverage exceeds 50%; and (4) 4 points: The wound surface is bright red and ruddy, the base is flat without protrusions, granulation tissue grows well, and the coverage rate reaches 100%.

Psychological health level: The "Positive Psychological Capital Questionnaire (PPQ)"[10] was used. This included four dimensions of optimism (42 points), hope (42 points), self-efficacy (49 points), and psychological resilience (49 points), with 28 items, a total score of 182 points. Further, the score was directly proportional to the level of psychological health.

Statistical analysis

All data collected in this study were analyzed using SPSS Windows software version 26.0. The following statistical methods were employed for measurement data that conform to a normal distribution: (1) Data were presented as mean ± SD; (2) Between-group comparisons were conducted using the independent samples *t*-test; (3) Within-group comparisons were conducted using the paired samples *t*-test; (4) Count data were primarily analyzed using the χ^2 test, with results presented as number (*n*) and percentage (%); and (5) Ordinal data were primarily analyzed using the rank sum test, also presented as number (*n*) and percentage (%). The baseline data of the two groups were compared ($P > 0.05$), indicating no statistically significant differences.

Table 1 Comparative analysis of laboratory parameters (mean ± SD) for the two groups

Groups	hs-CRP (mg/L)		WBC (× 10^9/L)		LDH (U/L)	
	Before 1 day	After 1 week	Before 1 day	After 1 week	Before 1 day	After 1 week
Observation (n = 51)	24.22 ± 1.12	4.70 ± 0.22[a]	12.01 ± 0.25	5.42 ± 0.20[a]	191.10 ± 20.18	133.84 ± 13.36[a]
Control (n = 51)	24.35 ± 1.22	5.39 ± 0.31[a]	11.89 ± 0.36	7.23 ± 0.18[a]	191.86 ± 20.20	160.86 ± 14.41[a]
t	0.561	12.963	1.955	48.039	0.190	9.820
P value	0.576	< 0.001	0.053	< 0.001	0.850	< 0.001

[a]P < 0.05, comparisons within the same group before and after treatment.
hs-CRP: High-sensitivity C-reactive protein; WBC: White blood cell; LDH: Lactate dehydrogenase.

Table 2 Comparison of wound granulation scoring between the two groups, *n* (%)

Groups	1 point	2 points	3 points	4 points
Observation (n = 51)	1 (1.96)	6 (11.76)	28 (54.90)	16 (31.37)
Control (n = 51)	5 (9.80)	12 (23.53)	23 (45.10)	11 (21.57)
Z	1.977			
P value	0.048[a]			

[a]P < 0.05, comparisons within the same group before and after treatment.

Table 3 Comparison of psychological health levels between the groups (mean ± SD, score)

Groups	Optimism		Hope		Self-efficacy		Psychological resilience	
	Before	After	Before	After	Before	After	Before	After
Observation (n = 51)	25.24 ± 3.66	35.35 ± 2.61[a]	25.19 ± 3.75	36.46 ± 2.69[a]	33.71 ± 2.51	40.29 ± 3.51[a]	32.30 ± 3.61	40.26 ± 2.66[a]
Control (n = 51)	25.31 ± 3.72	31.84 ± 2.50[a]	25.25 ± 3.72	32.87 ± 2.65[a]	33.39 ± 2.81	37.82 ± 3.57[a]	32.35 ± 3.59	35.80 ± 2.61[a]
t	0.096	6.936	0.081	6.790	0.607	3.523	0.070	8.547
P value	0.924	< 0.001	0.936	< 0.001	0.546	0.001	0.944	< 0.001

[a]P < 0.05, comparisons within the same group before and after treatment.

RESULTS

Laboratory indicators

A comparison of laboratory indicators between the two groups 1 day before treatment showed no significant difference (P > 0.05). However, 1 week after treatment, both groups exhibited significant changes in laboratory indicators compared to baseline, with notable differences (P < 0.05). Furthermore, the laboratory indicators of the observation group were significantly different from those of the control group (P < 0.05) (Table 1).

Wound granulation scoring

Following treatment with SFBT therapy combined with VSD, the granulation scoring of the wounds in the observation group was significantly higher compared to the control group (P < 0.05) (Table 2).

Psychological health status

Before treatment, the two groups had no significant difference in psychological health status (P > 0.05). However, after treatment, both groups showed a significant improvement in psychological health status compared to baseline (P < 0.05), with the observation group demonstrating a statistically significant difference compared to the control group (P < 0.05) (Table 3).

DISCUSSION

It is well-documented in the literature that in the medical field, physical recovery often comes with psychological challenges, especially for patients with wounds[11,12]. Pain, changes in appearance, social phobia, and self-identity issues can lead to a range of psychological issues, such as anxiety, depression, and post-traumatic stress disorder, affecting mental health. Their path to recovery is not limited to the physiological level but is also a profound experience of psychological reconstruction and social readjustment.

Traditional concepts suggest that wounds should be exposed to the air to promote healing. In contrast, modern medical research indicates that a moist environment is more conducive to wound healing. In clinical practice, the growth and coverage of granulation tissue over the wound indicate good repair. Moreover, LDH is an essential indicator of granulation growth's oxygen environment, while hs-CRP and WBC reflect the body's degree of infection and trauma. This study shows that one week after treatment, the tissue oxygen partial pressure, LDH, hs-CRP, and WBC in the observation group were all lower than those in the control group, and the wound granulation score was higher, with a significant difference between the two groups ($P < 0.05$). VSD is an effective method for treating wounds. Whether it is significant soft tissue defects, open fractures, burns, or other difficult-to-heal wounds, VSD can achieve significant therapeutic effects. It mainly uses controllable negative pressure to make the wound tissue fluid flow to the drainage tube, quickly discharge exudate, make the drainage area "zero accumulation", ensure blood supply to the wound, accelerate local blood circulation, stimulate tissue regeneration and granulation tissue growth, and speed up the wound healing rate. Simultaneously, it avoids the drawbacks of traditional wound treatment methods that require frequent dressing changes. Thus, it significantly reduces the number of dressing changes. Hence, it converts open wounds into closed wounds. Subsequently, this prevents external bacterial infections and makes patients more comfortable during treatment[13,14]. Therefore, focusing on the psychological problems of wound patients and applying SFBT therapy can further improve the mental health level of patients. SFBT therapy is a goal-oriented, short-term psychological treatment that emphasizes starting from a positive and proactive perspective. It focuses on the possibility of problem-solving rather than the problem itself. Consequently, it taps into the patient's resources and abilities and promotes individual self-growth and change[15]. During the implementation of SFBT therapy in this study, medical staff focused on cooperative communication with patients, thus promoting a trust-based cooperative relationship between the two parties to explore and solve problems jointly. Simultaneously, they guided patients to focus on their own resources and strengths. They emphasized the role of emotions in problem-solving and made them understand the harm of negative emotions to wound treatment. Further, they jointly formulated feasible solutions and encouraged them to practice and apply them. This helped patients learn effective emotional regulation skills. Thus, they improved patients' emotional management ability, better controlling negative emotions, reducing mental and psychological burden and pain, regaining confidence, and improving self-mental health. The limitation of this study is the data presented in this article. In the future, it would be best to include a more diverse patient population to examine the effectiveness across different sexes, ages, and backgrounds.

CONCLUSION

The combined application of SFBT and VSD treatment can accelerate the wound healing speed of patients undergoing wound treatment. It can also promote granulation growth and improve mental health, which is worth applying clinically.

FOOTNOTES

Author contributions: Shi WJ designed the study; Shi WJ and Zhou J analyzed the data; Shi WJ, Zhou J, Xu QL, Jiang Y, and Dai Q were involved in the data and writing of this article. All authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Wuling capsule combined with sertraline in the therapy of anxiety and depression with insomnia in adolescents

Li-Li Duo, Gao-Feng Rao

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Abstract

BACKGROUND

The treatment of adolescent patients with anxiety, depression and insomnia is challenging, and there is no ideal treatment method.

AIM

To evaluate the clinical efficacy of Wuling capsule combined with sertraline in the treatment of adolescent anxiety, depression and insomnia.

METHODS

Eighty adolescent patients with anxiety, depression with insomnia who were admitted to our hospital from April 1, 2022 to March 30, 2024. And the subjects were randomly classified into the control group (n = 40) and the observational group (n = 40). The control group was treated with a combination of sertraline and placebo. The observation group was treated with Wuling capsule in addition to sertraline. The two groups were cured continuously for 8 weeks. Insomnia severity index (ISI), Hamilton Anxiety Scale (HAMA) and Hamilton Depression Scale (HAMD) were used to evaluate the clinical symptoms before treatment and at 2, 4, 6 and 8 weeks after treatment. The Treatment Emergent Symptom Scale (TESS) was used to evaluate adverse reactions during treatment.

RESULTS

There was no obvious difference in HAMD, HAMA and ISI scores between the two groups before treatment (P > 0.05). After treatment, the HAMD, HAMA and ISI scores of patients in both groups decreased compared with before treatment, and HAMD, HAMA and ISI scores of patients in the observation group were

remarkedly lower than those in the control group at each time point after treatment ($P < 0.05$). Compared with the control group, the TESS score of the study group were sharply lower ($t = 18.239$, $P < 0.001$).

CONCLUSION

Wuling capsule can further alleviate the insomnia symptoms of adolescents with anxiety and depression, and the efficacy and safety are high. It is recommended to promote the application.

Key Words: Adolescent; Depression; Anxiety; Insomnia symptom; Sertraline; Wuling capsules

Core Tip: This study discusses the clinical effect of Wuling capsule combined with Sertraline in the treatment of anxiety and depression with insomnia symptoms, and emphasizes that Wuling capsule can further alleviate the insomnia symptoms of anxiety and depression in adolescents, with high efficacy and safety. Therefore, this study proposed a combination treatment method, which can effectively improve the depression state and sleep quality of patients, and is conducive to improving the treatment compliance of patients, and it is recommended to be popularized.

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INTRODUCTION

Depressive disorder refers to a group of mood disorder syndromes mainly manifested by low mood, anhedonia, reduced interest with decreased initiative, slow thinking and other symptoms of psychomotor retardation[1]. Depressive episodes are mainly manifested by depressed mood, which can be triggered by obvious causes, and can develop from depressed mood to grief, or even depressive rigidity. In severe cases, delusions, hallucinations, hallucinations, mania and other psychotic symptoms can occur[2]. Depressive disorder has a tendency to recur, although each episode can be controlled by medication. But after repeated episodes, it is easy to become chronic or leave the corresponding symptoms. The incidence of adolescent depression has been rising in recent years, and some data suggested that the prevalence of depression in adolescence (12 to 18 years old) was increasing year by year, which was mainly related to the heavy burden of homework, learning pressure and inadequate sleep duration for physical function recovery[3,4]. And most of the patients have a tendency to relapse, and some of them can last until adulthood, which has a serious adverse effect on their growth and development and social functioning to bring serious mental pressure and economic burden to the family and society. Therefore, there is an urgent need to carry out research on adolescent depression to better understand the occurrence and development of depression in various age groups and provide a basis for clinical diagnosis and therapy [5]. Insomnia is a characteristic phenomenon of depressive disorders, which may increase the risk of depressive episodes, and 60% to 80% of patients with depressive disorders are accompanied by sleep disorders. Therefore, insomnia and depression are highly co-existing[6]. It is clinically proven that strengthening the co-morbidity therapy of depression and insomnia is of great significance for clinical prevention and therapy[7]. Generalized anxiety disorder is a neurosis characterized by subjective anxiety. It is expressed as a fearfulness that is not based on concrete evidence and lacks objective goals and concrete concepts, and is accompanied by behavioral disorders such as vegetative nervous system dysfunction and motor restlessness[8]. Anxiety secondary to other psychiatric disorders (such as hallucinations, delusions, depression and phobias) or other physical illnesses (such as coronary heart disease, hypertension and hyperthyroidism) can be collectively referred to as anxiety syndromes. In recent years, with the increase of life pressure, its incidence has gradually increased, which has brought serious impact on the life quality and physical and mental health of patients[9]. A survey of sleep problems associated with mental disorders found that sleep problems are significantly correlated with anxiety disorders[10]. The previous study found that many social anxiety disorder patients also meet the diagnostic criteria for insomnia, in which early waking is insomnia and anxiety levels associated with the highest degree of manifestation[11]. At the same time, insomnia can appear as the most prominent prodrome of anxiety disorders, which can increase the risk of anxiety disorders by more than several times. Therefore, there is a clear practical need and important clinical significance to actively treat anxiety insomnia and to conduct clinical research on anxiety insomnia[12,13]. The modern medicine believes that the pathological factors of the disease are closely related to the abnormal rise of neurotransmitters, especially 5-hydroxytryptamine is the most closely related to the onset of anxiety and depression, and the rest such as norepinephrine, dopamine and γ-aminobutyric acid can also affect the onset of anxiety and depression. At present, the clinical therapy of anxiety and depression disorders with insomnia symptoms is mainly based on drug, including benzodiazepines, tricyclic anti-anxiety drugs, selective serotonin reuptake inhibitors, serotonin and norepinephrine dual reuptake inhibitors and other drugs. However, the drug therapy has different degrees of side effects in the application process, which directly affects the therapeutic effect[14,15]. Sertraline is commonly used in the therapy of adolescent

depressive disorders, which can effectively improve depression and anxiety[16]. However, in the patient's sleep disorder symptoms of improvement, the therapeutic effect of the drug is slightly worse than other drugs. It is generally necessary to combine sedation and hypnosis drugs. Although it can achieve certain efficacy, the concern about the adverse effects of the drug can affect the patient's adherence to treatment[17]. Traditional Chinese medicine has been gradually adopted clinically in recent years for its remarkable efficacy and few adverse reactions. Wuling capsule is a kind of biotechnology refined pure traditional Chinese medicine preparation, which has obvious effects on insomnia and depressive disorder. In order to further analyze the effectiveness and safety of sertraline combined with Wuling capsule in the therapy of mild to moderate anxiety and depression patients with insomnia symptoms[18]. A control study was conducted on 80 adolescent patients with anxiety, depression with insomnia who were admitted to our hospital from April 1, 2022 to March 30, 2024. The results were as follows.

MATERIALS AND METHODS

General information about patients

Eighty adolescent patients with anxiety, depression with insomnia who were admitted to our hospital from April 1, 2022 to March 30, 2024. And the subjects were randomly classified into the control group (n = 40) and the observational group (n = 40) according to random number table method. According to the sample size calculation formula: n = (Uα + Uβ) 22 P (1 - P)/(P1 - P0) 2 and 5% loss of follow-up rate of "optimal clinical trial", at least 39 samples should be included in each group in this study. In control group, patients ranged in age from 12 to 18 years, with an average age of 15.31 ± 2.08 years. There were 18 males and 22 females. The average course of disease was 3.44 ± 0.15 months, ranging from 1 to 5 months. In observation group, patients aged 12 to 18 years and mean aged 15.29 ± 2.06 years. There were 17 males and 23 females. The average course of disease was 3.46 ± 0.13 months, ranging from 1 to 6 months. There was no statistically significant difference between the two groups (P > 0.05), so the study could be conducted.

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients with definite clinical diagnosis of anxiety or depression disorder; (2) Patients with insomnia severity index (ISI) score ≥ 8, accompanied by insomnia symptoms; (3) Adolescents aged 12-18 years old; (4) Patients with normal laboratory indicators; (5) Patients with Hamilton Depression Scale (HAMD) score ≥ 20 or Hamilton Anxiety Scale (HAMA) score ≥ 14; and (6) Patients and guardians were informed of this study and participated voluntarily.

Exclusion criteria: (1) Patients with serious tendency of suicide and self-injury; (2) Patients with severe symptoms (ISI score ≥ 22), HAMA score ≥ 29, HAMD score ≥ 35; (3) Patients with bipolar affective disorder; (4) Patients with allergic reactions to the drugs used in this study; (5) Those with serious physical and organic diseases such as kidney, lung, brain and heart; (6) Those with immune function diseases; (7) Those with mental illness; and (8) Patients who could not cooperate with the study and lost to follow-up.

Methods

The control group was treated with a combination of sertraline (Manufacturer: Zhejiang Huahai Pharmaceutical Co., LTD; Specification: 50 mg) and placebo. Sertraline application method: Oral, 25-50 mg per day as the starting dose, and the dose was adjusted appropriately according to the patient's condition after 2 weeks of treatment, the maximum dose is 100 mg per day. The observation group was treated with Wuling capsule (Manufacturer: Zhejiang Zoli Pharmaceutical Co., LTD.; Specification: 0.33 g per capsule) in addition to sertraline. The capsules were taken orally, 1-3 capsules each time, 3 times a day. The two groups were cured continuously for 8 weeks.

Observation index

Clinical effect: ISI and HAMD scores were used as the basis to judge the treatment effect. Judging criteria: ISI score ≤ 7 points, HAMD score ≤ 8 points are judged to be cured; ISI score and HAMD score reduced by 50% or more are considered effective; The reduction of ISI score and HAMD score < 50% are considered as ineffective, effective rate + cure rate = total effective rate.

ISI, HAMA and HAMD were used to evaluate the clinical symptoms before treatment and at 2, 4, 6 and 8 weeks after treatment.

The Treatment Emergent Symptom Scale (TESS) was used to evaluate adverse reactions during treatment.

Statistical analysis

SPSS 27.0 analysis software was applied. The measurement data expressed by mean ± SD, and t-test was adopted. The count data were statistically described by percentages, and the comparison of rates between groups was performed using the χ^2 test. P < 0.05 indicating that the difference was statistically significant.

RESULTS

Comparison of improvement of clinical symptoms

Tables 1, 2 and 3 suggested that there was no obvious difference in HAMD, HAMA and ISI scores between the two groups before treatment ($P > 0.05$). After treatment, the HAMD, HAMA and ISI scores of patients in both groups decreased compared with before treatment, and HAMD, HAMA and ISI scores of patients in the observation group were remarkedly lower than those in the control group at each time point after treatment ($P < 0.05$). The results indicated that Wuling capsule combined with Sertraline could effectively improve the depressive symptoms, anxiety degree and insomnia of adolescent patients with anxiety, depression and insomnia.

Comparison of treatment effect

Table 4 indicated that compared with the control group, the total effective rate of the observation group was apparently higher ($P < 0.05$). The results indicated that Wuling capsule combined with sertraline could effectively improve the depressive symptoms, anxiety degree and insomnia of adolescent patients with anxiety, depression and insomnia.

Comparison of TESS scores

The TESS scores of the observation group and the control group were 2.15 ± 0.43 and 5.85 ± 1.21, respectively. Compared with the control group, the TESS score of the study group were sharply lower ($t = 18.239$, $P < 0.001$). The results indicated that Wuling capsule combined with sertraline could effectively reduce the occurrence of adverse reactions in adolescent patients with anxiety, depression and insomnia.

DISCUSSION

With the development of many aspects of society, the pressure brought by work, life and study is increasing, and the incidence of anxiety and depressive insomnia is growing[19]. Relevant studies have shown that insomnia occurs in 90% of adolescents with depressive disorders. It often as the first symptom, and residual insomnia after acute therapy is also a major component of persistent depressive episodes[20]. Anxious insomnia can seriously affect people's life quality, but also lead to a series of physical and mental illnesses, such as the circulatory system (common hypertension, tachycardia), the digestive system (common peptic ulcer and anorexia nervosa), the endocrine system (common diabetes mellitus, obesity), and the urinary system (common menstrual disorders, impotence and premature ejaculation)[21]. At present, the effective therapy of adolescent anxiety and depression disorders with insomnia symptoms has gradually gained clinical attention, and the research on them has gradually deepened and diversified.

Currently, adolescents with depressive disorders are mainly cured with medications, and the preferred drugs are selective serotonin reuptake inhibitors[22]. Sertraline, as a selective and potent serotonin reuptake inhibitor, is supported by sufficient evidence-based medical evidence in the therapy of adolescent depression at home and abroad, which can effectively improve anxiety and depression. However, the drug has obvious affinity for benzodiazepine receptors and γ-amino-butyric acid receptors, so it cannot effectively improve insomnia symptoms[23,24]. The combination of sedative-hypnotic drugs (such as benzodiazepine agonists, non-benzodiazepine agonists, melatonin agonists, antidepressants with hypnotic effect, antihistamines) is commonly used to improve sleep, which not only increases the risk of suicide and the experience of depression, but also has more adverse effects and poor patient compliance. To some extent, it restricts the clinical application of the drug[25].

According to Chinese medicine, insomnia is related to the liver, heart, spleen, stomach and kidney. The heart, as the commander of the blood and the seat of consciousness, controls emotional activities. The emotional disorders and restlessness of the heart and mind are the main causes of insomnia. The Chinese medicine believes that the disorder between the internal organs and the heart is also the cause of insomnia[26,27]. The common causes include deficiency of kidney yin, weakness of the spleen and stomach and insufficiency of blood in the heart. The pathogenesis of depression and anxiety mainly involves liver qi stagnation, and it is also related to the imbalance between the internal organs of the heart, spleen and kidneys. The core of Chinese medicine is to improve the patient's sleep condition by adjusting the function of qi and blood in the body's internal organs. The clinical treatments are often used to nourish the heart and tranquillize the mind, and nourish the kidney and yin. The Chinese medicine treats insomnia mainly with Chinese herbs, acupuncture and other non-pharmacological therapies. For thousands of years, Chinese medicine has played an important role in the healthcare of insomnia patients in China[28,29]. The main ingredient of Wuling Capsules is fermented powder of Wuling Mushroom, containing adenosine, adenine, uridine, guanosine, polysaccharides, mannitol, ergosterol and 19 kinds of amino acids, such as aspartic acid, glutamic acid and lysine. It belongs to the kidney meridian, and has the effect of nourishing the kidney[30,31]. It has the function of nourishing kidney yin and lowering heart fire, especially suitable for insomnia caused by heart fire and kidney water insufficiency. At the same time, it has the effect of nourishing the heart and tranquilizing the mind, which can greatly alleviate the symptoms of anxiety caused by the loss of the heart and the mind[32].

For adolescents with mild-to-moderate depressive disorder and anxiety with insomnia, the concept of prevention is better than cure is adopted to reduce the possibility of recurrence of the disease. Our study found that the therapeutic effect of sertraline combined with Wuling capsule was better. Compared with the control group, the total effective rate of the observation group was apparently higher, and the HAMD score, HAMA score, ISI, and TESS score were significantly lower at 2, 4, 6, and 8 weeks after the treatment ($P < 0.05$), which indicated that the effectiveness and safety of sertraline combined with Wuling capsule is higher, and it effectively improved the clinical symptoms of patients. The effective

Table 1 Comparison of Hamilton Depression Scale between the two groups

HAMD score	Control group (*n* = 40)	Observation group (*n* = 40)	*t* value	*P* value
Before treatment	24.23 ± 2.02	24.40 ± 1.52	0.438	0.662
2 weeks after treatment	18.58 ± 2.39	16.78 ± 2.69	3.158	0.002
4 weeks after treatment	15.67 ± 4.02	12.85 ± 3.71	3.268	0.002
6 weeks after treatment	12.60 ± 2.38	9.05 ± 2.09	7.086	< 0.001
8 weeks after treatment	8.63 ± 1.05	6.65 ± 1.19	7.861	< 0.001

HAMD: Hamilton Depression Scale.

Table 2 Comparison of Hamilton Anxiety Scale between the two groups

HAMA score	Control group (*n* = 40)	Observation group (*n* = 40)	*t* value	*P* value
Before treatment	22.87 ± 2.43	23.12 ± 2.59	0.445	0.658
2 weeks after treatment	18.07 ± 3.12	15.53 ± 3.71	3.326	0.001
4 weeks after treatment	14.78 ± 3.72	12.03 ± 4.28	3.067	0.003
6 weeks after treatment	11.63 ± 2.52	8.35 ± 2.38	5.976	< 0.001
8 weeks after treatment	8.75 ± 1.26	5.68 ± 1.31	10.723	< 0.001

HAMA: Hamilton Anxiety Scale.

Table 3 Comparison of Insomnia severity index between the two groups

ISI score	Control group (*n* = 40)	Observation group (*n* = 40)	*t* value	*P* value
Before treatment	17.85 ± 2.74	17.78 ± 2.76	0.122	0.903
2 weeks after treatment	15.63 ± 3.65	12.63 ± 4.01	3.499	< 0.001
4 weeks after treatment	13.75 ± 2.42	10.83 ± 3.15	4.658	< 0.001
6 weeks after treatment	11.90 ± 2.31	7.58 ± 2.15	8.679	< 0.001
8 weeks after treatment	8.73 ± 1.11	5.63 ± 1.00	13.101	< 0.001

ISI: Insomnia severity index.

Table 4 Comparison of treatment effect between the two groups, *n* (%)

Index	Control group (*n* = 40)	Observation group (*n* = 40)	χ^2	*P* value
Cure	15 (37.50)	27 (67.50)		
Effective	14 (35.00)	11 (27.50)		
Ineffective	11 (27.50)	2 (5.00)		
Total effective rate	29 (72.50)	38 (95.00)	7.440	0.006

therapeutic effect can be seen from the pharmacological mechanism that Wuling capsule is a supplement to the pharmacological mechanism of sertraline. Wuling Capsule is a pure Chinese medicine preparation with a single ingredient, which is diuretic and tonic to the heart and mind, and it has medicinal value for insomnia, vomiting of blood and postpartum blood loss. It can nourish the heart, tranquillize the mind and tonify the kidneys and the brain.

The drug has obvious effect of calming the center, it can effectively regulate the nerve function, improve the effect of memory disorders[33,34]. The brain-healthy and brain-protecting effect is better. Wuling Capsules can promote neuropeptide Y and 5-hydroxytryptamine content, reduce the content of substance P, so as to balance the monoamine neurotransmitters, in order to effectively improve the patient's insomnia symptoms. The drug is safe and has no adverse effects[35]. Our results indicated that both Wuling capsule and sertraline have anti-anxiety, anti-depression and sedative

hypnotic effects. After combined administration, patients' anxiety, depression and insomnia symptoms are remarkedly improved, suggesting that Wuling capsule can regulate natural sleep rhythm by regulating central neurotransmitter and neurophysiological balance, and at the same time enhance the function of viscera. The clinical symptoms of insomnia patients with anxiety and depression have been improved.

CONCLUSION

Sertraline combined with Wuling capsule has ideal effect on adolescent patients with anxiety, depression and insomnia symptoms, which can effectively improve the depressive state and sleep quality of patients, and is conducive to improving the treatment compliance of patients.

FOOTNOTES

Author contributions: Duo LL and Rao GF contribute equally to this study as co-corresponding authors. Duo LL designs research; Duo LL conducts case collection; Rao GF guide the research.

Institutional review board statement: The study was reviewed and approved by the Taizhou Hospital of Integrated Chinese and Western Medicine Institutional Review Board.

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ORIGINAL ARTICLE

Retrospective Study

Relationship between gestational body mass index, blood pressure variability, and postpartum depression in pregnant women with pre-eclampsia

Fang-Fang Wu, Hong Xu

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Abstract

BACKGROUND

Pre-eclampsia has long been proven to be an independent risk factor for postpartum depression (PPD). Excessive increase in body mass index (BMI) during pregnancy is an important factor inducing pre-eclampsia. Increased blood pressure is the main symptom of patients with pre-eclampsia. However, whether there is a correlation between BMI and blood pressure variability during pregnancy and PPD occurrence in pregnant women with pre-eclampsia remains unclear.

AIM

To investigate the relationship between BMI, blood pressure variability, and PPD in pregnant women with pre-eclampsia.

METHODS

Using a cross-sectional survey research, 201 pregnant women with pre-eclampsia who were treated and delivered in Suzhou Ninth People's Hospital from May 2016 to June 2024 were selected as this study's subjects. At 42 days after delivery, the subjects were re-examined in the hospital's outpatient department. The Edinburgh Postnatal Depression Scale (EPDS) was used to evaluate whether PPD symptoms, divided the subjects into two groups: The PPD and non-PPD groups. We analyzed clinical data, changes in BMI during pregnancy, and blood pressure variability in the two groups. The Pearson method was used to test the correlation between BMI increase, blood pressure variability during pregnancy, and EPDS score in patients with pre-eclampsia. Logistic regression analysis was performed to explore whether increased BMI and blood pressure variability during preg-

nancy are influencing factors for PPD occurrence in patients with pre-eclampsia.

RESULTS

Of the 201 pre-eclamptic women who underwent an outpatient review 42 days after delivery, 37 had PPD symptoms based on the EPDS scale evaluation, resulting in an incidence rate of 18.41% (37/201). The differences between the PPD and non-PPD groups in terms of age, educational level, place of residence, reproductive history, gestational age, mode of delivery, newborn gender, and newborn birth weight were not statistically significant ($P > 0.05$). The gestational BMI increase, 24-hour systolic blood pressure (SBP) variability, and 24-hour diastolic blood pressure (DBP) variability in the PPD group were significantly higher than those in the non-PPD group; the differences were statistically significant ($P < 0.001$). Pearson correlation analysis showed that BMI increase, SBP variability, and DBP variability during pregnancy correlated positively with the EPDS score of pregnant women with pre-eclampsia ($r = 0.349$, 0.336, and 0.241; $P < 0.001$). Logistic regression analysis showed that a high increase in BMI during pregnancy [odds ratio (OR) = 4.614, 95% confidence interval (CI): 1.749-12.170, $P = 0.002$], large variability in 24-hour SBP (OR = 2.910, 95%CI: 1.322-6.404, $P = 0.008$), and large variability in 24-hour DBP (OR = 2.347, 95%CI: 1.138-4.831, $P = 0.021$) were factors affecting PPD occurrence in patients with pre-eclampsia.

CONCLUSION

Increased BMI and blood pressure variability during pregnancy can increase the risk of PPD in patients with pre-eclampsia. Strengthening pregnancy guidance and controlling fluctuations in BMI and blood pressure variability during pregnancy within a reasonable range can help reduce the risk of PPD in patients with pre-eclampsia.

Key Words: Pre-eclampsia; Pregnancy; Body mass index; Blood pressure variability; Postpartum depression

Core Tip: Postpartum depression (PPD) is a mental illness that affects family and social harmony. This study found that increased body mass index and blood pressure variability during pregnancy can increase the risk of PPD in patients with pre-eclampsia. This suggests that controlling body mass index increase and blood pressure fluctuations during pregnancy in patients with pre-eclampsia is crucial to prevent these factors from negatively affecting their psychological well-being. Additionally, it plays an important role in reducing the overall incidence of maternal PPD.

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INTRODUCTION

Postpartum depression (PPD) is a puerperium mental syndrome characterized by sadness, anxiety, and difficulty in emotional control[1]. It can cause adverse effects on maternal physical and mental health, neonatal feeding, and even negative behaviors, including self-mutilation and suicide, thereby affecting family and social harmony. In addition to common social and physiological factors such as age, parity, and economic status[2], the individual health factors of pregnant women during pregnancy are closely linked to PPD occurrence. The International Academy of Medicine has promoted the ideal range of weight gain during pregnancy based on body mass index (BMI). Several studies have investigated the relationship between pregnancy-related psychiatric symptoms and BMI[3]. Some studies have found that pre-pregnancy obesity is a risk factor for PPD[4]. However, there are few reports on the relationship between BMI and PPD during pregnancy. Pre-eclampsia is a common pregnancy-specific disease. Overweight/obesity is an important trigger for its onset[5,6], with elevated blood pressure being the primary clinical feature of pre-eclampsia. Some studies have suggested a correlation between changes in dynamic blood pressure rhythm and organ diseases in various body systems and that blood pressure variability is closely linked to negative emotions[7]. Given that the primary clinical features of pre-eclampsia are new-onset hypertension and proteinuria after 20 weeks of pregnancy, which can lead to multi-system and organ involvement of varying severity, and the condition can progress and worsen unpredictably, the risk of adverse pregnancy outcomes is high[8]. Consequently, pregnant women with pre-eclampsia often experience psychological stress during pregnancy, which is significantly higher than that in normal pregnant women, making them more susceptible to PPD. Therefore, understanding the relationship between BMI, blood pressure variability, and PPD during pregnancy in the context of pre-eclampsia is crucial for guiding clinical measures to reduce overall maternal PPD. However, to date, there is little to no literature exploring the mechanisms linking pregnancy BMI, blood pressure variability, and PPD in patients with pre-eclampsia. This study explored the relationship between changes in BMI, blood pressure variability, and PPD in pregnant women with pre-eclampsia to provide a reference for the prevention and treatment of PPD in pregnant women with pre-eclampsia.

MATERIALS AND METHODS

Research subjects

A cross-sectional survey was conducted involving 201 pregnant women with pre-eclampsia who received treatment and successfully gave birth at Suzhou Ninth People's Hospital from May 2016 to June 2024. These women were the research subjects. The Edinburgh Postnatal Depression Scale (EPDS) was used to assess the presence of PPD symptoms at 42 days postpartum. Based on the results, the women were categorized into PPD and non-PPD groups.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) 20-40 years of age; (2) All prenatal checkups were conducted in our hospital; (3) Met the diagnostic criteria for pre-eclampsia in the "Guidelines for the Diagnosis and Treatment of Pregnancy-induced Hypertension (2020)"[9] namely: After 20 weeks of pregnancy, systolic blood pressure (SBP) ≥ 140 mmHg (1 mmHg = 0.133 kPa), diastolic blood pressure (DBP) ≥ 90 mmHg, and elevated proteinuria; (4) No major life changes during pregnancy; (5) The newborn survived, and no deformity was observed; and (6) Informed of this study, and signed informed consent.

The exclusion criteria were as follows: (1) Other than pre-eclampsia, other pregnancy complications existed; (2) Pre-pregnancy or lineal relatives had a history of mental illness; (3) Pregnancy *via* assisted reproductive technology; and (4) During pregnancy and before delivery, a depression screening questionnaire (PHQ-9) was used to identify individuals who were already depressed[10].

Research methods

General information collection: A general information collection form was created. The collected information included age, pre-pregnancy BMI, educational level, place of residence, birth history, gestational age, delivery mode, newborn gender, and birth weight of the subjects.

Changes in BMI during pregnancy: The height and weight of the subjects were measured. BMI was calculated according to the following formula: BMI = [weight (kg)/height (m^2)]; changes in BMI during pregnancy = pre-delivery BMI - pre-pregnancy BMI[11].

Pregnancy blood pressure variability: Because blood pressure exhibits certain physiological fluctuations and circadian rhythm changes, its dynamic adjustments to these changes are one of the most basic physiological characteristics of the human body. Therefore, we selected the third trimester (28-30 weeks) to observe the 24-hour ambulatory blood pressure (diastolic and SBP) in pregnant women with pre-eclampsia using a non-invasive portable ambulatory blood pressure monitor. To obtain accurate blood pressure values while considering physiological fluctuations and circadian rhythm changes, we selected 6:00 a.m. to 21:59 p.m. as the daytime, measured once every 15 minutes. The night period was from 22:00 p.m. to 5:59 a.m., measured once every 30 minutes. We ensured that monitoring frequency of patients was > 80% effective, otherwise, we re-measured. The blood pressure variability of patients with pre-eclampsia was calculated based on the daily average blood pressure and standard deviation: Blood pressure variability = standard deviation/mean blood pressure × 100%.

PPD diagnosis: The EPDS was used to assess whether pregnant women with pre-eclampsia who went to the hospital's outpatient department for follow-up 42 days after delivery had PPD symptoms. This scale comprises 10 items, each of which is rated on four levels: Never scored; 0: Occasionally scored; 1: Frequently scored; 2: And always scored; 3: The total score is 0-30 points. PPD symptoms are present when EPDS score is ≥ 9 points in women with pre-eclampsia[12].

Statistical analysis

SPSS 25.0 statistical software was used for data analysis. The measurement data were first verified using the S-W method to conform to a normal distribution expressed as mean ± SD. The two groups were compared using an independent *t*-test. The utilization rate and composition ratio of count data [*n* (%)] were expressed. The two groups were compared using the χ^2 test. Pearson's correlation method was used to analyze the correlation between BMI increase during pregnancy, blood pressure variability, and EPDS score in patients with pre-eclampsia. Multiple logistic regression analysis was used to investigate the effects of changes in BMI and blood pressure variability during pregnancy on PPD in patients with pre-eclampsia. $P < 0.05$ indicates statistically significant differences.

RESULTS

Occurrence and general information of PPD in patients with pre-eclampsia

Among the 201 pregnant women with pre-eclampsia who attended outpatient follow-up on the 42nd day after delivery, 37 were found to have depressive symptoms based on the EPDS scale evaluation (PPD group), with an incidence rate of 18.41% (37/201) and an EPDS score of 17.23 ± 3.65. The remaining 164 women had no depressive symptoms (non-PPD group), with an EPDS score of 6.93 ± 1.58. The differences between the PPD and non-PPD groups in terms of age, educational level, place of residence, reproductive history, gestational age, delivery mode, newborn gender, and newborn birth weight were not statistically significant ($P > 0.05$) (Table 1).

Table 1 General information comparison

Characteristics	PPD group (*n* = 37)	Non-PPD group (*n* = 164)	t/χ^2 value	*P* value
Age (years), mean ± SD	28.03 ± 3.55	27.46 ± 3.17	0.966	0.335
Pre-pregnancy BMI (kg/m^2), mean ± SD	24.29 ± 2.85	23.43 ± 2.91	1.630	0.105
Degree of education, *n* (%)			1.710	0.191
High school or below	22 (59.46)	78 (47.56)		
College degree or above	15 (40.54)	86 (52.44)		
Place of residence, *n* (%)			0.162	0.687
Rural area	13 (35.14)	52 (31.71)		
Cities and towns	24 (64.86)	112 (68.29)		
Birth history, *n* (%)			0.363	0.547
Primipara	9 (24.32)	48 (29.27)		
Multipara	28 (75.68)	116 (70.73)		
Delivery gestational weeks (weeks), mean ± SD	38.74 ± 1.25	38.69 ± 1.31	0.211	0.833
Delivery method, *n* (%)			0.163	0.686
Vaginal delivery	16 (43.24)	65 (39.63)		
Cesarean birth	21 (56.76)	99 (60.37)		
Gender of newborn, *n* (%)			0.114	0.735
Male baby	23 (62.16)	97 (59.15)		
Female infant	14 (37.84)	67 (40.85)		
Newborn birth weight (kg), mean ± SD	3.70 ± 0.72	3.48 ± 0.65	1.823	0.069

PPD: Postpartum depression; BMI: Body mass index.

Comparison of BMI increase and blood pressure variability during pregnancy

BMI increase, 24-hour SBP variability, and 24-hour DBP variability during pregnancy in pregnant women with pre-eclampsia in the PPD group were significantly higher than those in the non-PPD group, difference was statistically significant ($P < 0.05$) (Table 2). This suggests that increased BMI and blood pressure variability during pregnancy are associated with PPD in pregnant women with pre-eclampsia.

Pearson correlation analysis

The increase in BMI, SBP variability, and DBP variability during pregnancy in pregnant women with pre-eclampsia correlated positively with their EPDS scores ($r = 0.349$, 0.336, and 0.241; $P < 0$ 001) (Figure 1). This indicates a positive linear trend between BMI change and blood pressure variability during pregnancy and PPD in pregnant women with pre-eclampsia.

Logistic regression analysis of the factors influencing PPD in patients with pre-eclampsia

PPD occurrence in pregnant women with pre-eclampsia after delivery was used as the dependent variable (0 = no; 1 = yes). The statistically significant indicators presented in Table 2 were used as the independent variables (original value input). Logistic regression analysis showed that a high increase in BMI during pregnancy, large variability in 24-hour SBP, and large variability in 24-hour DBP were the influencing factors of PPD in patients with pre-eclampsia ($P < 0.05$) (Table 3).

DISCUSSION

Pre-eclampsia is a common complication of pregnancy. Srajer *et al*[13] reported that pre-eclampsia is associated with increased risk and severity of cognitive impairment, psychological stress, and mental disorders, including depression, anxiety, and post-traumatic stress disorder. Holland and Richmond[14] reported that pregnant women diagnosed with pre-eclampsia have a significantly higher risk of PPD. This emphasizes that pre-eclampsia can exacerbate the risk of PPD development because it may involve multiple systems and organs to varying degrees, thereby affecting fetal development and causing adverse psychological effects on patients with pre-eclampsia, making them more prone to PPD. A meta-analysis showed that the overall rate of depression in healthy pregnant women without a history of depression is 17%

Table 2 Comparison of increased body mass index and blood pressure variability during pregnancy

Characteristics	PPD group (n = 37)	Non-PPD group (n = 164)	t value	P value
Increase in BMI during pregnancy (kg/m^2)	6.45 ± 1.73	4.21 ± 1.07	10.120	< 0.001
24-hour systolic blood pressure variability (mmHg)	28.19 ± 6.48	21.58 ± 4.35	7.557	< 0.001
24-hour diastolic blood pressure variability (mmHg)	20.27 ± 4.16	17.13 ± 3.84	4.424	< 0.001

PPD: Postpartum depression; BMI: Body mass index.

Table 3 Results of multivariate Logistic regression analysis

Variable	β	SE	Wald χ^2	P value	OR (95%CI)
Increased BMI during pregnancy	1.529	0.495	9.541	0.002	4.614 (1.749-12.170)
24-hour systolic blood pressure variability	1.068	0.403	7.023	0.008	2.910 (1.322-6.404)
24-hour diastolic blood pressure variability	0.853	0.369	5.343	0.021	2.347 (1.138-4.831)

BMI: Body mass index; OR: Odds ratio; CI: Confidence interval.

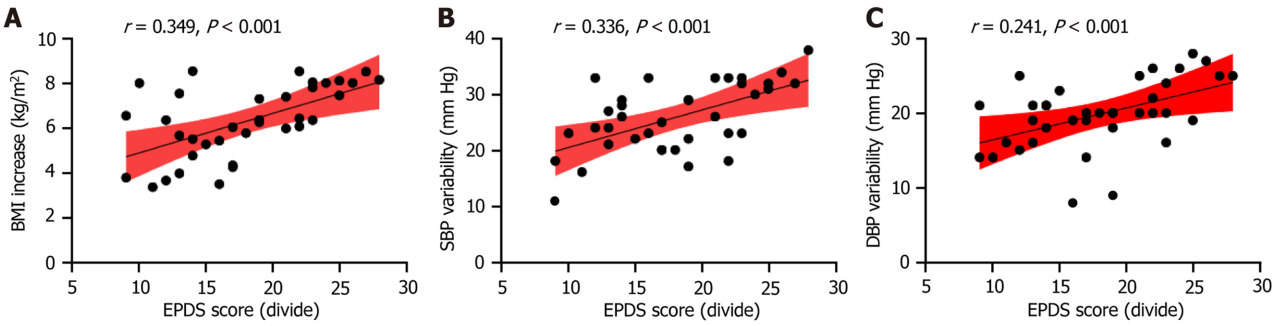

Figure 1 Correlation between increased body mass index during pregnancy, blood pressure variability, and Edinburgh Postnatal Depression Scale score. A: Correlation analysis between increased body mass index during pregnancy and Edinburgh Postnatal Depression Scale (EPDS) score; B: Correlation analysis between systolic blood pressure variability and EPDS score; C: Correlation analysis between diastolic blood pressure variability and EPDS score). EPDS: Edinburgh Postnatal Depression Scale; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

[15]. This study found that the incidence of PPD in pregnant women with pre-eclampsia at 42 days postpartum was 18.41%, slightly higher than that in the abovementioned report. It may be that the pathogenesis of pre-eclampsia or its symptoms increases the risk of PPD in pregnant women. Therefore, for the study of PPD in patients with pre-eclampsia, it is necessary to explore the relationship between PPD and the etiology and symptoms of pre-eclampsia in pregnant women to take early clinical measures to reduce PPD incidence in pregnant women with pre-eclampsia.

Being overweight and obese are important factors in pre-eclampsia pathogenesis[16]. They can lead to complications in pregnant women, including hyperlipidemia, hyperinsulinemia, pathological and physiological changes in the placenta, causing systemic vascular endothelial damage, systemic small artery spasm, and, ultimately, pre-eclampsia. This is evidenced by the fact that most patients with pre-eclampsia were overweight or obese before pregnancy. Furthermore, high BMIs before pregnancy often lead to weight gain during pregnancy that exceeds the reasonable range. Wu *et al*[17] found that an excessive increase in BMI during pregnancy is an important influencing factor of PPD. Howard *et al*[18] reported that the BMI of postpartum women correlates positively with PPD. Qiu *et al*[19] found that excessive weight gain during pregnancy is significantly associated with a high risk of developing PPD. This study found that the gestational BMI increase in patients with pre-eclampsia in the PPD group was significantly higher than that in the non-PPD group. BMI increase during pregnancy correlated positively with the EPDS score of patients with pre-eclampsia in the PPD group, suggesting that BMI increase during pregnancy is a contributing factor to PPD occurrence in patients with pre-eclampsia, consistent with the abovementioned report. The reason may be that the excessive increase in BMI in pregnant women with pre-eclampsia can cause endocrine disorders, increase the incidence of macrosomia, affect normal vaginal delivery, increase cesarean section and forceps rates, and may adversely affect newborns[20]. Therefore, it significantly affects the psychological state of pregnant women, leading to tension and fear before delivery. This exacerbates the condition, hinders postpartum recovery, and creates a vicious cycle that can ultimately trigger PPD. Second, an excessive increase in BMI during pregnancy can easily lead to postpartum weight and fat retention[21], affecting the mother's body shape and worsening her psychological burden, thereby making them prone to PPD.

Additionally, the psychological state of postpartum women is more sensitive compared to the sensitive period. Will pay more attention to postpartum body shape recovery. However, excessive weight gain during pregnancy is associated with many endocrine problems[22]. It often leads to difficulty in restoring weight and body shape after childbirth to the pre-pregnancy state[23]. This can cause the mothers to become prone to negative emotions, increasing their risk of PPD.

Elevated blood pressure is the main clinical manifestation of pre-eclampsia[24]. Harskamp and Zeeman[25] reported that pregnant women with pre-eclampsia are more likely to develop cardiovascular and cerebrovascular diseases than those with normal blood pressure. This may be due to elevated blood pressure variability in pregnant women with pre-eclampsia, which can easily trigger several cardiovascular and cerebrovascular diseases[26]. This will undoubtedly cause a greater physical and psychological burden on pregnant women. When the psychological state is relatively fragile during pregnancy, PPD is often prone to occur[27]. Artinian *et al*[28] reported that the higher the blood pressure level in women, the greater the risk of developing depression. This study found that the 24-hour SBP and DBP variabilities in patients with pre-eclampsia in the PPD group were significantly higher than those in the non-PPD group. The 24-hour SBP and DBP variabilities correlated positively with the EPDS score of patients with pre-eclampsia in the PPD group. These findings suggest that the 24-h SBP and DBP variabilities are influencing factors for PPD occurrence in patients with pre-eclampsia, consistent with the abovementioned conclusion. Blood pressure variability and PPD occurrence in patients with pre-eclampsia are related. The reason may be the increased blood pressure variability during pregnancy in patients with pre-eclampsia, causing small artery spasms in some cerebral blood vessels[29], damaging the endothelial function of the blood-brain barrier, and leading to long-term structural and functional brain changes. These changes may lead to subsequent mental health damage and increase the risk of PPD. Additionally, blood pressure variability during pregnancy may trigger several cardiovascular and cerebrovascular diseases, which can cause psychological stress[30] and stimulate negative emotions such as tension, fear, and anxiety. These negative emotions can cause sympathetic nervous system excitement, elevated blood pressure, exacerbate blood pressure fluctuations, and induce a relatively stable hypertension level for a long time. This forms a vicious cycle that causes certain mental and psychological abnormalities, thereby increasing the risk of PPD occurrence.

CONCLUSION

In summary, the BMI and blood pressure variability of pregnant women with pre-eclampsia during pregnancy were closely related to their PPD occurrence. In other words, increased BMI and high blood pressure variability during pregnancy can increase the risk of PPD in patients with pre-eclampsia. Although an increasing number of researchers are paying attention to the psychological problems of postpartum women, the clinical management system for these problems remains imperfect. Therefore, we suggest the monitoring of BMI and blood pressure fluctuations during pregnancy in patients with pre-eclampsia during routine prenatal checkups and the importance of health education and guidance during pregnancy to take proper measures to control the increase in BMI and blood pressure fluctuations in pregnant women with pre-eclampsia, thereby reducing the risk of PPD. We also strongly urge pregnant women to maintain a healthy weight through a reasonable diet and appropriate exercise, to maintain a comfortable mood as much as possible, and to avoid blood pressure stimulation by psychological tension. Furthermore, medical workers need to strengthen prenatal health education, control the weight gain of pregnant women during pregnancy while ensuring the nutritional needs of the mother and fetus, and do a good job in psychological counseling during pregnancy to alleviate tensions in pregnant women. Nevertheless, this study has some limitations. First, this study is a single-center survey data analysis with a limited sample size and representativeness. Second, there may be some residual confounding factors affecting the variable analysis. Therefore, it is necessary to improve and expand the sample size in future research to validate our conclusions.

FOOTNOTES

Author contributions: Wu FF and Xu H researched and wrote the manuscript; Wu FF and Xu H contributed to conceiving the research and analyzing data, conducted the analysis and provided guidance for the research; and all authors reviewed and approved the final manuscript.

Institutional review board statement: This study was approved by the Ethic Committee of Suzhou Ninth People's Hospital (Suzhou Ninth Hospital Affiliated to Soochow University), No. SZLY0160768.

Informed consent statement: All research subjects provided informed written consent regarding personal and medical data collection prior to enrollment in the study.

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Retrospective Study

Mindfulness-based stress reduction training and supplemented Jinshui Liujun decoction promote recovery in patients with non-small cell lung cancer

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Abstract

BACKGROUND

Conventional chemotherapy (CC) administered to patients with non-small cell lung cancer (NSCLC) often causes adverse effects, such as cardiopulmonary dysfunction and immune system imbalance. Patients may experience anxiety and depression during the perioperative period due to various factors, such as treatment costs and cancer recurrence risks, thereby compromising the overall quality of life. Consequently, we hypothesized that integrating mindfulness-based stress reduction training (MSRT) with Jinshui Liujun decoction may mitigate negative emotions and promote recovery in patients with NSCLC.

AIM

To explore the effects of MSRT and Jinshui Liujun decoction on the immune function and emotional state of NSCLC patients.

METHODS

A retrospective clinical study was conducted involving 92 patients with stage IIIb-IV NSCLC; 35 patients in the control group (CG) received CC therapy (combination of pemetrexed and carboplatin), and 57 patients in the treatment group (TG) received MSRT-assisted flavored Jinshui Liujun decoction (FJLD) in addition to CC. We evaluated the survival time, Karnofsky performance status, treatment efficacy, traditional Chinese medicine syndrome score, immune function, negative emotional level, and adverse reactions of the CG and TG.

RESULTS

Median progression-free survival, Karnofsky performance status, and clinical

efficacy of the TG were superior to those of the CG ($P < 0.05$). Symptoms of cough, weakness, bloody sputum, shortness of breath, and chest pain significantly decreased in the TG compared to that in the CG ($P < 0.05$). In the TG, MSRT + FJLD treatment increased the numbers of $CD3^+$ and $CD4^+$ immune cells, effectively reduced the number of $CD8^+$ cells, and enhanced the $CD4^+/CD8^+$ ratio, thereby restoring the immune function of patients. In the TG, the self-rating anxiety scale and self-rating depression scale scores decreased significantly. There was no statistically significant difference in the incidence of adverse reactions between the CG and TG ($P > 0.05$).

CONCLUSION

MSRT + FJLD proved to be an effective treatment for patients with NSCLC.

Key Words: Non-small cell lung cancer; Mindfulness-based stress reduction training; Flavored Jinshui Liujun decoction; Curative effect; Immune function; Negative emotion

Core Tip: The combined effects of mindfulness-based stress reduction training with flavored Jinshui Liujun decoction and conventional chemotherapy on survival time, Karnofsky performance status, traditional Chinese medicine syndrome score, immune function, negative emotion levels, and incidence of adverse reactions in patients with non-small cell lung cancer were evaluated. We found that combining mindfulness-based stress reduction training + flavored Jinshui Liujun decoction with conventional chemotherapy for patients with non-small cell lung cancer extended survival time, improved Karnofsky performance status scores, increased $CD3^+$ and $CD4^+$ immune cells, reduced $CD8^+$ cells, and improved the $CD4^+/CD8^+$ ratio, thereby restoring immune function.

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INTRODUCTION

Lung cancer, also known as primary bronchopulmonary carcinoma, is one of the deadliest malignancies among patients with cancer worldwide[1]. Non-small cell lung cancer (NSCLC), a subtype of lung cancer, accounts for approximately 85% of cases. It includes several different types of cancers, such as lung adenocarcinoma and lung squamous cell carcinoma, with lesion foci mainly in the alveolar epithelium and bronchial mucosal epithelium[2]. Stages I-IIIa are considered the initial phases of lung cancer, during which clinical features do not manifest. At the time of diagnosis, most patients have already progressed to intermediate and late stages (stages IIIb-IV) and can only be treated with conservative methods, such as chemotherapy[3].

Chemotherapy is a widely used treatment for NSCLC that aims to kill or slow the growth of cancer cells using chemical agents[4]. However, chemotherapeutic agents act systemically, affecting not only cancer cells but also healthy cells. This can cause side effects, such as myelosuppression, alopecia, cardiotoxicity, and pulmonary toxicity, as well as perioperative stresses, such as prolonged hospitalization, high treatment costs, and cancer recurrence with metastasis, increasing the risk of passive mood (anxiety and depression) in patients[5]. In addition, the combination therapy of pemetrexed and carboplatin is mainly used for the treatment of late-onset NSCLC. Although it has low toxicity and is well tolerated, long-term use of pemetrexed is likely to induce drug resistance, leading to poor therapeutic efficacy. Therefore, it is necessary to identify effective treatments based on conventional chemotherapy (CC) to maintain patient health and improve survival[6].

Mindfulness-based stress reduction training (MSRT) is a variation of progressive muscle relaxation training based on the concept of self-movement and alternating cycles of muscle "contraction-relaxation-reduction". The repetitive muscle relaxation regimen trains people to tense and relax different muscle groups, relieves negative emotions such as anxiety, and has been widely used in recent years to treat lung cancer and other cancers[7]. Additionally, traditional Chinese herbal therapy can reduce the toxic effects of chemotherapy in patients with NSCLC. This approach not only reduces toxicity, improves efficacy, and promotes recovery but also promotes the recovery of the patient's immune system by improving the levels of the body's immune function indicators[8].

Flavored Jinshui Liujun decoction (FJLD) is commonly used in clinical practice to treat lung diseases, such as chronic obstructive pulmonary disease, asthma, and chronic bronchitis. It comprises prepared Rehmannia root, Pinellia ternata rhizome, chenpi, licorice, Poria cocos, and milkvetch root. Its pharmacological actions include blood-supplementing and yin-supplementing effects, and has blood-nourishing, diuretic, expectorant, anti-inflammatory, and immunomodulating properties[9]. In a combined treatment regimen of traditional Chinese medicine (TCM) and Western medicine, FJLD has been shown to have a positive impact on the T lymphocyte subsets of patients with NSCLC after chemotherapy and to improve the immune function of patients[10]. However, most existing treatment protocols for patients with NSCLC focus

on the effects of Chinese and Western medical treatments on physical health. Moreover, only a few studies have examined the combination of MSRT and CC to mitigate negative emotions and promote recovery in patients with NSCLC. This study selected 92 patients with NSCLC for a retrospective clinical trial to investigate the effect of MSRT + FJLD in addition to CC for the treatment of NSCLC.

MATERIALS AND METHODS

Physical data

Ninety-two patients with NSCLC admitted to the First Affiliated Hospital of Hebei North University between December 2022 and December 2023 were retrospectively selected and divided into the control group (CG) and the treatment group (TG) according to treatment modalities. Telephone follow-up was conducted to improve case data. The study was reviewed and approved by the Institutional Review Board of the First Affiliated Hospital of Hebei North University (Approval No. K2020227).

The inclusion criteria were as follows: (1) Patients who met diagnostic criteria for NSCLC with clinical stage IIIb-IV, as confirmed by imaging, histological specimens, and other pathological tests[6]; (2) Patients who provided informed consent and had complete clinical data; (3) Patients newly diagnosed with NSCLC; (4) Patients with Karnofsky performance status (KPS) ≤ 60 points; (5) Patients with a follow-up period for case data of 2 years; and (6) Patients with no serious immunological or other diseases[3]. The exclusion criteria were as follows: (1) Individuals with drug allergies; (2) Individuals with complications from other cancers; (3) Patients with bronchial asthma and lung diseases such as chronic obstructive pulmonary disease; (4) Individuals with mental or consciousness disorders; and (5) Patients who received treatment for less than one cycle or dropped out midway.

The disease control rate (DCR) of the subjects was the outcome index. According to the literature review, the DCR of the intervention group is expected to be 80%, that of the CG is expected to be 45%, the bilateral $\alpha = 0.05$, and the test efficacy β is 90%. According to the sample size calculation formula $N = [2P \times (1-P) \times (Z_{\alpha} + Z_{\beta})^2]/(p1 - p2)^2$, a total of 78 subjects in the intervention group and the CG were estimated to be required. The 92 patients included in this study met the statistical requirements.

Procedures

CG: Thirty-five patients were treated with CC, including pemetrexed and carboplatin. Pemetrexed disodium, administered by injection (Jiangsu Osaikang Pharmaceutical Co., Ltd., State Pharmaceutical License No. H20080624, specification: 0.2 g), was administered intravenously on the first day at a dose of 500 mg/m^2, while carboplatin (Yunnan Phyto-Pharmaceutical Co. H10950273, specification: 50 mg) was also administered by injection on the first day. The area under the curve was controlled at 5. Another course of treatment was administered after 3 weeks, totaling two courses of treatment.

TG: Fifty-seven cases were treated using MSRT[11] supplemented with FJLD. The FJLD consisted of prepared Rehmannia root (1 g), Pinellia ternata rhizome (12 g), chenpi (12 g), licorice (9 g), Poria cocos (9 g), milkvetch root (15 g), Radix Pseudostellariae (12 g), coastal glehnia root (15 g), and dwarf lilyturf tuber (9 g). It was administered as a 300-mL juice, taken with warm water twice daily in the morning and evening, along with two cycles of chemotherapy treatment.

Observational index

Evaluation indicators: Primary evaluation index: Progression-free survival (PFS) to investigate the patient's disease progression or death. Secondary evaluation index: Overall survival (OS) to investigate the patient's death or the last follow-up visit.

KPS score: 100 points: Indicates normalcy, with no discomfort. 90 points: Indicates the ability to perform normal activities with mild illness. 80 points: Indicates having few symptoms. 70 points: Indicates an inability to maintain normal activities or heavy work. 60 points: Indicates living independently most of the time and needing some assistance. 50 points: Indicates needing more assistance. 40 points: Indicates poor self-care ability and needing special care or assistance. 30 points: Indicates an inability to live independently. 20 points: Indicates the patient is critically ill and needs hospitalization. 10 points: Indicates closeness to death. 0 points: Indicates death.

Clinical efficacy: The treatment efficacy in the CG and TG was evaluated after the two treatment courses. Complete remission: Complete disappearance of symptoms, maintained for ≥ 4 weeks. Partial remission: ≥ 30% decrease in the sum of the largest diameters of the lesions, maintained for ≥ 4 weeks. Stable disease: < 30% decrease or < 20% increase in the sum of the largest diameters of the lesions. Progressive disease: ≥ 20% increase in the sum of the largest diameters of the lesions or appearance of new lesions. DCR = complete remission + partial remission + stable disease.

TCM syndrome score: The TCM syndrome scores of the CG and TG were compared before and after treatment, with a maximum score of 3. Lower scores indicate a better treatment effect.

Measurement of the immune function index: 5 mL of venous blood was collected before and after treatment from the CG and TG. The percentages of $CD3^+$, $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ cells in the CG and TG were measured using a flow cytometer (BriCyte E6, Myriad BioMedical Electronics Co. Ltd., Shenzhen, China).

Negative mood assessment: The self-rating anxiety scale (SAS) was used to assess anxiety in patients in the CG and TG. The judging criteria were as follows: Severe anxiety ≥ 70 points, general anxiety 60-69 points, less anxiety 50-59 points, and no anxiety < 50 points. The self-rating depression scale (SDS) was used to assess depression status before and after treatment in the CG and TG. The judging criteria were as follows: Severe depression ≥ 70 points, general depression 60-69 points, less depression 50-59 points, and no depression < 50 points.

Adverse reactions: The incidences of dyspnea, diarrhea, vomiting, and proteinuria after treatment in the CG and TG were statistically analyzed.

Statistical analysis

SPSS 26.0 (IBM, NY, United States) statistical analysis software was used for data analysis. The measurement data were analyzed using the *t*-test, and the results were expressed as mean ± SD. Count data were tested using the χ^2 test and expressed as *n* (%). Kaplan-Meier analysis was used to enumerate the PFS and OS of each group, and survival curves were compared between the groups. $P < 0.05$ indicated statistical significance.

RESULTS

Baseline data

The TG ($n = 57$) included 38 men and 19 women, with a mean age of 59.77 ± 5.22 years. The mean body mass index was 21.44 ± 1.84 kg/m^2. Eight patients had a history of hypertension, and 49 patients had no history of hypertension. Four patients had diabetes, and 53 patients had no history of diabetes. The NSCLC disease course was 6-12 months (8.82 ± 6.04 months). Pathological staging comprised 23 cases of IIIb, 15 cases of IIIc, and 8 cases of IV. Pathological classification included 16 cases of adenocarcinoma, 32 cases of squamous cell carcinoma, and 9 cases of others. The mean lesion diameter was 3.14 ± 1.16 cm.

The CG ($n = 35$) included 23 men and 12 women, with an average age of 60.74 ± 6.18 years and an average body mass index of 21.20 ± 2.00 kg/m^2. There were 5 cases with a history of hypertension and 30 cases without hypertension. There were three cases with a history of diabetes and 32 cases without a history of diabetes. The NSCLC disease course was 6-12 months (9.00 ± 2.20 months). Pathological staging comprised 10 cases of IIIb, 20 cases of IIIc, and 5 cases of IV. Pathological classification included 16 cases of adenocarcinoma and 14 cases of squamous cell carcinoma (Table 1).

Survival time

The median PFS in the TG and CG significantly differed at 20.50 and 13.10 months, respectively ($\chi^2 = 4.138$, $P < 0.05$). The median OS was 22.00 months in the TG and 19.10 months in the CG, with no statistically significant difference between the two groups ($\chi^2 = 0.291$, $P > 0.05$) (Figure 1).

KPS score

Before treatment, there was no difference in the KPS scores between the TG and CG ($P > 0.05$). After treatment, the KPS score of the TG was significantly higher than that of the CG ($P < 0.05$) (Table 2).

Clinical efficacy

Compared to the CG, the TG had a higher DCR value (71.94% *vs* 51.43%) ($P < 0.05$), indicating that MSRT + FJLD improved treatment efficacy in NSCLC (Table 3).

TCM syndrome score

There were no significant differences in TCM syndrome scores for cough (CG: 2.02 ± 0.66, TG: 2.03 ± 0.63), weakness (CG: 1.97 ± 0.59, TG: 1.97 ± 0.61), bloody sputum (CG: 2.01 ± 0.69, TG: 1.93 ± 0.59), shortness of breath (CG: 2.06 ± 0.53, TG: 2.08 ± 0.50), and chest pain (CG: 1.91 ± 0.56, TG: 1.96 ± 0.62) between the CG and the TG, respectively. After two courses of treatment, the TCM syndrome scores in the TG and the CG decreased to some extent. In the TG, the scores for cough (0.91 ± 0.50), weakness (0.94 ± 0.58), bloody sputum (0.89 ± 0.55), shortness of breath (0.83 ± 0.48), and chest pain (0.90 ± 0.62) were significantly lower than those in the CG (1.14 ± 0.57, 1.20 ± 0.57, 1.17 ± 0.57, 1.10 ± 0.53, 1.25 ± 0.57, respectively) ($P < 0.05$). These results suggest that MSRT + FJLD significantly improves cough, weakness, bloody sputum, shortness of breath, and chest pain in patients with NSCLC (Figure 2).

Immunological function

Before treatment, there were no significant differences in the percentages of $CD3^+$, $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ between the CG (62.21% ± 4.58%, 37.52% ± 4.57%, 35.20% ± 3.27%, 1.08% ± 0.19%) and the TG (62.91% ± 4.87%, 37.51% ± 4.44%, 35.92% ± 2.93%, 1.05% ± 0.15%) after statistical analysis. After two courses of treatment, the percentages of immune function indices in the CG and TG changed. The percentages of $CD3^+$, $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ in the TG (70.86% ± 3.36%, 43.67% ± 4.86%, 24.95% ± 3.46%, 1.78% ± 0.30%, respectively) were significantly higher than those in the CG (64.90% ± 3.32%, 39.62% ± 3.83%, 30.75% ± 3.35%, 1.30% ± 0.17%, respectively) ($P < 0.05$) (Figure 3). This indicates that MSRT + FJLD can improve immune system function in patients with NSCLC.

Table 1 Baseline data of patients with non-small cell lung cancer

Projects	*n*	TG (*n* = 57)	CG (*n* = 35)	χ^2/t	*P* value
Sex, *n* (%)				0.009	0.925
Male	61	38 (66.67)	23 (65.71)		
Female	31	19 (33.33)	12 (34.29)		
Age, mean ± SD		59.77 ± 5.22	60.74 ± 6.18	-0.807	0.422
BMI (kg/m^2), mean ± SD		21.44 ± 1.84	21.20 ± 2.00	0.584	0.561
Hypertension history, *n* (%)				0.001	0.973
Find	13	8 (14.04)	5 (14.29)		
Nil	79	49 (85.96)	30 (85.71)		
History of diabetes, *n* (%)				0.074	0.785
Find	7	4 (7.02)	3 (8.57)		
Nil	85	53 (92.98)	32 (91.43)		
Duration of disease (month), mean ± SD		8.82 ± 6.04	9.00 ± 2.20	-0.389	0.698
Pathological stage, *n* (%)				0.038	0.981
IIIb	26	16 (28.07)	10 (28.57)		
IIIc	52	32 (56.14)	20 (57.14)		
IV	14	9 (15.79)	5 (14.29)		
Pathological classification, *n* (%)				0.025	0.988
Adenocarcinoma	43	27 (47.37)	16 (45.71)		
Squamous carcinoma	36	22 (38.60)	14 (40.00)		
Others	13	8 (14.04)	5 (14.29)		
Tumor diameter (cm), mean ± SD		3.14 ± 1.16	3.17 ± 1.13	-0.122	0.903

CG: Control group; TG: Treatment group; BMI: Body mass index.

Table 2 Karnofsky performance status scores

Group	*n*	KPS scores	
		Before treatment	After treatment
TG	57	50 (40, 60)	60 (40, 70)
CG	35	50 (40, 60)	50 (40, 60)
χ^2		0.015	12.394
P value		0.992	0.006

CG: Control group; TG: Treatment group; KPS: Karnofsky performance status.

Negative emotion

Before treatment, the SAS and SDS scores of the CG (58.86 ± 4.82 and 59.09 ± 5.43, respectively) and the TG (58.44 ± 5.47 and 58.72 ± 5.05, respectively) were not significantly different. After two courses of treatment, the SAS and SDS scores in both the CG and the TG decreased; however, the scores in the TG (47.37 ± 4.69 and 47.63 ± 4.79, respectively) were significantly lower than those in the CG (53.31 ± 5.07 and 54.54 ± 4.59, respectively) ($P < 0.05$) (Figure 4). This indicates that MSRT + FJLD can effectively improve the emotional state of patients with NSCLC and maintain their mental health.

Adverse reactions

Compared to the CG, the TG had a lower occurrence rate of adverse reactions (breathing difficulties, diarrhea, vomiting, and proteinuria) after two courses of treatment. No statistically significant differences were observed in the overall response rate between the TG (10.52%) and the CG (11.44%) (Table 4).

Table 3 Therapeutic efficacy in the treatment group and control group, *n* (%)

Group	*n*	CR	PR	SD	PD	DCR	χ^2	*P* value
TG	57	13 (22.81)	15 (26.32)	13 (22.81)	16 (28.06)	41 (71.94)	3.962	0.047
CG	35	3 (8.57)	5 (14.29)	10 (28.57)	17 (48.57)	18 (51.43)		

CR: Complete remission; PR: Partial remission; SD: Stable disease; PD: Progressive disease; DCR: Disease control rate; CG: Control group; TG: Treatment group.

Table 4 Occurrence rate of adverse reactions in the treatment group and control group, *n* (%)

Group	*n*	Breathing difficulties	Diarrhea	Vomiting	Proteinuria	Overall response rate	χ^2	*P* value
TG	57	1 (1.75)	2 (3.51)	2 (3.51)	1 (1.75)	6 (10.52)	0.018	0.893
CG	35	1 (2.86)	1 (2.86)	1 (2.86)	1 (2.86)	4 (11.44)		

CG: Control group; TG: Treatment group.

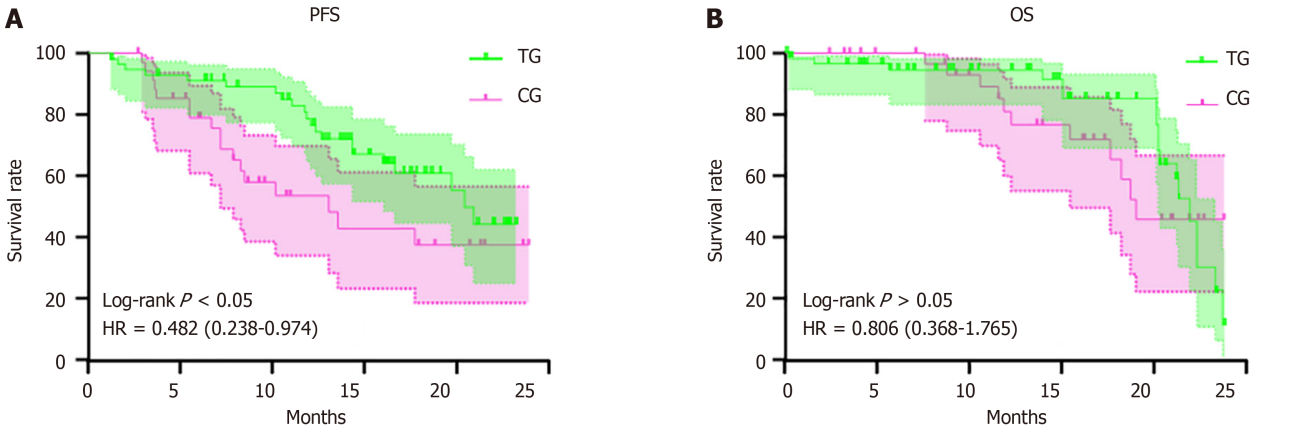

Figure 1 Survivorship curve. A: Progression-free survival; B: Overall survival. PFS: Progression-free survival; OS: Overall survival; TG: Treatment group; CG: Control group; HR: Hazard ratio.

DISCUSSION

This study retrospectively examined the clinical efficacy of MSRT + FJLD in the treatment of patients with NSCLC. Our results showed that MSRT + FJLD significantly prolonged median PFS ($P < 0.05$) and improved the KPS score of patients with NSCLC, indicating the potential long-term efficacy of MSRT + FJLD for these patients. Patients with NSCLC typically experience faster tumor progression and shorter survival times. However, the survival curve showed that the median OS of the TG was higher than that of the CG. Further studies with larger sample sizes should be conducted to validate these statistical results. Additionally, this study found that administering MSRT + FJLD in addition to CC in patients with NSCLC exhibited significant therapeutic efficacy, a significant decrease in TCM syndrome scores, and an improvement in immune function-related indicators ($CD3^+$, $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$).

MSRT is generally administered by specific professionals who guide mindfulness exercises for the target participants, including body scanning, mindfulness breathing, mindfulness meditation, mindfulness eating, mindfulness walking, and compassion meditation exercises. It focuses on the connection between cognitive categories, such as thinking, attention, emotions, and the body[12]. MSRT is a product of Eastern Zen thought and Western quantitative science. It is often used to address the recurrence of psychological diseases, such as depression, autism, and schizophrenia. MSRT is a psychological intervention that can influence an individual's psychological cognition, physical health, and social relationships.

FJLD is a type of TCM with advantages, such as reduced toxicity, increased efficiency, safe medication, and a low recurrence rate. It also delays tumor recurrence and metastasis, balances the proportion of immune cells, and regulates the immune system. The components of FJLD can enhance the body's immune function in the treatment of NSCLC, inhibit tumor cell growth, prolong patient survival time, and reduce the clinical treatment risk index[13]. For example, Pinellia has anti-inflammatory and anti-tumor effects; it may negatively impact the survival and proliferation of tumor cells by regulating related proteins in the phosphatidylinositol 3-kinase (PI3K)-protein kinase B (Akt) signaling pathway. The active ingredients in orange peel may inhibit the PI3K-Akt signaling pathway, reduce the invasion and metastasis of

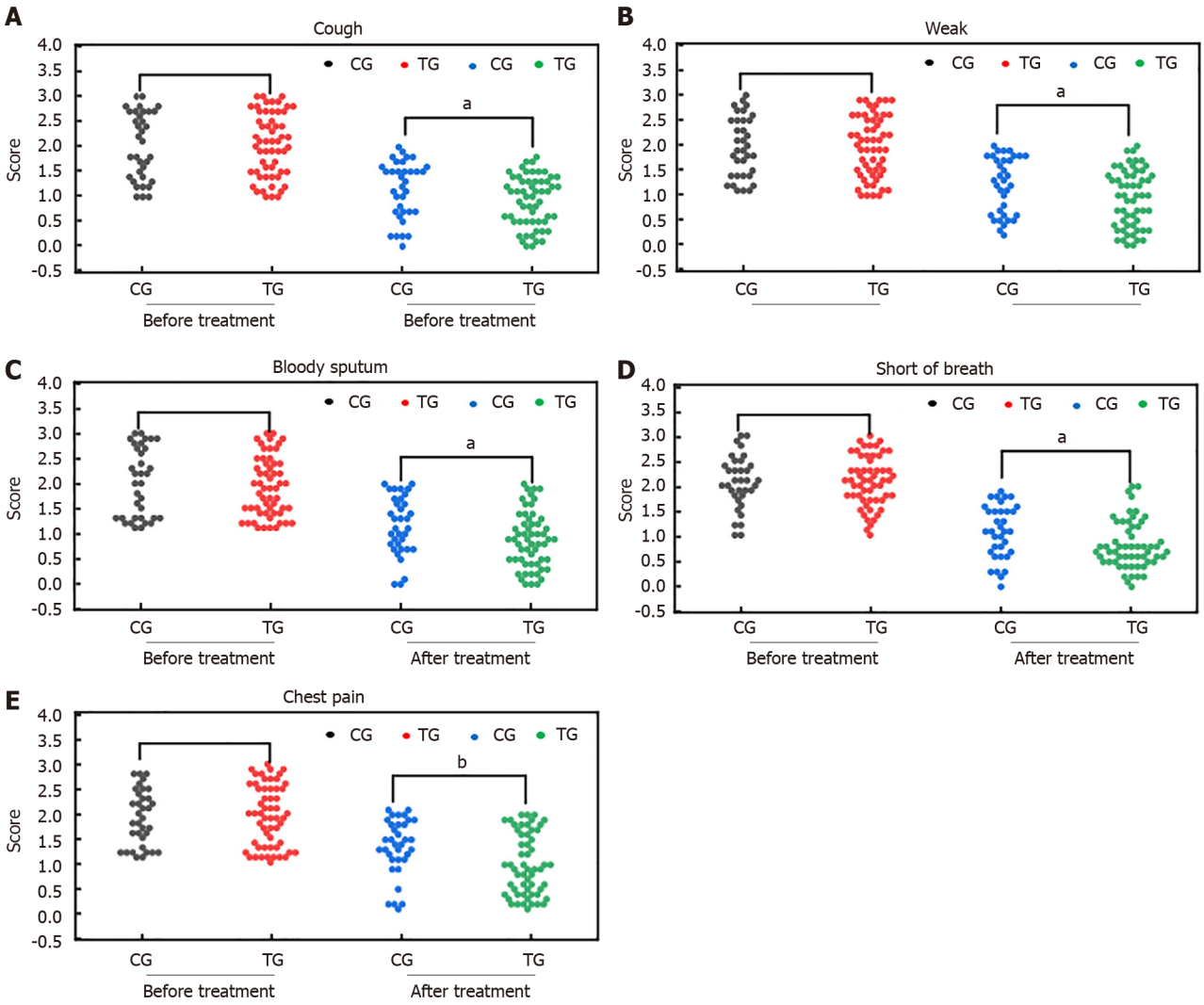

Figure 2 Traditional Chinese medicine syndrome scores of patients with non-small cell lung cancer before and after treatment. A: Cough; B: Weakness; C: Bloody sputum; D: Shortness of breath; E: Chest pain. $^{a}P < 0.05$; $^{b}P < 0.01$. CG: Control group; TG: Treatment group.

tumor cells, and improve the immune response of the body. Glycyrrhizic acid and other components in licorice may reduce the proliferation of tumor cells by inhibiting the PI3K-Akt signaling pathway and have anti-inflammatory and immunomodulatory effects. Poria polysaccharide from Poria poria may enhance the immune function of the body, increase the proportion of $CD3^+$ and $CD4^+$ cells, and reduce the number of $CD8^+$ cells by activating the Akt protein in the PI3K-Akt signaling pathway. Astragaloside and other components in milkvetch root may promote the activation of immune cells and augment the anti-tumor function of the body by activating the PI3K-Akt signaling pathway. $CD3^+$, $CD4^+$, and $CD8^+$ cells are surface markers of T cells. CD3 is part of the T-cell receptor complex, which participates in cell-mediated immune responses, helps B cells produce antibodies, directly kills cells infected by pathogens, and regulates immune responses to avoid autoimmune reactions[14]. $CD4^+$ T cells recognize antigens presented by major histocompatibility complex class II molecules and play a coordinating role in the immune response by activating other immune cells, such as B cells and macrophages, through the secretion of cytokines. $CD4^+$ T cells can further differentiate into different subsets, such as T helper type 1 (Th1), Th2, and Th17, each playing different roles in the immune response[15]. $CD8^+$ T cells, usually known as cytotoxic T cells or killer T cells, help regulate the immune response and prevent excessive attacks on the body[16]. Negative emotions, such as anxiety, depression, and stress, are believed to reduce survival and weaken immune system function. These emotional states may lead to excessive activation or inhibition of the immune system, thereby affecting the distribution and function of immune cells (*e.g.*, a decrease in $CD3^+$ and $CD4^+$ cells and an increase in $CD8^+$ cells).

Long-term psychological stress is associated with a decrease in the number and activity of immune cells[17]. A study by Chen *et al*[18] revealed that using TCM syndrome and long-term treatment with intravenous administration of TCM and oral Chinese patent medicine can prolong the survival time of patients with advanced NSCLC. Cheng *et al*[19] also reported that an increase in $CD3^+$ and $CD4^+$ levels and a decrease in $CD8^+$ levels help restore immune function, which is in accordance with the results of our study.

Chemotherapy drugs affect rapidly dividing healthy cells and cancer cells simultaneously, leading to pulmonary fibrosis, heart damage, tumor lysis syndrome, immune system disorders, and other symptoms. This can also increase psychological pressure on patients, causing anxiety, depression, and other emotional changes during chemotherapy,

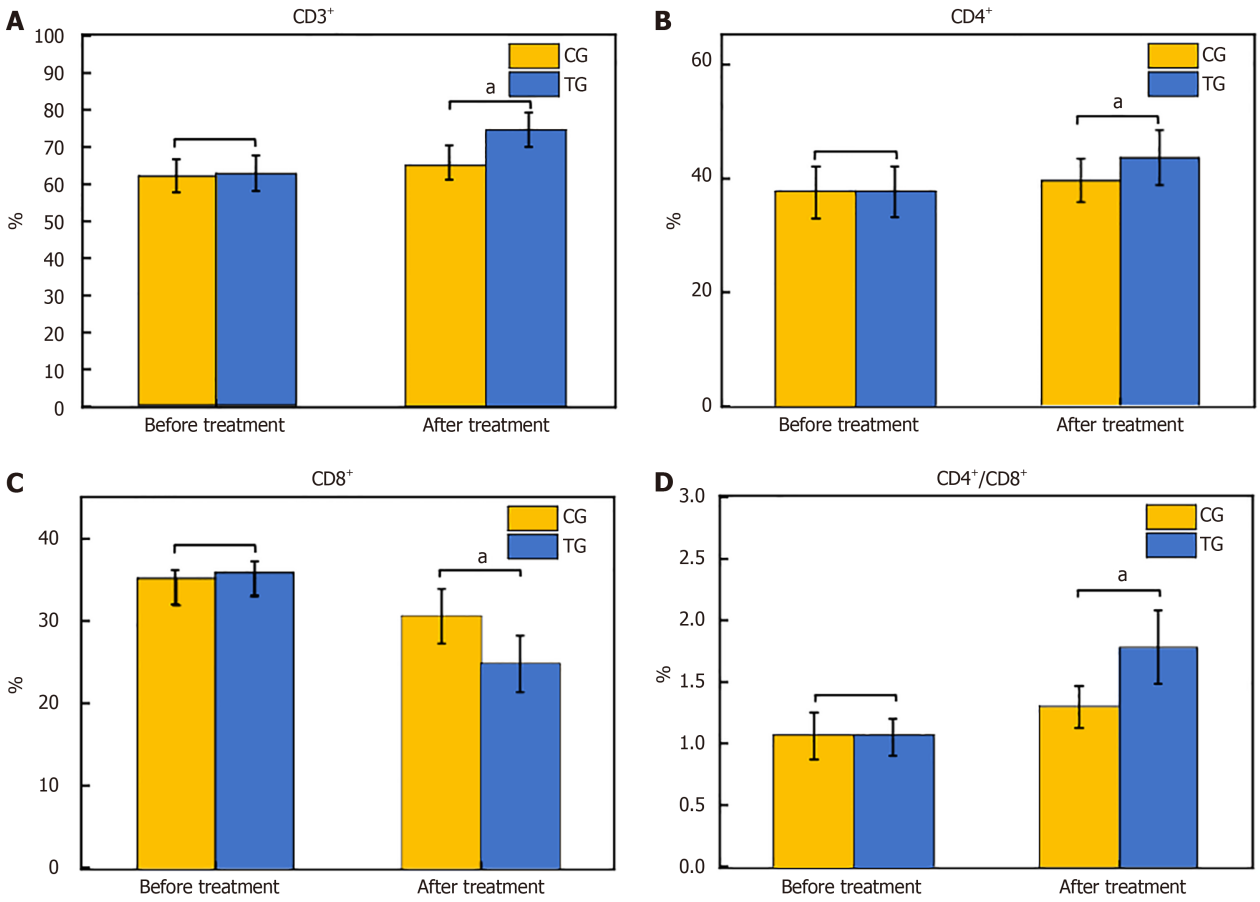

Figure 3 Changes in immune function indices in patients with non-small cell lung cancer before and after treatment. A: $CD3^+$; B: $CD4^+$; C: $CD8^+$; D: $CD4^+/CD8^+$. $^aP < 0.05$. TG: Treatment group; CG: Control group.

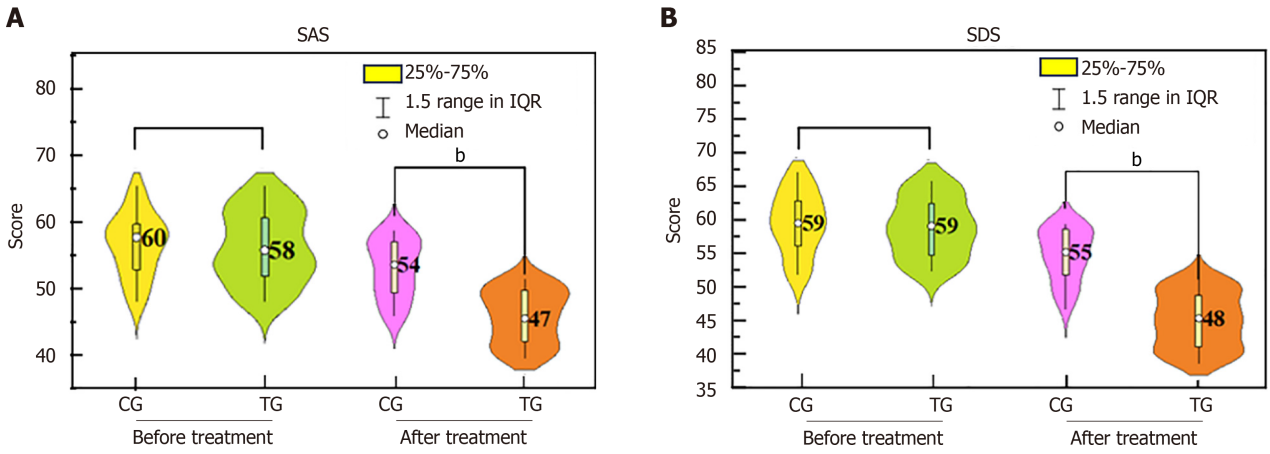

Figure 4 Negative emotion scores of patients with non-small cell lung cancer before and after treatment. A: Self-rating anxiety scale; B: Self-rating depression scale. $^bP < 0.01$. IQR: Interquartile range; CG: Control group; TG: Treatment group; SAS: Self-rating anxiety scale; SDS: Self-rating depression scale.

which require psychological support and appropriate intervention[20]. Our findings showed that the SAS and SDS scores of patients with NSCLC treated only with CC were higher than those in the TG, indicating a possibility of mild anxiety and mild depression. Compared with the CG, the SAS and SDS scores of the TG decreased after MSRT + FJLD treatment, indicating that MSRT + FJLD had a positive effect on improving the negative emotions of patients with NSCLC. McDonnell *et al*[21] used MSRT intervention therapy for patients with lung cancer and found that the SAS and SDS scores of the patients were better than those in the CG[21,22], which aligned with our study's results. MSRT + FJLD augments immune function and treatment efficacy in NSCLC patients through both psychological and physiological effects.

In summary, this study confirms that MSRT + FJLD has certain therapeutic effects on NSCLC; however, limitations such as the inability of the study design to control the experimental conditions, as in prospective studies, as well as the small sample size may limit the generalization and reliability of the results. Therefore, further studies with increased sample size and improved study design are warranted to obtain more reliable study results.

CONCLUSION

This retrospective clinical study found that MSRT + FJLD, in addition to CC, prolonged the survival time of patients with NSCLC, improved the KPS score, increased the number of $CD3^+$ and $CD4^+$ immune cells, effectively reduced the number of $CD8^+$ cells, and increased the $CD4^+$ and $CD8^+$ ratio, thereby restoring the immune function of patients. Additionally, it alleviated symptoms such as cough, weakness, bloody sputum, shortness of breath, and chest pain, and improved the patients' SAS and SDS scores. Therefore, this study suggests that MSRT + FJLD combined with CC is an effective treatment for patients with NSCLC.

FOOTNOTES

Author contributions: Liu DW and Zhou XA wrote the paper; Wu XY, Wang YX, and Fan JT performed data extraction; Li ZL supervised the paper; and all authors read and approved the final version.

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ORIGINAL ARTICLE

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Music therapy combined with motivational interviewing

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Abstract

BACKGROUND

Percutaneous coronary intervention (PCI) is one of the main treatment methods for myocardial infarction (MI). Despite its positive effects, patients often experience different degrees of anxiety and depression after the intervention. Therefore, effectively changing the emotional state of patients with MI during PCI remains a focus of clinical research.

AIM

To assess the effect of music therapy and motivational interviewing in young and middle-aged patients with anxiety and depression after PCI.

METHODS

We collected data from January 2022 to December 2023 from 86 young and middle-aged patients with MI after PCI. They were divided into observation and control groups according to the random throwing method. The observation group consisted of 43 patients undergoing music therapy and motivational interviewing, and the control group (43 cases) underwent music therapy and conventional communication. The two groups were then compared on mood status [Chinese Brief Mood Status Scale (POMS)], coping methods [Medical Coping Methods Questionnaire (MCMQ) Chinese version], and healthy lifestyle behaviors [Heart Health Self-Efficacy and Self-Management (HH-SESM) scale].

RESULTS

Two weeks post-intervention, the observation group had lower POMS scores, improved MCMQ scores, and higher HH-SESM scores than the control group ($P < 0.05$).

CONCLUSION

The combined intervention of music therapy and motivational interviewing for young and middle-aged patients with anxiety and depression after MI can effectively regulate their mood, reduce anxiety and depression symptoms, and stimulate patients to actively face their condition. It also encourages the formation

of healthy behavioral habits.

Key Words: Music therapy; Motivational interviewing; Young and middle-aged; Myocardial infarction; Percutaneous coronary intervention; Anxiety; Depression

Core Tip: Music therapy combined with motivational interviewing can stabilize mood states, reduce negative mood, and improve coping styles and healthy lifestyle behaviors. The intervention has the potential to achieve a sustained, stable, and effective impact, which is especially suitable for patients with anxiety and depression after percutaneous coronary intervention for myocardial infarction.

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INTRODUCTION

Myocardial infarction (MI) is a prevalent acute coronary syndrome, typically precipitated by coronary artery occlusion, leading to myocardial ischemia and necrosis[1]. When young or middle-age, individuals are often subjected to the dual demands of their careers and families, coinciding with a period of physiological senescence and functional decline[2]. Lifestyle factors, such as smoking and improper diet, together with various conditions, including being overweight or obese, further exacerbate the risk of MI. Percutaneous coronary intervention (PCI) is a widely acknowledged treatment of MI as it alleviates the symptoms of myocardial ischemia and hypoxia by directly targeting stenotic or occluded coronary arteries[3-5].

However, research has demonstrated a significant association of post-PCI anxiety and depression with patient prognosis, with negative emotional states potentially undermining the efficacy of PCI and impeding the postoperative recovery process[6]. Thus, examining effective psychological interventions is crucial for enhancing post-PCI rehabilitation. Music therapy, an emerging psychological intervention, stimulates patients' physiological potential and modulates their emotional states through the frequency, rhythm, and acoustic vibrations of music[7,8]. Moreover, motivational interviewing employs unique interviewing principles and communication skills to evoke patients' internal motivation and foster corresponding changes in their external behaviors[9].

Currently, there is a paucity of clinical research on the combined application of music therapy and motivational interviewing in young and middle-aged patients with anxiety and depression following MI[10]. This study aimed to analyze the effects of the combined application of these two interventional measures and provide additional evidence-based support for clinical practice. We examined the efficacy of the joint intervention of music therapy and motivational interviewing in improving the psychological state of patients post-MI. Accordingly, we propose recommendations for further research and clinical applications.

MATERIALS AND METHODS

General information

Between January 2022 to December 2, 2023, we selected 86 young and middle-aged patients with anxiety and depression after patient medication instruction treatment in our hospital as study participants. They were then grouped according to the random throwing method. The control group (n = 43), consisted of 41 male patients and 2 female patients, with their age distribution between 35 and 55 years, mean age of (45.08 ± 3.32) years, and time from onset to admission between 2 and 8 hours (mean = 5.06 ± 1.04 hours). In this group, the 14-item Hamilton Anxiety Scale (HAMA) scores were between 14 and 25 (mean of 19.28 ± 1.82 points), and the 24-item Hamilton Depression Scale (HAMD) scores were between 20 and 31 (mean of 25.87 ± 1.80 points). The Killip Cardiac function was classified as grade I in 14 patients and grade II in 29 patients. A total of 15 participants in the control group had a high school education or lower, and 28 patients had higher qualifications. The observation group (n = 43) included 39 male and 4 female patients, with their age distribution between 35 and 55 years, mean age of (45.17 ± 3.35) years, and time from onset to admission between 2 and 8 hours (mean = 5.11 ± 1.03 hours). In this group, the 14 HAMA scores ranged between 14 and 23 (mean = 18.93 ± 1.57 points), and the 24 HAMD scores were between 20 and 33 (mean = 26.54 ± 2.22 points). The Killip Cardiac function was classified as grade I in 16 patients and grade II in 27 patients. A total of 18 patients in this group had a high school education or lower, and 25 had higher education. There were no statistically significant differences between the baseline data of the two patient groups, and the results were comparable (P > 0.05).

The inclusion criteria were as follows: (1) Meet the determination criteria for MI, combined with electrocardiogram examination and coronary angiography[4]; (2) The first PCI treatment without treatment contraindications; (3) PCI combined with anxiety, depression, or any mood; (4) Clear awareness and no cognitive, audiovisual, or speech impairment; and (5) Voluntary participation after providing a written agreement.

The exclusion criteria were as follows: (1) Having organic lesions in vital organs other than the heart; (2) Having other types of cardiac disease, malignant tumors, and so on; (3) Having a mental illness or a history of mental illness; (4) Has taken antidepressants, antipsychotics, or other such medicines; and (5) Withdrawal from the study or participation in other studies.

Methods

All patients in the two groups underwent music therapy. A psychological evaluation was first conducted to select music tracks corresponding to the patients' emotional state. Subsequently, they were allowed to assume a comfortable position and adjust the volume to 50-60 dB while keeping the surrounding environment quiet; the duration was controlled at approximately 30 minutes once at noon and night each. Using a music player to play the soothing tracks chosen by the patients, such as natural white noise and light music, we verbally guided the patients through breathing exercises, allowing them to relax. For patients with emotions such as fear, we played music such as "High Moon" and "Spring River Flower Moon Night". For patients experiencing anger, we chose "General Order", "The Yellow River", or something similar. For patients with depression, "Blue Danube" or "Jiangnan Good" was played. Patients experiencing pessimism listened to music such as "Backgam" and "Happy Goat". For patients with emotions such as anxiety, we played "Butterfly Lovers", "Two Springs Reflect the Moon", or something similar. This intervention lasted for two weeks.

The control group received routine communication. According to the relevant contents of the Postoperative Health Education Manual for PCI after MI, the diet, exercise, medication, and other precautions for PCI were thoroughly explained to the patients. The patients' and their families' questions were patiently answered.

The observation group underwent the following motivational interviewing stages: (1) Pre-intention stage: To evaluate the knowledge level of patients with MI after PCI treatment and the status of their healthy life-related behaviors, they were reminded of and/or warned about the harm of healthy lifestyle behaviors; (2) Intention stage: In addition to the Health Education Manual, other resources such as videos, graphic data, and presentations informed the patients with MI about the precautions and self-management methods of PCI. Consequently, clinical data and successful cases were combined to guide the participants to express their genuine thoughts and concerns and understand the causes of anxiety and depression after PCI. This also taught them the skills of self-motivation and seeking support from family and friends; (3) Preparation stage: According to the patient's actual condition, PCI recovery, and emotional state, the phased PCI rehabilitation plan and feasibility goals taught patients to record life diaries and specified guidelines for medical compliance, a healthy diet, regular exercise, emotional management, regular physical monitoring, smoking cessation, and other behaviors; (4) Action stage: This involved identifying the existing or potential risk factors affecting PCI rehabilitation and establishing a hospital-family dual supervision system to supervise the changes in behaviors related to a healthy life. Moreover, patients were actively informed to avoid smoking and a diet high in salt or sugar and to manage their mood swings. They were offered positive verbal encouragement for their external behavior efforts to relieve anxiety and depression; and (5) Maintenance stage: This included summarizing the entire postoperative rehabilitation plan of periodic PCI. This stage involved affirming the changes made by the patient, pointing out their shortcomings while providing targeted suggestions, repeatedly emphasizing the importance and necessity of maintaining healthy lifestyle behaviors, and using positive and negative examples for further education.

Observing indicators

We observed the following three key indicators in our study: (1) Mood state: The Chinese Brief Mood Status Scale (POMS)[5] was used, which contains 40 items across 7 categories-tension (6 items, 0-24 points), anger (7 items, 0-28 points), fatigue (5 items, 0-20 points), depression (6 items, 0-24 points), energy (6 items, 0-24 points), panic (5 items, 0-20 points), and mood (5 items, 0-20 points). Higher scores indicate worse patient mood. The evaluation was conducted before and two weeks after the intervention; (2) Coping methods: The Chinese version of the Medical Coping Methods Questionnaire (MCMQ)[6] was used. It yields 3 subscales (face, avoid, and surrender) and 20 items, with 8, 7, and 5 items for each subscale. Items are scored from 0 to 3, with the patient's coping being positively correlated with the score. The evaluation time nodes were before and two weeks after the intervention; (3) Healthy lifestyle behaviors: The Heart Health Self-Efficacy and Self-Management (HH-SESM) scale[7] was used. It consists of 12 items across 6 dimensions-activities (2 items), diet (4 items), medication (2 items), social mentality (2 items), body mass index (BMI) management (1 item), and smoking (1 item). Each item is rated between 1 and 4 points, with higher scores indicating a better and healthier lifestyle of the patient. The evaluation time nodes were pre-intervention and two weeks post-intervention.

Statistical analysis

All data in this study were analyzed using the SPSS 27.0 software and applied to perform the measurement data as (mean ± SD). All data conform to the normal distribution. By employing a self-sample *t*-test and *t*-test, computing the data with percentage (%), and using a χ^2 test, the results would be statistically significant at $P < 0.05$.

RESULTS

Comparison of mood state between the two groups

This study evaluated emotional changes in 43 participants in both the control and observation groups before and after the intervention. Four dimensions were covered—nervousness, anger, fatigue, and depression. The results showed that the observation group's scores on all emotional dimensions significantly decreased after the intervention ($P < 0.05$), whereas the control group exhibited less significant improvements. There was no significant difference in emotional changes between the two groups ($P > 0.05$), indicating that the intervention had a similar positive effect on both groups. These findings provide important evidence for further research on the effectiveness of emotion interventions (Table 1).

Comparison of coping methods between the two groups

We analyzed the energy levels, confusion, and self-related discomfort of all participants before and after the intervention. The observation group showed a significant increase in energy and self-related discomfort ($P < 0.05$) and a significant decrease in confusion after the intervention. The control group also demonstrated a trend toward increased energy and decreased confusion; however, the improvement was not as significant as in the observation group. There were no statistically significant differences in the changes between the two groups, indicating that the intervention had a positive effect on participants in both groups (Table 2).

Comparison of healthy lifestyle behaviors between the two groups

This study further compared the activity levels, dietary habits, medication use, social mentality, BMI management, and smoking behavior of the two groups before and after the intervention. The results indicated significant improvements in activity levels, dietary habits, and medication use in both groups after the intervention ($P < 0.05$), with the observation group showing more notable progress. Additionally, positive changes were observed in social mentality, BMI management, and smoking behavior particularly in the observation group, which showed significant improvements in social mentality and BMI management ($P < 0.05$). These findings suggest that the comprehensive intervention measures effectively promoted improvements in the lifestyle habits and psychological states of the participants (Table 3).

DISCUSSION

This study was conducted to assess the efficacy of an intervention program on the emotional well-being, coping methods, and healthy lifestyle behaviors of young and middle-aged individuals following MI. The findings of this study provide valuable insights into the impact of the intervention on the participants' emotional and behavioral health.

Our analysis revealed significant reductions in nervousness, anger, fatigue, and depression in the observation group following the intervention, with much more pronounced improvements than in the control group[11]. These results are consistent with those of previous studies that have reported positive effects of psychological interventions on emotional health after acute cardiac events[12]. The non-inferiority of the control group's emotional improvement suggests that the intervention may have largely had a positive impact, potentially through the Hawthorne effect or other nonspecific treatment factors[13].

The observation group exhibited a significant increase in energy levels and decrease in confusion post-intervention, indicating an enhanced capacity to cope with psychological demands following a cardiac event. This is particularly important as effective coping strategies are crucial for long-term psychological adjustment and quality of life[14]. The control group also demonstrated improvements, albeit to a lesser extent, suggesting that the intervention may have had a generalized positive effect on participants' coping methods[15].

The intervention led to significant improvements in activity levels, dietary habits, and medication adherence in both groups but with greater improvements in the observation group. These findings are consistent with a growing body of evidence supporting the role of lifestyle modifications in cardiac rehabilitation[16]. The significant improvements in social mentality and BMI management in the observation group underscore the potential of the intervention to foster comprehensive lifestyle changes, which extend beyond individual behaviors to include social and self-management aspects.

The findings of this study highlight the potential benefits of a multifaceted intervention in improving emotional and behavioral outcomes post-MI. The progress observed in the observation group suggests that targeted interventions may be effective in promoting long-term behavioral changes and emotional well-being. Future research should explore the specific components of interventions that contribute to these improvements and investigate the long-term sustainability of these effects.

CONCLUSION

In conclusion, the intervention program assessed in this study has demonstrated a clear positive influence on emotional states, coping methods, and healthy lifestyle behaviors among individuals post-MI. These results encourage further investigations into the mechanisms underlying these improvements and the development of tailored intervention strategies to enhance patients' cardiac recovery and quality of life.

Table 1 Comparison of mood status between the two groups (mean ± SD, score)

Group	*n*	Nervous		Anger		Tired		Depression		Energy		Confusion		Eds related to the self	
		Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Control	43	17.18 ± 2.42	13.83 ± 2.31[a]	9.29 ± 1.30	6.95 ± 1.28[a]	12.57 ± 2.41	8.65 ± 2.24[a]	15.08 ± 2.36	12.12 ± 2.23[a]	12.52 ± 2.47	10.21 ± 2.38[a]	11.36 ± 2.28	9.05 ± 2.12[a]	13.79 ± 2.54	10.25 ± 2.43[a]
Observation	43	17.25 ± 2.36	12.47 ± 2.23[a]	9.16 ± 1.27	6.24 ± 1.12[a]	12.49 ± 2.38	7.23 ± 2.15[a]	15.16 ± 2.21	10.84 ± 2.16[a]	12.39 ± 2.50	8.82 ± 2.26[a]	11.43 ± 2.31	7.79 ± 2.06[a]	13.63 ± 2.49	8.78 ± 2.32[a]
t value		0.136	2.778	0.469	2.737	0.155	2.999	0.162	2.704	0.243	2.777	0.141	2.795	0.295	2.869
P value		0.892	0.007	0.64	0.008	0.877	0.004	0.871	0.008	0.809	0.007	0.888	0.006	0.769	0.005

[a]*P* < 0.05 compared with the specific values in the same group.

Table 2 Comparison of coping methods between the two groups (mean ± SD, score)

Group	*n*	Face		Avoid		Surrender	
		Before	After	Before	After	Before	After
Control	43	12.69 ± 2.25	16.74 ± 2.39[a]	15.42 ± 2.31	11.59 ± 2.24[a]	10.09 ± 2.27	7.93 ± 2.14[a]
Observation	43	12.58 ± 2.17	18.12 ± 2.46[a]	15.53 ± 2.47	10.35 ± 2.16[a]	10.18 ± 2.30	6.72 ± 2.05[a]
t value		0.231	2.638	0.213	2.613	0.183	2.677
P value		0.818	0.010	0.832	0.011	0.856	0.009

[a]*P* < 0.05 compared with the same group before the intervention.

Table 3 Comparison of healthy lifestyle behaviors between the two groups (mean ± SD, score)

Group	*n*	Activity		Diet		Medication use		Social mentality		BMI management		Smoking	
		Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Control	43	3.18 ± 0.26	6.19 ± 0.54[a]	8.29 ± 1.15	12.35 ± 1.28[a]	3.07 ± 0.32	6.05 ± 0.41[a]	3.29 ± 0.47	6.34 ± 0.52[a]	2.13 ± 0.21	2.89 ± 0.38[a]	2.09 ± 0.18	2.89 ± 0.23[a]
Observation	43	3.25 ± 0.30	6.57 ± 0.63[a]	8.16 ± 1.27	13.24 ± 1.40[a]	3.14 ± 0.26	6.38 ± 0.54[a]	3.33 ± 0.54	6.73 ± 0.61[a]	2.08 ± 0.19	3.12 ± 0.43[a]	2.12 ± 0.09	3.06 ± 0.35[a]
t value		1.156	3.003	0.498	3.077	1.113	3.192	0.366	3.191	1.158	2.628	0.978	2.662
P value		0.251	0.004	0.62	0.003	0.269	0.002	0.715	0.002	0.25	0.01	0.331	0.009

[a]*P* < 0.05 compared with specific values before the intervention in the same group.
BMI: Body mass index.

FOOTNOTES

Author contributions: Meng DF designed the study; Meng DF, Bao J, Cai TZ, Ji YJ, and Yang Y analyzed the data; Meng DF was involved in collecting the data and writing this article; all authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Clinical Trials Study

Effects of remote support courses on parental mental health and child development in autism: A randomized controlled trial

Jia-Hui Lu, Hua Wei, Yu Zhang, Fan Fei, Hai-Yan Huang, Qiu-Jun Dong, Jing Chen, Dong-Qin Ao, Li Chen, Ting-Yu Li, Yan Li, Ying Dai

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Abstract

BACKGROUND

Sustaining the mental health of autistic children's parents can be demanding.

AIM

To determine the effect of remote support courses on the mental health of parents and the development of autistic children.

METHODS

Parents of 140 autistic children were randomly assigned to two groups receiving a 2-week intervention: The control group received caregiver-mediated intervention (CMI); the experimental group received CMI with remote family psychological support courses (R-FPSC). The Parenting Stress Index-Short Form, Parenting Sense of Competence Scale, Generalized Anxiety Disorder-7, and Patient Health Questionnaire-9 were used to measure parents' mental health. The Childhood Autism Rating Scale and Gesell Developmental Schedules were used to evaluate children's development.

RESULTS

Improved parenting stress, sense of competence, depression, and anxiety were found in both groups, but improvements in parenting stress (81.10 ± 19.76 *vs* 92.10

± 19.26, $P < 0.01$) and sense of competence (68.83 ± 11.23 *vs* 63.91 ± 10.86, $P < 0.01$) were greater in the experimental group, although the experimental group showed no significant reduction in depression or anxiety. Children's development did not differ significantly between the groups at follow-up; however, experimental group parents exhibited a short-term increase in training enthusiasm (12.78 ± 3.16 *vs* 11.57 ± 3.15, $P < 0.05$).

CONCLUSION

Integrating R-FPSC with CMI may be effective in reducing parenting stress, enhancing parents' sense of competence, and increasing parents' training enthusiasm.

Key Words: Autism spectrum disorder; Parenting stress; Parenting sense of competence; Caregiver-mediated intervention; Family psychological intervention

Core Tip: This study emphasizes the crucial impact of parental mental health on therapeutic interventions for children with autism spectrum disorder (ASD). Integrating remote family psychological support courses with traditional caregiver-mediated interventions (CMI) enhances parental competence and reduces stress more effectively than CMI alone. Employing a robust, single-blinded randomized controlled trial design, the findings demonstrate that remote interventions effectively support parental mental health, essential for managing ASD care. The research suggests mental health professionals incorporate remote psychological support into family interventions to expand access to crucial resources and potentially improve outcomes for both children and parents. Further research is needed to explore the long-term effects of such interventions and their direct impact on ASD symptoms in children, advocating for holistic, family-centered care models in psychiatry.

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INTRODUCTION

Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders characterized by difficulties in social interaction and verbal and nonverbal communication, as well as narrow interests, and repetitive behaviors. Long-term therapeutic training and special education are the main treatments for ASD[1]. An increasing amount of attention has been paid to family-oriented intervention models[2].

The literature shows that caregivers of children on the autism spectrum often experience more severe mental health issues than caregivers of children with other disabilities or those of typically developing children[3,4]. Some parents continuously worry about their child's prognosis. Due to the particularity of the child's performance and limited communication[5-7], parents will face numerous challenges in caring for their child[8], coupled with the added financial strain of long-term treatment[9]. These difficulties contribute to heightened levels of fatigue, anxiety, and depression, resulting in a decline in the parents' overall health and quality of life. Moreover, negative emotions can have a direct impact on the parent's ideas, attitudes, and methods related to parenting, ultimately having an indirect effect on their child's rehabilitation training[10]. The effects of these challenges indicates that interventions designed only for children diagnosed with ASD might not be sufficient[11]. As the primary implementers of the family intervention model, parents must be able to prioritize their physical and mental health, maintain a positive attitude[12], and believe in the positive effect of therapeutic training on their child's symptoms, which is crucial for the child's progress and the functional well-being of the entire family[13]. However, very few of the interventions include specific attention to the psychological health of caregivers. For the optimal development of children on the autism spectrum, it is imperative to adopt more holistic approaches that include interventions for both children and parents. Therefore, the integration of family psychological support with the existing family intervention model is required because it has significant implications for families with autistic children and for society. The current pilot study aimed to examine the efficacy of remote family psychological support courses for improving the mental health of parents and improving the therapeutic outcomes of children on the autism spectrum.

MATERIALS AND METHODS

Design

The present study used a single-blinded randomized controlled trial design.

Participants

From February to June 2023, parents of children on the autism spectrum, who were scheduled to participate in a caregiver-mediated intervention (CMI) program were recruited *via* convenience sampling, from the Department of Child Health Care, Children's Hospital of Chongqing Medical University in Chongqing City, China.

The inclusion criteria for the prospective participants were as follows: (1) The children met the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition diagnostic criteria for ASD; (2) The children were 24 to 72 months old; (3) The children were newly diagnosed with ASD and did not receive any prior training; (4) The parents were able to understand and complete questionnaires independently; and (5) The parents volunteered to participate in the study and signed an informed consent form.

The exclusion criteria consisted of the following characteristics: (1) Parent with a serious physical or mental illness; (2) A child diagnosed with cerebral palsy, epilepsy, hearing impairment, genetic metabolic disease, or other serious disease; (3) Had other children in the family with a serious or chronic disease; (4) Had a parent and child dyad who withdrew from the study; or (5) Parents who had received any other psychological treatment within the past six months.

Sample size calculation

In this study, the total score of the parenting stress index-short form (PSI-SF) was used as the main evaluation index, and the formula[14] was used to calculate the sample size, which was suitable for the calculation of sample size in randomized controlled trials. N_1 and N_2 are the sample sizes of the experimental group and the control group, respectively. In our pre-test, the standard deviation was approximately 7.75, the difference between the mean numbers of the two samples was approximately 5.13, was 0.05, was 0.10; yielding a sample size of $N_1 = N_2 = 48$. Considering a loss rate of 30%, the overall sample size needed for both groups was at least 138. A total of 140 parents of children on the autism spectrum who agreed to participate in the study were included in the analysis.

Randomization and allocation concealment

The 140 participants were randomly divided into two groups using random numbers generated by SPSS software (V26, IBM Corporation, Armonk, NY, United States). The seed number was 20211207. Participants were assigned random numbers in the order in which they were enrolled in the study. Participants with odd random numbers were assigned to the control group, and those with even random numbers were assigned to the experimental group. A total of 71 participants were included in the experimental group, and 69 participants were included in the control group. The resulting random assignments were placed in sequential order, coded, sealed, and stored in opaque envelopes for safekeeping by a third party who was blinded to the trial. After the investigator determined the eligibility of the participants, the third party opened the envelopes in order and assigned the participants to the appropriate groups.

Intervention

The individuals in the control group participated in the CMI project[15], which was a family-oriented intervention model for autistic children and parents who had not previously received professional training, but did not participate in any family psychological support courses. There were two specific content areas of the CMI. First, theory teaching videos explaining CMI theory, with each video lasting approximately 20 minutes, were sent to one parent once a day through the WeChat online platform from Monday to Friday for two weeks; these videos included: (1) Training strategies for interventions; (2) Helping your child learn how to participate in a game; (3) Understanding and promoting communication; (4) Providing auxiliary skills; (5) Providing challenging behavior and coping strategies; (6) Training methods for cognitive development; (7) Training methods for fine motor skills; (8) Training methods for gross motor skills; (9) Training methods for social contact; and (10) Training methods for language comprehension and expression. Second, practical operation lessons consisted of a practical demonstration of the CMI to the parent and child and were conducted from Monday to Friday in the treatment room (90 minutes a day for two weeks); these lessons included: (1) Guidance from the theoretical courses, in which the parents learned how to help their children establish a learning routine and how to correct challenging behavior; (2) The integration of language, cognition, and movement training with children's play and life activities; (3) The improvement of parents' skills and confidence levels during family interventions; and (4) The help of children learn new skills. The practitioners were professional therapists who had undergone uniform training, were qualified to practice, and had a minimum of five years of work experience.

The experimental group participated in remote family psychological support courses (R-FPSC) in addition to the CMI. Researchers, psychologists, and psychotherapists produced and revised the R-FPSC, which was rooted in mindfulness-based cognitive therapy[16], acceptance and commitment therapy (ACT)[17], Bowen's family systems therapy[18], and Minuchin's structured family therapy[19]. As a combination of cognitive therapy and mindfulness-based stress reduction therapy, mindfulness-based cognitive therapy was to manage the recurrence of long-term depression. Rayan and Ahmad [20] demonstrated that the implementation of mindfulness-based interventions could alleviate psychological distress among Arab parents of children on the autism spectrum. The main premise of ACT is about accepting what one cannot control and making a commitment to take action to improve one's quality of life. A study by Marino[21] used ACT for parents of children on the autism spectrum and showed that ACT could improve parents' psychological flexibility, awareness states, personal values in everyday life, and parenting stress. Family systems therapy is guided by systems

theory, cybernetics, information theory, and the radical constructivism epistemology. The main principle of structured family therapy is to rebuild the family structure and seek to change the patterns of the family's interactions that sustain family problems or symptoms. Previous studies have confirmed the effectiveness of family therapy for treating ASD[22]. The R-FPSC included the following steps: (1) Recognize ASD; (2) Recognize common emotional and psychological changes in parents; (3) Accept emotions and respond kindly; (4) Improve time management; (5) Engage in career planning; (6) Establish a system for child assistance; (7) Promote ourselves; (8) Care for yourself and be kind to yourself; (9) Establish a good parent–child relationship; and (10) Practice the saying "right here, right now". The specific procedure entailed delivering one session of the R-FPSC to parents *via* the WeChat online platform daily, with a reading duration of approximately 15 minutes, Monday through Friday, over a two-week period.

The professional therapist supervised parents to ensure daily viewing of the CMI theory teaching videos and the R-FPSC content.

Primary outcome

PSI-SF: The PSI-SF[23], a 36-item self-report questionnaire with a 5-point Likert scale that is designed to measure impressions and difficulties related to the role of parents. The PSI-SF consists of three subscales: The parenting distress (PD), parent-child dysfunctional interaction (PCDI), and difficult child (DC) subscales. The total score ranges from 36 to 180 points, with higher scores indicating higher levels of parenting stress and scores higher than 90 representing a positive threshold. This scale has high reliability and validity. An examination of the internal consistency of the PSI-SF revealed that = 0.91 for the PD subscale, = 0.85 for the PCDI subscale, and = 0.82 for the DC subscale[24].

Secondary outcomes

Parenting sense of competence scale: The parenting sense of competence (PSOC) is a questionnaire consisting of 17 items [25], which are divided into two subscales: Efficacy and satisfaction. Each item is rated on a 6-point scale (1 to 6 points), ranging from strongly agree to strongly disagree. The efficacy subscale, reflecting feelings of familiarity, competence, and problem-solving capability in the parenting role, contains 8 items, with a total possible score of 8 to 48. The Satisfaction subscale, which reflects feelings of anxiety, frustration, and motivation in the parenting role, contains 9 items, with a total possible score ranging from 9 to 54. Studies have shown the internal consistency of the PSOC to be acceptable: = 0.79-0.85 for the total score, = 0.75-0.80 for the Satisfaction subscale, and = 0.80-0.88 for the Efficacy subscale[26,27].

Generalized anxiety disorder-7: The generalized anxiety disorder-7 (GAD-7) includes 7 items in total and uses a 4-point scale (0 to 3 points)[28]. The total possible score ranges from 0 to 21. A score of 0 to 4 indicates no anxiety or no clinical significance, 5-9 indicates mild anxiety, 10-14 indicates moderate anxiety, and ≥ 15 is classified as severe anxiety. The GAD-7 has been found to be a valid and efficient tool in research on the Chinese population[29].

Patient health questionnaire-9: The patient health questionnaire-9 (PHQ-9) consists of 9 items scored on a 4-point scale (1 to 6 points). The total score ranges from 0 to 27. A total possible score of 0 to 5 indicates no depression or no clinical significance; 6-9 indicates mild depression, 10-14 indicates moderate depression, 15-21 indicates moderate depression, and ≥ 22 indicates severe depression. The Chinese version of the PHQ-9 has been developed and validated[30].

Childhood autism rating scale: The childhood autism rating scale (CARS), which was compiled by Schopler *et al*[31], was designed to diagnose ASD and evaluate the core symptoms of children. Using 15 items that are scored on a 4-point scale, the CARS is suitable for children older than 2 years. A score < 30 indicates no autism, 30-36 indicates mild to moderate autism, and a score of 37-60 with at least five items higher than 3 indicates severe autism.

Gesell developmental schedules: The Gesell developmental schedules (GDS) assess adaptive behavior, gross motor skills, fine motor skills, language, and personal-social behavior dimensions and are used to evaluate the development capability of children from 0 to 6 years of age[32]. The results of the evaluations are presented in the form of a developmental quotient (DQ). A score of 55-75 is classified as a mildly abnormal DQ, 40-55 is classified as a moderately abnormal DQ, 25-39 is classified as a severely abnormal DQ, and < 25 is classified as an extremely abnormal DQ.

Data collection procedure

The evaluator, who was blinded to the study allocation and had received professional training in psychological assessments of parents and children, provided instructions to the parents regarding the completion of the questionnaires and assessed the children in the hospital's treatment room. The demographic information of the participants was recorded before the intervention, while the duration of children's engagement in therapeutic training was documented following the intervention. Data were collected to assess parents' levels of mental health before and after the intervention. Three months after the intervention, the CARS and GDS scores were analyzed to evaluate the progress of the children.

Statistical analysis

This study used SPSS software (V26, IBM Corporation, Armonk, NY, United States) for the data analysis. Independent 2-sample t tests, χ^2 tests, and Mann-Whitney U tests were used to analyze the information of the participants. Independent 2-sample t-tests were used to compare differences between the two study groups on each scale before and after the intervention. Paired-sample t tests were used to compare differences within the control group as well as between the experiment group before and after the intervention. A P value < 0.05 indicated a statistically significant difference. The explanation of statistical symbols: Lowercase letter n for sample number; italicized uppercase letter P for probability; italicized uppercase letter P for probability, and mean ± SD is expressed as mean ± SD.

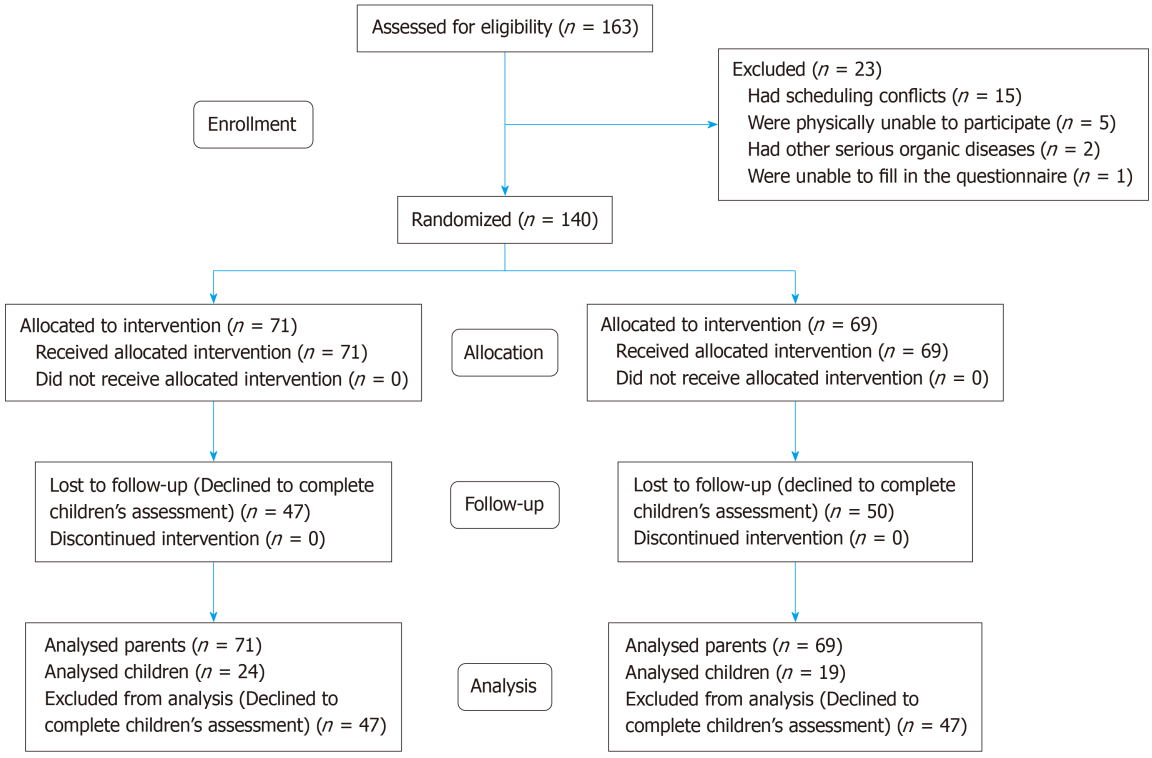

Figure 1 Flowchart of the study.

RESULTS

Participant enrollment

A total of 163 child-parent dyads were recruited to participate in the study. Of these, 14.1% (n = 23) were ineligible for participation. Subsequently, 140 dyads were enrolled in the study and randomized into two groups. All of the parents completed the post-assessment; 71 and 69 of them were in the intervention group and control group, respectively. However, only 43 children completed the follow-up assessment after three months; 24 were in the intervention group, and 19 were in the control group (see Figure 1).

Demographic characteristics of the two groups

The demographic and clinical characteristics of the participants in this study are reported in Table 1. No significant differences in participants' demographic or clinical variables were found between the two groups at baseline (all P > 0.05).

Primary outcomes

Comparisons of parenting stress between the two groups of parents: Table 2 shows no significant differences between the two groups in the total score or in the three subscale scores on the PSI-SF prior to the intervention (all P > 0.05). The total PSI-SF scores of both groups were greater than 90, indicating clinically elevated levels of stress. After the intervention, we observed a greater reduction in parenting stress in the experimental group than in the control group (all P < 0.05). The parenting stress of both groups decreased significantly compared with the parenting stress observed before the intervention (all P < 0.05), but a high stress level persisted among the parents in the control group (= 92.10). This finding implies that CMI had a partial effect on the reduction in parental stress among parents of children on the autism spectrum. Thus, adding R-FPSC to CMI interventions may significantly reduce parenting stress.

Secondary outcome

Comparison of parents' sense of competence in the evaluation between the two groups: No significant differences were found in the PSOC scale score between the two groups before the intervention (Table 3). After the intervention, parents in the experimental group had greater parenting efficacy and greater satisfaction than did those in the control group (all P < 0.05). In comparison to the pre-experimental results, both groups of parents experienced a significant increase in parenting efficacy and satisfaction after the intervention (all P < 0.05). These findings suggest that CMI can enhance the sense of competence among parents of children with ASD. However, the inclusion of the R-FPSC was more effective at improving parents' sense of competence and subsequently increasing their happiness as parents.

Comparisons of the anxiety and depression of parents between the two groups: The initial assessments of the parents' anxiety and depression revealed no significant differences between the experimental and control groups (Table 4).

Table 1 Comparisons of the demographic characteristics between the two groups at baseline, *n* (%)/mean ± SD

Variable	Experimental group (*n* = 71)	Control group (*n* = 69)	$\chi^2/t/Z$	*P* value
Children's gender				
Boy	57 (80.28)	58 (84.06)	[1]0.340	0.560
Girl	14 (19.72)	11 (15.94)		
Children's age in months	33.66 ± 8.60	32.83 ± 8.35	[2]-0.583	0.561
Parents				
Father	15 (21.13)	17 (24.64)	[1]0.245	0.621
Mother	56 (78.87)	52 (75.36)		
Parents' age in years	32.41 ± 4.41	32.86 ± 4.26	[2]0.609	0.544
Educational level				
Senior high school or below	18 (25.35)	23 (33.33)	[3]-0.795	0.427
College or undergraduate	50 (70.42)	42 (60.87)		
Postgraduate or above	3 (4.23)	4 (5.80)		
Occupation				
Employed	61 (85.92)	54 (78.26)	[1]1.398	0.237
Unemployed	10 (14.08)	15 (21.74)		
Average annual household income in RMB				
≤ 50000	13 (18.31)	20 (28.99)	[3]-1.388	0.165
50000-100000	21 (29.58)	20 (28.99)		
100000-200000	26 (36.62)	19 (27.54)		
> 200000	11 (15.49)	10 (14.49)		
Residence				
Urban	37 (52.11)	39 (56.52)	[1]0.274	0.601
Rural	34 (47.89)	30 (43.48)		
Family structure				
Nuclear family	25 (35.21)	24 (34.78)	[1]1.697	0.428
Immediate family 1	38 (53.52)	32 (46.38)		
Immediate family 2	8 (11.27)	13 (18.84)		
Number of children	1.35 ± 0.56	1.54 ± 0.68	[2]1.752	0.082
CARS	35.92 ± 5.08	36.42 ± 5.22	[2]0.580	0.563
GDS				
Adaptability	64.11 ± 18.22	64.62 ± 20.23	[2]0.157	0.875
Gross motor skills	71.92 ± 14.95	74.99 ± 16.72	[2]1.146	0.254
Fine motor skills	67.17 ± 18.95	70.12 ± 17.79	[2]0.948	0.345
Language	44.32 ± 19.19	40.84 ± 16.66	[2]-1.145	0.254
Personal-social behavior	52.92 ± 13.76	51.68 ± 15.30	[2]-0.502	0.616

[1]χ^2 test.
[2]*t* test.
[3]Mann-Whitney *U* test.
Nuclear family: Parents and minor children live together; Immediate family 1: Nuclear family and grandparents who can offer some help; Immediate family 2: Nuclear family and grandparents who cannot offer any help; CARS: Childhood autism rating scale; GDS: Gesell developmental schedules.

Table 2 Comparisons of scores on the parenting stress index-short form between two groups before and after the intervention, mean ± SD

Variable	Experimental group (*n* = 71)	Control group (*n* = 69)	*t*	*P* value
PD				
Pre-intervention	33.30 ± 9.16	33.48 ± 9.16	0.118	0.906
Post-intervention	28.03 ± 9.64	31.84 ± 8.57	0.267	0.015[a]
t/*P* value	7.225/< 0.001[b]	2.755/< 0.001[b]		
PCDI				
Pre-intervention	28.51 ± 7.95	28.41 ± 6.60	-0.082	0.935
Post-intervention	24.28 ± 8.00	27.20 ± 6.79	0.075	0.021[a]
t/*P* value	6.319/< 0.001[b]	2.483/0.015[a]		
DC				
Pre-intervention	32.94 ± 7.28	35.10 ± 7.02	1.785	0.076
Post-intervention	28.79 ± 8.29	33.06 ± 7.63	0.364	0.002[b]
t/*P* value	6.157/< 0.001[b]	4.613/< 0.001[b]		
Total score				
Pre-intervention	94.75 ± 20.95	96.99 ± 19.53	0.654	0.514
Post-intervention	81.10 ± 19.76	92.10 ± 19.26	0.476	0.001[b]
t/*P* value	9.540/< 0.001[b]	4.663/< 0.001[b]		

[a]$P < 0.05$.
[b]$P < 0.01$.
PD: Parenting distress; PCDI: Parent-child dysfunctional interaction; DC: Difficult child.

Following the interventions, both groups of parents experienced a significant reduction in their levels of anxiety and depression compared to their levels before the experiment (all $P < 0.05$), and the degree of reduction was similar in both groups. These findings showed that the R-FPSC intervention had no obvious effect on the alleviation of parents' anxiety or depression.

Comparisons of the training durations between the two groups of children: To evaluate parental motivation to engage their children in therapeutic training, we measured the children's weekly training durations, which encompassed all the hours they spent receiving training in various settings, such as hospitals, institutions, homes, communities, and more. Prior to the intervention, none of the children had received any therapeutic training. As indicated in Table 5, the parents of the experimental group exhibited a significantly greater level of enthusiasm about taking their children for therapeutic training than did the parents of the control group ($P < 0.05$).

Comparisons of the core symptoms and developmental abilities of the children between the two groups: Table 6 reveals that the severity of the core symptoms, adaptability, gross motor skills, fine motor skills, language development, and personal-social behavior levels were comparable between the two groups of children prior to the intervention (all $P > 0.05$). No significant improvement in core symptoms or developmental abilities was observed in the experimental group at the three-month follow-up (all $P > 0.05$). At the follow-up, the children in the experimental group had fewer core symptoms than they had before the intervention ($P < 0.05$), and the children in the control group had more progress in language development ($P < 0.05$).

DISCUSSION

In this study, the R-FPSC was added to the CMI of the experimental group as part of the intervention. Parents' mental health was assessed using the PSOC, GAD-7, and PHQ-9 scales, as well as the PSI-SF, as outcome measures. The CARS and GDS were used to evaluate the efficacy of the interventions among the children. The children's training time was investigated to determine their parents' motivation to engage them in therapeutic training. This study revealed that the R-FPSC effectively relieved parenting pressure, increased parents' willingness to raise children on the autism spectrum, and promoted parents' care for children on the autism spectrum. These activities had a positive effect on the mental health of the parents.

Table 3 Comparisons between two groups on the parenting sense of competence scale before and after the intervention, mean ± SD

Variable	Experimental group (*n* = 71)	Control group (*n* = 69)	*t*	*P* value
Efficacy				
Pre-intervention	26.66 ± 5.88	27.54 ± 5.20	0.931	0.353
Post-intervention	30.65 ± 6.49	28.45 ± 5.64	-2.137	0.034[a]
t/*P* value	8.334/< 0.001[b]	1.907/< 0.001[b]		
Satisfaction				
Pre-intervention	32.72 ± 8.17	33.94 ± 6.89	0.957	0.340
Post-intervention	38.18 ± 7.06	35.46 ± 7.01	-2.286	0.024[a]
t/*P* value	6.414/< 0.001[b]	2.508/0.015[a]		
Total score				
Pre-intervention	59.38 ± 11.59	61.48 ± 9.94	1.148	-2.634
Post-intervention	68.83 ± 11.23	63.91 ± 10.86	0.253	0.009[b]
t/*P* value	8.092/< 0.001[b]	2.807/0.005[b]		

[a]*P* < 0.05.
[b]*P*< 0.01.

Table 4 Comparisons of scores on the generalized anxiety disorder-7 and patient health questionnaire-9 between two groups before and after the interventions, mean ± SD

Variable	Experimental group (*n* = 71)	Control group (*n* = 69)	*t*	*P* value
GAD-7				
Pre-intervention	5.85 ± 4.67	4.91 ± 4.63	-1.186	0.238
Post-intervention	2.89 ± 3.19	3.67 ± 3.92	0.124	0.199
t/*P* value	7.323/< 0.001[b]	3.599/0.001[b]		
PHQ-9				
Pre-intervention	5.48 ± 4.86	5.04 ± 4.77	-0.535	0.594
Post-intervention	2.77 ± 3.00	3.48 ± 4.27	0.090	0.260
t/*P* value	6.590/< 0.001[b]	4.725/< 0.001[b]		

[b]*P* < 0.01.
GAD-7: Generalized anxiety disorder-7; PHQ-9: Patient health questionnaire-9.

Table 5 Comparisons of the training duration between two groups after the intervention, mean ± SD

Variable	Experimental group (*n* = 71)	Control group (*n* = 69)	*t*	*P* value
Training duration in hours				
Pre-intervention	0	0		
Post-intervention	12.78 ± 3.16	11.57 ± 3.15	-2.266	0.025[a]

[a]*P* < 0.05.

The influence of the R-FPSC on the parenting stress of those raising children on the autism spectrum

Compared to parents who only received CMI, those who received CMI + R-FPSC experienced a significantly greater decrease in parenting stress, which refers to the pressure that parents feel while fulfilling their parental role and engaging in parent–child interactions. The level of parenting stress is mainly determined by three factors: Parents' personality traits, characteristics of the child's diagnosis, and overall family situation[33,34]. Both of the study groups experienced

Table 6 Comparisons of scores on the childhood autism rating scale and the Gesell developmental schedules between two groups before the intervention and at the follow-up, mean ± SD

Variable		Experimental group (*n* = 24)	Control group (*n* = 19)	*t*	*P* value
GDS					
Adaptability	Pre-intervention	70.67 ± 17.75	73.74 ± 16.19	0.585	0.562
	Post-intervention	75.88 ± 20.14	78.74 ± 14.79	0.518	0.607
	t/*P* value	-1.403/0.174	-1.485/0.155		
Gross motor skills	Pre-intervention	79.88 ± 16.00	80.11 ± 15.61	0.047	0.962
	Post-intervention	82.17 ± 16.45	79.21 ± 13.84	-0.627	0.534
	t/*P* value	-0.792/0.436	0.516/0.612		
Fine motor skills	Pre-intervention	77.79 ± 16.14	75.21 ± 14.97	-0.537	0.594
	Post-intervention	83.17 ± 21.60	78.16 ± 14.26	-0.871	0.389
	t/*P* value	-1.411/0.172	-0.923/0.368		
Language	Pre-intervention	51.25 ± 21.27	46.00 ± 14.89	-0.950	0.348
	Post-intervention	59.33 ± 23.38	60.16 ± 18.15	0.126	0.900
	t/*P* value	-1.745/0.094	-4.453/< 0.001[b]		
Personal-social behavior	Pre-intervention	61.25 ± 14.189	57.84 ± 12.668	-0.819	0.417
	Post-intervention	68.88 ± 19.447	63.00 ± 13.772	0.146	0.272
	t/*P* value	-1.758/0.092	-1.665/0.113		
CARS	Pre-intervention	34.17 ± 5.895	35.16 ± 6.930	0.507	0.615
	Post-intervention	30.54 ± 7.437	33.05 ± 6.980	1.129	0.265
	t/*P* value	2.476/0.021[a]	1.284/0.216		

[a]$P < 0.05$.
[b]$P < 0.01$.
CARS: Childhood autism rating scale; GDS: Gesell developmental schedules

high levels of parenting stress prior to the intervention, reaching clinically elevated stress levels, which aligns with the findings of Staunton *et al*[35]. After the intervention, there was a significantly lower level of parenting stress in both study groups. Other studies have suggested that parent training programs may stabilize or reduce parenting stress[36,37]. Our results showed that providing parents with R-FPSC may enhance this potential. This finding is consistent with that of the study by Weitlauf *et al*[38], which might be related to parents' correct understanding of ASD[39], their active seeking of assistance from multiple resources[40], their proper allocation of time[41], and their tendency to pay more attention to the present[42]. Despite the positive findings of this study regarding the effectiveness of R-FPSC in alleviating parenting stress, it is necessary to determine whether this effect can be sustained over the long term. Additionally, further research is needed to understand the mechanisms underlying the effects of R-FPSC on parenting stress. This approach will enable us to enhance the content and format of R-FPSC in order to offer more effective psychological support.

The influence of R-FPSC on the PSOC among parents of children on the autism spectrum

The use of R-FPSC has the potential to enhance parents' sense of competence, which has been defined as the sense of self-perception and satisfaction during the process of raising children[43]. Researches have demonstrated that parents with higher parenting self-efficacy are more likely to employ positive parenting techniques, increase their confidence in educating their children, engage in active and effective parent-child interactions, and reduce their own psychological stress[44-46]. In the present study, the control group significantly improved their PSOC through the CMI, which is consistent with the results of a pilot trial conducted in Italy that evaluated the effectiveness of the parent skills training [47]. We also found that the R-FPSC could further improve parents' efficacy and satisfaction in raising their children on the autism spectrum. First, the R-FPSC provides guidance for helping parents effectively address their children's emotional difficulties and challenging behaviors[48], so that their difficulties in parent-child interactions are alleviated, parents' views of the children's behaviors improve, and parents are better able to regulate their own negative cognitions [37]. Moreover, as reported by Arellano *et al*[46], parents' level of competence in parenting can be influenced by various factors, including overall family dysfunction, interpersonal tension, lack of family cohesion, and inadequate family support. Through the provision of psychological support, parents can prioritize the promotion of cooperation within the entire family, mobilize family resources, strengthen family cohesion, and obtain increased support from family members [49]. Consequently, their parenting competence is more likely to increase.

The influence of the R-FPSC on the anxiety and depression of parents of children on the autism spectrum

Anxiety and depression improved during active treatment in both study groups. However, the parents who received R-FPSC did not have a greater reduction in anxiety or depression symptoms than did the parents in the other group. A study[38] that compared the parent-implemented early start denver model (P-ESDM) to the P-ESDM + mindfulness-based stress reduction model in two intervention groups of parents of children on the autism spectrum yielded similar results, with both groups of parents experiencing a reduction in symptoms of depression and anxiety, but the positive effects of the intervention wore off at follow-up after 6 months, approaching initial baseline levels. Therefore, the study suggested that ongoing psychological interventions might help sustain the initial improvements in parents' mental health. It also reminded us of the importance of continuous intervention. At the same time, short-term improvements in children's autism symptoms and neuropsychological development might not have been sufficient to alleviate parental anxiety or depression. Furthermore, the durations of psychological support were relatively short, and the differences in the needs of parents at different stages should have been taken into consideration. For instance, during the early intervention stage, parents may require more emotional support and guidance to cope with the confusion and anxiety they may experience. As the training stage progresses, parents may benefit more from practical skill training and access to resources. Therefore, further exploration and development of customized support measures for different stages are necessary.

The influence of R-FPSC on the training duration of children on the autism spectrum

After receiving the R-FPSC intervention, the parents' motivation to engage their children in training increased, which may be attributed to the emotional support and connection experienced during the R-FPSC. Parents' emotional state became more stable, which enhanced their willingness to interact with their children and engage in their training[49]. Furthermore, the R-FPSC showed parents the benefits of persisting in training for children on the autism spectrum, bringing them hope. As a result, they were more willing to invest more effort and time in their children's training. Future studies should further increase the follow-up time to see if this positive effect persists.

The influence of the R-FPSC on the development of children on the autism spectrum

The R-FPSC did not show obvious advantages in terms of improving children's developmental levels or reducing their autism symptoms. First, the follow-up sample size was small, which may have affected the reliability and generalizability of the results. Second, as ASD is a complex neurodevelopmental disorder that is influenced by various factors, some autistic children may even experience regression during development[50]. Individual differences, specific training methods and quality, the qualifications of rehabilitation therapists, and parents' proficiency in training skills can also influence a child's developmental progress. Therefore, influenced by these factors, R-FPSC might not be associated with significant effects. Finally, the assessment tools used in the study may have certain limitations, as they may not comprehensively measure the efficacy of the R-FPSC in children. Hence, we recommend that future studies consider selecting alternative assessment tools, such as the Autism Treatment Evaluation Checklist, to evaluate the effectiveness of interventions for children.

CONCLUSION

Our findings indicate that using high-quality, low-cost, comprehensive R-FPSC is associated with reduced parental stress and increased confidence in parenting competence, which can help improve parent–child relationships, family atmosphere, and quality of life for families of children on the autism spectrum. The R-FPSC provides psychological support to parents through the WeChat online platform, not only by offering them professional knowledge and training skills related to ASD but also by providing emotional understanding and support. Additionally, it eliminates the geographical and temporal limitations faced by traditional face-to-face psychological therapy, offering parents a more convenient and economical way of receiving psychological support and further expanding the audience of psychotherapy. Therefore, offering psychological support to parents through online platforms appears to be a promising and feasible therapeutic approach. These findings may serve as a valuable reference for current family intervention models and have significance for families of children on the autism spectrum. However, we also need to recognize the limitations of this study. Given the study's limited duration and small number of children at follow-up, the effectiveness of the R-FPSC in facilitating children's core symptoms and developmental levels remains uncertain, and the long-term effects on parents' mental health require further investigation. Future research should employ robust methodologies, larger sample sizes, and longer follow-up periods to ascertain the durability and stability of the effects of R-FPSC on parental mental health and intervention outcomes for children on the autism spectrum.

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FOOTNOTES

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Observational Study

Analysis of anxiety and depression status and their influencing factors in patients with diabetic retinopathy

Sheng Gao, Xia Liu

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Abstract

BACKGROUND

Diabetic retinopathy (DR) is a common complication of diabetes and the leading cause of visual impairment and blindness. It has a serious impact on the mental and physical health of patients.

AIM

To evaluate the anxiety and depression status of patients with DR, we examined their influencing factors.

METHODS

Two hundred patients with DR admitted to the outpatient and inpatient departments of ophthalmology and endocrinology at our hospital were selected. A questionnaire was conducted to collect general patient information. Depression and anxiety were assessed using the Patient Health Questionnaire-9 and Seven-item Generalized Anxiety Disorder scale, respectively. The diabetes specific quality of life scale and Social Support Rating Scale were used to assess the quality of life of patients with DR and their social support, respectively. Logistic regression analysis was used to assess the correlations.

RESULTS

The prevalence of depression and anxiety were 26% (52/200) and 14% (28/200), respectively. Regression analysis revealed that social support was associated with depression [odds ratio (OR) = 0.912, 95% confidence interval (CI): 0.893-0.985] and anxiety (OR = 0.863, 95%CI: 0.672-0.994). Good quality of life (diabetes specific quality of life scale score < 40) was a protective factor against anxiety (OR = 0.738, 95%CI: 0.567-0.936) and depression (OR = 0.573, 95%CI: 0.4566-0.784). Visual impairment significantly increased the likelihood of depression (OR = 1.198, 95%CI: 1.143-1.324) and anxiety (OR = 1.746, 95%CI: 1.282-2.359). Additionally, prolonged diabetes duration and history of hypertension were significant risk factors for both conditions, along with a family history of diabetes.

CONCLUSION
Key factors influencing anxiety and depression in patients with DR include social support, quality of life, visual impairment, duration of diabetes, family history of diabetes, and history of hypertension.

Key Words: Diabetic retinopathy; Depression; Anxiety; Influencing factors; Regression analysis

Core Tip: Diabetic retinopathy (DR) is a common complication of diabetes and the leading cause of visual impairment and blindness, which has a severe impact on the patient's mental and physical health. We evaluated anxiety and depression status and their influencing factors in patients with DR. We conclude that social support, good quality of life, visual impairment, duration of diabetes, family history of diabetes, and history of hypertension are critical factors for anxiety and depressive symptoms in patients with DR. Health managers should screen for these risk factors to implement early prevention strategies to reduce depression and anxiety in patients with DR.

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INTRODUCTION

Diabetic retinopathy (DR) is a common microvascular complication in patients with diabetes mellitus. DR can cause irreversible visual impairment or even blindness, which has a severe impact on mental and physical health[1]. According to the 2019 statistics of the International Diabetes Federation, there are 463 million patients with diabetes worldwide, including 116 million in China[2,3]. The prevalence of DR among patients with diabetes in China is 18.1%-35.0%[4]. Relevant literature indicates that patients with DR are prone to negative emotional reactions, such as anxiety, depression, fear, anger, and loss of confidence, which not only threaten their physical and mental health but also reduce their quality of life[5-7].

Studies have shown that depression and/or anxiety may be risk factors for diabetes. Patients with depression are more likely to develop diabetes than those without depression. Depression and anxiety are common mental disorders that affect different patient groups. The incidence of diabetes caused by depression is approximately 6.87%[8]. Compared with healthy people, depression and/or anxiety are more likely to occur in patients with chronic health conditions, such as diabetes. Depression and/or anxiety can negatively affect patients' health-related quality of life, healthcare utilization, and healthcare costs can also be negatively affected by depression and/or anxiety[9]. Patients with DR and depression often have a negative attitude towards treatment, which often leads to poor blood sugar control, reduced treatment compliance, an increased incidence of proliferative diabetic retinopathy, and higher medical expenses[10]. Patients with depression are three times more likely to have reduced compliance than other patients, less likely to undergo surgery, and more likely to miss follow-up examinations. Although the impacts of myopia and glaucoma on the psychological state of patients have been reported[11], few studies have examined the psychological state of patients with DR. Therefore, screening for anxiety and depression in patients with DR is essential for effective patient management.

The Seven-item Generalized Anxiety Disorder Scale (GAD-7) and the Patient Health Questionnaire-9 (PHQ-9) are rapid, reliable, and effective tools[12,13]. The GAD-7 was used to assess anxiety, and the PHQ-9 was used to assess depression. These scales together can better determine whether anxiety is accompanied by depression. Some ophthalmologists use the PHQ-9 and GAD-7, which are considered effective screening tools for assessing mental health status, primarily to assess anxiety and depression in patients with chronic eye disease. Therefore, in this study, we used GAD-7 and PHQ-9 to assess anxiety and depression, respectively. To evaluate the interaction between anxiety, depression, and DR treatment, we examined the anxiety and depression statuses of patients with DR and their influencing factors to provide a reference for corresponding psychological interventions for patients with DR in clinical practice.

MATERIALS AND METHODS

Study design and participants

Two hundred patients with DR admitted to our hospital's outpatient and inpatient Departments of Ophthalmology and Endocrinology between March 2023 and April 2024 were selected for this cross-sectional study. Diagnostic criteria for DR in the "Guidelines for the Clinical Management of Diabetic Retinopathy in China" was met[14]. Data were collected within six months following the patients' diagnosis of DR to enhance the understanding of the potential temporal associations between their DR status and their psychological state. Relevant information was obtained from electronic medical

records and questionnaires of the hospital.

To ensure adequate statistical power, we calculated the sample size based on a preliminary survey of prevalence rates of anxiety and depression in diabetic patients in our region, aiming for a power of 0.80 and a significance level of 0.05. The survey process: (1) Before the survey, all assessors received formal training and were instructed to use standardized language to explain the contents of the scale. They were also required to strictly abide by their duties, avoid discrimination between respondents, and refrain from asking personal questions. The researchers were also evaluated for consistency; (2) Each questionnaire was collected and completed by two clinical researchers; (3) All content in the questionnaire was filled in and collected accurately and comprehensively; and (4) When guiding patients to fill in the form, a quiet environment was provided to avoid interference. If a patient had severe visual impairment, the scale was completed face-to-face with the help of an assessor. The assessor read and explained the items to patients and recorded their answers.

The inclusion criteria were as follows: (1) Participants must be between 18 and 80 years old; (2) Diagnosed with DR; (3) Able to speak and write Chinese well; and (4) Conscious and cognitively capable. The exclusion criteria were as follows: (1) Patients with acute complications of diabetes; (2) Patients with acute cardiovascular and cerebrovascular diseases, severe infections, tumors, severe water and electrolyte disorders, and immune and blood system diseases; (3) Patients with dementia, various mental illnesses, or those who were unwilling to cooperate; (4) Patients with a history of drug or alcohol dependence, or those who had used antidepressants and anxiety drugs in the past; and (5) Pregnant or lactating women.

Ethical approval

This study was approved by the Research Ethics Committee, and all patients voluntarily participated.

Demographic information and clinical data

The collected data included age, sex, duration of diabetes, family history of diabetes, history of hypertension, history of diabetes medication use, smoking, alcohol consumption, educational level, marital status, place of residence (rural or urban), and glycemic control. Hemoglobin A1c (HbA1c) levels were used as indicators of glycemic control and measured using high-performance liquid chromatography. In accordance with the Chinese guidelines for the secondary prevention of ischemic stroke and transient ischemic attack 2010[15], an HbA1c level of 53 mmol/mol (< 7.0%) was classified as indicative of good glycemic control, whereas a level of HbA1c ≥ 7.0% (53 mmol/mol) was deemed indicative of poor glycemic control[15]. As less than 5% of the data were missing, no handling of the missing data was necessary.

Assessment of visual impairment

Visual acuity was measured using a standard logarithmic visual acuity chart. "VI" was defined as the presenting visual acuity of the better eye. We used this definition because it reflects the vision in real life. According to the International Classification of Diseases criteria, the VI level was classified as blindness, severe VI, moderate VI, mild VI, or no VI. The patients were classified as blind [logarithmic minimum angle of resolution (logMAR) ≥ 1.30], severe VI (1 ≤ logMAR < 1.30), moderate VI (0.48 ≤ logMAR < 1), mild VI (0.30 ≤ logMAR < 0.48), and no VI (logMAR < 0.30). We judged mild or no VI as no visual impairment or blindness and moderate or severe VI as visual impairment.

Assessment of depression

In this study, we assessed depression using the PHQ-9[13], which consists of nine items rated on a four-point Likert scale ranging from zero (never) to three (every day). Scores on this scale can range from zero to 27, with a score of ≥ 10 indicating the presence of depression. The Chinese edition of the PHQ-9 has been demonstrated to exhibit strong reliability and validity, as indicated by a Cronbach's α coefficient of 0.834 in our study.

Assessment of anxiety

The GAD-7 scale was used to evaluate anxiety levels[12]. This scale comprises seven symptom items aimed at gauging the severity and functional impact of anxiety symptoms experienced over the preceding two weeks. Responses were rated on a four-point Likert scale, ranging from zero (never) to three (every day), leading to a total score ranging from zero to 21. A score of ≥ 10 indicates the presence of anxiety. The Chinese version of GAD-7 is frequently used to evaluate the severity of anxiety symptoms in the Chinese population. In the current study, the Cronbach's α coefficient for the scale stood at 0.938.

Assessment of social support

Social support was evaluated using the Social Support Rating Scale, specifically tailored to the Chinese context[16]. This scale comprised three subscales: Subjective support (perceived support level), objective support (visible support level), and support utilization (utilization of available support). Subjective support was gauged through four items, scored between eight and 32; objective support through three items, scored between one and 22; and support utilization through three items scored between three and 12. The total score ranges from 12 to 66, with higher scores indicating greater social support. The scale demonstrated a Cronbach's α coefficient of 0.89 and a test-retest reliability of 0.92 in previous studies. Scores of 12 to 22 signify low support, 23 to 44 moderate support, and 45 to 66 high support[17].

Assessment of quality of life

Individuals with type 2 diabetes mellitus in China were evaluated using a diabetes specific quality of life scale (DSQL) [18]. This validated questionnaire comprises 24 items that assess physiological, social, psychological, and therapy-related

aspects that affect the quality of life. The scores on the four domains range from 24 to 120 points, with higher scores indicating a lower quality of life. When identifying the good and poor quality of life-based on DSQL scores below 40, the diagnostic sensitivity and specificity were 94.5% and 91.0%[18]. In this study, a DSQL score of < 40 was considered to indicate a good quality of life.

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 26.0. Descriptive statistics were used to present continuous variables with means and standard deviations, while categorical variables were expressed as counts and percentages. Pearson's χ^2 test was used for categorical variables. Based on binary logistic regression analysis, we evaluated the factors influencing negative emotions in patients with DR using odds ratios (ORs) and 95% confidence intervals (CIs). Negative emotions were defined as the outcome variable, and the participants were categorized into two groups: Those experiencing negative emotions and those without. Two-sided tests were used in the regression model with a significance level of $P < 0.05$.

RESULTS

Demographic and clinical characteristics

The demographic and clinical information of patients with DR are shown in Table 1. Among the 200 patients, 52 (26.0%) had depression, 28 (14.0%) had anxiety, the mean age (standard deviation) was 54.62 (10.85) years, 104 (52.0%) were women, and 42 (21.0%) had a college degree or above. Fifty-eight patients had diabetes for less than 5 years, and 142 had diabetes for ≥ 5 years. Among these patients, 84.5% had visual impairment. Thirty-nine (19.5%) patients had good quality of life, 48 (24.0%) had high social support, 74 (37.0%) had a history of drinking, 68 (34.0%) had a history of smoking, and 172 (86.00%) had a family history of diabetes. A total of 136 patients (68.0%) had hypertension.

Univariate analysis of depression

Table 2 shows the results of univariate analysis for each factor and depression. The results showed significant differences between patients with and without depression in terms of education level, duration of diabetes, visual impairment, quality of life, social support, and hypertension ($P < 0.05$). There were no significant differences in age, marital status, place of residence, smoking, drinking, or type of diabetes between the groups ($P > 0.05$).

Univariate analysis of anxiety

Table 3 presents the results of univariate analysis for each factor and anxiety level. The results showed that there were significant differences between anxious patients and non-anxious patients in terms of smoking history, duration of diabetes, visual impairment, good quality of life, social support, family history of diabetes, combined hypertension, and blood sugar control levels ($P < 0.05$). No notable variations were found in age, education level, marital status, location of residence, smoking habits, alcohol consumption, or type of diabetes ($P > 0.05$).

Logistic regression analysis of depression

Considering depression as the dependent variable (0 = no, 1 = yes), and according to the results of the univariate analysis in Table 2, the variables with statistically significant differences (education level, duration of diabetes, visual impairment, good quality of life, social support, and hypertension) were used as independent variables. Binary logistic regression was used to analyze the independent factors influencing depression in patients with DR. The results showed that the longer the duration of diabetes, the higher the risk of depression (OR = 1.943, 95%CI: 1.826-2.139). Visual impairment (OR = 1.198, 95%CI: 1.143-1.324) and high blood pressure (OR = 1.307, 95%CI: 1.113-2.194) are risk factors for depression. Good quality of life and social support are protective factors against depression (OR = 0.573, 95%CI: 0.456-0.784). As shown in Table 4, patients with high social support were less likely to experience depression than those with low social support (OR = 0.912, 95%CI: 0.893-0.985).

Logistic regression analysis of anxiety

Considering anxiety as the dependent variable (0 = no, 1 = yes), and according to the results of the univariate analysis in Table 3, variables with statistically significant differences (smoking history, duration of diabetes, visual impairment, quality of life, social support, hypertension, family history of diabetes, and blood sugar control level) were used as independent variables. Binary logistic regression was used to analyze the independent factors influencing anxiety in patients with DR. The results showed that the longer the duration of diabetes, the higher the risk of anxiety (OR = 1.526, 95%CI: 1.451-1.863), and visual impairment was a risk factor for anxiety (OR = 1.746, 95%CI: 1.282-2.359). High blood pressure was also a risk factor for anxiety (OR = 1.836, 95%CI: 1.517-2.592), while a good quality of life was a protective factor for anxiety (OR = 0.738, 95%CI: 0.567-0.936). Social support is also a protective factor against anxiety. A family history of diabetes (OR = 2.065, 95%CI: 1.792-3.571) was an independent risk factor for anxiety. Patients with high social support were less likely to experience anxiety (OR = 0.863, 95%CI: 0.672-0.994). Figure 1 illustrates the visualization results for the independent influencing factors listed in Table 5.

Table 1 Demographic and clinical characteristics of diabetic retinopathy patients

Variable	Patients (*n* = 200)	Percentage (%)
Sex		
Male	96	48.0
Female	104	52.0
Age (year)	54.62 ± 10.85	/
Education		
Primary	23	11.5
Secondary	37	18.5
Senior high school	98	49.0
College or above	42	21.0
Duration of diabetes, year		
< 5	58	29.0
≥ 5	142	71.0
Depression		
Yes	52	26.0
No	148	74.0
Anxiety		
Yes	28	14.0
No	172	86.0
Visual impairment		
Yes	169	84.5
No	31	15.5
Good quality of life (DSQL score < 40)		
Good	39	19.5
Poor	161	80.5
Social support		
Low support	69	34.5
Moderate support	83	41.5
High support	48	24.0
History of smoking		
Yes	68	34.0
No	132	66.0
History of drinking		
Yes	74	37.0
No	126	63.0
Complicated with hypertension		
Yes	136	68.0
No	64	32.0
Diabetes history		
Yes	172	86.0
No	28	14.0
Residence		

Rural	89	44.5
Urban	111	55.5
Diabetes type		
Type 1 diabetes	5	2.5
Type 2 diabetes	195	97.5
Diabetes medication		
Oral hypoglycemic drugs	63	31.5
Insulin injection	41	20.5
Both	96	48.0
Marital status		
Married	115	57.5
Single	32	16.0
Divorced/widowed	53	26.5
Blood glucose control		
Good	37	18.5
General	96	48.0
Bad	67	33.5

DSQL: Diabetes specificity quality of life scale.

DISCUSSION

In the present study, we found that the overall mental health of patients with DR was poor. Among all patients, 52 (26.0%) had symptoms of depression, and 28 (14.0%) had symptoms of anxiety. The prevalence of depression was higher in the current population than in the general population[19]. The prevalence of depression in the present study was higher than that reported in another study[20]. However, another study reported a higher prevalence of depression and anxiety in patients with diabetes[21]. Prevalence disparities may arise from variations in measurement instruments and study populations. Although there were no notable disparities in the prevalence of depression and anxiety symptoms among individuals with diabetes, significant variations were observed when compared to those in the general population. Accordingly, the mental well-being of patients with DR warrants continued monitoring.

Social support also plays a vital role in psychological adaptation[22]. Previous studies have shown that social support is indirectly associated with mental health in patients with diabetes[23]. In a study by Chiu *et al*[24], health behaviors accounted for 13% of the association between depressive symptoms and glycemic control. The results showed a negative correlation between social support and depression (OR = 0.912, 95%CI: 0.893-0.985) and anxiety (OR = 0.863, 95%CI: 0.672-0.994), which is consistent with the results of previous studies[25]. However, a higher quality of life reduced the odds of depression (OR = 0.573, 95%CI: 0.456-0.784) and anxiety (OR = 0.738, 95%CI: 0.567-0.936) in patients with DR, which is consistent with the results of other studies on patients[26].

In addition, vision loss and DR treatment methods are issues of great concern for patients with DR in ophthalmology outpatient clinics and inpatient settings and deserve further discussion. Patients with vision-threatening DR may experience greater social and emotional stress than those without it. Previous studies have found that visual changes are important factors associated with changes in mental health[27]. There was a positive correlation among vision loss, depression, and anxiety symptoms[28]. The results of this study showed that patients with visual impairments had a higher risk of depression (OR = 1.198, 95%CI: 1.143-1.324) and anxiety (OR = 1.746, 95%CI: 1.282-2.359), which is consistent with previous research results.

In addition, the results of this study indicated that patients with hypertension were more likely to experience depression (OR = 1.307, 95%CI: 1.113-2.194) and anxiety (OR = 1.836, 95%CI: 1.517-2.592) than those without hypertension. These results were consistent with those reported by Geldsetzer *et al*[29] that depression and anxiety are associated with hypertension in patients with type 2 diabetes[30]. This may be because patients with hypertension require more direct and indirect medical care, resulting in greater economic and psychological burdens[31]. Additionally, patients with hypertension often experience severe physical pain and functional disorders that cause more severe depression and anxiety than a single disease[32].

Our research indicates that patients with a familial predisposition to diabetes display heightened levels of anxiety compared with those without such a history. Furthermore, another study revealed that individuals at risk for type 2 diabetes reported more subjective stress than their non-diabetic counterparts[21]. Although previous studies have linked the incidence of DR to a family history of diabetes, the potential causal relationship between familial diabetes history and anxiety symptoms in patients with DR remains unclear[33]. Our findings suggest that a family history of diabetes

Table 2 Univariate analysis of depression

Variable	Without depression (*n* = 148)	Depression (*n* = 52)	χ^2	*P* value
Sex				
Male	76	20	3.257	0.083
Female	72	32		
Education			12.841	0.006
Primary	18	5		
Secondary	28	9		
Senior high school	63	35		
College or above	39	3		
Duration of diabetes, year			4.423	0.035
< 5	37	21		
≥ 5	111	31		
Visual impairment			9.556	< 0.001
Yes	132	37		
No	16	15		
Good quality of life (DSQL score < 40)			27.379	< 0.001
Good	16	23		
Poor	132	29		
Social support			13.274	0.001
Low support	57	12		
Moderate support	65	18		
High support	26	22		
History of smoking			1.568	0.211
Yes	54	14		
No	94	38		
History of drinking			0.105	0.745
Yes	43	31		
No	105	21		
Complicated with hypertension			12.421	< 0.001
Yes	109	27		
No	39	25		
Diabetes history			3.293	0.696
Yes	149	23		
No	7	21		
Residence			0.046	0.829
Rural	72	17		
Urban	76	35		
Diabetes type			1.367	0.618
Type 1 diabetes	3	2		
Type 2 diabetes	145	50		
Diabetes medication			2.632	0.355
Oral hypoglycemic drugs	35	28		

Insulin injection	26	15		
Both	87	9		
Marital status			0.938	0.626
Married	88	27		
Single	23	9		
Divorced/widowed	37	16		
Blood glucose control			1.438	0.487
Good	24	5		
General	69	25		
Bad	55	22		

DSQL: Diabetes specificity quality of life scale.

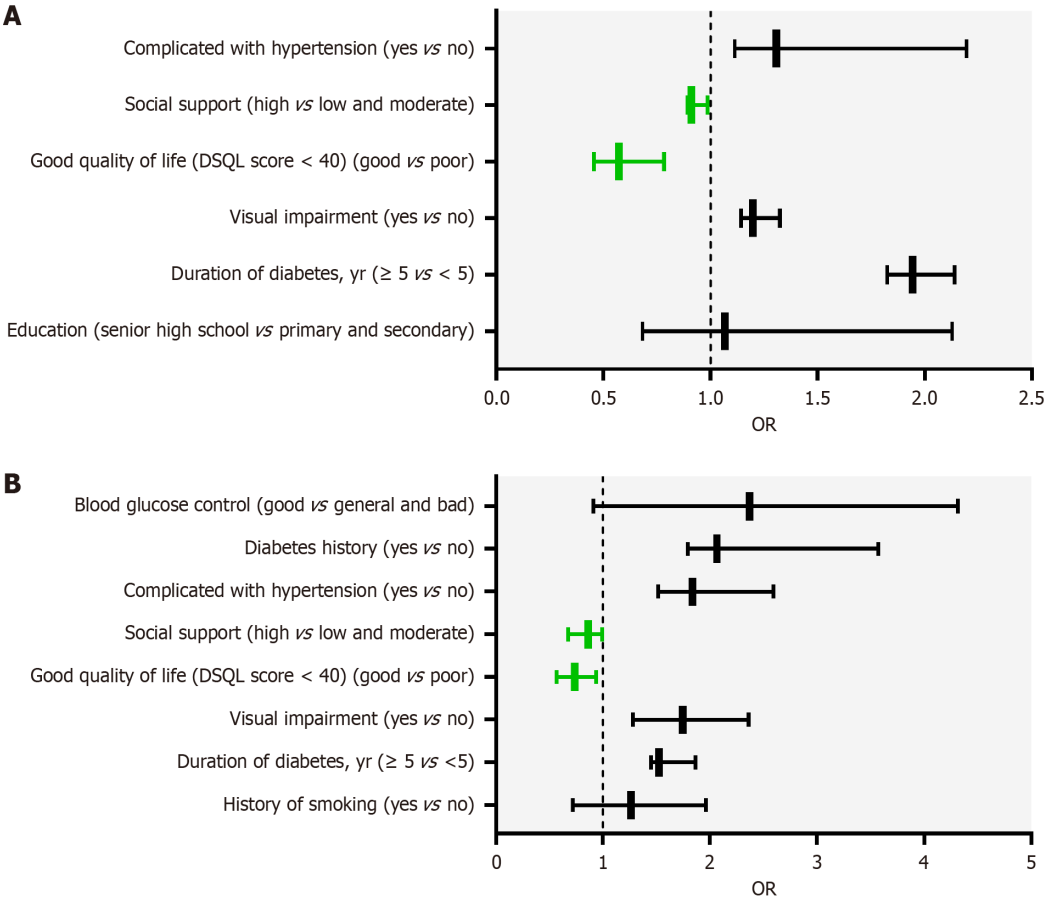

Figure 1 Binary logistic regression forest plot of independent influencing factors of depression and anxiety. A: Binary logistic regression forest plot of independent influencing factors of depression; B: Binary logistic regression forest plot of independent influencing factors of anxiety. DSQL: Diabetes Specificity Quality of Life Scale; OR: Odds ratio.

independently increases the risk of anxiety (OR = 2.065, 95%CI: 1.792-3.571), which is in line with the existing research.

Our findings can help clinicians provide more personalized support and counseling and clinically incorporate mental health support into treatment plans for patients with chronic eye diseases such as DR. For example, the PHQ-9 was integrated into the routine visits of DR Patients. Healthcare providers should use the tool at the initial diagnosis and each follow-up appointment. GAD-7 was administered during the same visit. Patients diagnosed with DR Were evaluated at least every 6 months, or more frequently, for those with scores above the established cutoff (PHQ-9 and GAD-7 ≥ 10 points). In cases of mild to moderate depression and anxiety, a brief cognitive behavioural therapy intervention was offered as part of the care plan. Consider referring a trained mental health clinician to the ophthalmology or endocrinology department for treatment. It also promotes a collaborative care model integrating eye and mental health services to ensure patients receive comprehensive care. In conclusion, structured screening, integrated care models, and

Table 3 Univariate analysis of anxiety

Variable	Without anxiety (*n* = 172)	Anxiety (*n* = 28)	χ^2	*P* value
Sex				
Male	78	18	3.459	0.063
Female	94	10		
Education			5.885	0.117
Primary	21	2		
Secondary	32	5		
Senior high school	79	19		
College or above	40	2		
Duration of diabetes, year			33.459	< 0.001
< 5	37	21		
≥ 5	135	7		
Visual impairment			39.489	< 0.001
Yes	157	12		
No	15	16		
Good quality of life (DSQL score < 40)			29.389	< 0.001
Good	23	16		
Poor	149	12		
Social support			21.445	< 0.001
Low support	67	2		
Moderate support	73	10		
High support	32	16		
History of smoking			5.558	0.018
Yes	53	15		
No	119	13		
History of drinking			0.388	0.534
Yes	67	7		
No	151	21		
Complicated with hypertension			12.337	< 0.001
Yes	125	11		
No	47	17		
Diabetes history			46.252	< 0.001
Yes	160	12		
No	12	16		
Residence			0.832	0.362
Rural	125	18		
Urban	47	10		
Diabetes type			0.288	0.592
Type 1 diabetes	4	1		
Type 2 diabetes	168	27		
Diabetes medication			5.354	0.069
Oral hypoglycemic drugs	49	14		

Insulin injection	36	5		
Both	87	9		
Marital status			0.445	0.801
Married	98	17		
Single	27	5		
Divorced/widowed	47	6		
Blood glucose control			7.928	0.019
Good	29	8		
General	79	17		
Bad	64	3		

DSQL: Diabetes specificity quality of life scale.

Table 4 Binary logistic regression analysis of diabetic retinopathy combined with depression

Variable	Reference	*P* value	OR	95%CI
Education				
Senior high school	Primary and secondary	0.926	1.067	0.683-2.128
Duration of diabetes, year				
≥ 5	< 5	0.041	1.943	1.826-2.139
Visual impairment				
Yes	No	0.048	1.198	1.143-1.324
Good quality of life (DSQL score < 40)				
Good	Poor	0.046	0.573	0.456-0.784
Social support				
High support	Low and moderate support	0.021	0.912	0.893-0.985
Complicated with hypertension				
Yes	No	0.035	1.307	1.113-2.194

DSQL: Diabetes specificity quality of life scale; OR: Odds ratio; CI: Confidence interval.

Table 5 Binary logistic regression analysis of diabetic retinopathy combined with anxiety

Variable	Reference	*P* value	OR	95%CI
History of smoking				
Yes	No	0.876	1.264	0.721-1.965
Duration of diabetes, year				
≥ 5	< 5	0.032	1.526	1.451-1.863
Visual impairment				
Yes	No	0.028	1.746	1.282-2.359
Good quality of life (DSQL score < 40)				
Good	Poor	0.013	0.738	0.567-0.936
Social support				
High support	Low and moderate support	0.029	0.863	0.672-0.994
Complicated with hypertension				

Yes	No	< 0.001	1.836	1.517-2.592
Diabetes history				
Yes	No	0.017	2.065	1.792-3.571
Blood glucose control				
Good	General and bad	1.525	2.369	0.915-4.317

DSQL: Diabetes specificity quality of life scale; OR: Odds ratio; CI: Confidence interval.

targeted support programs can address the mental health needs of patients with DR and improve overall patient outcomes.

In addition, future studies should implement randomized controlled trials that focus on specific interventions designed to reduce anxiety and depression in patients with DR. Potential interventions could include cognitive-behavioral therapy, mindfulness-based stress reduction, or group therapy sessions targeting diabetes management and emotional support. Multiple interventions, including medical and psychological care, should be explored simultaneously. Integrating diabetes education, regular mental health assessments, and a collaborative care model that includes endocrinologists, ophthalmologists, and mental health professionals can provide holistic treatment strategies. Tailoring interventions according to the individual needs of patients, such as the severity of visual impairment, duration of diabetes, and previous mental health history, will improve the effectiveness of treatment strategies. Future studies should also evaluate the comorbidities that may affect anxiety and depression in patients with DR, such as obesity, hypertension, and other diabetes-related complications. Understanding how these factors interact can inform comprehensive treatment strategies to improve overall patient care and outcomes.

Limitations

This study has several limitations. First, the reliance on self-administered questionnaires for patient assessment may have introduced a data recall bias and potentially inadequately captured the full spectrum of mental health conditions. Second, the use of a cross-sectional design precludes the establishment of causal relationships between the variables. Future research should address these limitations. Third, the association between family history of DR and anxiety symptoms, which served as a confounding factor in this study, warrants further investigation. Finally, this study was conducted at a single-center hospital in China, which limits the generalizability of the findings to Chinese patients with DR. We included standardized clinical assessments of visual acuity and objective measures of glycemic control (HbA1c levels) as part of our data collection. This dual approach enhances the validity of our findings and allows for a more comprehensive understanding of the relationships between DR, visual impairment, anxiety, and depression. Future studies should consider integrating additional objective assessments and focus on longitudinal studies and randomized controlled trials to evaluate the effectiveness of specific interventions aimed at reducing anxiety and depression in patients with DR while also exploring the adverse effects of treatments and the role of comorbid conditions, such as standardized clinical evaluations of DR severity using retinal imaging techniques and detailed ocular examinations, to support the reliability of the findings further.

CONCLUSION

This study shows that some patients with DR exhibit symptoms of depression and anxiety. Social support and a good quality of life were negatively correlated with depression and anxiety. Diabetes duration, visual impairment, and hypertension are the risk factors for depression and anxiety in patients with DR. A family history of diabetes is a risk factor for anxiety. Therefore, treating patients with DR should focus on controlling blood sugar levels and improving vision. Encouraging patients to take care of themselves as much as possible, strengthening psychological counseling, and providing psychotherapy and behavioral intervention for patients with anxiety and depression can help them achieve maximum recovery from the disease, obtain the best psychological comfort, and improve their quality of life.

FOOTNOTES

Author contributions: Gao S was the guarantor and designed the study, and revised the article critically for important intellectual content; Gao S and Liu X participated in the acquisition, analysis, and interpretation of the data, and drafted the initial manuscript.

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ORIGINAL ARTICLE

Observational Study

Impact of anxiety symptoms on dialysis adherence and complication rates: A longitudinal observational study

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Abstract

BACKGROUND

Anxiety is a common psychological comorbidity in patients undergoing dialysis, yet its impact on treatment adherence and complication rates remains understudied. We designed a longitudinal observational study to investigate these relationships, based on the hypothesis that higher anxiety symptoms would be associated with increased complication rates and negatively associated with adherence to the dialysis regimen.

AIM

To investigate the relationship between anxiety symptoms, dialysis adherence, and complication rates in patients undergoing dialysis over a 24-month period.

METHODS

This observational study analyzed data from 250 adult patients who underwent hemodialysis or peritoneal dialysis at three Affiliated Hospitals of Youjiang Medical University for Nationalities over a period of 24 months. Anxiety symptoms were assessed using the Hospital Anxiety and Depression Scale-Anxiety subscale at baseline and every 6 months. Dialysis adherence was evaluated through attendance records, interdialytic weight gain, and patient-reported medication adherence. We recorded complications (infections, cardiova-

scular events, and hospitalizations) and used mixed-effects models and survival analyses to infer associations between anxiety symptoms, adherence measures, and complication rates.

RESULTS

Higher anxiety symptoms were significantly associated with poorer dialysis adherence, including increased missed sessions [incidence rate ratio = 1.32, 95% confidence interval (CI): 1.18-1.47, $P < 0.001$], greater interdialytic weight gain ($\beta = 0.24$, 95%CI: 0.15-0.33, $P < 0.001$), and lower medication adherence (odds ratio = 0.85, 95%CI: 0.78-0.93, $P < 0.001$). Patients with clinically significant anxiety (Hospital Anxiety and Depression Scale-Anxiety subscale ≥ 8) had a higher risk of complications [hazard ratio (HR) = 1.68, 95%CI: 1.32-2.14, $P < 0.001$], particularly infections (HR = 1.89, 95%CI: 1.41-2.53, $P < 0.001$) and cardiovascular events (HR = 1.57, 95%CI: 1.18-2.09, $P = 0.002$). The relationship between anxiety and complications was partially mediated by adherence measures.

CONCLUSION

Anxiety symptoms in patients undergoing dialysis are associated with poorer treatment adherence and increased complication rates. Regular screening and targeted interventions to address symptoms may improve adherence and clinical outcomes.

Key Words: Anxiety; Dialysis; Adherence; Complications; End-stage renal disease

Core Tip: This study highlights the significant impact of anxiety symptoms on adherence to treatment and complication rates in patients who undergo dialysis. The findings reveal that higher anxiety is associated with increased missed treatment sessions, greater interdialytic weight gain, and lower adherence to medication. Consequently, anxiety leads to a higher risk of infections, cardiovascular events, and hospitalization. Addressing anxiety through regular screening and targeted interventions could improve adherence and reduce complications, enhancing overall patient outcomes.

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INTRODUCTION

End-stage renal disease (ESRD) is a chronic condition affecting millions of people worldwide, and has a considerable impact on the quality of life and long-term health outcomes[1]. Dialysis, either hemodialysis or peritoneal, is a life-sustaining treatment for patients with ESRD. However, the dialysis regimen is complex and demanding, requiring strict adherence to treatment schedules, dietary restrictions, and medication regimens[2]. Psychological comorbidities, particularly anxiety and depression, are prevalent among patients who undergo dialysis treatment[3]. The prevalence of anxiety in this population ranges from 12% to 52%, depending on the assessment method and study population[4]. The high prevalence of anxiety in patients who require dialysis can be attributed to various factors, including stress from chronic illness, fear of complications, lifestyle restrictions, and uncertainty about the future[5]. While the impact of depression on dialysis outcomes has been investigated extensively[6], the specific role of anxiety in dialysis adherence and complication rates remains understudied. Anxiety symptoms may interfere with the patient's ability to adhere to the complex dialysis regimen, potentially leading to adverse health outcomes[7]. Despite this knowledge, the mechanisms through which anxiety affects dialysis adherence and complications are not well understood.

Adherence to dialysis treatment is crucial for optimal outcomes in patients with ESRD. Non-adherence can manifest in various forms, including skipping or shortening dialysis sessions, excessive interdialytic weight gain (IDWG), and poor medication adherence[8]. Previous studies have shown that non-adherence to dialysis is associated with increased morbidity and mortality[9], but the relationship between anxiety symptoms and specific adherence behaviors in patients who receive dialysis has not been thoroughly investigated. Complications are a significant concern in patients undergoing dialysis, contributing to increased healthcare utilization, reduced quality of life, and mortality[10]. Common complications include infections (particularly access-related infections), cardiovascular events, and hospitalizations[11]. While several risk factors for complications have been identified, the potential role of anxiety as a modifiable risk factor has received limited attention.

Understanding the relationship between anxiety symptoms, dialysis adherence, and complication rates is crucial for several reasons. First, it can help identify patients at higher risk of poor outcomes, allowing for targeted interventions. Second, addressing anxiety symptoms may be a modifiable factor to improve adherence and reduce complications. Lastly, elucidating the mechanisms through which anxiety affects outcomes can inform the development of more effective and integrated care approaches for patients. Previous research in this area has been limited by cross-sectional

designs, small sample sizes, and a focus on either adherence or complications, but not both[12,13]. A longitudinal study examining the relationships between anxiety, adherence, and complications over time is needed to provide a more comprehensive understanding of these complex interactions. The primary objective of this study was to investigate the effects of anxiety symptoms on dialysis adherence and complication rates in a cohort of patients undergoing dialysis over a 24-month period. We hypothesized that higher levels of anxiety would be associated with poorer dialysis adherence and increased complication rates. Furthermore, we expected that the relationship between anxiety and complications would be partially mediated by adherence measures.

MATERIALS AND METHODS

Study design and participants

This prospective, longitudinal observational study was conducted at three dialysis centers affiliated with Affiliated Hospital of Youjiang Medical University for Nationalities in Baise, China between January 2021 and December 2022. The study protocol was approved by the Institutional Review Board of Affiliated Hospital of Youjiang Medical University for Nationalities, Baise (approval number: YYFY-LL-2022-241), and all participants provided written informed consent. Eligible participants were adults aged 18 years or older with ESRD who had been on either hemodialysis or peritoneal dialysis for at least 3 months prior to enrollment. The exclusion criteria were as follows: (1) Cognitive impairment that would interfere with the ability to provide informed consent or complete study assessments; (2) Active psychosis or severe mental illness; (3) Terminal illness with life expectancy of less than 6 months; (4) Inability to understand or communicate in the local language; and (5) Planned living donor kidney transplantation within the next 6 months. A total of 250 patients were enrolled in the study. The sample size was determined based on power calculations to detect clinically meaningful associations between anxiety symptoms, adherence measures, and complication rates.

Data collection

Baseline assessment: At enrollment, the participants underwent a comprehensive baseline assessment that included: (1) Demographic information: Age, sex, education level, marital status, and employment status; (2) Clinical characteristics: Dialysis modality, vintage (time on dialysis), primary cause of ESRD, comorbidities, and medications; (3) Laboratory values: Hemoglobin, albumin and phosphate levels, and Kt/V (a measure of dialysis adequacy, where K refers to clearance, t to time, and V to volume); and (4) Psychosocial measures: Social support, assessed using the Multidimensional Scale of Perceived Social Support[14].

Anxiety assessment: Anxiety symptoms were assessed using the Hospital Anxiety and Depression Scale-Anxiety subscale (HADS-A)[15]. HADS-A is a widely used and validated 7-item self-report measure that assesses anxiety symptoms in the previous week. Each item is scored on a 4-point Likert scale (0-3), with total scores ranging from 0 to 21. Higher scores indicate greater anxiety symptoms, with scores ≥ 8 considered indicative of clinically significant anxiety. HADS-A was administered at baseline and every 6 months throughout the 24-month study period, resulting in a total of five anxiety assessments per participant.

Adherence measures: Adherence to dialysis was assessed using multiple measures: (1) Attendance: The number of missed or shortened (by > 10 minutes) dialysis sessions was recorded monthly for the patients in hemodialysis. For the patients undergoing peritoneal dialysis, adherence to the prescribed number of exchanges was documented through self-reports and verified *via* dialysis logs; (2) IDWG: For the patients in hemodialysis, IDWG was calculated as the difference between the pre-dialysis weight and the weight at the end of the previous session, averaged over each month. For the patients in peritoneal dialysis, daily weight fluctuations were recorded and averaged monthly; and (3) Medication adherence: The 8-item Morisky Medication Adherence Scale (MMAS-8)[16] was used to assess self-reported medication adherence at baseline and every 6 months.

Complication assessment: Complications were recorded throughout the study period and categorized as follows: (1) Infections: Access-related infections (such as catheter-related bloodstream infections and peritonitis) and other infections requiring medical attention or hospitalization; (2) Cardiovascular events: Myocardial infarction, stroke, heart failure exacerbation, and other cardiovascular events requiring hospitalization; (3) Hospitalizations: All-cause hospitalizations, excluding scheduled admissions for procedures; and (4) Complications were verified through medical record review and confirmed by the treating nephrologist.

Statistical analysis

All statistical analyses were performed using R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided *P*-value < 0.05 was considered to indicate statistical significance. The statistical methods of this study were reviewed by Si-Dan Wang from Affiliated Hospital of Youjiang Medical University for Nationalities.

Descriptive statistics: The baseline characteristics were summarized using mean ± SD for continuous variables, and frequencies and percentages for categorical variables. Changes in anxiety scores over time were examined using repeated-measures ANOVA.

Anxiety and adherence: The association between anxiety symptoms and adherence measures was analyzed using mixed-effects models to account for the repeated measures design. For missed dialysis sessions, a generalized linear mixed

model with a Poisson distribution was used, with the number of missed sessions per month as the outcome. For IDWG, a linear mixed model was employed, with the monthly average IDWG as the outcome. For medication adherence, an ordinal mixed model was used, with MMAS-8 categories as the outcome. All models included anxiety scores as the primary predictor, adjusting for relevant covariates (age, sex, dialysis vintage, comorbidities, and social support). Random intercepts for participants and dialysis centers were included to account for clustering.

Anxiety and complications: The relationship between anxiety symptoms and complication rates was examined using Cox proportional hazards models with time-varying covariates. Separate models were constructed for each complication category (infections, cardiovascular events, and hospitalizations) and all complications. The anxiety scores were treated as a time-varying predictor, updated at each 6-month assessment. The models were adjusted for baseline demographics, clinical characteristics, and time-varying adherence measures.

RESULTS

Participant characteristics

Of the 250 patients enrolled in the study, 235 (94%) completed the 24-month follow-up assessment. The baseline characteristics of the study population are presented in Table 1.

Anxiety symptoms over time

The mean HADS-A score at baseline was 6.8 ± 4.2, with 92 participants (36.8%) meeting the criteria for clinically significant anxiety (HADS-A ≥ 8). Over the 24-month study period, there was a slight overall decrease in anxiety symptoms [$F(4, 930) = 3.72$, $P = 0.005$]. The proportion of participants with clinically significant anxiety at each time point was: 36.8% (baseline), 34.4% (6 months), 33.2% (12 months), 31.6% (18 months), and 30.8% (24 months).

Anxiety and adherence to dialysis

Missed dialysis sessions: Higher anxiety symptoms were significantly associated with an increased rate of missed dialysis sessions [incidence rate ratio = 1.32, 95% confidence interval (CI): 1.18-1.47, $P < 0.001$] (Table 2). For each one-point increase in the HADS-A score, the rate of missed sessions increased by 32%. Patients with clinically significant anxiety had, on average, 2.1 times the rate of missed sessions compared to those without clinically significant anxiety (incidence rate ratio = 2.13, 95%CI: 1.76-2.58, $P < 0.001$).

Assessment of IDWG: Anxiety symptoms were positively associated with IDWG ($\beta = 0.24$, 95%CI: 0.15-0.33, $P < 0.001$) (Table 2). For each one-point increase in the HADS-A score, IDWG increased by 0.24 kg. Patients with clinically significant anxiety had, on average, 0.78 kg higher IDWG than those without clinically significant anxiety (95%CI: 0.51-1.05, $P < 0.001$).

Adherence to medication: Higher anxiety symptoms were associated with lower medication adherence, as measured using MMAS-8 (odds ratio = 0.85, 95%CI: 0.78-0.93, $P < 0.001$) (Table 2). For each one-point increase in the HADS-A score, the odds of being in a higher adherence category decreased by 15%. Patients with clinically significant anxiety had 2.6 times higher odds of being in the low adherence category than those without clinically significant anxiety (odds ratio = 2.62, 95%CI: 1.89-3.64, $P < 0.001$).

Anxiety and complication rates

Overall complications: Patients with clinically significant anxiety (HADS-A ≥ 8) had a significantly higher risk of experiencing any complication during the study period [hazard ratio (HR) = 1.68, 95%CI: 1.32-2.14, $P < 0.001$] (Table 3).

Infections: Clinically significant anxiety was associated with an increased risk of infections (HR = 1.89, 95%CI: 1.41-2.53, $P < 0.001$) (Table 3). The incidence rate of infections was 0.42 per patient-year in those with clinically significant anxiety compared to 0.23 per patient-year in those without.

Cardiovascular events: Patients with clinically significant anxiety had a higher risk of cardiovascular events (HR = 1.57, 95%CI: 1.18-2.09, $P = 0.002$) (Table 3). The incidence rate of cardiovascular events was 0.31 per patient-year in those with clinically significant anxiety compared to 0.20 per patient-year in those without.

Risk of hospitalization: Clinically significant anxiety was associated with an increased risk of all-cause hospitalization (HR = 1.45, 95%CI: 1.15-1.83, $P = 0.002$) (Table 3). The incidence rate of hospitalization was 0.89 per patient-year in those with clinically significant anxiety compared to 0.63 per patient-year in those without.

DISCUSSION

This longitudinal observational study provides compelling evidence for the significant impact of anxiety symptoms on dialysis adherence and complication rates in patients with ESRD. Our findings demonstrate that higher levels of anxiety are associated with poorer treatment adherence across multiple domains and an increased risk of infections, cardio-

Table 1 Baseline characteristics of the study participants

Characteristic	Value (*n* = 250)
Age, years (mean ± SD)	58.3 ± 14.7
Sex, *n* (%)	
Male	142 (56.8)
Female	108 (43.2)
Dialysis modality, *n* (%)	
Hemodialysis	187 (74.8)
Peritoneal dialysis	63 (25.2)
Dialysis vintage, months, median (IQR)	36 (18-72)
Primary cause of ESRD, *n* (%)	
Diabetic nephropathy	95 (38.0)
Hypertensive nephrosclerosis	62 (24.8)
Glomerulonephritis	45 (18.0)
Polycystic kidney disease	23 (9.2)
Other/unknown	25 (10.0)
Comorbidities, *n* (%)	
Diabetes mellitus	128 (51.2)
Hypertension	218 (87.2)
Cardiovascular disease	87 (34.8)
Baseline HADS-A score (mean ± SD)	6.8 ± 4.2
Clinically significant anxiety (HADS-A ≥ 8), *n* (%)	92 (36.8)

IQR: Interquartile range; ESRD: End-stage renal disease; HADS-A: Hospital Anxiety and Depression Scale-Anxiety subscale.

Table 2 Association between anxiety symptoms and dialysis adherence measures

Adherence measure	Effect size	95%CI	*P* value
Missed dialysis sessions (IRR)	1.32	1.18-1.47	< 0.001
Interdialytic weight gain (β)	0.24	0.15-0.33	< 0.001
Medication adherence (OR)	0.85	0.78-0.93	< 0.001

IRR: Incidence rate ratio; OR: Odds ratio; CI: Confidence interval.

Table 3 Complication rates in patients with and without clinically significant anxiety

Complication	Clinically significant anxiety	No clinically significant anxiety	HR (95%CI)	*P* value
Overall complications	0.89 per patient-year	0.53 per patient-year	1.68 (1.32-2.14)	< 0.001
Infections	0.42 per patient-year	0.23 per patient-year	1.89 (1.41-2.53)	< 0.001
Cardiovascular events	0.31 per patient-year	0.20 per patient-year	1.57 (1.18-2.09)	0.002
Hospitalization	0.89 per patient-year	0.63 per patient-year	1.45 (1.15-1.83)	0.002

HR: Hazard ratio; CI: Confidence interval.

vascular events, and hospitalization. The prevalence of clinically significant anxiety in our cohort (36.8% at baseline) is consistent with previous reports on populations undergoing dialysis[14-17]. The slight decrease in anxiety symptoms over the 24-month study period may reflect adaptation to the dialysis regimen over time or the effects of routine clinical care. Despite this observation, the persistently high prevalence of anxiety underscores the need for ongoing psychological assessment and support in this population.

Our results showed a strong association between anxiety symptoms and various measures of dialysis non-adherence. The 32% increase in missed dialysis sessions for each one-point increase in the HADS-A score is particularly concerning, given the critical importance of regular dialysis treatments for maintaining health in patients with ESRD. Similarly, the positive association between anxiety and IDWG suggests that patients who experience anxiety may have difficulty adhering to fluid restrictions, a crucial aspect of dialysis management[18]. The negative impact of anxiety on medication adherence is consistent with findings in other populations with chronic disease[19]. Poor medication adherence in patients who receive dialysis treatment can lead to inadequate control of comorbid conditions, electrolyte imbalances, and increased risk of complications[20]. Our findings highlight the need to address anxiety as a potential barrier to medication adherence in this population.

The observed association between anxiety and increased complication rates is particularly noteworthy. The 68% higher risk of overall complications in patients with clinically significant anxiety underscores the clinical significance of anxiety symptoms in patients in dialysis. The strongest association was observed for infections, with patients with anxiety having nearly twice the risk of developing infectious complications. This finding may be related to the known effects of chronic stress and anxiety on immune function[21], as well as potential behavioral factors such as poor adherence to hygiene practices or delayed reporting of symptoms.

The increased risk of cardiovascular events in patients with high anxiety burden is consistent with the growing body of evidence linking psychological distress to cardiovascular outcomes in various populations[22]. In dialysis, patients who are already at a high risk for cardiovascular disease, anxiety may represent an additional modifiable risk factor that warrants attention. The higher rate of hospitalization among patients with anxiety likely reflects the cumulative impact of poor adherence and increased complications. Frequent hospitalizations not only affect the patients' quality of life but also contribute significantly to healthcare costs in the population with ESRD[23].

Several limitations of our study should be acknowledged. First, while the longitudinal design allows for temporal associations to be established, causality cannot be definitively inferred. Second, reliance on self-reported measures for some variables, particularly adherence to medication, may be subject to recall bias or social desirability effects. Third, while we adjusted for several potential confounders, residual confounding due to unmeasured factors cannot be ruled out. Lastly, our study was conducted in a single geographical region, which may limit the generalizability of our findings to other settings or populations. Despite these limitations, our study has several strengths, including its longitudinal design, comprehensive assessment of both adherence and complications, and use of validated measures of anxiety and adherence. The inclusion of both patients in hemodialysis and peritoneal dialysis enhances the generalizability of our findings to the broader population with ESRD demonstrates that anxiety symptoms in patients in dialysis are associated with poorer treatment adherence and increased rates of infections, cardiovascular events, and hospitalizations.

CONCLUSION

Regular screening for anxiety symptoms and targeted interventions to address high anxiety levels may improve adherence and clinical outcomes in this vulnerable population.

FOOTNOTES

Author contributions: Huang P, Liang XZ, and Wang J designed and are the guarantors of this study; Huang HT, Ma J, and Pang J participated in the data collection, analysis, and interpretation; Huang P drafted the initial version; Zhang YY, Ma CH, Wang SD, and Wang J made critical revisions to this article for important intellectual content. All authors participated in this study and jointly reviewed and edited the manuscript.

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ORIGINAL ARTICLE

Observational Study

Predictive value of nutritional status and serological indicators in elderly patients with mild cognitive impairment

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Abstract

BACKGROUND

Mild cognitive impairment (MCI) in elderly individuals is a transitional stage between normal cognition and dementia. Understanding the risk factors for MCI and identifying those at high risk are extremely important for the elderly population.

AIM

To analyze the risk factors for MCI in the elderly population and construct a clinical prediction model.

METHODS

Total 295 elderly individuals presenting with memory loss diagnosed at Wuxi People's Hospital between March 2021 and March 2024 were included. Comprehensive demographic, clinical, and serological data were collected for analysis. Participants were categorized into either an MCI group or a normal group based on their performance on the Montreal Cognitive Assessment Scale. An elaborate clinical predictive model was developed to predict the likelihood of MCI in stroke patients; its accuracy was evaluated using area under curve values and calibration curves.

RESULTS

The results of the study showed that old age, hypertension, diabetes, hyperlipidemia, smoking, high-salt diet, high-cholesterol diet, decreased red blood count, increased neutrophil lymphocyte ratio and increased low-density lipoprotein cholesterol were risk factors for the onset of MCI, with A high vitamin diet and

elevated high-density lipoprotein cholesterol being protective factors. In addition, the prediction model constructed in this study exhibits good degrees of differentiation and calibration.

CONCLUSION
The risk factors for MCI are diverse. Early identification of individuals at high risk of MCI can better intervene and improve their quality of life of MCI patients.

Key Words: Nutritional status; Serum detection; Cognitive impairment; Mild symptom; Forecast; Risk factor

Core Tip: The degree of cognitive impairment in the elderly is affected by many factors, which makes its early diagnosis still a certain challenge. Nutritional status and serological indicators are believed to be closely related to changes in cognitive function. Therefore, exploring the predictive value of nutritional status and serological indicators in elderly patients with mild cognitive impairment can not only provide a new scientific basis for early diagnosis, intervention and treatment of patients, but also help promote health management strategies in the field of public health.

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INTRODUCTION

Mild cognitive impairment (MCI) is a transitional phase between normal aging and dementia in which people experience mild declines in memory or other cognitive functions that go beyond normal aging but do not yet meet the diagnostic criteria for dementia[1]. MCI is often considered a precursor stage to types of dementia such as Alzheimer's disease (AD), in which patients may show functional decline in one or more areas of memory, language, attention, executive function, or visuospatial ability[2]. MCI currently has a prevalence of more than 15% in older age groups and progresses to dementia at a rate of 8% to 15% per year[3]. As a precursor symptom of various neurodegenerative diseases, early diagnosis and intervention of MCI are of vital significance to delay or prevent cognitive decline and improve the quality of life of the elderly[4]. However, the current diagnosis of MCI primarily depends on clinical assessment and neuropsychological tests, which, although sensitive and specific, are often constrained by subjective judgment, time consumption, and operational complexity[5]. Therefore, the exploration of more objective, convenient, and cost-effective methods for predicting MCI has emerged as a focal point in neuroscience and gerontology research.

In recent years, significant progress has been made in the study of nutrition in the field of senile cognitive impairment [6]. Previous studies have shown that there is a close correlation between nutritional status and cognitive function in the elderly[7,8]. Insufficient food, poor nutrition, and unbalanced nutrient intake may lead to cognitive decline in the elderly, thereby increasing the risk of MCI[9]. In terms of nutritional status, a number of clinical trials and epidemiological investigations have shown that a balanced diet and increased intake of foods rich in unsaturated fatty acids, antioxidants and B vitamins can help improve or delay cognitive decline[10]. For example, the Mediterranean diet pattern, which is high in healthy fats, whole grains, vegetables and fruits, has been shown to have a positive effect on protecting cognitive function [11]. This may be because malnutrition leads to an inadequate supply of energy to neurons, affecting the synthesis and release of neurotransmitters, which impairs cognitive function[12]. And certain nutrients, such as vitamins, cholesterol, minerals, *etc.* are essential for maintaining the normal structure and function of the nervous system, and their deficiency can accelerate cognitive decline[13,14]. In addition, some objective indicators that can reflect the physiological and pathological state of the body, such as red blood cell count, neutrophil count, total cholesterol, low density lipoprotein, interleukin, *etc.*, have gradually attracted attention in the diagnosis and prediction of MCI[15,16]. Although existing studies have initially revealed the relationship between nutritional status and serological indicators and cognitive function, their predictive value in elderly patients with MCI needs to be further explored.

In this study, elderly patients presenting for memory decline were divided into MCI group and normal group using the Montreal Cognitive Assessment Scale (MoCA). Through comprehensive analysis of demographic information, diet information and serological information between the two groups, to explore the predictive effect of these factors on the occurrence of MCI. This study can provide scientific basis for the development of personalized nutritional intervention programs for patients with MCI, which can help delay or prevent the further deterioration of cognitive function. This study is expected to provide clinicians with a simple and practical method for early identification and intervention of elderly patients with MCI, so as to reduce the risk of AD occurrence and improve the quality of life of the elderly.

MATERIALS AND METHODS

Patient population

A total of 295 elderly patients who came to Wuxi People's Hospital for memory loss were included in this study. Patients were collected from March 2021 to March 2024. Their inclusion criteria are as follows: (1) Patients were ≥ 50 years old; (2) Patients complained of memory loss, or family members reported memory loss; (3) Patients without serious underlying diseases or organ failure; (4) Patients without other neurological disorders that may cause cognitive impairment; and (5) Patients with complete clinical data. These patients all met the following exclusion criteria: (1) Patients who have been diagnosed with dementia[17]; (2) Patients with severe neurological diseases, such as Parkinson's disease, stroke, multiple sclerosis, encephalitis, *etc.*; (3) Patients with severe mental illness, such as depression, schizophrenia, bipolar disorder, *etc.*; (4) Patients with a history or current use of psychotropic drugs; and (5) Patients with severe speech impairment.

Grouping standard

The MoCA scale was used to assess patients' cognitive function. The MoCA scale covers multiple cognitive domains, including attention, executive function, memory, language, visuospatial ability, abstract thinking, computation, and orientation[18]. The total score of the MoCA scale is 30 points, and subjects with less than 12 years of education are added 1 point to the total score to adjust for the effect of education level on the score. Patients with a final score below 26 were assigned to the MCI group, otherwise they were assigned to the normal group.

Information collection

The data of all patients were collected and analyzed through structured questionnaire and medical record system. The patient data collected mainly included demographic information, dietary information and serological test results. Demographic information included age, sex, body mass index (BMI), hypertension, diabetes, hyperlipidemia, cardiovascular disease, lung disease and kidney disease. Dietary information includes smoking, alcohol consumption, tea, coffee, spicy diets, high-sugar diets, high-fried diets, high-salt diets, high-cholesterol diets, high-vitamin diets, and types of cooking oil. Serological measures include red blood cell (RBC) count, white blood cell count, neutrophil lymphocyte ratio (NLR), interleukin-6, total cholesterol (TC), triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).

Statistical analysis

SPSS 23.0 was used to statistically analyse the data. Data included for continuous variables that met normal distribution were expressed as mean ± SD and comparisons between groups were made using the independent samples *t*-test. Data that did not conform to normal distribution were expressed as median (quartiles) and comparisons between groups were made using the Kruskal-Wallis test, categorical count data were expressed as percentages and comparisons between groups were made using the chi-square test. Univariate and multivariate logistic regression was used to analyse the extent of the influence of each factor on MCI, and the odds ratio (OR) values and their 95% confidence intervals (95%CI) were calculated. Variables with $P < 0.05$ in univariate Logistic regression will be included in multivariate Logistic regression analysis. $P < 0.05$ was considered as statistically significant difference, and tests were two-sided.

Clinical prediction model

A clinical prediction model was constructed based on Logistic regression to predict the risk of MCI in the elderly. The 295 patients were randomly divided into a train set (206 patients) and a text set (89 patients) at a ratio of 7:3 for internal validation of the model. Then *t*-test or Pearson χ^2 test was used to check the balance between the train set and the test set. A nomogram model was drawn based on multivariate Logistic regression. The variance inflation factor (VIF) was calculated for collinearity diagnosis. VIF < 5 was considered to be non-multicollinearity. The area under curve (AUC) of receiver operating characteristic (ROC) was used to evaluate the differentiation of the model. Hosmer-Lemeshow was used to evaluate the calibration degree of the model. When $P > 0.05$, it indicated that there was no statistical difference between the predicted value and the observed value, and the model fit was good. Calibration curve was used to evaluate the calibration degree of the model, and decision acceptance curve (DAC) was used to evaluate the clinical application value of the model. In addition, computational accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were used to evaluate the performance of the model and evaluate the cost-effectiveness of different interventions.

RESULTS

General information

Among 295 elderly patients, 161 (54.58%) were diagnosed with MCI by MoCA scale and 134 (45.42%) were normal (Table 1). The mean age of the MCI group was 72.63 ± 8.71, and that of the normal group was 68.33 ± 7.56, and the disparity observed between the two groups was found to be statistically significant. ($P < 0.05$). No statistical differences in gender composition ($P > 0.05$) and BMI ($P > 0.05$) were observed between the two groups (Table 1).

Table 1 Difference of demographic information, dietary information and serological information between two groups

Variables	Total (*n* = 295)	NMCI group (*n* = 134)	MCI group (*n* = 161)	Statistic	*P* value
Demographic information					
Age, mean ± SD	70.68 ± 8.47	68.33 ± 7.56	72.63 ± 8.71	t = -4.49	< 0.001
Sex, *n* (%)				χ^2 = 0.42	0.516
Male	137 (46.44)	65 (48.51)	72 (44.72)		
Female	158 (53.56)	69 (51.49)	89 (55.28)		
BMI, mean ± SD	22.57 ± 4.15	22.75 ± 3.78	22.43 ± 4.45	t = 0.65	0.514
Hypertension, *n* (%)				χ^2 = 4.47	0.035
No	211 (71.53)	104 (77.61)	107 (66.46)		
Yes	84 (28.47)	30 (22.39)	54 (33.54)		
Diabetes, *n* (%)				χ^2 = 10.18	0.001
No	228 (77.29)	115 (85.82)	113 (70.19)		
Yes	67 (22.71)	19 (14.18)	48 (29.81)		
Hyperlipemia, *n* (%)				χ^2 = 4.23	0.040
No	233 (78.98)	113 (84.33)	120 (74.53)		
Yes	62 (21.02)	21 (15.67)	41 (25.47)		
Cardiovascular disease, *n* (%)				χ^2 = 4.59	0.032
No	225 (76.27)	110 (82.09)	115 (71.43)		
Yes	70 (23.73)	24 (17.91)	46 (28.57)		
Pulmonary disease, *n* (%)				χ^2 = 0.35	0.554
No	256 (86.78)	118 (88.06)	138 (85.71)		
Yes	39 (13.22)	16 (11.94)	23 (14.29)		
Kidney disease, *n* (%)				χ^2 = 0.06	0.808
No	265 (89.83)	121 (90.30)	144 (89.44)		
Yes	30 (10.17)	13 (9.70)	17 (10.56)		
Dietary information					
Smoking, *n* (%)				χ^2 = 7.10	0.008
No	178 (60.34)	92 (68.66)	86 (53.42)		
Yes	117 (39.66)	42 (31.34)	75 (46.58)		
Drinking, *n* (%)				χ^2 = 0.10	0.750
No	190 (64.41)	85 (63.43)	105 (65.22)		
Yes	105 (35.59)	49 (36.57)	56 (34.78)		
Tea, *n* (%)				χ^2 = 3.32	0.069
No	232 (78.64)	99 (73.88)	133 (82.61)		
Yes	63 (21.36)	35 (26.12)	28 (17.39)		
Coffee, *n* (%)				χ^2 = 4.55	0.033
No	250 (84.75)	107 (79.85)	143 (88.82)		
Yes	45 (15.25)	27 (20.15)	18 (11.18)		
Spicy diet, *n* (%)				χ^2 = 0.11	0.735
No	204 (69.15)	94 (70.15)	110 (68.32)		
Yes	91 (30.85)	40 (29.85)	51 (31.68)		
High-sweet diet, *n* (%)				χ^2 = 0.05	0.815

No	236 (80.00)	108 (80.60)	128 (79.50)		
Yes	59 (20.00)	26 (19.40)	33 (20.50)		
High fried diet, *n* (%)				χ^2 = 0.67	0.413
No	236 (80.00)	110 (82.09)	126 (78.26)		
Yes	59 (20.00)	24 (17.91)	35 (21.74)		
High-salt diet, *n* (%)				χ^2 = 7.42	0.006
No	203 (68.81)	103 (76.87)	100 (62.11)		
Yes	92 (31.19)	31 (23.13)	61 (37.89)		
High cholesterol diet, *n* (%)				χ^2 = 4.69	0.030
No	220 (74.58)	108 (80.60)	112 (69.57)		
Yes	75 (25.42)	26 (19.40)	49 (30.43)		
High-vitamin diet, *n* (%)				χ^2 = 5.62	0.018
No	176 (59.66)	70 (52.24)	106 (65.84)		
Yes	119 (40.34)	64 (47.76)	55 (34.16)		
Edible oil type, *n* (%)				χ^2 = 0.47	0.494
Vegetable oil	192 (65.08)	90 (67.16)	102 (63.35)		
Animal oil	103 (34.92)	44 (32.84)	59 (36.65)		
Serological indicators					
RBC, mean ± SD	4.65 ± 1.02	4.83 ± 1.05	4.51 ± 0.96	*t* = 2.80	0.005
WBC, mean ± SD	7.17 ± 3.37	6.97 ± 3.45	7.33 ± 3.32	*t* = -0.91	0.362
NLR, mean ± SD	2.25 ± 0.61	2.02 ± 0.53	2.43 ± 0.61	*t* = -6.12	< 0.001
PLT, mean ± SD	168.71 ± 29.96	171.31 ± 31.69	166.54 ± 28.37	*t* = 1.36	0.174
IL-6 increases, *n* (%)				χ^2 = 2.18	0.140
No	219 (74.24)	105 (78.36)	114 (70.81)		
Yes	76 (25.76)	29 (21.64)	47 (29.19)		
TC, mean ± SD	5.01 ± 1.21	4.92 ± 1.17	5.10 ± 1.25	*t* = -1.27	0.204
TG, mean ± SD	1.29 ± 0.40	1.25 ± 0.36	1.32 ± 0.43	*t* = -1.31	0.191
HDL-C, mean ± SD	1.36 ± 0.25	1.41 ± 0.27	1.33 ± 0.21	*t* = 2.74	0.007
LDL-C, mean ± SD	3.29 ± 0.41	3.22 ± 0.31	3.35 ± 0.47	*t* = -2.96	0.003

NMCI: Non-mild cognitive impairment; MCI: Mild cognitive impairment; BMI: Body mass index; RBC: Red blood cell; WBC: White blood cell; NLR: Neutrophil lymphocyte ratio; PLT: Platelet; IL-6: Interleukin-6; TC: Total cholesterol; TG: Triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol.

Difference analysis between MCI group and normal group

There were significant differences in the prevalence of hypertension (33.54% *vs* 22.39%, $P < 0.05$), diabetes (29.81% *vs* 14.18%, $P < 0.005$), hyperlipidemia (25.47% *vs* 15.67%, $P < 0.05$) and cardiovascular disease (28.57% *vs* 17.91%, $P < 0.05$) between MCI group and normal group (Table 1). In relation to dietary information, significant differences were observed between the two groups in the proportion of patients with smoking (46.58% *vs* 31.34%, $P < 0.05$), coffee (11.18% *vs* 20.15%, $P < 0.05$), high-salt diet (37.89% *vs* 23.13%, $P < 0.05$), high-cholesterol diet (30.43% *vs* 19.40%, $P < 0.05$), and high-vitamin diet (34.16% *vs* 47.76%, $P < 0.05$; Table 1). In addition, there were notable discrepancies between the two groups with regard to RBC ($P < 0.05$), NLR ($P < 0.05$), HDL-C ($P < 0.05$), and LDL-C ($P < 0.05$; Table 1). No statistical differences were found between the two groups in other factors.

Logistic regression analysis between MCI group and normal group

Univariate Logistic regression showed that old age, hypertension, diabetes, hyperlipidemia, cardiovascular disease, smoking, high-salt diet, high-cholesterol diet, decreased RBC, increased NLR, and elevated LDL-C were associated with increased risk of MCI (Table 2). These variables were included in multivariate Logistic regression analysis, and the results showed that advanced age was significantly correlated with an elevated risk of MCI (OR = 1.12, 95%CI: 1.08-1.17, $P < 0.05$; Table 2). Elderly patients with basic diseases, such as hypertension (OR = 3.28, 95%CI: 1.50-7.16, $P < 0.05$), diabetes

Table 2 Logistic regression analysis of demographic information, dietary information and serological information between the two groups

Variables	Univariate Logistic analysis					Multivariate Logistic analysis				
	β	SE	Z	*P* value	OR (95%CI)	β	SE	Z	*P* value	OR (95%CI)
Age	0.06	0.02	4.23	< 0.001	1.07 (1.03-1.10)	0.12	0.02	5.25	< 0.001	1.12 (1.08-1.17)
Hypertension										
No					1.00 (Reference)					1.00 (Reference)
Yes	0.56	0.27	2.10	0.036	1.75 (1.04-2.95)	1.19	0.40	2.98	0.003	3.28 (1.50-7.16)
Diabetes										
No					1.00 (Reference)					1.00 (Reference)
Yes	0.94	0.30	3.13	0.002	2.57 (1.42-4.64)	1.07	0.40	2.65	0.008	2.91 (1.32-6.40)
Hyperlipemia										
No					1.00 (Reference)					1.00 (Reference)
Yes	0.61	0.30	2.04	0.041	1.84 (1.02-3.30)	0.83	0.39	2.14	0.032	2.30 (1.07-4.92)
Cardiovascular disease										
No					1.00 (Reference)					1.00 (Reference)
Yes	0.61	0.28	2.13	0.033	1.83 (1.05-3.20)	0.55	0.38	1.42	0.154	1.73 (0.81-3.66)
Smoking										
No					1.00 (Reference)					1.00 (Reference)
Yes	0.65	0.24	2.65	0.008	1.91 (1.18-3.08)	0.70	0.32	2.19	0.029	2.02 (1.08-3.80)
Coffee										
No					1.00 (Reference)					1.00 (Reference)
Yes	-0.70	0.33	-2.11	0.035	0.50 (0.26-0.95)	-0.14	0.45	-0.31	0.758	0.87 (0.36-2.11)
High-salt diet										
No					1.00 (Reference)					1.00 (Reference)
Yes	0.71	0.26	2.70	0.007	2.03 (1.21-3.38)	1.25	0.36	3.45	< 0.001	3.47 (1.71-7.05)
High cholesterol diet										
No					1.00 (Reference)					1.00 (Reference)
Yes	0.60	0.28	2.15	0.031	1.82 (1.05-3.13)	0.88	0.37	2.37	0.018	2.41 (1.16-4.98)
High-vitamin diet										
No					1.00 (Reference)					1.00 (Reference)
Yes	-0.57	0.24	-2.36	0.018	0.57 (0.35-0.91)	-0.71	0.32	-2.18	0.029	0.49 (0.26-0.93)
RBC	-0.33	0.12	-2.74	0.006	0.72 (0.57-0.91)	-0.60	0.17	-3.59	< 0.001	0.55 (0.39-0.76)
NLR	1.25	0.23	5.48	< 0.001	3.50 (2.24-5.48)	1.95	0.34	5.78	< 0.001	7.05 (3.64-13.65)
HDL-C	-1.35	0.50	-2.73	0.006	0.26 (0.10-0.68)	-2.04	0.65	-3.14	0.002	0.13 (0.04-0.46)
LDL-C	0.84	0.30	2.77	0.006	2.31 (1.28-4.18)	0.76	0.38	1.99	0.047	2.14 (1.01-4.53)

OR: Odds ratio; 95%CI: 95% confidence interval; RBC: Red blood cell; NLR: Neutrophil lymphocyte ratio; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol.

(OR = 2.91, 95%CI: 1.32-6.40, $P < 0.05$), and hyperlipidemia (OR = 2.30, 95%CI: 1.07-4.92, $P < 0.05$), were also associated with an increased risk of MCI (Table 2). Smoking (OR = 2.02, 95%CI: 1.08-3.80, $P < 0.05$), high salt diet (OR = 3.47, 95%CI: 1.71-7.05, $P < 0.05$), high cholesterol diet (OR = 2.41, 95%CI: 1.16-4.98, $P < 0.05$) were associated with a high risk of MCI. High vitamin diet (OR = 0.49, 95%CI: 0.26-0.93, $P < 0.05$) were protective factors for MCI. Decreased RBC (OR = 0.55, 95%CI: 0.39-0.76, $P < 0.05$) and increased NLR (OR = 7.05, 95%CI: 3.64-13.65, $P < 0.05$) and increased LDL-C (OR = 2.14, 95%CI: 1.01-4.53, $P = 0.05$) in elderly patients may be risk factors for MCI and increased LDL-C (OR = 0.13, 95%CI: 0.04-0.46, $P < 0.05$) may be protective factors (Table 2).

Construction of clinical prediction model

A prediction model for MCI risk in the elderly was constructed based on Logistic regression. The nomograph was constructed using nine factors: Hypertension, diabetes, smoking, high-salt diet, age, NLR, TC, HDL-C and LDL-C (Figure 1). In the training set, the AUC of the ROC plotted by the prediction model was 0.86 (95%CI: 0.81-0.91; Figure 2A). Calibration curve results showed that the model fits well and there was no significant difference between predicted and observed values (Hosmer-Lemeshow $P > 0.05$; Figure 2B). The DAC curve showed that when the risk threshold exceeds 0.1, the corresponding intervention had a positive benefit (Figure 2C). When the cut-off value was 0.595, the model has the best prediction effect, and the accuracy was 0.80 (95%CI: 0.73-0.85), the sensitivity was 0.87 (95%CI: 0.80-0.94), the specificity was 0.73 (95%CI: 0.65-0.81), the PPV was 0.73 (95%CI: 0.65-0.81), and the NPV was 0.87 (95%CI: 0.80-0.84; Table 3).

Validation of clinical predictive models

In this study, internal validation was used to test the stability of the prediction model. Before internal validation, the balance check results showed no significant difference between the training set and the validation set (Supplementary Table 1). Moreover, the VIF values of the variables included in the prediction model were all less than 5, indicating that there was no multicollinearity between the variables (Supplementary Table 2).

In the validation set, the AUC was 0.79 (95%CI: 0.70-0.89; Figure 2D). The results of the calibration curve indicated that the model demonstrated a strong fit (Hosmer-Lemeshow $P > 0.05$; Figure 2E). The DAC results showed that when the risk threshold was greater than 0.1, the intervention can obtain a good return effect (Figure 2F). When the cutoff value was 0.595, the model of validation set had the best prediction effect. At this time, the accuracy was 0.73 (95%CI: 0.63-0.82), the sensitivity was 0.80 (95%CI: 0.68-0.92), the specificity was 0.67 (95%CI: 0.54-0.80), the PPV was 0.67 (95%CI: 0.53-0.80), and the NPV was 0.80 (95%CI: 0.68-0.93; Table 3).

DISCUSSION

MCI, as an intermediate state between normal aging and dementia, is characterized by a slight decline in cognitive functions (such as memory, language, attention, reasoning, *etc.*), but the decline is not large enough to affect an individual's ability to function in daily life[19]. MCI is relatively common in older people, especially in those over 65 years of age[20]. MCI may cause psychological disorders, social disorders, and impaired functional independence in elderly patients, and once it progresses to dementia, it will put a huge burden on the patient's family and society[21]. Since MCI is in an intervenable stage, early identification and treatment are important to delay the process of cognitive decline and avoid deterioration into dementia[22]. In this study, nutritional status, dietary factors and serological indicators were used to investigate their ability to predict the risk of MCI. The results showed that old age, combined with hypertension, diabetes or hyperlipidemia, smoking, high-salt diet, high-cholesterol diet, decreased RBC, increased NLR, and elevated LDL-C may be independent risk factors for the increased risk of MCI in the elderly. High vitamin diet and high HDL-C may be protective factors for MCI. The results of this study can provide theoretical support for more accurate identification of high-risk groups of MCI and timely implementation of targeted intervention measures.

The results of this study found that advanced age is an important risk factor for the onset of MCI. As we age, the brain undergoes a series of structural and functional changes[23]. For example, a decrease in the number of brain cells, decreased levels of neurotransmitter substances, and reduced blood circulation in the brain can all lead to a decline in cognitive function[24]. Previous studies have shown that aging leads to the accumulation of more neurofibrillary tangles and amyloid plaques in the brain[25]. These are key pathological features of AD and other forms of dementia, and are also associated with susceptibility to MCI[26]. In addition, this study also found that some underlying diseases in the elderly group are also risk factors for MCI. Previous studies have reported that high blood pressure, diabetes, and high blood lipids increase the risk of cognitive impairment, which is consistent with the findings of this study[27,28]. Long-term hypertension can lead to hardening of the small artery wall, especially the small blood vessels in the brain, and then lead to changes in the structure and function of cerebral vessels, such as thickening of the blood vessel wall, narrowing of the lumen, and decreased vascular elasticity[29]. The alterations lead to a reduction in cerebral blood supply, resulting in hypoxia and malnutrition of the brain tissue, thereby impacting the normal functioning of neurons and potentially leading to cognitive decline. This study also found that a high-salt diet was associated with an increased risk of developing MCI, possibly because of the strong association between a high-salt diet and high blood pressure, and because a high-salt diet itself can also affect inflammatory responses and oxidative stress levels in the body. Abnormal blood glucose metabolism in diabetic patients not only directly damages blood vessels, but also leads to systemic inflammation and oxidative stress through insulin resistance and hyperinsulinemia. These processes can promote brain microvascular disease, neuronal damage, and cognitive decline[30]. In addition, the results of the study also showed that hyperlipidemia is an important risk factor for the onset of MCI, which is similar to previous studies[31]. In addition, factors associated with hyperlipidemia, such as a high-cholesterol diet and high LDL-C, were also found to be associated with an increased risk of MCI. High levels of cholesterol and LDL-C are associated with an increased risk of atherosclerosis[32]. Atherosclerosis affects not only large blood vessels, but also small blood vessels in the brain, resulting in reduced blood flow to the brain and impaired cognitive function. In addition, dyslipidemia may damage neurons directly or indirectly by promoting inflammatory responses, oxidative stress, and apoptosis[33]. However, its specific mechanism and molecular principle are worthy of further investigation.

Table 3 Confusion matrix analysis of clinical predictive models

Data	AUC (95%CI)	Accuracy (95%CI)	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	Cut off
Train	0.86 (0.81-0.91)	0.80 (0.73-0.85)	0.87 (0.80-0.94)	0.73 (0.65-0.81)	0.73 (0.65-0.81)	0.87 (0.80-0.94)	0.595
Test	0.79 (0.70-0.89)	0.73 (0.63-0.82)	0.80 (0.68-0.92)	0.67 (0.54-0.80)	0.67 (0.53-0.80)	0.80 (0.68-0.93)	0.595

95%CI: 95% confidence interval; AUC: Area under curve; PPV: Positive predictive value; NPV: Negative predictive value.

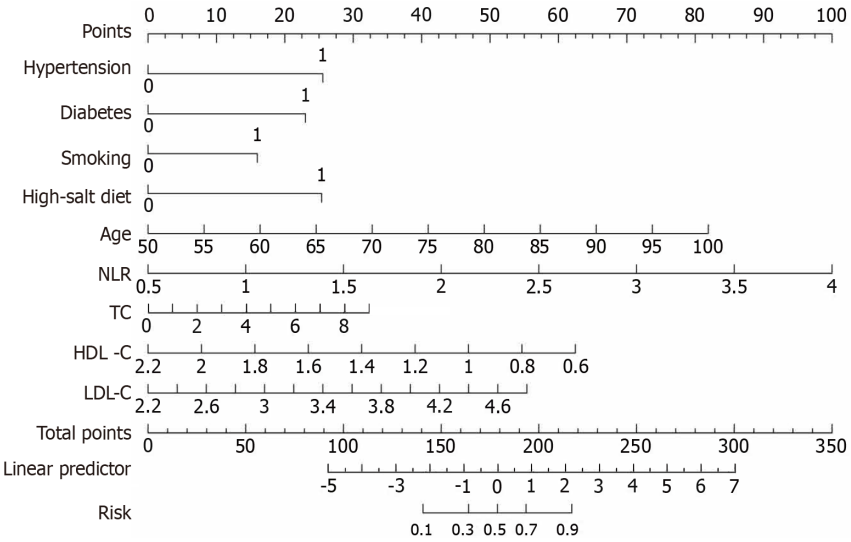

Figure 1 The nomogram model for predicting the risk of mild cognitive impairment onset. NLR: Neutrophil lymphocyte ratio; TC: Total cholesterol; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol.

In addition, this study found that smoking was associated with an increased risk of MCI. Smoking has been widely recognized to have a negative impact on cognitive function. Nicotine and other harmful chemicals can affect brain function through a variety of mechanisms, including promoting oxidative stress, inflammatory responses, and cerebrovascular dysfunction. These processes may accelerate neuronal degeneration and cognitive decline, thereby increasing the risk of MCI[34]. Long-term smoking may also cause hardening and narrowing of blood vessels, reduce the blood supply to the brain, affect the oxygen and nutrient supply to the brain, and further exacerbate the decline in cognitive function[35]. This study found that a high-vitamin diet and high levels of HDL-C were protective factors for MCI. Vitamin D strengthens the connections between neurons and is essential for maintaining normal cognitive function. Studies have shown that vitamin D deficiency makes neural networks more vulnerable to the effects of enzyme degradation, reducing the number and strength of connections between neurons in the hippocampus, which can lead to cognitive decline[36]. Vitamin E is an antioxidant that protects nerve cells from oxidative stress and has a protective effect on cognitive function[37]. And folic acid promotes the synthesis of neurotransmitters in the brain, such as dopamine and serotonin, which are essential for maintaining normal cognitive function. In addition, folic acid also helps reduce harmful substances that damage brain vessels, and assists in DNA synthesis and improves memory. Vitamin B2 (riboflavin) plays an important role in brain cell development and regeneration, and can activate brain function[38]. The decrease of RBC and the increase of NLR may be related to the inflammatory response in the body, which may aggravate the decline of neurological function in elderly patients. However, further research is needed to explore the specific mechanisms.

However, there are some limitations to this study. First of all, this study is a retrospective analysis, and there is a tendency of recall bias in the process of collecting patients' lifestyle and dietary habits. Second, the sample source of this study is single, resulting in limited extrapolation of results. Finally, changes in nutritional status and serological indicators in older adults are often influenced by multiple factors, including physiological aging, chronic disease, and drug use. In addition, the lack of in-depth research on the mechanism of the influence of the identified risk factors on MCI limits the clinical application value of the findings. At the same time, most of the existing studies were cross-sectional designs and failed to include longitudinal follow-up data, resulting in insufficient understanding of the evolution of risk factors over time and their impact on the progression of MCI. Moreover, the research is mainly focused on specific populations and environments, and the applicability of the model in different ethnic and regional populations is not fully tested, which may lead to the generality and accuracy of the model being questioned. Therefore, when evaluating the relationship between these indicators and cognitive function, it is necessary to consider a variety of factors in order to reach a more accurate conclusion.

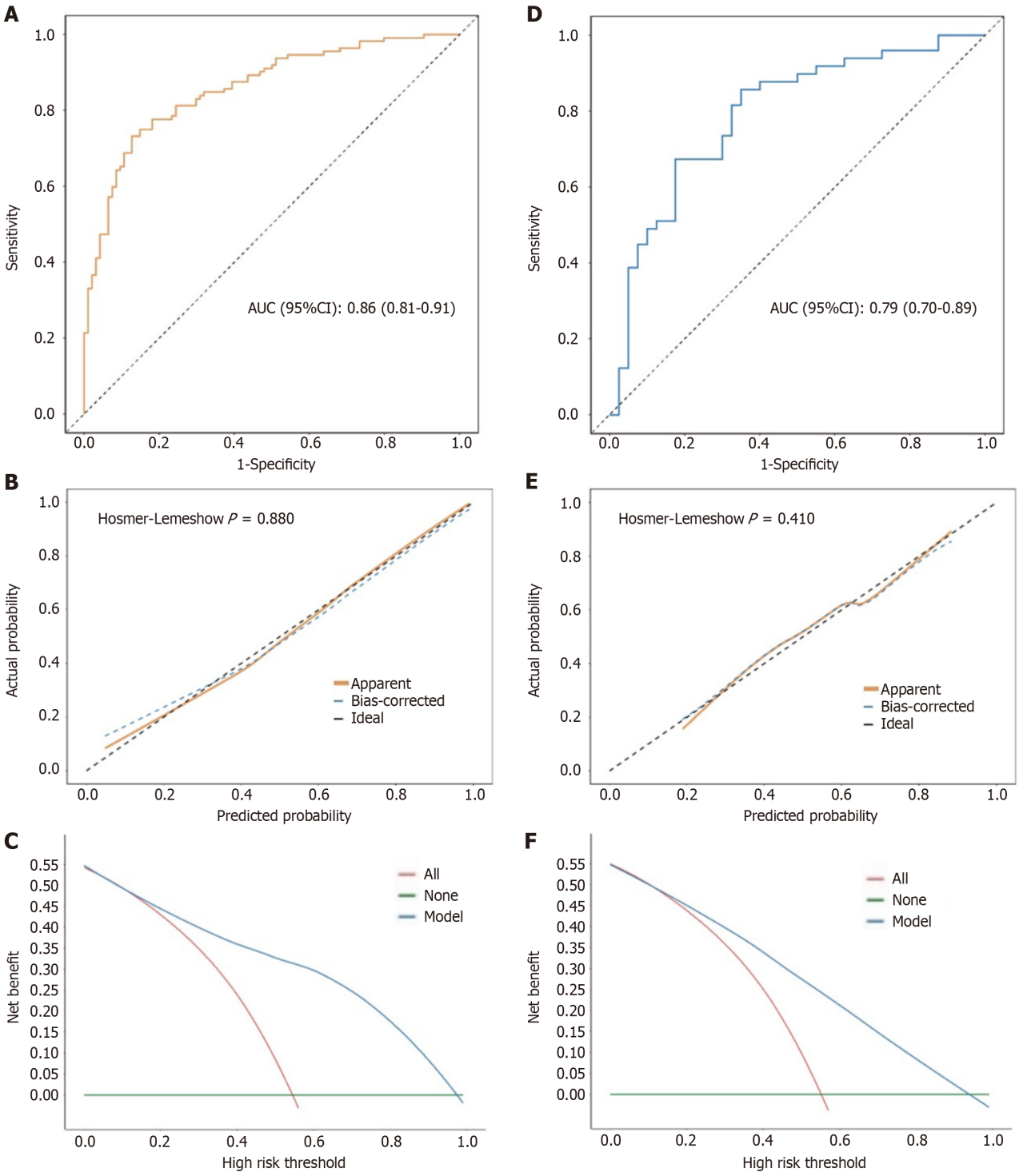

Figure 2 Receiver operating characteristic curves, calibration curves and decision acceptance curve analysis for training and testing sets. A-C: Receiver operating characteristic (ROC), calibration curve, and decision acceptance curve (DAC) for the training set; D-F: ROC, calibration curve, and DAC for the testing set. AUC: Area under curve.

CONCLUSION

Through comprehensive analysis of demographic information, dietary information and serological test results in the elderly population, this study discussed the risk factors of MCI in the elderly population, and built a prediction model for predicting the incidence of MCI in elderly patients. The results of the study showed that old age, hypertension, diabetes, hyperlipidemia, smoking, high-salt diet, high-cholesterol diet, decreased RBC, increased NLR and increased LDL-C were risk factors for the onset of MCI. High vitamin diet and elevated HDL-C were protective factors. In addition, the prediction model constructed in this study has good differentiation and calibration degree. The findings of this study uncover numerous risk factors contributing to the heightened susceptibility to MCI in the elderly population, offering crucial theoretical insights for etiological exploration and clinical management of MCI. Furthermore, leveraging the

predictive model enables accurate identification of high-risk cohorts for MCI, facilitating timely implementation of targeted interventions and averting further progression into dementia. The outcomes of this study hold significant clinical and practical implications for managing and preventing MCI in patients.

FOOTNOTES

Author contributions: Hong K designed research; Yang Y performed research; Lu SR, Xu Q and Yu J contributed new reagents or analytic tools; Wang Z analyzed data; Yang Y and Zhang BS wrote the paper.

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Prospective Study

Network analysis of adolescent non-suicidal self-injury subgroups identified through latent profile analysis

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Abstract

BACKGROUND

Non-suicidal self-injury (NSSI) is common among adolescents and frequently co-occurs with depression. Understanding the distinct patterns of NSSI behaviors, along with their associated risk and protective factors, is crucial for developing effective interventions.

AIM

To classify NSSI behaviors and examine interactions between risk and resilience factors in Chinese adolescents.

METHODS

A cross-sectional study involving 3967 Chinese students (51.7% female, mean age 13.58 ± 2.24 years) who completed questionnaires on parenting styles, bullying, childhood maltreatment, depression, resilience, and NSSI. Latent profile analysis (LPA) was used to identify NSSI subtypes, and network analysis explored interactions between risk and resilience factors.

RESULTS
Three NSSI subtypes were identified: NSSI with depression (18.8%), NSSI without depression (12.3%), and neither (68.9%). Bullying was the central risk factor across subtypes, while emotional control and family support were key protective factors. Statistical analyses showed significant differences between groups ($P < 0.001$).

CONCLUSION
This study identified three NSSI subtypes among Chinese adolescents. Bullying emerged as a central risk factor, while emotional control and family support were key protective factors. Targeting these areas may help reduce NSSI behaviors in this population.

Key Words: Non-suicidal self-injury; Adolescent; Network analysis; Latent profile analysis; Resilience

Core Tip: Latent profile analysis (LPA): Utilized LPA based on self-injury and patient health questionnaire-9 depression assessments to uncover distinct non-suicidal self-injury (NSSI) profiles in adolescents, addressing the hypothesized heterogeneity between NSSI with and without depression. Network analysis insights: Identified differences in risk and resilience factors across NSSI subgroups. Bullying and depression connection: Demonstrated a strong link between bullying and depressive symptoms in NSSI subgroups. Intervention focal points: Pinpointed emotional control and family support as key areas for targeted interventions derived from LPA findings.

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INTRODUCTION

Non-suicidal self-injury (NSSI), defined as deliberate self-harm without suicidal intent, is an escalating public health concern, particularly among adolescents. Common methods include cutting, scratching, and hitting oneself-behaviors prevalent worldwide. Studies indicate that approximately 17.2% of adolescents in non-clinical settings engage in NSSI, with rates as high as 27.4% reported among Chinese adolescents aged 13-18 years[1,2]. The high incidence of NSSI in China highlights the urgent need for effective interventions, as individuals engaging in NSSI have a 66-fold increased risk of suicide[3].

The etiology of NSSI is complex, involving genetic, psychological, and sociocultural factors. Significant contributors include chronic stress, adverse childhood experiences, and digital media use[4]. Emotional dysregulation resulting from childhood trauma and a lack of parental support are key predictors of NSSI[5,6]. In China, societal factors such as academic pressure, filial piety, and traditional family dynamics further exacerbate these risks.

Despite extensive research on NSSI risk factors, a gap remains in understanding how these factors interact within specific adolescent subgroups. Existing studies often employ binary classifications, which fail to capture the complexity of these behaviors. This oversimplification overlooks the interplay between risk factors and protective factors-such as resilience and emotional regulation-that are crucial for developing effective interventions[7].

Latent profile analysis (LPA) offers a more nuanced method for identifying NSSI subtypes by classifying adolescents based on their behaviors and associated factors. Network analysis further explores the interactions among risk and resilience factors[8], revealing how these elements interrelate across different subtypes.

This study fills a critical gap by integrating LPA and network analysis to examine NSSI among Chinese adolescents. We identify distinct NSSI subtypes and analyze how risk factors-such as bullying, parenting style, and digital media use-interact with protective factors such as emotional control (EC) and SF within these subtypes. Our research provides new insights into the underlying mechanisms of NSSI, offering implications for tailored interventions to meet the diverse needs of adolescent subgroups.

MATERIALS AND METHODS

Participants

Participants were recruited from the Yuxi cohort of the Mental Health Survey for Children and Adolescents, which is part of the broader Yunnan Mental Health Survey. We employed a two-stage cluster sampling technique to obtain a representative sample of adolescents aged 10-18 years. In the first stage, schools were randomly selected using probability proportional to size sampling. In the second stage, within each selected school, 2-4 classes from each grade level were

chosen through random sampling to participate in the study. The survey was conducted in two phases: Initially, participants completed a self-administered questionnaire, followed by a diagnostic assessment for those who screened positive, conducted by qualified psychiatric professionals. The study was conducted in accordance with ethical standards, with approval from the Ethics Committee of Kunming Medical University (Approval Number: KMMU2020MEC047). Written informed consent was obtained from the legal guardians of all participants in September 2021.

Measures

Table 1 presents the key details regarding the measures used in this study.

Statistical analysis

Our statistical analysis comprised several key steps: Handling missing data, performing LPA, and conducting network analysis, which included network estimation, inference, stability assessment, and comparison. All analyses were conducted using R version 4.3.1. Specific packages used included "qgraph" for network visualization "bootnet" for network stability[9], and "NetworkComparisonTest" for network comparison.

Missing data handling: Missing data were addressed using full information maximum likelihood (FIML) estimation, allowing the use of all available data without imputing values[10]. FIML provides unbiased parameter estimates under the assumption of data missing at random, avoiding biases from methods like listwise deletion. Sensitivity analyses confirmed that missing data did not significantly affect the findings, ensuring the robustness of the results.

LPA: We conducted LPA to classify adolescent subgroups based on NSSI behaviors and depressive symptoms measured by the modified adolescents' self-harm survey and the patient health questionnaire-9. LPA is suitable for identifying hidden subgroups, providing a nuanced understanding of heterogeneity in NSSI behaviors and depression levels.

To determine the optimal number of latent profiles, we explored models with varying profile numbers. Model selection was guided by the Akaike information criterion (AIC), Bayesian information criterion (BIC), and adjusted BIC (aBIC), where lower values indicate better fit[11]. We used the Lo-Mendell-Rubin adjusted likelihood ratio test and bootstrapped likelihood ratio test to compare models, considering P values less than 0.05 as a significant improvement in fit. An entropy value assessed classification accuracy; our entropy of 0.89 suggested excellent classification quality.

Network analysis: Network analysis explored interactions between risk and resilience factors across the NSSI subgroups, following these steps: (1) Network Estimation: The Gaussian graphical model with graphical LASSO was used to capture partial correlations among variables[12]. LASSO regularization prevents overfitting by shrinking weaker edges; (2) Inference: Centrality measures-node strength, closeness, and betweenness-were calculated to assess each variable's role within the network[13], identifying key factors for intervention; (3) Stability: Bootstrapping through the "bootnet" package provided confidence intervals for edge weights and centrality measures, ensuring the stability of results. Stability coefficients above 0.5 confirmed robustness; (4) Comparison: The network comparison test (NCT) evaluated differences in network structure across NSSI subgroups[14]. Holm-Bonferroni corrections were applied to adjust for multiple comparisons, ensuring reliable inferences; and (5) Network density: Network density, defined as the average strength of all edges, was compared between subgroups. Higher density indicates a more interconnected network, which may have implications for the persistence and resilience of NSSI behaviors within subgroups.

RESULTS

Descriptive analyses

This study included 3967 participants (51.7% female, mean age = 13.58, SD = 2.24). Table 2 presents the means and standard deviations for each variable. Bonferroni correction revealed significant differences in paternal warmth (PW), maternal warmth (MW), and bullying between NSSI subgroups, with the NSSI-D group showing the lowest levels. These findings suggest that targeted interventions focusing on family dynamics and bullying may be critical for these subgroups.

LPA

LPA identified three subgroups: NSSI with depression (NSSI-D; 18.8%), NSSI without depression (NSSI-ND; 12.3%), and no NSSI (NNSSI-ND; 68.9%). Model fit indices (AIC = 353719.4, BIC = 371608.7, aBIC = 282288.2) supported the three-profile solution, with an entropy value of 0.89 indicating high classification accuracy.

The NSSI-D group had higher depressive symptoms and emotional dysregulation, while the NSSI-ND group exhibited impulsive and externalizing behaviors, pointing to the need for distinct interventions for each subgroup (Table 3).

Network analysis

Network estimation: Figure 1 illustrates the networks for the NSSI-ND, NSSI-D, and NNSSI-ND groups. The network densities were 0.490 (NSSI-ND, 4/529 edges), 0.451 (NSSI-D, 12/529 edges), and 0.585 (NNSSI-ND, 2/529 edges), reflecting varying levels of connectivity. Mean absolute edge weights were 0.094 (NSSI-ND), 0.079 (NSSI-D), and 0.055 (NNSSI-ND), indicating different strengths of associations within each group.

Across all groups, strong positive correlations were observed between MW and PW, with edge weights ranging from 0.639 to 0.712. Negative correlations revealed unique family dynamics, such as the -0.165 edge between family support

Table 1 Measures of variables in risk factor-resilience networks across all study participants

Measure	Description	Scoring	Total score/subscales	α
PHQ-9 (Martin *et al* [34], 2006)	Measures the severity of depression	9 items 4-point scale ranging from "never" (1 point) to "very often" (4 points)		0.886
MASHS (Feng *et al*[35], 2008)	Measure the method and severity of self-harming behavior in an adolescent's lifetime	18-item, the first part: A 4-point scale ranging from (0, 1, 2–4, 5, and more); the second part: A 5-point scale (0 = none to 5 = extremely severe	The frequency of NSSI behavior is categorized into two parts (frequency and severity)	0.84
S-EMBU-C (Jiang *et al* [36], 2010)	Assess parenting styles experienced during childhood years	21 items. 4-point scale ranging from "Never" (1 point), "Occasionally" (2 points), "Frequently" (3 points), and "Always" (4 points)	Two parts to three dimensions: Rejection, emotional warmth, and overprotection	0.827
CTQ-SF (Bernstein and Fink[37], 1998)	Measure traumatic childhood experiences	28-item 5-point scale (1 = never, 2 = once, 3 = twice to four times, 4 = five times or more)	PA, EA, SA, PN, and EN	0.871
OBVQ (Solberg and Olweus[38], 2003)	Evaluate traditional school bullying, encompassing physical, verbal, and relation and attitude to bully	14 item 5-point Likert scale (1 = never happened, 2 = altogether once or twice, 3 = 2–3 times per month, 4 = once a week, 5 = several times a week)	Traditional bullying, another to physical bullying, and a third to attitudes towards bullying behaviors	0.72
RSCA (Hu and Gan [39], 2008)	Assess resilience	27-item 5-point scale (1 = never, 2 = once, 3 = twice to four times, 4 = five times or more)	Five components of resilience (goal concentration, emotion regulation, positive perception, FS, and interpersonal help)	0.82
MPAI(Leung[40], 2008)	Assess the levels of mobile phone addiction among the participants, and it has good reliability and validity	17 items 5-point Likert scale (1 = never, 5 = always)	4 subscales: ICCS, FALS, WES, and PLS	0.86

PHQ-9: The Patient Health Questionnaire nine-item depression scale; MASHS: Modified adolescents self-harm survey; S-EMBU-C: The short Chinese Egna Minnen av Barndoms Uppfostra; CTQ-SF: The Childhood Trauma Questionnaire-Short Form; OBVQ: The Chinese version of the Orvis Bullying/Victimization Questionnaire; RSCA: Resilience Scale for Chinese Adolescents; MPAI: The mobile phone addiction index scale amended by Leung; PLS: The productivity loss subscale; WES: The withdrawal and escape subscale; FALS: The feeling anxious and lost subscale; ICCS: The inability to control cravings subscale; FS: Family support; EN: Emotional neglect; PN: Physical neglect; SA: Sexual abuse; EA: Emotional abuse; PA: Physical abuse; NSSI: Non-suicidal self-injury.

(FS) and father reject in the NSSI-ND group and the -0.218 edge between FS and PW in the NSSI-D group. These findings highlight how family dynamics vary across NSSI subgroups, suggesting different intervention targets depending on family structure and relationships.

Network inference: Bridge strength analyses provided key insights into the influence of risk and resilience factors across NSSI subgroups. As presented in Table 4, PW, MW, and FS exhibited high centrality and bridge strength, emphasizing their crucial roles in shaping NSSI behaviors, particularly concerning EC. These factors consistently emerged as central nodes across the NSSI-ND, NSSI-D, and NNSSI-ND groups.

Predictability scores, which indicate the proportion of variance explained by neighboring nodes, were 47.3% for NSSI-D, 48.1% for NSSI-ND, and 49.3% for NNSSI-ND, highlighting how risk factors interact within the network. Additionally, correlations between centrality strength and predictability were strong, with values of 0.826 (NSSI-ND), 0.590 (NSSI-D), and 0.730 (NNSSI-ND), suggesting varying impacts of these factors across different groups.

These findings highlight the importance of family dynamics and EC in addressing NSSI behaviors, particularly for adolescents with co-occurring depressive symptoms (NSSI-D) (Table 4 and Figure 2).

Network stability: Stability analysis revealed that edge weights had slight to moderate confidence intervals, with a correlation stability coefficient for strength centrality of 0.75 in all networks, exceeding the recommended 0.50 threshold [15]. Detailed information is available in Figure 3.

Network comparison: Spearman correlations revealed high network similarity: 0.95 between NSSI-ND and NSSI-D, and 0.97 between NSSI-ND and NNSSI-ND. The NCT found no significant global strength differences across networks (NSSI-ND: 8.67, NSSI-D: 9.09, NNSSI-ND: 10.97; $S = 0.418$, $P = 0.39$), indicating overall connectivity consistency. However, significant structural differences were observed between the NSSI-ND and NSSI-D networks ($M = 0.301$, $P < 0.001$), with one significantly different edge and four specifically identified edges. Centrality invariance tests ($C = 0.05$, $P = 0.007$) revealed distinct centrality patterns, particularly in bullied nodes within the NSSI-D network.

A noteworthy finding was the unique centrality of bullying in the NSSI-D group, suggesting that bullying plays a more prominent role in adolescents with both NSSI and depression, compared to those without depression. This insight highlights the need for targeted anti-bullying interventions in this subgroup.

Table 2 Overview of influence factors (including means and standard deviations) from subgroup data

No.	Risk factor	Short codes	M (SD)		
			X1	X2	X3
1	Paternal warmth	PW	19.73 (4.99)	21.21 (5.03)	20.85 (5.04)
2	Maternal warmth	MW	20.68 (5.05)	20.71 (4.82)	21.89 (4.66)
3	Father reject	FR	8.17 (2.76)	7.54 (2.44)	7.7 (2.49)
4	Mother reject	MR	9.94 (2.28)	9.7 (2.01)	9.73 (2.15)
5	Father overprotective	FO	15.91 (3.8)	15.18 (4.01)	15.39 (3.9)
6	Mother overprotective	MO	16.85 (4.05)	16.16 (4.44)	16.21 (4.18)
7	Emotional abuse	EA	6.78 (2.53)	6.68 (2.53)	6.81 (2.62)
8	Physical abuse	PA	5.71 (1.48)	5.72 (1.6)	5.84 (1.8)
9	Sexual abuse	SA	5.12 (0.6)	5.15 (0.66)	5.14 (0.67)
10	Emotional neglect	EN	10.5 (4.01)	10.4 (4.19)	10.41 (4.23)
11	Physical neglect		6.71 (2.29)	6.62 (2.43)	6.74 (2.47)
12	Bullied	BL	8.56 (2.76)	7.26 (0.67)	8.04 (2.44)
13	Attitudes bullying	AB	17.08 (3.4)	17.45 (3.16)	17.46 (3.29)
14	Bullying	PB	6.5 (1.21)	6.07 (0.53)	6.17 (0.65)
15	Targeted focus	TF	17.95 (4.52)	19.38 (4.28)	18.72 (4.67)
16	Emotional control	EC	19.39 (4.05)	20.47 (4.04)	20.3 (4.02)
17	Positive cognition	PC	14.53 (3.72)	15.32 (3.47)	14.97 (3.73)
18	Interpersonal interactions	II	20.84 (5.92)	22.33 (5.79)	22.25 (5.77)
19	Family support	FS	23.82 (4.56)	23.42 (4.68)	23.3 (4.67)
20	Smartphone addiction - withdrawal	SW	6.9 (3.76)	5.84 (3.01)	6.35 (3.54)
21	Smartphone addiction - out of control	SO	17.23 (7.31)	15.72 (7.25)	15.89 (7.39)
22	Smartphone addiction - avoidance	SV	7.41 (3.59)	6.52 (3.35)	6.92 (3.62)
23	Smartphone addiction - inefficiency	SI	5.42 (2.66)	4.89 (2.44)	5.08 (2.61)

Influence factor names and No. Short codes were applied completely by paper.

Table 3 Fit indices for three models using latent profile analysis (*n* = 3967)

M	*df*	χ^2	G^2	aBIC	AIC	Entropy	LMR	BLRT	Group size for each profile (%)			
									1	2	3	4
1	2963	16130	312372	386431	380120.1	-	-	-	3967 (100)			
2	2742	12040	290985.2	366874.6	359174.5	0.781	0.043	0.001	1225 (35.7)	2742 (64.3)		
3	1121	23910	282288.2	371608.7	353719.4	0.742	0.342	0.001	488 (12.3)	747 (18.8)	2732 (68.9)	
4	1292	26059	279126.3	367029.9	350215.5	0.670	0.471	0.001	1067 (26.9)	603 (15.2)	1944 (49)	353 (0.088)

Numbers in bold indicate "best" fit. AIC: Akaike information criterion; BIC: Bayesian information criterion; aBIC: Adjusted Bayesian information criterion; pLMR: *P* value for LoMendell-Rubin adjusted likelihood ratio test for K *vs* K-1 profiles; pBLRT: *P* value for bootstrapped likelihood ratio test.

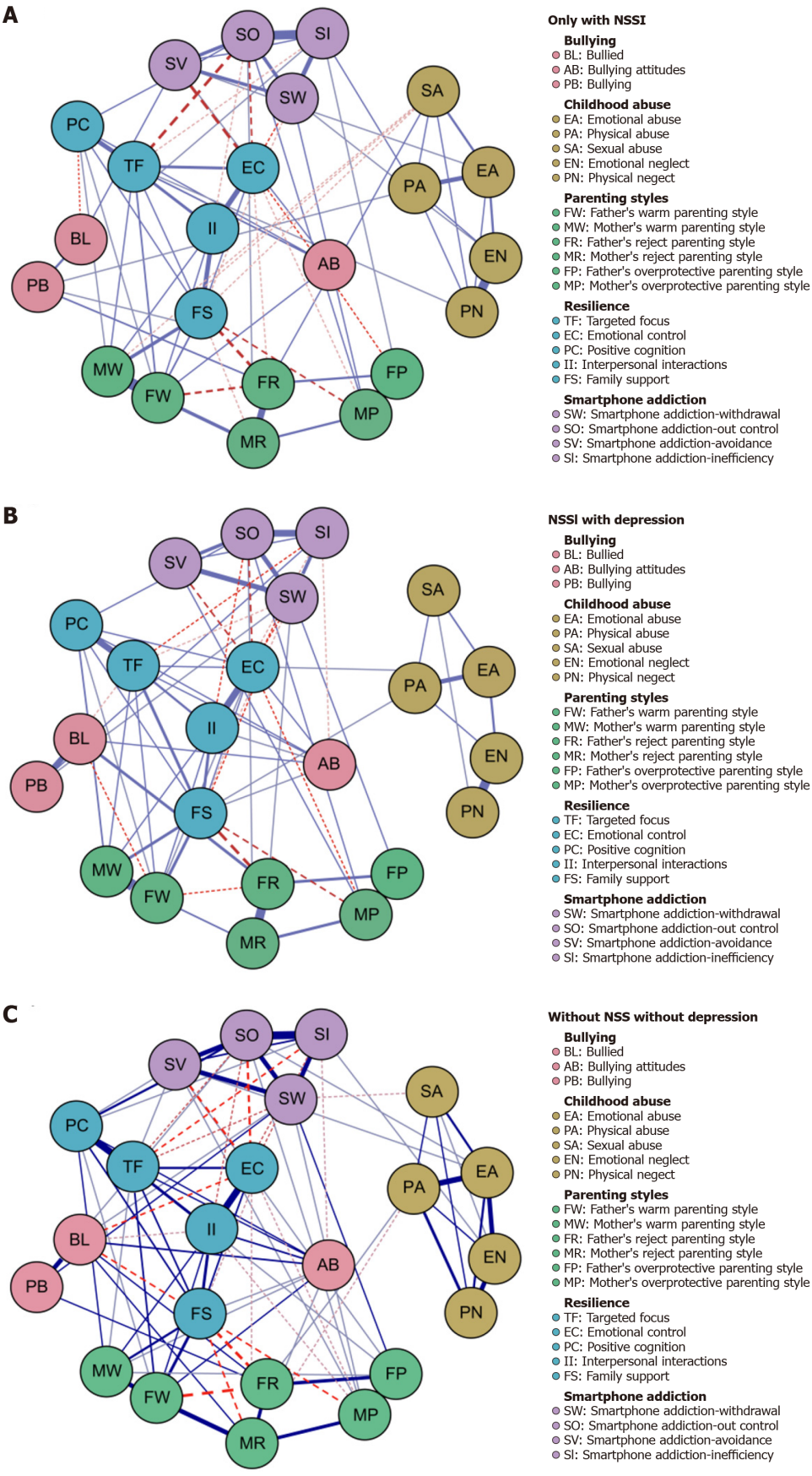

Figure 1 Regularized partial correlation influence factor-resilience network across three subgroups: Edge thickness represents the strength of association. Blue (solid) lines indicate positive relationships, whereas red (dashed) lines indicate negative relationships. Only edges with weights greater than 0.05 are displayed. Edge weights are scaled according to the maximum edge weight across all points (0.65). A: Subgroup designations: Non-suicidal self-injury (NSSI)-without depression (ND); B: Subgroup designations: NSSI-with depression; C: Subgroup designations: No NSSI-ND.

Table 4 Centrality measures of key risk and resilience factors across non-suicidal self-injury subgroups

Factor	NSSI-ND (strength)	NSSI-D (strength)	NNSSI-ND (strength)
Paternal warmth	0.72	0.68	0.75
Maternal warmth	0.69	0.71	0.74
Family support	0.63	0.60	0.70
Bullying	0.75	0.78	0.65

NSSI-ND: Non-suicidal self-injury-without depression; NSSI-D: Non-suicidal self-injury-with depression; NNSSI-ND: No non-suicidal self-injury-without depression.

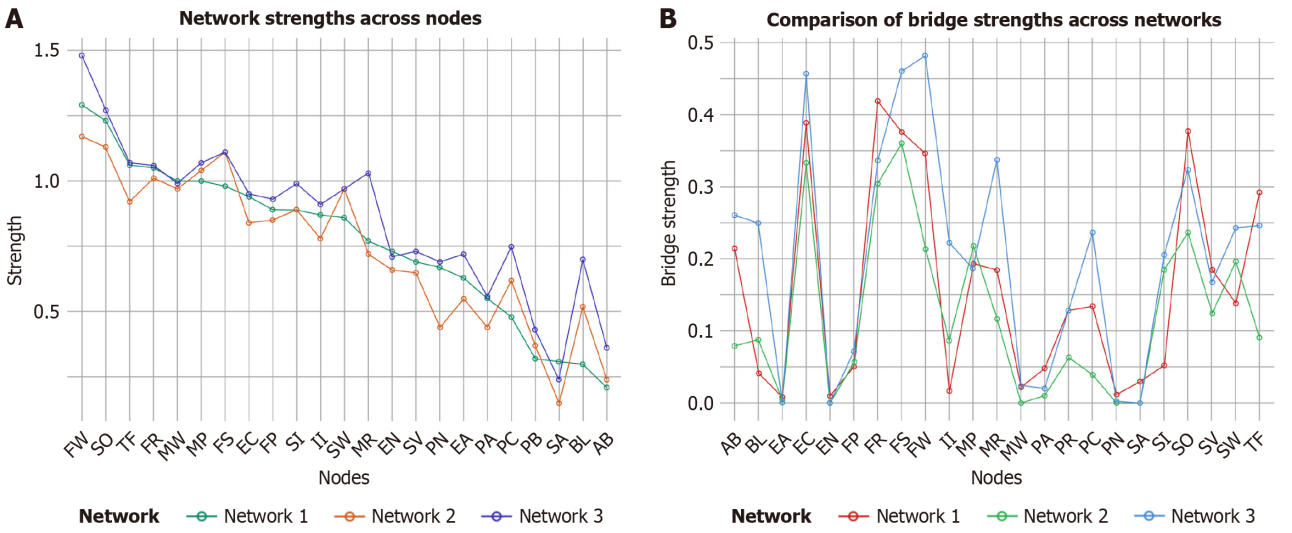

Figure 2 Standardized node strength centrality and bridge strength of influence factors across three non-suicidal self-injury datasets. A: Node strength; B: Bridge strength. The networks are labeled as follows: Network 1 = Non-suicidal self-injury (NSSI)-without depression (ND), Network 2 = NSSI-with depression, Network 3 = No NSSI-ND. Refer to Table 2 for the complete names of influence risk factors.

No significant global strength or structural differences were found between the NSSI-ND and NNSSI-ND, or between NSSI-D and NNSSI-ND networks. However, node centrality differences emerged between NSSI-ND and NNSSI-ND. Pairwise NCT analyses identified significant differences in 12 out of 529 edges (4.74%) between NSSI-ND and NNSSI-ND and in two pairs between NSSI-D and NNSSI-ND. For detailed comparisons of edge weights and significant variance, refer to Supplementary Tables 1-3.

DISCUSSION

This study provides significant insights into the complex nature of NSSI among Chinese adolescents by employing a combination of LPA and network analysis. By identifying distinct subgroups based on NSSI behaviors and depressive symptoms, and exploring the interactions between risk and protective factors, we have advanced the understanding of NSSI's multifaceted etiology.

Interpretation of key findings

The identification of three distinct subgroups-NSSI-D, NSSI-ND, and NNSSI-ND-highlights the heterogeneity of NSSI behaviors. This heterogeneity underscores the importance of not treating NSSI as a homogeneous behavior, as different subgroups may have unique underlying mechanisms and require tailored interventions[16].

Our network analysis revealed that bullying is a central risk factor, especially in the NSSI-D subgroup. This finding aligns with prior research indicating that experiences of bullying are significantly associated with both depressive symptoms and NSSI behaviors[17]. Adolescents who are bullied may internalize negative self-perceptions and experience heightened emotional distress, leading to depressive symptoms. Consequently, the likelihood of engaging in NSSI as a maladaptive coping mechanism increases[18].

In contrast, the NSSI-ND subgroup showed a distinct pattern where smartphone addiction emerged as a notable factor. This suggests that adolescents engaging in NSSI without concurrent depressive symptoms may be using excessive smartphone use as an alternative or complementary coping strategy to manage emotional distress[19]. The accessibility

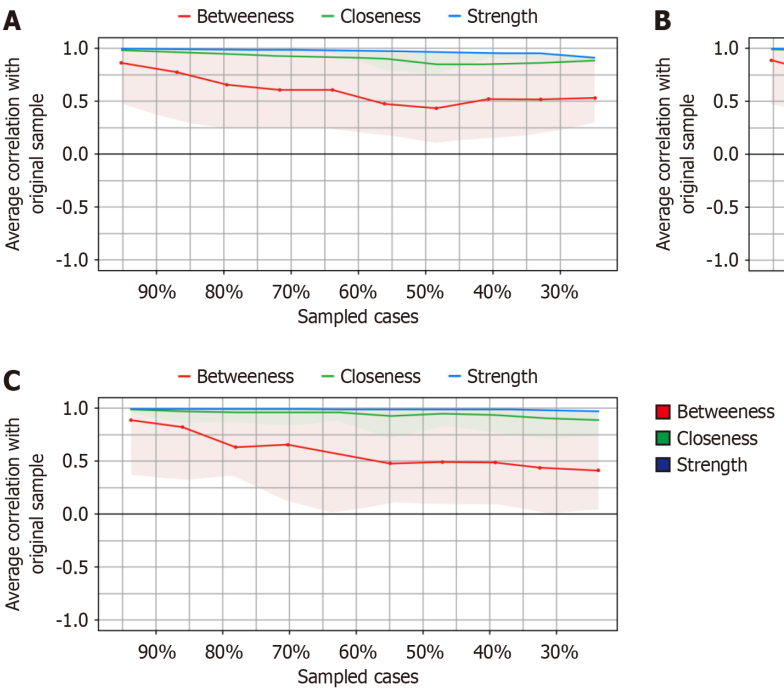

Figure 3 Estimated correlation stability coefficient (cs-coefficient) with bootstrapped 95%CI: The CS-coefficient ranges from 0 to 1, where values above 025 indicate moderate stability, and values above 05 indicate strong stability. Edge-weight difference tests and centrality difference tests were conducted for each network. A: Non-suicidal self-injury (NSSI)-without depression (ND); B: NSSI-with depression; C: No NSSI-ND. AB: Bullying Attitudes; BL: Bullied; EA: Emotional abuse; EC: Emotional control; EN: Emotional neglect; FP: Father's overprotective parenting style; FR: Father's reject parenting style; FS: Family support; FW: Father's Warm Parenting Style; II: Interpersonal interactions; MP: Mother's overprotective parenting style; MR: Mother's reject parenting style; MW: Mother's warm parenting style; PA: Physical abuse; PB: Bullying; PC: Positive cognition; PN: Physical neglect; SA: Sexual abuse; SI: Smartphone addiction-inefficiency; SO: Smartphone addiction-out control; SV: Smartphone addiction-avoidance; SW: Smartphone addiction-withdrawal; TF: Targeted focus.

and immediacy of digital media may provide temporary relief but could also reinforce avoidance behaviors and hinder the development of healthier coping mechanisms[20].

FS and EC were identified as key protective factors across all subgroups. High levels of FS may buffer the impact of stressors by providing emotional resources and a sense of belonging, which can mitigate the need for self-injurious behaviors[21]. EC, as an aspect of emotional regulation, enables adolescents to manage negative emotions more effectively, reducing the reliance on NSSI as a means of coping[22].

Theoretical implications

The findings support the interpersonal theory of NSSI, which posits that social factors such as bullying and family dynamics play a critical role in the initiation and maintenance of self-injurious behaviors[23]. The centrality of bullying in the NSSI-D subgroup suggests that negative interpersonal experiences are particularly detrimental when coupled with internalizing symptoms like depression.

Moreover, the study extends the application of the diathesis-stress model to NSSI by illustrating how individual vulnerabilities (*e.g.*, poor EC) interact with environmental stressors (*e.g.*, bullying) to influence the onset of self-injury[24]. The identification of protective factors such as FS highlights the potential moderating effects these elements can have on the stress-NSSI relationship.

Clinical implications

The differentiated profiles of NSSI behaviors have important implications for intervention strategies. For adolescents in the NSSI-D subgroup, interventions should involve a multi-faceted approach that addresses both depressive symptoms and experiences of bullying. Cognitive-behavioral therapy techniques can be effective in challenging negative thought patterns and enhancing problem-solving skills[25]. School-based programs that foster a positive social climate and implement anti-bullying policies may also reduce the prevalence of both bullying and NSSI[26].

For the NSSI-ND subgroup, interventions might focus on regulating technology use and promoting alternative coping strategies. Digital literacy programs that educate adolescents about the risks of excessive smartphone use and provide tools for managing screen time could be beneficial[27]. Incorporating mindfulness and stress management techniques can help adolescents develop healthier ways to cope with emotional distress[28].

Family-based interventions are crucial across all subgroups. Enhancing communication within the family, increasing parental awareness of NSSI, and fostering supportive relationships can strengthen the protective role of the family environment[29]. Parental training programs that focus on emotion coaching and responsive parenting may improve adolescents' emotional regulation abilities and reduce NSSI behaviors[30].

Cultural considerations

The cultural context in China, characterized by collectivism and strong familial ties, amplifies the influence of FS on adolescent behavior[31]. The emphasis on academic achievement and adherence to social norms may contribute to stress and emotional difficulties among adolescents[32]. Understanding these cultural factors is essential for designing interventions that are culturally sensitive and resonate with adolescents and their families.

Additionally, the stigma associated with mental health issues in Chinese society may hinder help-seeking behaviors. Efforts to destigmatize mental health problems through public education campaigns and integrating mental health services within schools could improve access to support and reduce the incidence of NSSI.

Limitations

This study has several limitations. The cross-sectional design limits the ability to infer causal relationships between risk factors, protective factors, and NSSI behaviors. Therefore, longitudinal studies are needed to examine how these relationships evolve and identify potential causal pathways.

The reliance on self-reported data may introduce biases, such as social desirability or recall inaccuracies. Future research could incorporate multiple data sources, including reports from parents, teachers, or clinical assessments, to enhance the validity of the findings.

The sample was drawn from a specific geographic region in China, which may limit the generalizability of the results to other regions or cultural contexts. Replication studies in diverse settings are necessary to confirm the applicability of these findings more broadly.

Future research directions

Building on the current findings, future research should employ longitudinal designs to explore the developmental trajectories of NSSI behaviors and the temporal dynamics between risk and protective factors. Investigating the mechanisms through which bullying leads to NSSI, particularly the mediating role of depression and emotional regulation, could inform more targeted interventions.

Examining the impact of digital media use in greater depth is also warranted, given the evolving nature of technology and its pervasive influence on adolescents' lives. Studies could explore how online interactions, cyberbullying, and social media exposure contribute to NSSI behaviors and mental health outcomes[33].

Additionally, qualitative research methods could provide richer insights into adolescents' subjective experiences of NSSI, capturing the nuances of their motivations, feelings, and contextual factors. Such insights could enhance the development of personalized intervention strategies that resonate with adolescents' lived experiences.

CONCLUSION

This study enhances the understanding of NSSI among Chinese adolescents by identifying distinct behavioral subgroups and elucidating the complex interplay of associated risk and protective factors. The findings emphasize the importance of considering individual differences and cultural contexts in both research and clinical practice. By tailoring interventions to address specific needs-such as bullying prevention, emotional regulation training, and FS enhancement-we can develop more effective strategies to reduce NSSI behaviors and promote mental well-being among adolescents.

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FOOTNOTES

Author contributions: Yang W and Xu XF conceptualized and designed the study, oversaw the entire project, and made the final decision to submit the manuscript; Yang W and Lian K have made critical and indispensable contributions to the completion of this project, thus qualifying as co-first authors; Duan XC contributed to the design of data collection tools, participated in data collection, and performed initial data analysis, which were critical in the early stages of the project; You X contributed to refining the data collection methodologies and ensured data integrity, enhancing the quality and reliability of the data; All authors have read and approved the final manuscript. Yang W was primarily responsible for drafting the manuscript, performing critical revisions, and ensuring the intellectual content and integrity of the work. Xu XF provided essential supervision, contributed significantly to data interpretation, and critically revised the manuscript for intellectual content. Cheng YQ and Xu XF served as co-corresponding authors. Lian K and Cheng YQ were involved in data curation. Yang W and Lian K played key roles in data verification and analysis, forming the backbone of the research findings. The collective efforts and collaboration of all authors were essential for the successful execution and publication of this research.

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ORIGINAL ARTICLE

Randomized Controlled Trial

Effect of comprehensive intervention model based on drug-psychology-society-skills on medication compliance and cognitive ability of chronic schizophrenia patients

Hai-Jun Wang, Wei Chen, Xiao-Lin Yan, Qian-Ying Huang, Wei-Dong Xu

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Abstract

BACKGROUND

The intervention value of a drug-psycho-social-skill model on medication compliance and cognitive ability in patients with chronic schizophrenia was unknown.

AIM

To explore the intervention value of a drug-psycho-social-skill model on medication compliance and cognitive ability in patients with chronic schizophrenia.

METHODS

Overall, 98 out-patients and in-patients with chronic schizophrenia treated in our hospital from February 2022 to January 2023 were included and randomly divided into the study (50 patients) and control groups (48 patients). For 3 months, the control group was treated with conventional drugs, and the research group with a comprehensive intervention model of drug-psychology-society-skills. Data were obtained for the mini mental assessment scale (MMSE), Montreal cognitive assessment scale (MoCA), positive and negative symptom scale, insight and treatment attitude scale, cognitive ability scale and social skills [personal and social function scale (PSP)]. The adverse reactions were observed.

RESULTS

After the intervention, the MMSE and MoCA scores improved in both groups. MoCA scores in the study group (26.58 ± 3.21) were significantly ($P < 0.05$) higher than those in the control group (24.68 ± 3.02), MMSE scores were not significantly higher. Post-intervention, positive and negative symptom scores improved in both groups, and the positive and negative symptom scores in the study group [(12.01 ± 2.58) and (32.51 ± 2.11)] were significantly ($P < 0.05$) different than those in the control group [(14.54 ± 2.33) and (33.74 ± 2.55)]. Post-intervention, insight and treatment attitudes questionnaire scores of both groups were improved and compared with the control group (7.97 ± 3.02), the study group (13.56 ± 6.35) had significantly ($P < 0.05$) higher scores. Post-intervention, the MATRICS consensus cognitive battery score of both groups was improved and compared with the control group (38.44 ± 6.23), the score of the study group was significantly ($P < 0.05$) increased (43.51 ± 6.01). Post-intervention, the PSP score of the study group (78.38 ± 6.63) was significantly ($P < 0.05$) higher than that of the control group (74.52 ± 7.01). During the intervention period, the incidence of adverse reactions in the study group was 6.25%, not significantly different from that in the control group (8.33%). During the intervention, both groups experienced adverse reactions, with no significant difference between groups ($P > 0.05$).

CONCLUSION

The comprehensive intervention model based on drug-psychology-society-skills has obvious intervention effects on patients with chronic schizophrenia, which improves their cognitive ability and reduces their positive and negative symptoms. Simultaneously, it improves the self-knowledge of patients, improves their attitude toward treatment, effectively promotes the recovery of patients' social functions, and is safe. Therefore, it is worthy of being vigorously promoted and widely used in clinics.

Key Words: Drug-psychology-society-skill; Comprehensive intervention model; Medication compliance; Self-knowledge; Cognitive ability

Core Tip: The comprehensive intervention model based on drug-psychology-society-skills has obvious intervention effect on patients with chronic schizophrenia, which not only improves the cognitive ability of patients, but also reduces the positive and negative symptoms of patients.

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INTRODUCTION

Chronic schizophrenia, a disease in the field of mental health, is characterized by apathy, lack of motivation, and other negative symptoms[1]. With the gradual extension of the course of the disease, patients' cognitive ability is impaired to some extent, which affects their mental health and adversely affects their quality of life[2]. In China, patients with schizophrenia are treated centrally and managed in a closed manner. However, patients with schizophrenia generally have poor medication compliance owing to a lack of correct understanding of their own diseases and treatments, which leads to patients' unwillingness to cooperate, thus causing treatment difficulties[3]. Simultaneously, poor medication compliance is also one of the main reasons that directly lead to the gradual chronicity of the course of schizophrenia. To a certain extent, it not only reduces social function but also consumes many medical resources and imposes a burden on families[4]. Current treatment models tend to focus on medication and neglect psychological, social, and skill training interventions. This single treatment approach is difficult to meet the full needs of people with chronic schizophrenia, therefore, exploring a comprehensive intervention model is of great significance for the rehabilitation of patients with chronic schizophrenia. Recently, with changes in medical models, people have gradually realized the complexity of mental illnesses and their multidimensional treatment. Drug therapy, combined with psychotherapy, social support, and skill training, provides patients with a comprehensive, personalized treatment plan. This intervention model not only focuses on symptom relief but also emphasizes the recovery of patients' psychological and social functions and the improvement of their quality of life. With regard to drug therapy, patient symptoms can be effectively controlled through a scientific and reasonable medication scheme that lays the foundation for the implementation of other treatment measures[5]. Psychotherapy focuses on helping patients establish positive self-awareness and improve their ability to cope with stress and challenges, thus reducing the recurrence and deterioration of symptoms[6]. In terms of social support, family, community, and other forces are used to provide the necessary help and support for patients and

promote their reintegration into society. Skill training is designed to help patients improve their daily self-care ability, vocational skills, life skills, and social ability so that they can better adapt to the social environment and promote their rehabilitation[7]. Comprehensive interventions improve functional outcomes in patients with chronic schizophrenia[8]. However, there are few reports on integrated drug-psycho-social-skill intervention models. Therefore, this study aimed to explore the intervention value of a drug-psycho-social-skill integrated model for medication compliance and cognitive ability in patients with chronic schizophrenia to provide a new perspective and practical basis for the clinical treatment of chronic schizophrenia. This study also aimed to provide a reference for future mental health policy formulation and service system improvement to achieve more comprehensive and humanized care and support for patients with schizophrenia. The remainder of this paper is organized as follows.

MATERIALS AND METHODS

General information

In this study, 98 patients with chronic schizophrenia who were treated at our hospital between February 2022 and January 2023 were selected as research subjects, and the study was approved by the ethics committee of the hospital. Inclusion criteria: (1) Patients satisfying the diagnostic criteria of the international classification of diseases[9], 10th edition, and diagnosed as chronic schizophrenia by psychiatrists; (2) Age ≥ 18 years old, regardless of sex or education level; (3) Patient should be in a relatively stable period of the disease; (4) Have certain cognitive function, and be able to understand and abide by the research requirements; and (5) Patient or their legal guardian shall sign an informed consent form and agree to participate in the study. Exclusion criteria: (1) Patients with severe physical, nervous system, or infectious diseases; (2) Patients with a history of drug abuse or dependence; (3) Patients who had recently experienced major life events (such as divorce and bereavement); (4) Patients who switched to other antipsychotics or added other antipsychotics midway; (5) Serious adverse reactions that occurred, the disease obviously worsened, and the patient or his family refused to continue to treat the patient; and (6) Pregnant or lactating women. Patients were randomly divided into a study group (n = 50) and a control group (n = 48). As two patients in the study group were lost to follow-up, they were finally divided into a study group (48 cases) and a control group (48 cases).

Among the 48 patients in the control group, the ratio of men to women was 27:21. The age range was 33–45 years, with an average age of (40.21 ± 4.32) years. The course of disease is 5-10 years, with an average of 7 ± 2.5 years and an average of (3.36 ± 0.48) years. Of the 48 patients, 7, 14, and 9 had major depression, schizophrenia, and bipolar disorder, respectively.

Among the 48 patients in the research group, the men-to-women ratio was 29:19. The age range was 34-44 years, with an average age of (39.12 ± 4.54) years. The course of the disease was 5-9 years with an average of 6.5 ± 3.0 years. There was no significant difference in the clinical data between the two groups, therefore, a targeted clinical comparison could be made (P > 0.05).

Methods

Control group: Intervention with second-generation antipsychotics. The dosage of most clozapine tablets was 200-600 mg/day, the dosage of quetiapine combined with quetiapine was 400-600 mg/day, the dosage of risperidone tablets was 4-6 mg/day, or the dosage of ziprasidone tablets was 80-120 mg/day. The dosage was individualized, considering the effective dosage and safe blood concentration range. Further, patients adherence to the dosage schedule (timing and quantity) was supervised, their families were guided on how to take drugs accurately, any changes in patients' conditions were identified, community doctors were consulted on time under abnormal circumstances, patients' possession of drugs was observed, and patients with suicidal tendencies were closely monitored.

Study group: Based on the control group, a drug-psychological-social-skill comprehensive intervention was administered.

Drug intervention and drug management training: Treatment drugs and control groups. Simultaneously, the adverse reactions of drugs and basic knowledge of psychotropic drugs were explained to the patients and their families to improve patients' ability to manage drugs.

Psychological intervention: Patients were supported and encouraged to help them face reality faster and live actively. According to the individual mood and ideological changes of patients, humor and positive language was used to stimulate patients' interest in life, a self-reliant and confident outlook on life was established, patients were encouraged to establish support networks, actively expand social circles, and gradually return to normal life.

Socio-skill intervention: (1) Life skills training: Using one-to-one behavior correction guidance, patients were trained in terms of daily self-care ability such as diet, personal hygiene, dressing and grooming, 2-3 times a day, and each training time was controlled within half an hour. At the same time to actively participate in the patient to give timely encouragement and affirmation. Patients were trained in daily living activities such as shopping and washing clothes, and their family members accompanied and assisted them throughout the training process, training once or twice a day, and each time was controlled to about 15 minutes; (2) Social employment skills training: For patients with functional disabilities, based on their previous occupations, occupational therapy and systematic labor simulation training were used to carry out individualized training in combination with their individual conditions. Each training time lasted for 1 hour, twice a week. Patients were encouraged to use household work or community services accompanied by family members, and the

time was also controlled at approximately 1 hour each time; (3) Emotional control training: Patients' interests and hobbies were combined and they were encouraged to participate in recreational activities such as chess, playing ball, singing, *etc.*, to help patients integrate into the normal life track. The patients were guided in finding appropriate ways of emotional catharsis by playing tai chi, practicing Wuqin play, *etc.* Additionally, basic emotional regulation skills, such as, deep breathing, appropriate physical exercise, and other ways to control emotions were taught. Psychologists conducted a psychological intervention for patients once a week, and specialists explained the general symptoms and treatment measures of schizophrenia to patients and their families, and reflect to doctors when necessary to get active treatment; and (4) Social skills training: Patients were encouraged to introduce themselves and their interests and hobbies in an appropriate way. General life events such as birthdays, dining, shopping were simulated to let patients learn how to get along with others, express their inner thoughts, and master the method of praising others and self-praise. They were also allowed to learn how to regularly carry out team cooperation games by encouraging and praising the patients in order to affirm correct behavior.

Both groups underwent intervention continuously for 3 months.

Observation indicators

The mini mental status examination and Montreal cognitive assessment were used for joint assessment: Mini mental status examination (MMSE)[10] evaluates seven components: Language, attention, computing power, immediate memory, delayed memory, time orientation, spatial orientation, and visual space. The Montreal cognitive assessment (MoCA)[11] evaluates language, naming, memory, execution, attention, orientation, abstract thinking, and delayed recall. The total score on both scales was 30, and the higher the score, the stronger the cognitive ability.

Positive and negative syndrome scale: Positive and negative syndrome scale (PANSS)[12] scores before and after treatment were compared between the groups. Negative symptoms mainly include poor speech, concentration defects, emotional retardation, apathy, and social withdrawal, while positive symptoms mainly include hallucinations and delusions; each item is scored according to 1-7 grades. Grade 1 was asymptomatic, with symptoms worsening gradually, grade 7 was the most serious, and the final score was counted.

Insight and treatment attitudes questionnaire: The scale[13] has 11 questions, including the patients' knowledge of diseases and their attitudes towards treatment. The evaluation doctor asks each question to the patient and answers and explains the question. The doctor gave a score of 0-2 based on the patient's answers. The score 2 = completely self-aware, 1 = partially self-aware, and 0 = not self-aware. The lowest score on the questionnaire was 0 and the highest score was 22. The higher the score, the better the patient's insight into and attitude towards treatment.

Cognitive ability scale: Before and after the intervention, patients' cognitive ability was evaluated using the MATRICS consensus cognitive battery (MCCB)[14], which included eight subtests, including number symbol, number span, visual memory, maze, visual reproduction, verbal fluency, short-term language memory, and continuous operation, and cognitive functions of patients, such as association, perception, and memory.

Social skills: Through the personal and social performance scale (PSP)[15], activities, personal and social relationships, self-care, and disturbing and aggressive behaviors are useful to patients in society were evaluated. The first three items are scoring standards and the fourth item is a scoring standard. The total score ranges from 0 to 100. Divided into 10 grades, 71-100 points: The patient's social and interpersonal skills are good and only slightly affected; 31-70: There are different degrees of defects in social skills; < 30: Patient's ability is low and needs active support or monitoring.

Adverse reactions in the two groups during the intervention period were evaluated, including extrapyramidal reactions, weight gain, elevated blood sugar and blood lipid levels, abnormal liver function, and leukopenia.

Statistical analysis

Statistical product and service solutions 26.0 was used for data processing. The counting data obtained from the experiment is expressed as %, and the measurement data is expressed by the mean ± SD by the χ^2 test. Data were normally distributed, the variance was homogeneous, and the difference was statistically significant according to the *t*-test, $P < 0.05$.

RESULTS

MMSE and MoCA score comparison

Before the intervention, there were no significant differences in the MMSE and MoCA scores between the two groups ($P > 0.05$). After intervention, the scores of both groups significantly improved, and the MoCA score of the study group (26.58 ± 3.21) was significantly higher than that of the control group (24.68 ± 3.02), the difference was statistically significant ($P < 0.05$), but there was no statistically significant difference in MMSE score between the two groups ($P > 0.05$). See Table 1.

PANSS score comparison

Before the intervention, there was no significant difference in the scores of positive symptoms and negative symptoms between the two groups ($P > 0.05$). After intervention, both positive and negative symptom scores were improved in the two groups, and the positive symptom scores (12.01 ± 2.58) and negative symptom scores (32.51 ± 2.11) in the study

Table 1 Comparison of mini mental assessment scale and Montreal cognitive assessment scale scores between the two groups, mean ± SD

Group	Number of cases	MMSE score		MoCA score	
		Before intervention	After intervention	Before intervention	After intervention
Research group (n = 48)	48	22.25 ± 2.47	27.15 ± 2.58	23.31 ± 2.14	26.58 ± 3.21[a]
Control group (n = 48)	48	22.33 ± 2.71	26.24 ± 2.36	23.44 ± 2.09	24.68 ± 3.02[a]
t value		0.151	1.803	0.301	2.987
P value		0.880	0.075	0.764	0.004

[a]$P < 0.05$.

MMSE: Mini mental assessment scale; MoCA: Montreal cognitive assessment scale.

group were more significantly changed than those in the control group [(14.54 ± 2.33) and (33.74 ± 2.55)]. This difference was statistically significant ($P < 0.05$). See Table 2.

Insight and treatment attitudes questionnaire score comparison

Before the intervention, there was no significant difference in the insight and treatment attitudes questionnaire (ITAQ) scores between the two groups ($P > 0.05$). After intervention, ITAQ scores of both groups were improved, and compared with control group (7.97 ± 3.02) scores, the score of study group (13.56 ± 6.35) scores was significantly increased, and the difference was statistically significant ($P < 0.05$). See Table 3.

MCCB score comparison

Before the intervention, there was no significant difference in the MCCB scores between the two groups ($P > 0.05$). After intervention, the MCCB score of both groups was improved, and compared with the control group (38.44 ± 6.23), the score of the study group was significantly increased (43.51 ± 6.01), and the difference was statistically significant ($P < 0.05$). See Table 4.

Comparison of social skills

Before the intervention, there was no significant difference in PSP scores between the two groups ($P > 0.05$). After intervention, the PSP score of the study group (78.38 ± 6.63) was significantly higher than that of the control group (74.52 ± 7.01), and the difference was statistically significant ($P < 0.05$). See Table 5.

Comparison of adverse reactions

The incidence of adverse reactions in the study group was 6.25%, which was not significantly different from that in the control group (8.33%), $P > 0.05$. See Table 6.

DISCUSSION

The continuous prolongation of chronic schizophrenia can cause great damage to the patient's body and mind in the long run, especially in terms of cognitive ability and social adaptability. As patients with schizophrenia easily lose confidence in treatment after long-term medication, medication compliance is an important factor in the treatment of patients with schizophrenia[16]. The main factors that affect patients' medication compliance are a lack of cognitive ability, the importance of continuous treatment to a certain extent, and the wrong cognition of adverse drug reactions, which leads patients to refuse to take medication[17]. If patients take their medication on time, they can better control their symptoms and reduce the possibility of recurrence, thus improving their quality of life[18]. Currently, the universal free medication policy has increased medication compliance to some extent and reduced the recurrence of diseases and further aggravation of disabilities; however, other methods and strategies are still needed to further strengthen this effect. Therefore, this study explored medication compliance and cognitive ability in patients with chronic schizophrenia, using a comprehensive intervention model of drug, psychological, and social skills. In order to avoid the impact of confounding factors on the study results, this study randomly grouped the patients after inclusion and compared the baseline data of the two groups of patients. The results showed no significant difference in the baseline data between the two groups, which further provided the basis for the study and ensured its feasibility. At the same time, after the successful completion of this study, it also showed a relatively satisfactory result.

The MMSE and MoCA rating scales mainly evaluate patients' cognitive function. The comprehensive intervention of drug-psychology-society-skills can reduce the interruption rate of antipsychotic drug treatment, effectively improve the patient's disease status and quality of life and bring new hope to the treatment of chronic schizophrenia[19]. Insisting drugs are the most effective means of preventing the recurrence of chronic schizophrenia. Hattabi *et al*[20] reported that the combination of psychological, social, and skill intervention training based on drug treatment can reduce the

Table 2 Comparison of positive and negative syndrome scale score between two groups, mean ± SD

Group	Number of cases	Positive symptom score		Negative symptom score	
		Before intervention	After intervention	Before intervention	After intervention
Research group (n = 48)	48	15.38 ± 2.45	12.01 ± 2.58[a]	35.22 ± 2.65	32.51 ± 2.11[a]
Control group (n = 48)	48	15.66 ± 1.94	14.54 ± 2.33[a]	35.53 ± 2.01	33.74 ± 2.55[a]
t value		0.621	5.042	0.646	2.575
P value		0.536	0.000	0.520	0.012

[a]P < 0.05.

Table 3 Comparison of insight and treatment attitudes questionnaire scores before and after treatment, mean ± SD

Group	ITAQ score	
	Before intervention	After intervention
Research group (n = 48)	5.23 ± 3.45	13.56 ± 6.35[a]
Control group (n = 48)	5.79 ± 3.04	7.97 ± 3.02[a]
t value	0.843	5.508
P value	0.402	0.000

[a]P < 0.05.
ITAQ: Insight and treatment attitudes questionnaire.

Table 4 Comparison of MATRICS consensus cognitive battery scores between the two groups, mean ± SD

Group	Number of cases	Before intervention	After intervention
Research group (n = 48)	48	34.45 ± 5.22	43.51 ± 6.01[a]
Control group (n = 48)	48	34.24 ± 5.62	38.44 ± 6.23[a]
t value		0.190	4.058
P value		0.850	0.000

[a]P < 0.05.

Table 5 Comparison of personal and social performance scale scores between the two groups, mean ± SD

Group	PSP		t value	P value
	Before intervention	After intervention		
Research group (n = 48)	46.79 ± 7.31	78.38 ± 6.63	22.177	0.000
Control group (n = 48)	45.51 ± 7.26	74.52 ± 7.01	19.916	0.000
t value	0.861	2.772		
P value	0.382	0.007		

PSP: Personal and social performance scale.

recurrence rate of patients with chronic schizophrenia and restore their damaged social functions, such as life, work, and study. The results of this study showed that the MMSE score was not statistically significant, which may be related to the insensitivity of the indicators. Although chronic mental illness results in cognitive impairment, it has not yet reached the level of dementia. The MoCA score and the complete cognitive function test for schizophrenia (MCCB) in the study group were statistically higher than those in the control group, suggesting that the comprehensive intervention model of drug-

Table 6 Comparison of the incidence of adverse reactions during treatment, *n* (%)

Group	Extrapyramidal reaction	Put on weight	Elevated blood sugar	Hyperlipidemia	Incidence rate
Research group (n = 48)	1 (2.08)	0 (0.00)	0 (0.00)	2 (4.17)	3 (6.25)
Control group (n = 48)	2 (4.17)	0 (0.00)	0 (0.00)	2 (4.17)	4 (8.33)
χ^2	0.205				
P value	0.36				

psychology-society-skills has a certain positive significance for patients with chronic schizophrenia and the two scales may be more useful for evaluating cognitive impairment. The reason is that the second-generation antipsychotic drugs show high affinity for α1 and α2 receptors by acting on 5-hydroxy tryptamine (HT) 2 and D2 receptors. On the one hand, they block D2 receptors in the midbrain marginal pathway, thus changing patients' attention[21], on the other hand, they block 5-HT2 receptors in the midbrain cortical pathway and the substantia nigra striatum pathway, improving the functions of D1 receptors in the prefrontal cortex and D2 receptors in the striatum, thus improving the cognitive function of patients with chronic schizophrenia[22]. Through psychosocial and skill interventions, patients can learn to rationally vent their emotions and relax, and correctly express their emotions and needs. Simulation training of employment skills was developed according to the patients' own conditions to improve their ability to deal with problems and cultivate their learning habits and ability to accept new things. They must be encouraged to actively participate in social activities and naturally integrate into them[23] and foster self-affirmation, thereby helping them regain confidence in recovery and indirectly helping them improve their quality of life.

Cognitive impairment is a typical symptom in chronic schizophrenia[24]. An increase in the MMSE and MoCA scores indicates that the cognitive function of the patients has recovered to some extent. However, this study found that the scores of positive and negative symptoms in the study group were lower than those in the control group, indicating that the comprehensive drug-psychology-society-skills intervention can reduce positive and negative symptoms in patients with chronic schizophrenia. This is because clozapine can stimulate the serotonin receptor and promote dopamine release, thus increasing dopamine content in the synaptic cleft[25]. Clozapine also has an anticholinergic effect that can effectively improve the conversion efficiency of dopamine in the central nervous system and increase dopamine levels in the substantia nigra-striatum, thus strengthening dopamine nerve function and reducing cholinergic nerve function[26]. Furthermore, the drug can be taken for a long time. Training patients in society and skills, encouraging patients to communicate with others, and enhancing patients' confidence are conducive to the improvement of the disease.

There is a positive correlation between medication compliance and insight, and the improvement of insight is related to cognitive ability. Therefore, we can infer that improving cognitive ability can improve insight, and thus improve medication compliance. Improvements in cognitive ability are closely related to the rehabilitation of social functioning. The results of this study showed that the ITAQ and MCCB scores of patients in the study group were significantly higher than those in the control group after the comprehensive intervention of drug-psychology-society-skills, showing that the comprehensive intervention of drug-psychology-society-skills can improve patients' cognitive ability, improve patients' treatment attitudes, and relieve mental symptoms. This is because drug treatment can directly affect neurotransmitters in the brain and relieve patients' mental symptoms and psychological states[27]. Psychological intervention can effectively improve patients' cognition of their own diseases, improve their self-management ability, and help alleviate patients' negative emotions, such as anxiety and depression[28]. Moreover, through social intervention, providing patients with a good social support network can effectively reduce the sense of social isolation of patients; in addition, by training patients' drug management ability, life ability, interpersonal skills, work ability, *etc.*, patients can help to identify adverse drug reactions, and patients can be provided comprehensive health education and psychological treatment, which can help patients understand the importance of treatment and improve their self-care ability and social adaptability, so as to reduce patients' dependence. This will help them improve quality of life, thereby improving ITAQ and MCCB scores.

This study also found that, after treatment, the PSP score of patients in the study group was significantly higher than that in the control group. The reason for this was that the mental symptoms and psychological state of patients were effectively alleviated through the control and improvement of symptoms of severe mental illness by drugs. A comprehensive treatment system was formed with the intervention of society and skills to improve the symptoms of patients more comprehensively and improve the score on the social skills scale. Furthermore, the results of this study also showed no significant difference in adverse reactions between the two groups, which may be due to individual differences in patients related to personal physique, age, and long-term medication use.

CONCLUSION

In summary, the comprehensive intervention mode based on drug-psycho-social-skills can reduce the disease state of patients with chronic schizophrenia, enhance the cognitive ability of patients, reduce the positive and negative symptoms of patients, and improve the self-knowledge of patients and their attitude toward treatment. This model provides more comprehensive support for patients and new ideas and directions for the development of the mental health field. However, this study also has some limitations: (1) The sample size of patients was small, which may affect the universality of the study results, so it is still necessary to carry out further research and observation of large samples; (2)

Observation of results by means of scale statistics may cause the results to be affected by subjective factors, so the analysis of objective indicators should be added in subsequent studies; (3) Patients were not followed up, and the potential impact of comprehensive intervention on patients' long-term life could not be clarified. Therefore, the study period should be further extended to clarify the clinical application value of comprehensive intervention; and (4) This study only observed the clinical treatment outcome of patients, and the specific mechanism of action was not clearly explained. Therefore, further research should be conducted to improve intervention mechanisms.

FOOTNOTES

Author contributions: Wang HJ designed research, and performed research; Yan XL and Huang QY contributed new reagents or analytic tools; Xu WD analyzed data; Wang HJ and Chen W wrote the paper.

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META-ANALYSIS

Association of premature birth and maternal education level on attention deficit hyperactivity disorder in children: A meta-analysis

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Abstract

BACKGROUND

Attention deficit hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder in childhood. There is growing evidence that both preterm birth and maternal education levels substantially affect the likelihood of ADHD in children. However, there are limited systematic reviews and meta-analyses examining these associations.

AIM

To systematically review and conduct a meta-analysis on the association of preterm birth and maternal education level on the risk of ADHD in children.

METHODS

We conducted a comprehensive literature search across MEDLINE (PubMed), Web of Science, Embase, and the Cochrane Library, including studies published up to June 17, 2024. Data synthesis was performed using random-effect models, and the quality of studies was assessed using the Newcastle-Ottawa Scale.

RESULTS

This study included twelve studies, which revealed a significant association between premature delivery and an increased risk of ADHD in children [odds ratio (OR) = 2.76, 95% confidence interval (CI): 2.52-3.04, $P < 0.001$, $I^2 = 1.9\%$). Conversely, higher maternal education levels were significantly associated with a reduced risk of ADHD in children (OR = 0.59, 95%CI: 0.48-0.73, $P < 0.001$, $I^2 = 47.1\%$). Subgroup analysis further indicated that maternal education levels

significantly influenced ADHD risk, particularly in studies conducted in China (OR = 0.59, 95%CI: 0.46-0.75, $P < 0.001$, $I^2 = 81.2\%$), while no significant association was observed in studies from other regions (OR = 1.25, 95%CI: 0.66-2.40, $P = 0.495$, $I^2 = 92.3\%$). The sensitivity analysis confirmed the robustness of our findings, showing no significant publication bias.

CONCLUSION

This study found that preterm birth significantly increases the risk of ADHD in children, while a higher maternal education level serves as a protective factor against ADHD. To reduce the incidence of ADHD in children, public health policies should focus on early intervention for preterm infants and improving maternal education levels.

Key Words: Attention deficit hyperactivity disorder; Maternal education level; Meta-analysis; Preterm birth; Systematic review

Core Tip: Preterm birth significantly increases the risk of attention deficit hyperactivity disorder (ADHD) in children, with those born prematurely before 32 weeks facing even higher vulnerability due to neurodevelopmental challenges. Conversely, higher maternal education levels correlate with reduced ADHD risk, particularly noted in studies from China where maternal education of more than 12 years lowered the risk significantly. The intersection of these factors compounds ADHD risk, emphasizing the need for early identification and targeted interventions. Healthcare strategies should include enhanced prenatal care and parent education programs, while policy efforts should focus on improving maternal education to mitigate ADHD risks effectively. Future research should focus on longitudinal studies and underlying mechanisms to refine preventive strategies.

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URL: https://www.wjgnet.com/2220-3206/full/v14/i12/1956.htm
DOI: https://dx.doi.org/10.5498/wjp.v14.i12.1956

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder characterized by inattention, hyperactivity, and impulsive behavior[1,2]. In recent years, a growing number of studies have focused on the role of environmental and social factors in the etiology of ADHD. Maternal education level and preterm birth (defined as gestation under 37 weeks) are two significant potential risk factors that have garnered considerable attention and research [3-9].

Social factors are considered to play a significant role in the etiology of ADHD[10,11]. Low family socioeconomic status may expose children to adverse environments - such as malnutrition, inadequate medical resources, and insufficient educational support - thereby increasing the risk of ADHD[12]. Parental educational levels, especially those of mothers, are regarded as important socioeconomic indicators influencing children's health and development[13,14]. Lower maternal education is associated with insufficient cognitive stimulation for children and higher family stress, which may negatively impact children's neural development[15]. A cohort study showed that the lower the mother's level of education, the higher the probability that her child will develop ADHD. Specifically, children whose mothers have a middle school education, compared to those whose mothers hold a bachelor's degree, have a significantly higher risk of ADHD [odds ratio (OR) = 9.21, 95% confidence interval (CI): 1.25-67.62][16]. This correlation may be related to factors such as limited parenting resources, poor nurturing environments, unfavorable family economic conditions, high stress, and lack of parenting knowledge. Additionally, issues of emotional support and resource allocation within family structures - such as single-parent households or families with multiple children - as well as environmental factors like pollution, noise, and overcrowding in living environments, may also affect children's behavioral regulation abilities, thereby increasing the incidence of ADHD.

Preterm birth has been widely explored as a significant risk factor for ADHD[12,17]. Premature infants are predisposed to heightened physiological and neurodevelopmental risks, especially those born before 37 weeks of gestation[12]. Due to inadequate intrauterine development time, their nervous systems may remain incompletely matured, elevating the probability of neurodevelopmental disorders. The increased susceptibility to ADHD in preterm individuals may stem from disruptions in neurobiological brain development, including delayed or aberrant maturation of key regions such as the prefrontal cortex, basal ganglia, and cerebellum - structures crucial for attention regulation and impulse control[18]. Furthermore, preterm children may exhibit functional irregularities in neurotransmitter systems like dopamine and norepinephrine, which are essential for modulating attention, behavioral control, and cognitive functions[18]. Consequently, preterm birth may amplify the risk of ADHD through these neurobiological mechanisms.

Recent studies have revealed a significant increase in the risk of ADHD among preterm infants born to mothers with low educational levels, as compared to full-term infants born to mothers with higher educational levels[3,15]. Additionally, other research has indicated that low maternal education is not only associated with preterm birth but also with adverse birth outcomes such as low birth weight and small for gestational age infants[15]. These findings underscore the dual association of maternal education and preterm birth on the incidence of ADHD in children.

MATERIALS AND METHODS

Ethical approval

As this meta-analysis uses previously published data without involving individual-level data collection or analysis, ethical approval was not necessary. This research adheres to the ethical guidelines and best practices for meta-analyses, ensuring a rigorous and objective synthesis of existing evidence. The study has been registered with PROSPERO (https://www.crd.york.ac.uk/PROSPERO/), registration number (CRD42024569277).

Search strategy

We conducted a comprehensive literature search in MEDLINE (PubMed), Web of Science, Embase, and the Cochrane Library, covering the period from each database's inception to June 17, 2024. The search was limited to MeSH terms without additional restrictions. Our search strategy included combinations of keywords and medical subject headings related to "Preterm Births", "Birth, Premature", "Mother", "Mother's Clubs", "Educational Achievement", "Education Level", "Educational Status", "Paternal Education Levels", "Maternal Education Levels", "ADHD", "ADDH", "Attention Deficit Disorders with Hyperactivity", "Attention Deficit-Hyperactivity Disorders", "Hyperkinetic Syndrome", and "Minimal Brain Dysfunction", among others (Supplementary Table 1 for specific search steps). We also manually reviewed the reference lists of all identified studies and relevant reviews to ensure comprehensive coverage. Figure 1 illustrates the flowchart summarizing the identification and evaluation process of studies included in this review.

Study selection

After removing duplicate articles using EndNote, the author Yin-Kai Zhao reviewed the titles and abstracts of the studies. Studies that did not meet the inclusion and exclusion criteria were excluded. Subsequently, two authors (Yin-Kai Zhao and Miao-Miao Feng) independently screened the full texts of the papers based on the inclusion and exclusion criteria, conducting the reviews in a blinded manner. Upon completing this step, any decisions to include or exclude a study were re-evaluated. In cases of disagreement, a third researcher (Lu-Lu Hu) re-assessed the study. If the full text of a study was unavailable, an email or interlibrary loan request was sent to the primary author; studies that remained inaccessible were excluded.

In this study, the Newcastle-Ottawa Scale[19] was used as a tool to assess the methodological quality of observational studies. Based on the various criteria of this checklist, case-control or cohort studies were rated on a scale of 0 to 9, evaluating titles, abstracts, introductions, methods, and results (4 points for selection, 2 points for comparability, and 3 points for exposure or outcome). A Newcastle-Ottawa Scale score of ≥ 7 was considered indicative of high-quality research (low risk of bias), a score of 5-6 indicated moderate quality (moderate risk of bias), and a score below 5 indicated low quality (high risk of bias). However, no study was excluded due to low quality or high risk of bias; all studies were included in the analysis[20].

Data extraction

Data collection was conducted by two authors (Yin-Kai Zhao and Miao-Miao Feng) using the methods and results from preliminary studies. A table was created to extract information such as the first author's name, publication year, country, preterm birth details, maternal education level, diagnostic criteria, and the age of included children. Data were extracted by Meng Li and reviewed by Ting-Ting Shi.

Risk of bias assessment

We utilized Stata 18 to assess the risk of bias through funnel plots and Egger's quantitative analysis ($P > 0.05$ indicates no publication bias).

Statistical analysis

We employed meta-analysis techniques, utilizing the Mantel-Haenzel random effects model[21] to calculate the pooled estimates for each case. The resulting pooled estimates were expressed as the pooled OR along with the corresponding 95%CI. Heterogeneity among specific study estimates was assessed using the I^2 statistic[22], with values < 30%, 30%-60%, 61%-75%, and > 75% indicating low, moderate, substantial, and considerable heterogeneity, respectively. The quality of studies was evaluated using the Newcastle-Ottawa scale.

The comprehensive analysis revealed that most studies categorized preterm and term births into extremely preterm (< 28 weeks), very preterm (28-31 completed weeks), moderate-late preterm (32-36 completed weeks), and term (37-41 completed weeks). To standardize criteria and mitigate the association of subtle differences in preterm definitions across articles, we defined preterm status using very preterm (gestational age < 31 + 6 weeks), mid-late premature (gestational age 32-36 completed weeks), preterm (gestational age < 36 + 6 weeks), and term (gestational age 37-41 completed weeks) [23,24]. Maternal education levels were categorized as follows: Completion of primary education as 6 years, junior high

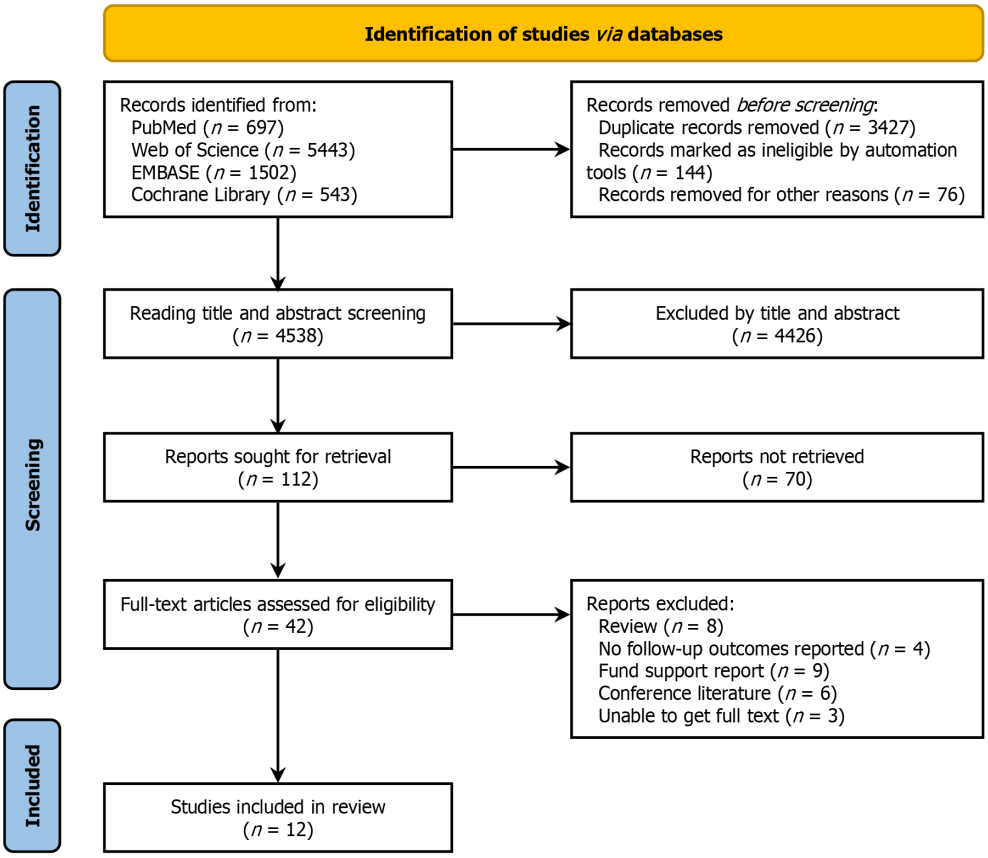


Figure 1 Flow diagram of study selection.

school as 9 years, high school as 12 years, and college or university and above as > 12 years.

Statistical heterogeneity was assessed using the Cochrane χ^2 test (Q test), with $P < 0.05$ indicating significant statistical heterogeneity. Study-specific risk estimates were combined through random effects meta-analysis. Forest plots were used to detail the associations between preterm birth, maternal education, and ADHD outcomes in children. Additionally, subgroup analyses and meta-regression were conducted based on child age stratification (above 10 years, below 10 years), study type (retrospective, other), geographic region (China, others), study design (single-center, multicenter), and different study periods to identify potential sources of heterogeneity. Sensitivity analyses were performed using the backward elimination method (removing one item at a time) to test the robustness of the results against the influence of specific studies. Potential publication bias was captured and its association on the validity of estimates was examined using funnel plots. Statistical analyses were conducted using SPSS 28.0 (IBM, Chicago, IL, United States) and Stata 18 software. $P < 0.05$ was considered statistically significant unless otherwise specified in the article.

RESULTS

Study characteristics

This article summarizes a meta-analysis aimed at evaluating the association of preterm birth and maternal education level on the prevalence of ADHD in children. A comprehensive literature search identified 697 articles from PubMed, 5443 from Web of Science, 1502 from Embase, and 543 from the Cochrane Library. Endnote software was used to remove 3427 duplicates. After screening and evaluation by reviewers, 12 studies were included in the meta-analysis. These studies were conducted in various regions, including 4 studies from China and 8 from other areas such as South Africa, the United States, and Finland. A total of 101612 samples were included, with most studies providing detailed follow-up data on preterm birth, maternal education, and ADHD prevalence in children. Detailed characteristics of the included studies are presented in Table 1. A summary of the meta-analysis results is presented in Table 2.

Qualitative assessment

The Newcastle-Ottawa Quality Assessment Scale was used to evaluate the quality of each study, with scores ranging from 5 to 9 (mean score: 7.583), indicating a generally accepted methodological approach. Table 1 lists the scores for each study, while Table 3 provides a detailed breakdown of the scoring criteria.

Table 1 Characteristics of the included studies

Ref.	Area	Sort	Intervention	Period	Age	Sample size	Sample source	NOS score	Language	Diagnostic basis
Kong *et al*[25], 2024	Finland	Prospective cohort study	Premature	1996-2018	4-22	57236	N/A	7	English	ICD-10 codes
Perapoch *et al* [27], 2021	Spain	Retrospective cohort study	Premature	1995-2007	7-19	7488	N/A	9	English	ICD-10
Bora *et al*[28], 2014	New Zealand	Retrospective cohort study	Premature	1998-2000	9	217	N/A	8	English	SDQ
Cherkes-Julkowski[26], 1998	N/A	Prospective cohort study	Premature	N/A	11	48	N/A	8	English	Stanford-Binet, 4th
Huang *et al* [16], 2018	China	Retrospective cohort study	Education level of mother	2013-2014	6-12	270	Multicenter	9	Chinese	DSM-5
St Sauver *et al* [33], 2004	United States	Case control study	Education level of mother	1976-1982	14-20	5701	Multicenter	7	English	DSM-4
Rydell[32], 2010	Sweden	Prospective cohort study	Education level of mother	None	10	1206	Single center	9	English	DSM-4
Chen *et al*[29], 2024	China	Retrospective cohort study	Education level of mother	2022-2023	6-12	11190	Multicenter	7	English	Parent Symptom Questionnaire
Hsu *et al*[31], 2022	Taiwan, China	Retrospective cohort study	Education level of mother	2000-2011	6-11	1855	Multicenter	5	English	DSM-IV-TR
Yan *et al*[35], 2018	China	Cross-sectional	Education level of mother	2014	3-6	15291	Single center	7	Chinese	Conners concise questionnaire
Cochran *et al* [30], 2022	United States	Prospective	Education level of mother	2002-2004	10-15	1010	Multicenter	9	English	Child Symptom Inventory-4
van Dyk *et al* [34], 2015	South Africa	Case control	Education level of mother	N/A	5-13	100	Single center	6	English	DSM-4

NOS: Newcastle-Ottawa Scale; N/A: Not applicable; ICD: International Classification of Diseases; SDQ: Strengths and Difficulties Questionnaire; DSM-4: Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition.

Table 2 Summary of meta-analysis results of the influence of premature delivery and mother's education level on attention deficit hyperactivity disorder

Intervention measure	Item	*Z*	OR	95%CI	*P* value	I^2
Premature	Premature *vs* term	21.13	2.76	2.52-3.04	< 0.001	1.9%
	Very premature *vs* mild-late premature	3.66	1.95	1.37-2.79	< 0.001	87.3%
Education level of mother	≥ 12 years *vs* < 12 years	1.56	0.78	0.57-1.07	0.119	91.7%
	≥ 12 years *vs* < 9 years	2.19	0.61	0.39-0.95	0.029	84.5%
	≥ 12 years *vs* < 9 years[1]	4.98	0.59	0.48-0.73	< 0.001	47.1%
	≥ 12 years *vs* 9-12 years	2.40	0.74	0.58-0.95	0.016	77.6%
	9-12 years *vs* < 9 years	1.44	0.74	0.49-1.11	0.150	59.2%

[1]Eliminate the literature with great heterogeneity.
OR: Odds ratio; CI: Confidence interval.

Preterm birth and childhood ADHD

Twelve articles were included in the analysis, with only four considered for examining the association between preterm birth and ADHD in children[25-28], as shown in Figure 2A. The meta-analysis revealed a significant association between preterm birth and an increased risk of ADHD compared to full-term birth (OR = 2.76, 95%CI: 2.52-3.04, $P < 0.001$, Figure 2A). No significant heterogeneity was observed among the included studies ($I^2 = 1.9\%$, $Q = 3.06$, heterogeneity $P = 0.383$). Additionally, only two studies[25,27] compared very preterm and mid-late preterm births, indicating that earlier preterm birth is associated with a higher risk of ADHD (OR = 1.95, 95%CI: 1.37-2.79, $P < 0.001$, Figure 2B). However,

Table 3 Assessment of quality of studies by the Newcastle-Ottawa scale

Ref.	Selection			Comparability			Outcome			Score
	1	2	3	4	5a	5b	6	7	8	
Kong *et al*[25], 2024	1	1		1	1		1	1	1	7
Perapoch *et al*[27], 2021	1	1	1	1	1	1	1	1	1	9
Bora *et al*[28], 2014	1	1	1	1	1	1	1		1	8
Cherkes-Julkowski [26], 1998	1	1	1	1	1	1		1	1	8
Huang *et al*[16], 2018	1	1	1	1	1	1	1	1	1	9
St Sauver *et al*[33], 2004	1	1	1		1	1	1		1	7
Rydell[32], 2010	1	1	1	1	1	1	1	1	1	9
Chen *et al*[29], 2024		1	1	1	1	1	1		1	7
Hsu *et al*[31], 2022	1		1		1	1			1	5
Yan *et al*[35], 2018	1		1	1	1	1		1	1	7
Cochran *et al*[30], 2022	1	1	1	1	1	1	1	1	1	9
van Dyk *et al*[34], 2015		1	1	1	1	1			1	6

1: The exposed cohort is representative; 2: Study cohort with unexposed; 3: Exposure factor identified; 4: No positive results at the start of the study; 5: Cohort comparability based on design or analysis (a: Study age controls; b: Study controls for any additional factors); 6: Outcome assessment is reliable; 7: Follow-up time is long enough; 8: Adequacy of cohort follow-up.

significant heterogeneity was found in this comparison (I^2 = 87.3%, Q = 7.85, P = 0.005), which may limit the conclusiveness of this finding (I^2 = 87.3%, Q = 7.85, heterogeneity P = 0.005).

Maternal education level and childhood ADHD

Twelve articles were included in the analysis, with only eight considered for examining the association between maternal education level and ADHD in children[16,29-35], as shown in Figure 3. The meta-analysis indicated that maternal education of ≥ 12 years was associated with a reduced risk of ADHD in children compared to < 12 years of education, with an OR of 0.78 (95%CI: 0.57-1.07, P = 0.119, Figure 3A), although significant heterogeneity was observed (I^2 = 91.7%, Q = 84.55, heterogeneity P < 0.001). Compared to maternal education of < 9 years, ≥ 12 years of education was significantly associated with a reduced risk of ADHD in children, with an OR of 0.61 (95%CI: 0.19-0.95, P = 0.029, Figure 3B), but significant heterogeneity was again observed (I^2 = 84.5%, Q = 32.25, heterogeneity P < 0.001). After manually excluding three studies with high heterogeneity[16,32,34], the meta-analysis showed more statistically significant results, with an OR of 0.59 (95%CI: 0.48-0.73, P < 0.001, Figure 3C) and no significant heterogeneity (I^2 = 47.1%, Q = 3.78, heterogeneity P = 0.151).

Additionally, we compared maternal education levels of ≥ 12 years with 9-12 years. The results were consistent with previous analyses, showing that higher maternal education was associated with a lower risk of ADHD in children (OR = 0.74, 95%CI: 0.58-0.95, P = 0.016, Figure 3D), despite significant heterogeneity (I^2 = 77.6%, Q = 22.29, heterogeneity P < 0.001). Finally, we analyzed the differences between maternal education levels of 9-12 years and < 9 years, revealing an OR of 0.73 (95%CI: 0.49-1.11, P = 0.150, Figure 3E), with significant heterogeneity observed (I^2 = 59.2%, Q = 7.36, heterogeneity P = 0.061).

Subgroup and sensitivity analyses

We also conducted a subgroup analysis (Figure 4 and Table 4) to explore the relationship between maternal education levels and the risk of ADHD in children under different influencing factors. Our subgroup analysis used 12 years of maternal education as the grouping variable, comparing studies from China and other regions (United States, Finland, South Africa, Spain, New Zealand, and Sweden). In China, maternal education significantly influenced ADHD risk, with an OR of 0.59 (95%CI: 0.46-0.75, P < 0.001, Figure 4A), though significant heterogeneity was observed (I^2 = 81.2%, Q = 15.95, heterogeneity P = 0.001). In other regions, maternal education levels showed no statistically significant association on the risk of ADHD (OR = 1.25, 95%CI: 0.66-2.40, P = 0.495, Figure 4A), with significant heterogeneity observed (I^2 = 92.3%, Q = 39.06, heterogeneity P < 0.001). We also compared single-center and multi-center studies, finding no statistically significant difference in the association of maternal education on the risk of ADHD. For multi-center studies, the OR was 0.67 (95%CI: 0.41-1.12, P = 0.128, Figure 4B), with significant heterogeneity observed (I^2 = 94.2%, Q = 69.11, heterogeneity P < 0.001). For single-center studies, the OR was 0.97 (95%CI: 0.59-1.61, P = 0.912, Figure 4B), with significant heterogeneity observed (I^2 = 81.2%, Q = 14.48, heterogeneity P < 0.001).

Table 4 Subgroup analysis summary table of mothers' education years ≥ 12 years *vs* < 12 years

Analysis specification	Z	OR	95%CI	*P* value	I^2
All	1.56	0.78	0.57-1.07	0.119	91.7%
China	4.21	0.59	0.46-0.75	< 0.001	81.2%
Other	0.68	1.25	0.66-2.40	0.495	92.3%
Multicenter	1.52	0.67	0.41-1.12	0.128	94.2%
Single	0.11	0.97	0.59-1.61	0.912	86.2%

OR: Odds ratio; CI: Confidence interval.

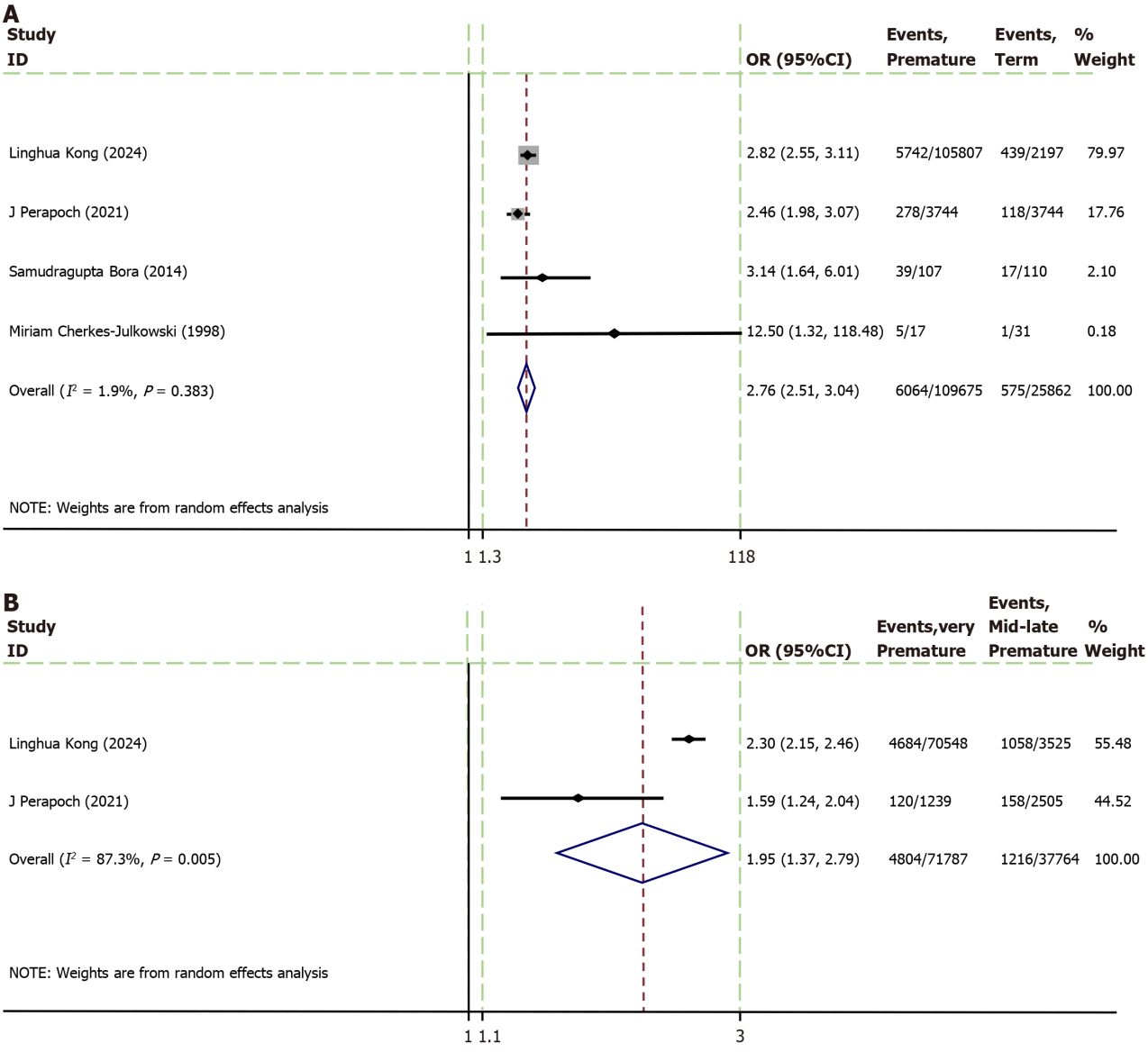
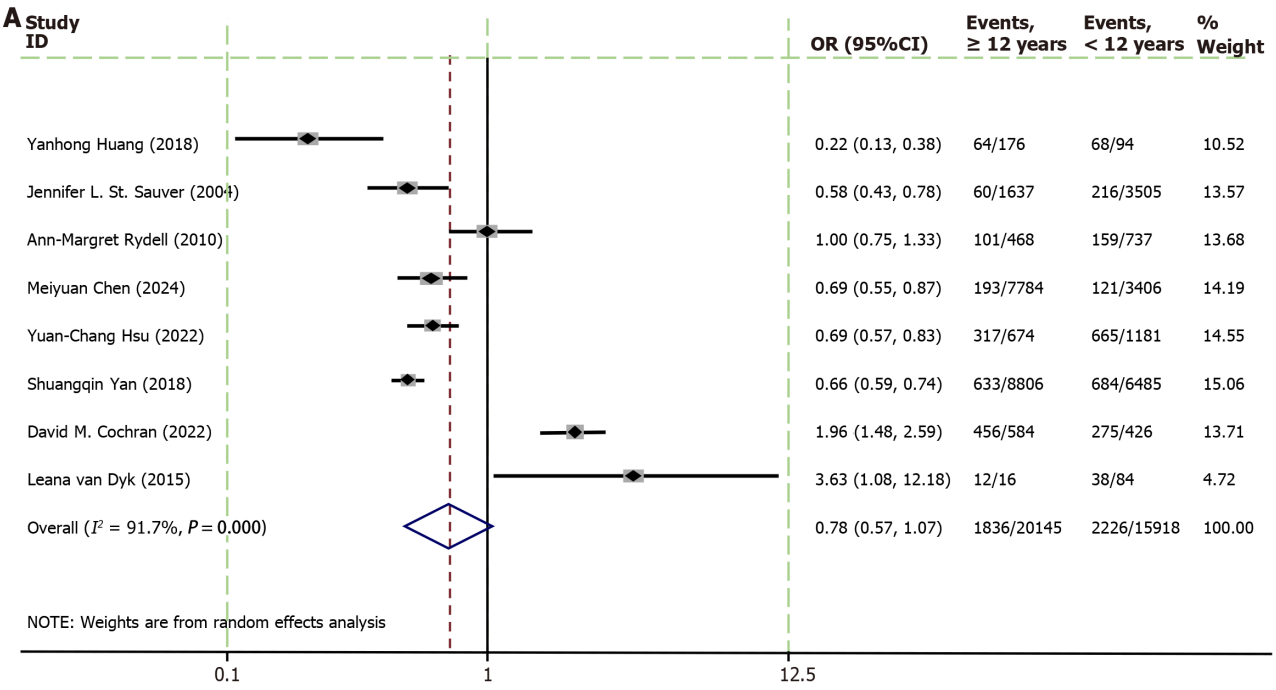
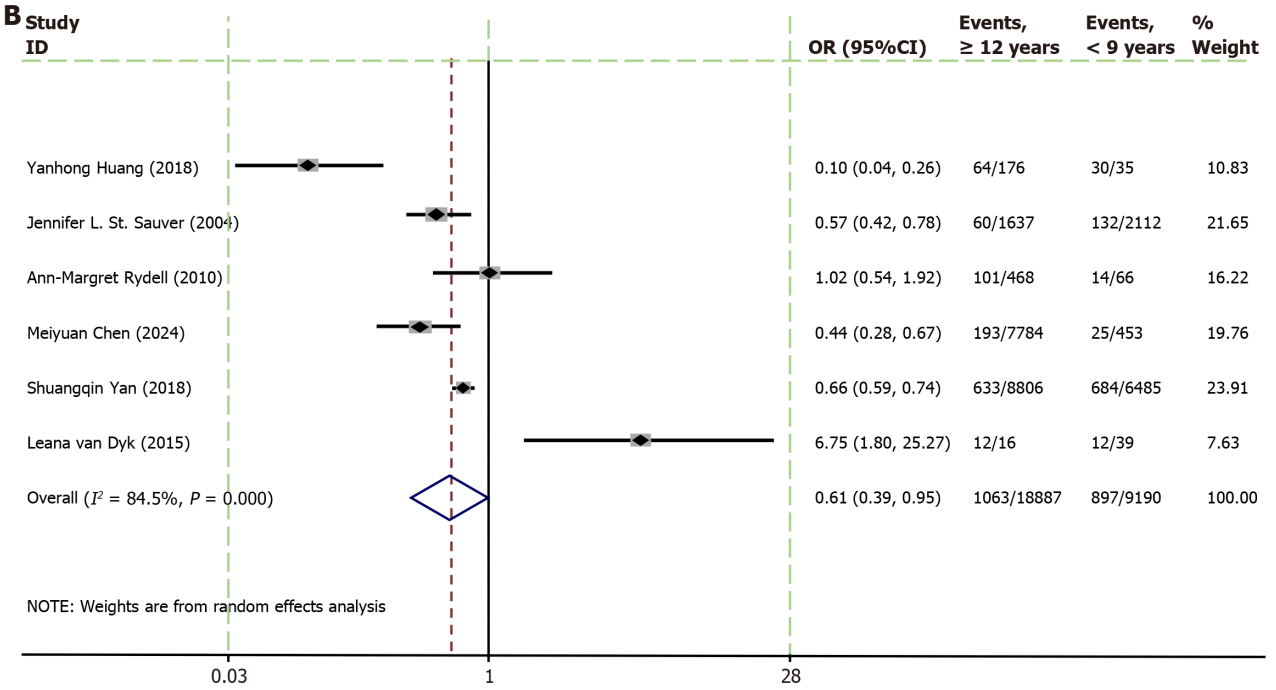
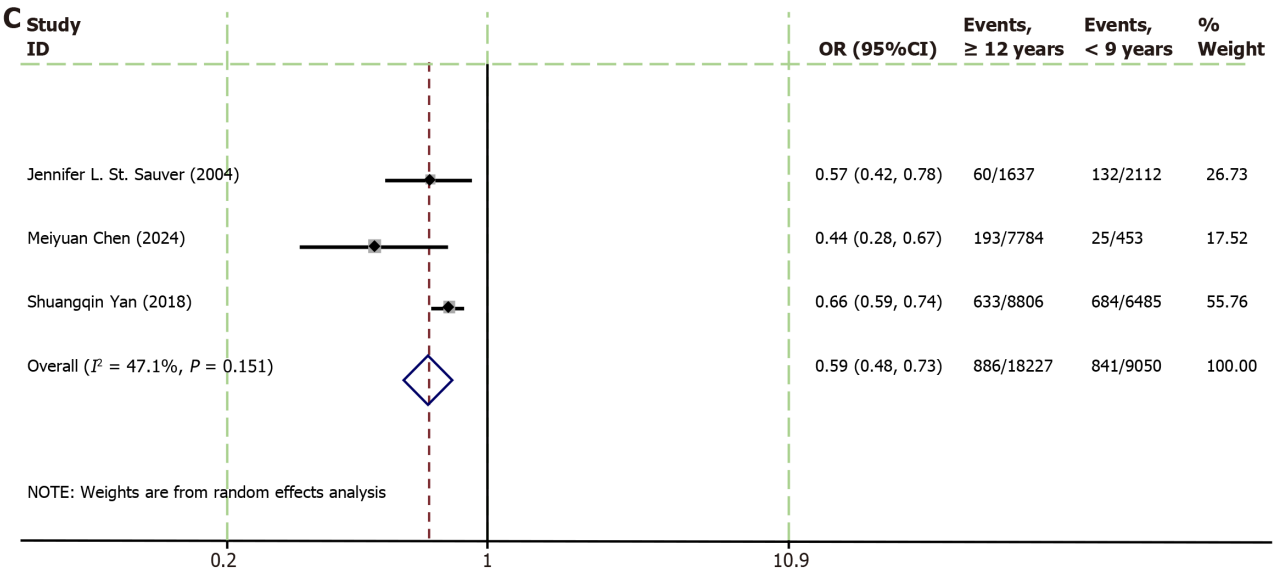


Figure 2 Meta-analysis of premature delivery and attention deficit hyperactivity disorder in children. A: Premature *vs* term; B: Very preterm *vs* mid-late premature. OR: Odds ratio; CI: Confidence interval.

We conducted a sensitivity analysis, through a step-by-step exclusion process, we found that the results did not show significant variation; all the outcomes after exclusion fell within the 95%CI of the pooled result (OR = 0.78, 0.57-1.07) in Figure 5. Results indicated that the significant association between preterm birth and the risk of ADHD in children is consistent and robust. Similarly, the significant association between maternal education level and the risk of ADHD in children is also consistent and robust. Therefore, despite observed heterogeneity, sensitivity analyses support the conclusion that both preterm birth and maternal education levels are associated with an increased risk of ADHD in


A
Study ID
OR (95%CI)
Events, ≥ 12 years
Events, < 12 years
% Weight
Yanhong Huang (2018) 0.22 (0.13, 0.38) 64/176 68/94 10.52
Jennifer L. St. Sauver (2004) 0.58 (0.43, 0.78) 60/1637 216/3505 13.57
Ann-Margret Rydell (2010) 1.00 (0.75, 1.33) 101/468 159/737 13.68
Meiyuan Chen (2024) 0.69 (0.55, 0.87) 193/7784 121/3406 14.19
Yuan-Chang Hsu (2022) 0.69 (0.57, 0.83) 317/674 665/1181 14.55
Shuangqin Yan (2018) 0.66 (0.59, 0.74) 633/8806 684/6485 15.06
David M. Cochran (2022) 1.96 (1.48, 2.59) 456/584 275/426 13.71
Leana van Dyk (2015) 3.63 (1.08, 12.18) 12/16 38/84 4.72
Overall (I^2 = 91.7%, P = 0.000) 0.78 (0.57, 1.07) 1836/20145 2226/15918 100.00
NOTE: Weights are from random effects analysis
0.1
1
12.5


B
Study ID
OR (95%CI)
Events, ≥ 12 years
Events, < 9 years
% Weight
Yanhong Huang (2018) 0.10 (0.04, 0.26) 64/176 30/35 10.83
Jennifer L. St. Sauver (2004) 0.57 (0.42, 0.78) 60/1637 132/2112 21.65
Ann-Margret Rydell (2010) 1.02 (0.54, 1.92) 101/468 14/66 16.22
Meiyuan Chen (2024) 0.44 (0.28, 0.67) 193/7784 25/453 19.76
Shuangqin Yan (2018) 0.66 (0.59, 0.74) 633/8806 684/6485 23.91
Leana van Dyk (2015) 6.75 (1.80, 25.27) 12/16 12/39 7.63
Overall (I^2 = 84.5%, P = 0.000) 0.61 (0.39, 0.95) 1063/18887 897/9190 100.00
NOTE: Weights are from random effects analysis
0.03
1
28


C
Study ID
OR (95%CI)
Events, ≥ 12 years
Events, < 9 years
% Weight
Jennifer L. St. Sauver (2004) 0.57 (0.42, 0.78) 60/1637 132/2112 26.73
Meiyuan Chen (2024) 0.44 (0.28, 0.67) 193/7784 25/453 17.52
Shuangqin Yan (2018) 0.66 (0.59, 0.74) 633/8806 684/6485 55.76
Overall (I^2 = 47.1%, P = 0.151) 0.59 (0.48, 0.73) 886/18227 841/9050 100.00
NOTE: Weights are from random effects analysis
0.2
1
10.9

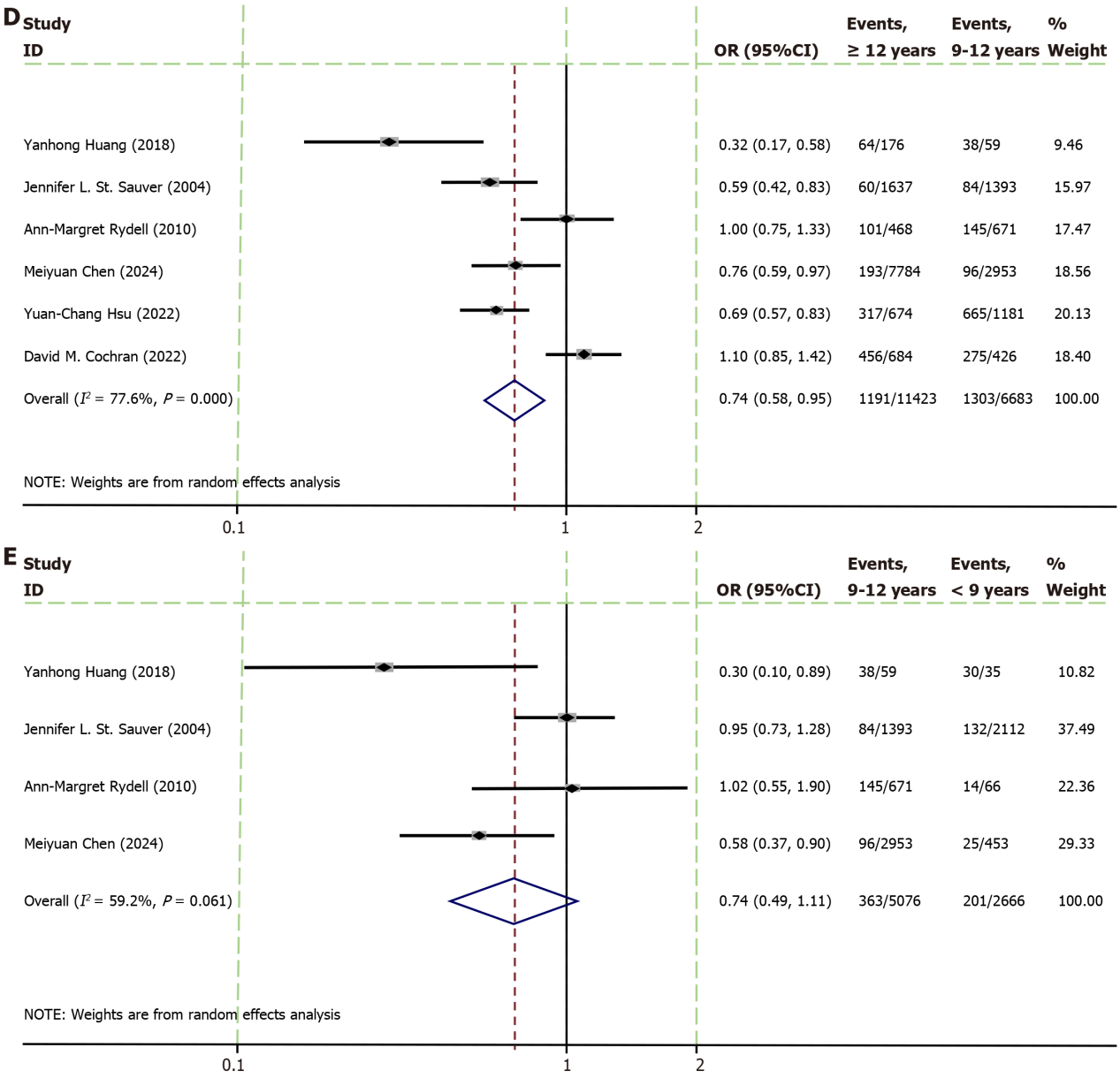


Figure 3 Meta-analysis forest map of mothers with different years of education. A: ≥ 12 years *vs* 12 years; B: ≥ 12 years *vs* 9 years; C: ≥ 12 years *vs* 9 years; D: ≥ 12 years *vs* 9-12 years; E: 9-12 years *vs* < 9 years. After the adjustment of meta-analysis, the studies with large heterogeneity were manually excluded. OR: Odds ratio; CI: Confidence interval.

children.

Publication bias assessment

Funnel plots were created and analyzed, along with Egger's quantitative analysis (Figure 6, Tables 4 and 5). In addition, we conducted a meta-regression analysis and did not identify any significant sources of heterogeneity (Table 6). All analyses revealed no evidence of publication bias, thereby supporting the reliability of the aggregated results.

DISCUSSION

This systematic review and meta-analysis identified a significant association between preterm birth and maternal education levels with the risk of developing ADHD in children. Our analysis, which included twelve studies, revealed that children born prematurely have a markedly increased risk of ADHD compared to full-term infants (OR = 2.76, 95%CI: 2.52-3.04, P < 0.001, I^2 = 1.9%). This risk was even more pronounced in those born before 32 weeks, indicating a gradient of vulnerability with the degree of prematurity. Additionally, our findings showed that higher maternal education serves as a protective factor against ADHD in children, with a notably reduced risk (OR = 0.59, 95%CI: 0.48-0.73, P < 0.001, I^2 = 47.1%). Subgroup analysis further suggested that this protective effect of maternal education was particularly significant in studies conducted in China (OR = 0.59, 95%CI: 0.46-0.75, P < 0.001, I^2 = 81.2%), while no

Table 5 Summary of publication bias

Intervention measure	Item	Incorporate literature	*t*	*P* value	95%CI
Premature	Premature *vs* term	4	0.67	0.570	-3.02 to 4.13
Education level of mother	≥ 12 years *vs* < 12 years	8	0.57	0.591	-4.91 to 7.88
	≥ 12 years *vs* < 9 years	6	-0.13	0.905	-4.90 to 4.49
	≥ 12 years *vs* < 9 years[1]	3	-3.29	0.188	-10.13 to 5.96
	≥ 12 years *vs* 9-12 years	6	-0.93	0.405	-10.85 to 5.41
	9-12 years *vs* < 9 years	4	-1.28	0.330	-9.43 to 5.11

[1]Eliminate the literature with great heterogeneity
CI: Confidence interval.

Table 6 Summary of meta-regression

Condition	*t*	*P* value	OR	95%CI
Merge	0.45	0.686	0.78	-4.81 to 6.38
Quality	0.21	0.894	0.04	-0.58 to 0.66
China	3.10	0.053	3.16	-6.40 to 0.09
Age[1]	2.33	0.102	2.60	-0.96 to 6.17
Multicenter	0.17	0.876	0.09	-1.56 to 1.74

[1]The groups were divided by age: Children aged 10 were included in the control group, while the intervention group consisted of samples with ages above 10.
OR: Odds ratio; CI: Confidence interval.

significant association was observed in studies from other regions (OR = 1.25, 95%CI: 0.66-2.40, $P = 0.495$, $I^2 = 92.3\%$). The sensitivity analysis confirmed the robustness of these findings and revealed no significant publication bias, underscoring the reliability of the results. This comprehensive evaluation highlights the importance of both biological and socioeconomic factors in the development of ADHD in children.

The study suggests that preterm birth and maternal education level may have a cumulative effect on the risk of ADHD in children, based on their independent and interactive influences on ADHD risk. Preterm children are more prone to neurodevelopmental issues[36,37], while lower maternal education is often associated with adverse environmental factors such as lower family socioeconomic status, insufficient cognitive stimulation, and a lack of parenting knowledge[38-40]. These factors can exacerbate the negative impact of preterm birth on a child's neurodevelopment. Consequently, when both preterm birth and low maternal education are present, the risk of ADHD in children may not only add up but could even exhibit a multiplicative effect.

The decision to combine these two risk factors for stratified analysis stems from their independently significant roles in ADHD risk, as well as their potential interrelation. Moreover, maternal education level is not only a key indicator of socioeconomic status but also directly influences parenting practices and cognitive stimulation within the home[40], offering a more targeted perspective for understanding ADHD risk in children. While other risk factors, such as family socioeconomic status, parental mental health, and environmental pollution, also exist, they are somewhat related to maternal education and preterm birth. Analyzing these two independent yet crucial factors together can help to unravel the complexity of ADHD risk in children and provide scientific support for the development of effective public health policies and early intervention strategies.

Preterm birth, defined as delivery before 37 weeks of gestation, is consistently linked to an increased risk of neurodevelopmental disorders, including ADHD) This meta-analysis consolidates findings from multiple studies to elucidate the relationship between preterm birth and the prevalence of ADHD in children. Our analysis included 12 studies that investigated the association between preterm birth and ADHD. The results indicated that, compared to full-term children, those born preterm have a significantly increased risk of developing ADHD. This suggests that the earlier the birth, the higher the risk of ADHD, potentially due to the increased vulnerability of the developing brain to extrauterine environmental and biological stress factors[41-44].

The neurodevelopmental pathways linking preterm birth to ADHD are intricate[45,46]. One hypothesized mechanism involves the incomplete development of neural circuits responsible for attention and executive functions, which are critical for impulse control and sustained attention. Additionally, preterm infants often experience a range of medical complications, such as intraventricular hemorrhage and periventricular leukomalacia, which may further disrupt brain development and contribute to the emergence of ADHD[41,47].

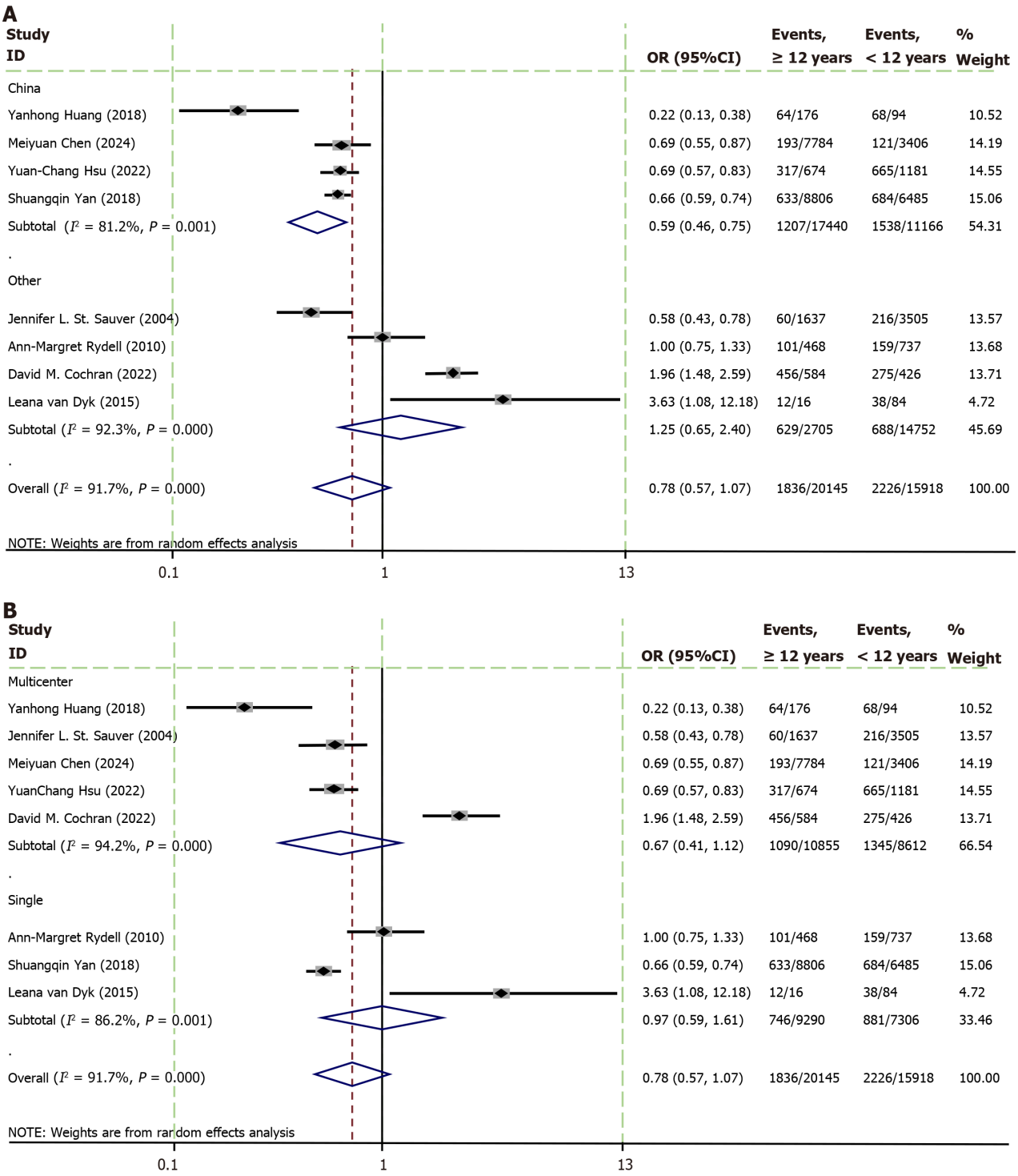


Figure 4 Subgroup analysis of the influence of mother's education level on attention deficit hyperactivity disorder in children forest map.
A: China *vs* other country; B: Multicenter *vs* single center. OR: Odds ratio; CI: Confidence interval.

Maternal education level is a key socioeconomic indicator influencing child health and development[48]. Our meta-analysis investigated the correlation between maternal education levels and the risk of ADHD in children, revealing that lower levels of maternal education are associated with an increased risk of ADHD. The studies included in this analysis indicate that children of mothers with lower educational attainment have an increased likelihood of developing ADHD. Specifically, in Chinese studies, the pooled OR for ADHD in children whose mothers have more than 12 years of education shows a significant difference compared to studies from other regions. This heterogeneity in findings suggests that the impact of maternal education on ADHD risk may vary depending on regional socioeconomic and cultural contexts.

The relationship between maternal education level and ADHD can be attributed to multiple factors. Lower maternal education levels are typically associated with reduced access to healthcare resources, insufficient knowledge about child development, and lower socioeconomic status[49]. These factors may create environments that are detrimental to

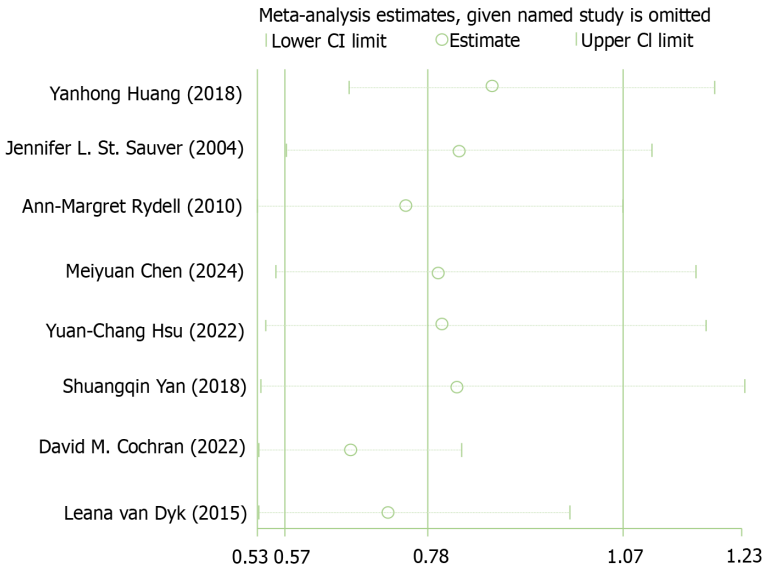


Figure 5 Sensitivity analysis chart of mother's education level. CI: Confidence interval.

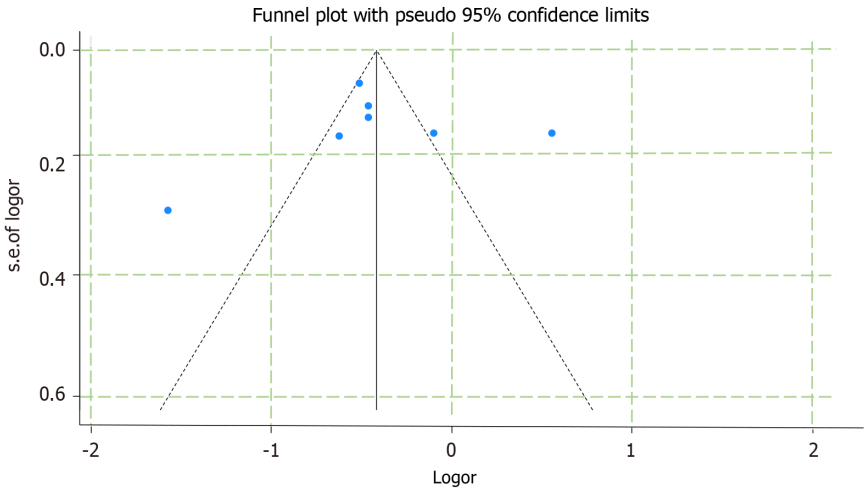


Figure 6 Funnel diagram of meta-analysis of mother's education level.

neurodevelopment, thereby increasing the risk of ADHD. For instance, children from low socioeconomic families may experience higher levels of stress, reduced cognitive stimulation, and poorer nutrition, all of which can negatively association brain development and function[15,50,51]. Additionally, maternal education level influences parenting practices and the ability to provide a supportive learning environment[52]. Educated mothers are more likely to engage in activities that promote cognitive and behavioral development, such as reading to their children and providing structured daily routines[52-54]. These activities are crucial for developing attention and self-regulation skills, which are often lacking in children with ADHD.

The joint association of prematurity and maternal low education on ADHD risk presents a compounded challenge. Our analysis indicates that these factors independently increase ADHD risk, but when combined, they may exhibit additive or even multiplicative effects. This intersectionality suggests that children who are both premature and have mothers with low education levels are particularly susceptible to ADHD. The interplay between the biological vulnerabilities associated with prematurity and the environmental disadvantages linked to low maternal education exacerbates the risk. Premature infants already face neurological immaturity and potential medical complications, which are further compounded by suboptimal developmental environments typically provided by mothers with low education, thereby increasing the likelihood of ADHD. The findings from this meta-analysis underscore the importance of risk mitigation strategies for premature infants and children of mothers with low educational attainment. Healthcare providers should prioritize early identification and support for these high-risk groups. Interventions may include enhanced prenatal and postnatal care for mothers and infants, the implementation of parent education programs, and ensuring access to early childhood development services.

Public health strategies should also focus on improving educational opportunities for women, as maternal education profoundly association children's health outcomes. Policies supporting maternal education can yield long-term benefits for both mothers and their children, reducing the incidence of ADHD and other developmental disorders. Furthermore, research should continue to explore the mechanisms linking prematurity, maternal education, and ADHD. Longitudinal studies tracking children from birth through adolescence can provide valuable insights, identifying critical periods for intervention.

CONCLUSION

In conclusion, this meta-analysis confirms that preterm birth and low maternal education levels are significant risk factors for ADHD in children. The evidence underscores the need for comprehensive strategies that address both medical and socioeconomic factors to effectively reduce the prevalence of ADHD. By understanding and addressing these risk factors, healthcare providers and policymakers can improve health outcomes for children and families affected by ADHD.

FOOTNOTES

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SCIENTOMETRICS

Bibliometric and visual study of narcolepsy from 2000 to 2023

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Abstract

BACKGROUND

More studies explored the prevalence, causes, associated conditions, and therapeutic strategies of narcolepsy. With an increasing focus on understanding narcolepsy's prevalence, associated conditions, and therapeutic strategies, there's a notable absence of bibliometric analyses summarizing trends in research and identifying emerging areas of focus within this field.

AIM

To conduct a bibliometric analysis to investigate the current status and frontiers of narcolepsy.

METHODS

The documents related to narcolepsy are obtained from the Web of Science Core Collection database (WoSCC) from January 1, 2000, to December 31, 2023, and VOS viewer 1.6.16, and the WoSCC's literature analysis wire were used to conduct the bibliometric analysis.

RESULTS

A total of 4672 publications related to narcolepsy were included, and 16182 authors across 4397 institutions and 96 countries/regions contributed to these documents in 1131 different journals. The most productive author, institution,

country and journal were Yves Dauvilliers, Stanford University, United States, and Sleep Medicine, respectively. The first high-cited document was published in *Nature* in 2005 by Saper *et al*, and this research underscores the role of certain neurons in ensuring the stability of sleep-wake transitions, offering insights into narcolepsy's pathophysiology.

CONCLUSION

In conclusion, the main research hotspots and frontiers in the field of narcolepsy are the diagnosis of narcolepsy, pathological mechanism of narcolepsy and the treatment of narcolepsy. More studies are needed to explore effective strategies for the diagnosis and treatment of narcolepsy.

Key Words: Narcolepsy; Diagnosis; Mechanisms; Treatment; Bibliometric analysis

Core Tip: This is the first bibliometric study to both quantitatively and qualitatively analyze publications in the field of narcolepsy. The main research hotspots and frontiers in the field of narcolepsy are the diagnosis of narcolepsy, pathological mechanism of narcolepsy and the treatment of narcolepsy. More studies are needed to explore effective strategies for the diagnosis and treatment of narcolepsy.

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INTRODUCTION

Narcolepsy is a long-term sleep disorder which is characterized by overwhelming daytime drowsiness, and this condition may be accompanied by cataplexy, vivid dreams or hallucinations upon falling asleep or waking, sleep paralysis, and disturbed sleep at night[1-5]. Narcolepsy is categorized into two primary forms: Narcolepsy type (NT) 1, marked by cataplexy and the depletion of orexin-producing neurons in the lateral hypothalamus, and NT2[1]. Diagnosis of narcolepsy is supported by reduced or absent levels of orexin in the cerebrospinal fluid. While some patients diagnosed with narcolepsy have shown a partial decrease in orexin neurons, orexin levels in the cerebrospinal fluid generally remain within the normal range for NT2, whose exact pathophysiological mechanisms are still under investigation[2,6-8]. Previous studies demonstrated that orexin receptor 1 and orexin receptor 2 (OX2R) are associated with narcolepsy[9-11]. These receptors participate in various physiological functions, such as sleep-wake regulation, maintaining energy balance, endocrine activities, and rewarding behaviors, with OX2R significantly involved in sustaining alertness and initiating rapid eye movement (REM) sleep. The consequences of narcolepsy are significant in both magnitude and severity, impacting nearly every aspect of a person's life. Frequent episodes of excessive daytime sleepiness (EDS) can severely impair daily functioning, affecting work performance, school activities, and social interactions. This can lead to issues like difficulty concentrating, memory lapses, and a decreased ability to complete tasks efficiently. Cataplexy, which is caused by narcolepsy, is a sudden loss of muscle tone triggered by strong emotions, adds further severity, potentially causing injuries from falls and contributing to social stigma and embarrassment. Narcolepsy also heightens the risk of accidents, such as car crashes, due to sudden sleep episodes. The cumulative impact on mental health is substantial, often resulting in anxiety, depression, and a diminished quality of life. Without effective management, these consequences can profoundly disrupt personal independence and overall well-being. Treatment options for narcolepsy currently include stimulants like modafinil, armodafinil, solriamfetol, methylphenidate, and amphetamines, along with medications such as pitolisant and hydroxybutyric acid[12-15]. The incidence of narcolepsy in estimated to range between 200 and 500 cases *per* million people[2].

With an increasing focus on understanding narcolepsy's prevalence, associated conditions, and therapeutic strategies, there's a notable absence of bibliometric analyses summarizing trends in research and identifying emerging areas of focus within this field. Bibliometric studies offer an in-depth review by examining various factors like publications, authorship, citation counts, h-index, geographical distribution, affiliating institutions, and prevailing themes in a given area of study [16,17]. Therefore, this research aims to conduct a bibliometric analysis to pinpoint the leading edges and focal points in narcolepsy research.

MATERIALS AND METHODS

Search strategy

As the most reliable citation-based database commonly used for bibliometric analysis, Web of Science Core Collection (WoSCC) was utilized in our study to download literature, and the search term was TS = "narcolepsy". The search was inclusive of all types of publications, imposing no restrictions on language, the documents published between January 1, 2000 and December 31, 2023 were included.

Data collection and bibliometric analysis

We downloaded the "Plain Text" versions of relevant records related to narcolepsy from WoSCC. For our analysis, we used the WoSCC literature analysis tool to identify the top 20 highly cited publications as well as the ten leading countries/regions, journals, authors, and institutions. Using VOS viewer, we created visual representations to illustrate the relationships among publications, including bibliometric networks of co-authorship for authors, institutions, countries, and journals, along with keyword co-occurrence.

RESULTS

Global publication trends

The bibliometric analysis revealed a total of 4672 publications related to "narcolepsy" after a thorough screening process, as illustrated in Figure 1. Among these, articles constituted the majority with 3766 entries (67.1%), followed by reviews numbering 906 (20%). In terms of subject categories, "Clinical Neurology" emerged as the predominant field with 1975 documents, making up 39.35% of the total, succeeded by "Neurosciences" with 1652 documents (17.42%), and "Pharmacology and Pharmacy" with 515 documents (16.67%). The temporal trend of publications from 2000 to 2023, as shown in Figure 2, indicates a steady growth in publication numbers, citations, and overall interest in narcolepsy research.

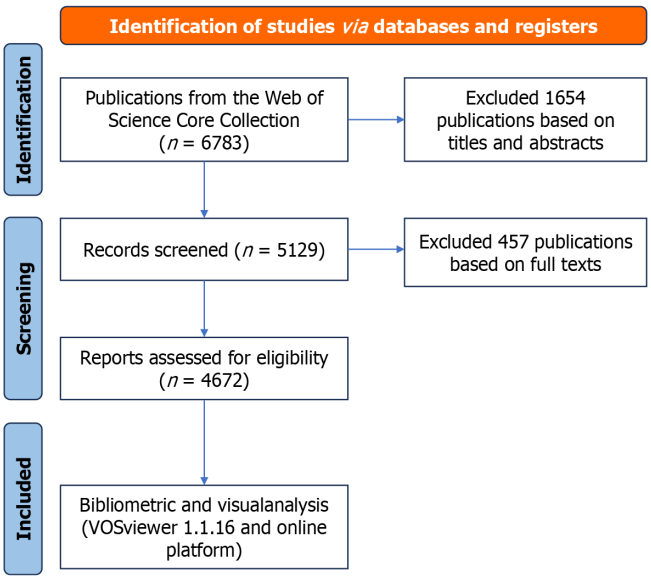

Figure 1 Flowchart of the inclusion and exclusion criteria.

Global contributions to narcolepsy research

The narcolepsy research domain has seen contributions from 16182 authors across 4397 institutions and 96 countries/regions, publishing in 1131 different journals. The United States leads in terms of publications with 1836 papers, which have attracted a noteworthy 105886 citations and achieved an H-index of 151, showcasing the significant volume and impact of its research contributions. France and Japan also stand out with 506 and 83 publications, respectively. Stanford University is at the forefront among institutions with 415 publications, closely followed by the Institut National De La Santé Et with 325 publications, and the University of Bologna with 254 publications. In terms of individual contributors, Yves Dauvilliers leads with 223 publications and 4046 citations, with Giuseppe Plazzi and Emmanuel Mignot also being notable for their substantial contributions of 222 and 191 publications, respectively. The journals "*Sleep Medicine*", "*Sleep*", and "*Journal of Clinical Sleep Medicine*" are the most prolific in the field, with 323, 318, and 149 publications, respectively. This illustrates the significant focus narcolepsy research has received from top-tier journals, as well as the collaborative effort spanning across various countries and institutions. The key figures and entities in narcolepsy research are detailed in Table 1 and Table 2, while network visualization maps showcasing the citation relationships among countries/regions,

Table 1 The productive 10 authors, institutions and countries

	Findings	Number	Ranking	Citation	H-index
Author	Carhart-Harris R	97	1	9188	45
	Griffiths RR	61	2	8713	39
	Roseman L	44	3	3289	26
	Nutt DJ	39	4	5257	26
	Ollenweider, FX	39	5	3925	29
	Erritzoe D	38	6	3920	20
	Liechti ME	32	7	1404	17
	Johnson M	31	8	6818	30
	Davis A	31	9	1831	20
	Hendricks PS	29	10	1067	13
Institution	Imperial College London	167	1	12490	59
	University of California System	155	2	5910	41
	Johns Hopkins University	145	3	11173	50
	University of London	95	4	5712	33
	Yale University	64	5	1721	22
	University of Zurich	63	6	3402	30
	University System of Ohio	63	7	1750	21
	Harvard University	56	8	2000	17
	King S College London	55	9	3774	23
	University of Toronto	53	10	1150	18
Country	United States	823	1	31979	86
	England	324	2	15473	64
	Canada	187	3	3392	32
	Germany	157	4	5873	43
	Switzerland	153	5	8685	54
	Australia	139	6	2861	29
	Netherlands	98	7	2555	28
	Brazil	83	8	3398	25
	Spain	79	9	3718	28
	Denmark	60	10	2273	23

institutions, authors and journals are presented in Figure 3A-D. This analysis highlights the global interest and collaborative nature of narcolepsy research, underscoring its importance and the contributions of leading researchers and institutions worldwide.

Visualization of citation networks and top-cited publications analysis

Figure 3E presents a network visualization map highlighting the citation relationships among publications in narcolepsy research. Table 3 summarizes the attributes of the top 20 most-cited publications, providing insights into pivotal findings in the field[18-37]. The foremost publication, appearing in *Nature* in 2005 by Saper *et al*[32], explores the intricate brain mechanisms governing sleep and wakefulness. The authors describe a network of cellular clusters activating the thalamus and cerebral cortex, vital for maintaining alertness, and a key hypothalamic mechanism that suppresses the arousal system during sleep. This research underscores the role of certain neurons in ensuring the stability of sleep-wake transitions, offering insights into narcolepsy's pathophysiology, the effects of medications on sleep patterns, and the influence of environmental factors on the sleep-wake cycle. The second notable publication by Peyron *et al*[29], published in *Nature Medicine* in 2000, investigates the role of hypocretins in narcolepsy through histopathological examination of brains from affected individuals and genetic screening. The study reveals a common deficiency in the hypocretin system

Table 2 The productive 10 journals based on publications

Journal	Number	Ranking	Citation	H-index
Sleep Medicine	323	1	9586	55
Sleep	318	2	16150	69
Journal of Clinical Sleep Medicine	149	3	3634	33
Journal of Sleep Research	126	4	4058	34
Journal of Neuroscience	80	5	10902	56
Sleep Medicine Reviews	71	6	5295	43
Plos One	69	7	2572	27
Neurology	61	8	4893	40
Neuroscience Letters	40	9	1329	22
Brain Research	38	10	1654	21

among narcolepsy patients, highlighted by a critical mutation affecting peptide trafficking in a case of early-onset narcolepsy, underscoring a universal hypocretin loss as a central aspect of the condition. The third highly-cited study, conducted by Thannickal *et al*[34] and published in *Neuron* in 2000, contrasts narcolepsy's genetic background in humans with that in animal models. The authors report a significant reduction in hypocretin neuron numbers in humans with narcolepsy, pointing to a selective degeneration of these neurons, as evidenced by surrounding gliosis, which implicates a degenerative process in the pathology of narcolepsy. Nishino *et al*[27], in a publication featured in *Lancet*, provide evidence of absent hypocretin levels in a majority of examined narcolepsy cases, suggesting a crucial impairment in hypocretin signaling as a feature of the disorder. Lastly, a study by Marcus *et al*[25], also in *Lancet*, discusses the varied roles of orexin receptors in body regulation and hints at the specific function of the OX2R receptor in maintaining stable sleep states, highlighting orexin's comprehensive role in sleep-wake regulation. These pivotal publications collectively enhance our understanding of narcolepsy, from its neurobiological underpinnings to genetic predispositions and pathophysiological mechanisms, illustrating the collaborative effort to unravel the complexities of this sleep disorder.

Analysis of keywords

Figure 3F displayed the visualization maps of keyword analysis. There were four distinct color-coded clusters, which likely represent thematic groups of keywords within the field. The central node labeled "narcolepsy" suggests it's the primary subject of the dataset from which this visualization is generated. It is closely associated with a cluster that likely represents the first thematic group, possibly focused on symptoms and related disorders, as suggested by terms such as "sleep", "cataplexy", and "excessive daytime sleepiness". The connections between "narcolepsy" and "orexin" or "hypocretin" indicate a second cluster, which may explore the biochemical or neurological aspects of the disorder, including research on neurons, neurotransmitters, and brain structures involved in sleep-wake regulation. Another cluster, identifiable by its distinct color and the proximity of certain keywords, may examine diagnostic tools, treatment methods, and the impact of narcolepsy on quality of life. This is evident from terms like "sleep latency test", "polysomnography", and "Epworth sleepiness scale", along with references to medications such as "modafinil" and "methylphenidate". A fourth cluster might cover the broader impacts and associations of narcolepsy, potentially addressing comorbidities, genetic factors, and epidemiological studies, as suggested by terms like "population", "genomics", and "prevalence".

DISCUSSION

General information

In general, 4672 publications related to "narcolepsy" were included. From 2000 to 2023, the number of publications increased steady, and this upward trajectory not only underscores the expanding research focus within the narcolepsy field but also mirrors the broader evolution of scientific inquiry. The most productive author, institution, country and journal were Dauvilliers Y, Stanford University, United States and *Sleep Medicine*, respectively. A landmark study by Saper *et al*[32], published in the *Nature* in 2005, stands out as a highly-cited publication, demonstrating the narcolepsy's pathophysiology. The keyword analysis further enriches this bibliometric perspective, revealing interconnected clusters around multifaceted research domain, from clinical symptoms to genetic predispositions of narcolepsy. The keyword analysis offers a comprehensive overview of the interconnected research topics within narcolepsy, showcasing the diversity of research areas from clinical to molecular studies, and providing insights into the most studied concepts and potential gaps in the literature.

Table 3 The top 20 highest cited references

Journal	Finding	Year	Ranking	Citation	Ref.
Nature	Hypothalamic regulation of sleep and circadian rhythms	2005	1	1752	Saper *et al*[32]
Nature Medicine	A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains	2000	2	1566	Peyron *et al*[29]
Neuron	Reduced number of hypocretin neurons in human narcolepsy	2000	3	1530	Thannickal *et al*[34]
Lancet	Hypocretin (orexin) deficiency in human narcolepsy	2000	4	1315	Nishino *et al*[27]
Journal of Comparative Neurology	Differential expression of orexin receptors 1 and 2 in the rat brain	2001	5	1246	Marcus *et al*[25]
Sleep	Practice parameters for the indications for polysomnography and related procedures: An update for 2005	2005	6	1118	Kushida *et al*[53]
Neuron	Genetic ablation of orexin neurons in mice results in narcolepsy, hypophagia, and obesity	2001	7	1085	Hara *et al*[19]
Trends in Neurosciences	The sleep switch: Hypothalamic control of sleep and wakefulness	2001	8	1081	Saper *et al*[30]
Nature	Neural substrates of awakening probed with optogenetic control of hypocretin neurons	2007	9	913	Adamantidis *et al*[18]
Neuron	Sleep state switching	2010	10	851	Saper *et al*[31]
Nature	A putative flip-flop switch for control of REM sleep	2006	11	810	Lu *et al*[24]
Archives of Neurology	The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias	2002	12	784	Mignot *et al*[26]
Sleep	Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. An American academy of sleep medicine report standards of practice committee of the American academy of sleep medicine	2005	13	724	Littner *et al*[23]
Neuron	Hypothalamic orexin neurons regulate arousal according to energy balance in mice	2003	14	694	Yamanaka *et al*[37]
Journal of Neuroscience	Discharge of identified orexin/hypocretin neurons across the sleep-waking cycle	2005	15	642	Lee *et al*[22]
Movement Disorders	The REM sleep behavior disorder screening questionnaire: A new diagnostic instrument	2007	16	634	Stiasny-Kolster *et al*[33]
Annual Review of Neuroscience	To eat or to sleep? Orexin in the regulation of feeding and wakefulness	2001	17	564	Willie *et al*[35]
Brain	Rapid eye movement sleep behaviour disorder: Demographic, clinical and laboratory findings in 93 cases	2000	18	558	Olson *et al*[28]
Journal of Sleep Research	Sensitivity and specificity of the MSLT, the maintenance of wakefulness test and the Epworth sleepiness scale: Failure of the MSLT as a gold standard	2000	19	556	Johns[20]
Journal of Neuroscience	Dopaminergic role in stimulant-induced wakefulness	2001	20	548	Wisor *et al*[36]

MSLT: Multiple sleep latency test; REM: Rapid eye movement.

Hotspots and frontiers

Based on the publications of narcolepsy, highly-cited documents, and important keywords with high frequency related to narcolepsy, the research hotspots in the field of narcolepsy were summarized as follows: (1) The diagnosis of narcolepsy. Narcolepsy often goes unrecognized or is incorrectly identified, with a significant delay in diagnosis[1-3,38-40]. Research conducted in Europe indicates the average time from when symptoms first appear to when narcolepsy is diagnosed can be up to 14 years. According to the global sleep disorder classification, NT1 diagnosis is considered when there is EDS persisting for over three months, paired with either low cerebrospinal fluid (CSF) orexin levels (less than 110 pg/mL) or cataplexy, plus a mean sleep latency under 8 minutes on the multiple sleep latency test (MSLT)[1]. Additionally, the presence of at least two sleep-onset REM periods (SOREMPs) either in MSLT or overnight sleep study is required. EDS typically emerges first, but only cataplexy is uniquely indicative of narcolepsy, making its accurate detection essential[2]. Cataplexy is not often seen and must be identified based on the patient's medical history, as there are no established diagnostic tools, though a standardized trigger test may be beneficial. There's limited evidence to support the effectiveness of video and neurophysiological recording to confirm cataplexy. NT2 is characterized by EDS persisting for over three months without cataplexy, a mean sleep latency of less than 8 minutes on the MSLT, and two or fewer SOREMPs on

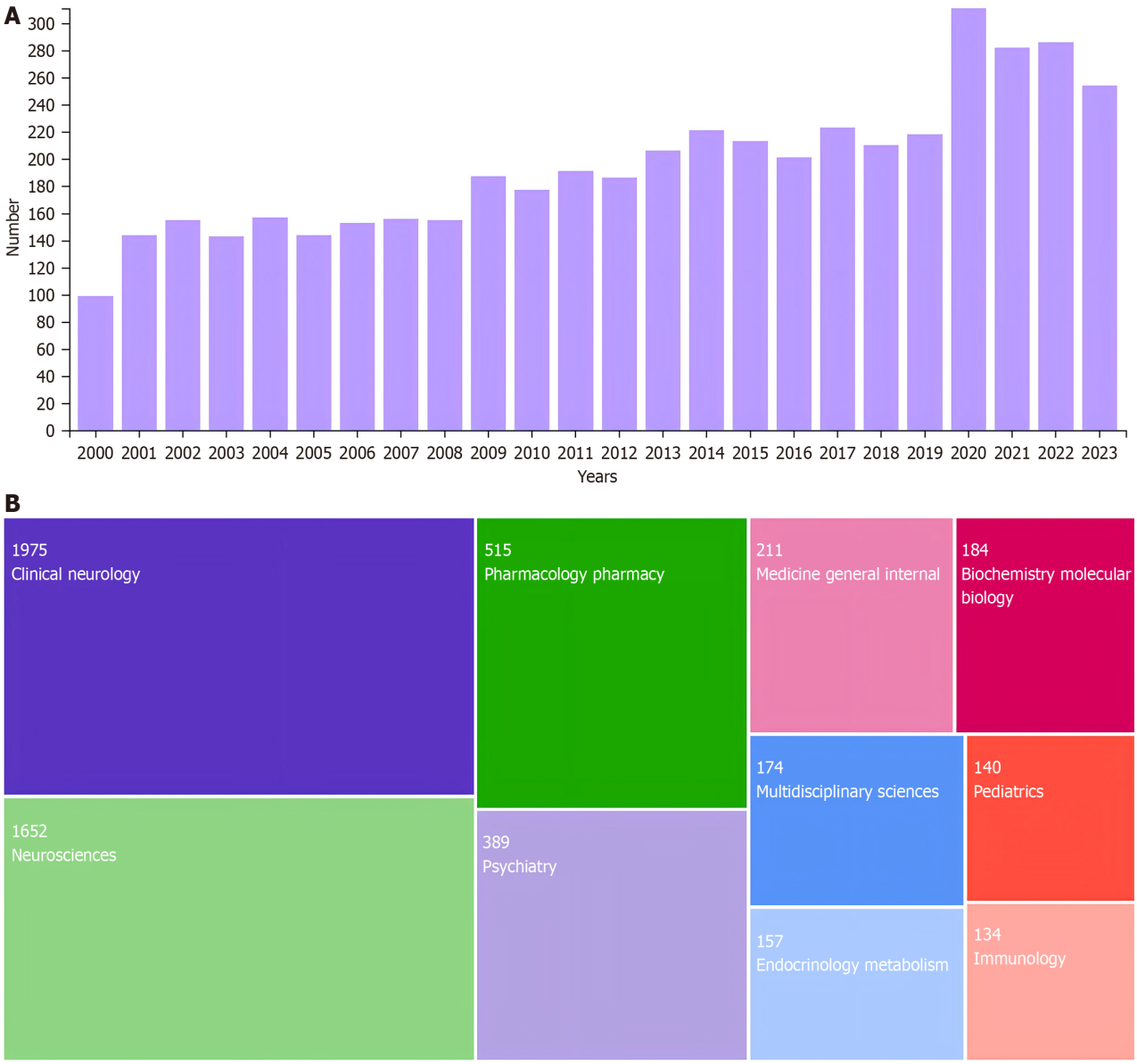

Figure 2 The yearly quantity and literature type of publications on narcolepsy. A: Annual publications; B: Subject categories.

the MSLT or nocturnal polysomnography, with CSF orexin levels above 110 pg/mL. Compared to NT1 patients, those with NT2 experience milder EDS and fewer REM sleep-related symptoms; (2) Pathological mechanisms of narcolepsy. Narcolepsy has been associated with the human leukocyte antigen (HLA) system, indicating a significant role of the immune system in the disease's development[41-44]. The observation that patients with narcolepsy often have reduced levels of orexin A in their CSF suggests that the disorder may involve an immune-mediated attack on the cells responsible for producing this neuropeptide. Orexin A and B are peptides that activate neurons through types 1 and 2 orexin receptors. The loss of orexin-producing neurons impacts several brain networks, leading to the various symptoms seen in narcolepsy. Type 1 narcolepsy, recognized by cataplexy and a lack of the neurotransmitter hypocretin, is believed to result from an interaction of genetic factors, environmental triggers, and a predisposition to immune system dysfunction that destroys the cells that produce hypocretin in the hypothalamus. The link between certain HLA alleles, notably HLA-DQB106:02, and narcolepsy underscores the immune system's involvement. Factors such as infections, vaccinations, and stress are thought to act as catalysts in those genetically at risk, triggering an autoimmune response that targets hypocretin neurons. This leads to the characteristic symptoms of narcolepsy. The progression of narcolepsy, therefore, stems from a complex interaction of genetic susceptibility and environmental influences, rather than a single causative agent; and (3) The treatment of narcolepsy. Management of narcolepsy utilizes a combination of lifestyle measures and medication to alleviate symptoms and enhance the well-being of individuals. Lifestyle modifications are essential for managing narcolepsy and include establishing a consistent sleep routine, practicing good sleep hygiene, incorporating brief, planned naps to combat daytime drowsiness, and adjusting daily habits to avoid triggering symptoms[45]. Psychological support and group therapy can be invaluable in addressing the social and mental challenges associated with narcolepsy[46]. Medically, wakefulness-promoting agents such as ritalin, modafinil and armodafinil are commonly prescribed[12,13,47-51], while sodium oxybate has been effective in reducing cataplexy episodes and improving sleep

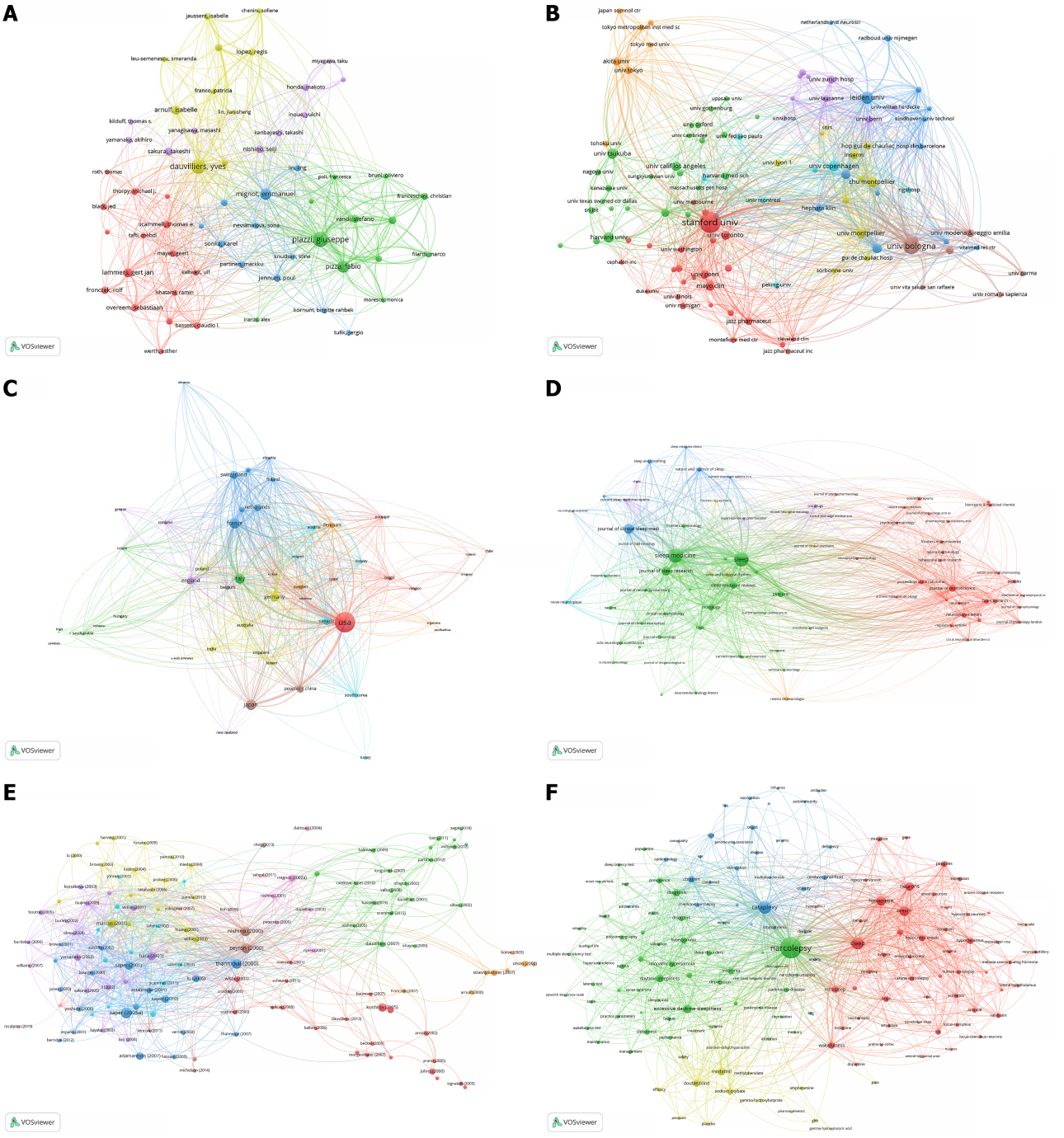

Figure 3 The visualization knowledge maps of co-authorship. A: Authors; B: Organizations; C: Countries; D: Journals; E: The citation relationships among publications in narcolepsy research; F: Keywords.

quality. Stimulants like methylphenidate and amphetamines are options for managing daytime sleepiness[15,52-54]. For symptoms like cataplexy, sleep paralysis, and hallucinations, selective serotonin reuptake inhibitors or serotonin and norepinephrine reuptake inhibitors may be beneficial[55,56]. Personalizing treatment is crucial, as different approaches work for different individuals, requiring tailored adjustments and close supervision by healthcare professionals.

Strengths and limitations

This is the first bibliometric study to both quantitatively and qualitatively analyze publications in the field of narcolepsy. The findings from this analysis provide valuable insights into the evolving landscape of scientific research on this complex sleep disorder. By thoroughly examining scholarly publications, the study has highlighted key advancements, major research centers, and influential authors who have significantly contributed to the understanding and management of narcolepsy. The data reveal a multidisciplinary approach, with the fields of neurology, psychiatry, genetics, and pharmacology converging to address the various challenges posed by narcolepsy. Despite progress in understanding the pathophysiology and developing therapeutic interventions, the analysis also identifies research gaps, particularly in long-term patient outcomes and personalized medicine. The global distribution of research efforts underscores the growing

recognition of narcolepsy's impact on diverse populations, while also pointing to the need for increased international collaboration and resource allocation to improve the quality of life for those affected by the disorder. Further research is essential to better understand the clinical spectrum of narcolepsy, the precise mechanisms behind orexin neuronal loss, and the potential of emerging treatments, including orexin agonists and immunomodulation. However, several limitations should be noted. First, the publications analyzed were exclusively retrieved from the WoSCC database, which may limit the generalizability of the findings. Additionally, the study focused on literature related to narcolepsy published between 2000 and 2023, excluding earlier publications before 2000, in order to capture the latest research trends and developments in the field of narcolepsy.

CONCLUSION

In conclusion, the main research hotspots and frontiers in the field of narcolepsy are the diagnosis of narcolepsy, pathological mechanism of narcolepsy and the treatment of narcolepsy. More studies are needed to explore effective strategies for the diagnosis and treatment of narcolepsy.

FOOTNOTES

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CASE REPORT

Effect of bright-light therapy on depression and anxiety of a patient with Alzheimer's disease combined with sleep disorder: A case report

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Abstract

BACKGROUND

Alzheimer's disease (AD) is a common type of dementia due to neuronal impairment. In addition, psychobehavioral symptoms including severe sleep disorders, depression and anxiety can occur in most patients with AD.

CASE SUMMARY

We report a case of a 68-year-old woman with a 2-year history of AD. She initially presented with memory loss, progressively more severe, leading to a depressive and anxious status. The clinical symptoms also included severe sleep disturbances. Considering the age and health state of the patient, a non-pharmacological treatment of bright light therapy was used to improve her sleep quality. The treatment was provided for 30 minutes twice a day, during 8:30 am to 9:00 am and 16:30 pm to 17:00 pm. After 4 weeks of therapy, the sleep quality notably improved, with a marked decrease in daytime sleep, increase in nighttime sleep, and disappearance of nocturnal activity. The depression and anxiety were also suppressed significantly.

CONCLUSION

This case report suggested that bright light therapy can have a positive effect on sleep quality in elderly patients with AD and can be used as an effective and safe non-pharmacological treatment.

Key Words: Bright-light therapy; Sleep disturbance; Alzheimer's disease; Dementia; Non-

pharmacological treatment; Case report

Core Tip: This report describes the case of a patient who developed Alzheimer's disease, accompanied by sleep disorders, depression and anxiety; we provided bright-light therapy (BLT) to improve her sleep quality. BLT can reduce the duration of daily sleep and nighttime restlessness, with a higher efficacy than medications in improving sleep. This case report suggested that BLT can have a positive effect on sleep quality in elderly patients with Alzheimer's disease and can be used as an effective and safe non-pharmacological treatment.

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INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder with various clinical manifestations, including cognitive decline, mental and behavioral alterations, and sleep disturbances[1]. The bidirectional relationship between AD and sleep disorders has been investigated extensively; sleep disturbances are a risk factor for AD and also a consequence of this disease[2]. A growing body of literature has examined sleep quality and cognitive function in elderly patients with AD[3]. Sleep disturbances exacerbate systemic inflammation and increase β-amyloid accumulation; β-amyloid a one of the major factors in AD pathogenesis[4]. Therefore, improving of sleep quality might have beneficial effect in AD. The cognitive decline cannot be completely eliminated; however, reducing sleep disturbances could prolong the cognitive abilities of patients with AD[5]. Multiple pharmacological and non-pharmacological approaches have been proposed for clinical treatment[6]. Bright-light therapy (BLT) is a non-pharmacological method usually adopted in elderly patients with sleep disorders[7,8]. Previous studies have shown that BLT can reduce depression and improve sleep quality in patients with mild cognitive impairment and neurodegenerative diseases[9-11]. Therefore, BLT is increasingly recommended as a first-line treatment for sleep disorders in patients with dementia, considering also its safety and efficacy [12]. This report describes the case of a patient who developed AD, accompanied by sleep disorders, depression and anxiety; we provided BLT to improve her sleep quality. BLT can reduce the duration of daily sleep and nighttime restlessness, with a higher efficacy than medications in improving sleep.

CASE PRESENTATION

Chief complaints

A 68-year-old woman presented with progressive memory loss, cognitive decline, and symptoms of dementia.

History of present illness

In the month before admission, she started having poor nighttime sleep quality or insomnia and being active in her room at night, heavily affecting her family's rest, and was accompanied to our hospital for treatment.

History of past illness

The patient's illness began 2 years prior, initially with short-term memory loss and incoherent speech. Later, the symptoms gradually worsened, and the patient started forgetting what she said immediately before, being unable to return home after a walk, and requiring assistance by the police and supervision from her family in daily life. She frequently believed her family stole her possessions and became depressed, irritable, and suspicious, often reprimanding her family members without reason.

Personal and family history

The patient denied any family history of AD.

Physical examination

At the initial consultation, the patient was conscious and cooperative in conversation; however, she could not recall immediate events or what she ate for her last meal and was not aware of being in the hospital. She was poorly oriented in time and space and towards other persons, with reduced volitional activity and lack of self-awareness.

Laboratory examinations

Blood counts, ultrasensitive C-reactive protein, and biochemistry were unremarkable.

Imaging examinations

A head computed tomography scan showed evident cerebral atrophy and no other organic lesions or cerebral infarct foci (Figure 1). No other somatic diseases possibly causing mental disorders were noted, and she had no history of hypertension, diabetes mellitus, or stroke.

FINAL DIAGNOSIS

The patient was diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, fifth edition criteria[13]. The patient was diagnosed with AD by two research psychiatrists and provision of informed consent. The cognitive level was evaluated by Mini-Mental State Examination (MMSE) score < 17, 20, and 24 in patient with education levels of illiteracy, primary school, and junior high school, respectively[14]. The disease course was more than 3 months. Donepezil or memantine was used to improve the cognitive level. The patient has no history of other severe mental illnesses. The MMSE of the patient score was 17. Based on these findings, the patient was diagnosed with AD accompanied by psychobehavioral symptoms and was subsequently hospitalized.

TREATMENT

BLT protocol

The phototherapy equipment (Figure 2) was designed by the Geriatrics Center of the Ningbo Kangning Hospital as described in our previous study[15]. It was mounted on a portable cart, and the intensity of the light source was adjustable from 0 to 20000 lux. The treatment was provided for 30 minutes twice a day, during 8:30 am to 9:00 am and 16:30 pm to 17:00 pm. The patient was seated 0.5-1 m from the light source; the light intensity provided was 14000 lux, for a 4-week course of treatment. The patient faced the light source and sited in a comfortable chair. After that, the nurse secures the portable cart and turns the light to patient, and reminds the patient that he or she is ready to begin treatment. During the course of treatment, patient was asked to remain quiet and not to get up and walk around. The patient was administered memantine oral solution 7.5 mL/quaque mane and carboplatin capsules 3 mg/bis in die, for intellectual stimulation, and olanzapine tablets 5 mg/day for antipsychotic treatment. Moreover, she underwent light therapy to improve the poor nighttime sleep quality.

OUTCOME AND FOLLOW-UP

After 4 weeks of hospitalization, the cognitive level was stable (MMSE: 18), whereas the psychiatric symptoms decreased, and the family reported improved mood and disappearance of paranoia. The patient's sleep quality markedly improved, with notable decrease in daytime sleep, increase in nighttime sleep, and absence of nocturnal activity.

DISCUSSION

We presented a case of severe AD complicated with sleep disturbances, treated with BLT. Sleep problems are common in patients with AD and place a high burden on their caregivers. Several medications can be used to increase sleep duration and improve its quality; however, the risk of side effects can also increase. Non-pharmacological treatment could be useful to avoid the risk of using multiple drugs in elderly patients with comorbidities. BLT can help regulate the sleep-wake cycle in older adults with dementia[16]. In a previous study, BLT was suggested to supplement daylight as a trigger for the suprachiasmatic nucleus (SCN)[17]. It can be used at any time during the day to promote wakefulness and reduce daytime sleep, realigning the patients' circadian rhythm to the typical sleep timings[18]. In this study, we provided BLT after breakfast and after dinner to maintain the wakeful state in the patient. There is a 4-hour interval between the time of BLT after dinner and the time of going to sleep at night, so it does not affect the patient's sleep. Additionally, an adequate sleep duration and circadian rhythm have a beneficial effect on the gut microbiota and digestive function[19].

Moreover, BLT is a well-established method to improve mood in seasonal affective disorder[20], and the effect of BLT on patients with non-seasonal depression has also been examined in a large number of clinical trials, as reported in a review[21]. In this case, the patient presented with depressive symptoms; with BLT, these symptoms markedly improved, though the cognitive dysfunction remained stable. The BLT mechanism of action has been investigated in previous studies; intrinsically photosensitive retinal ganglion cells project to the SCN and mediate the effects of light on learning. Mood regulation by light, on the other hand, requires an SCN-independent pathway linking intrinsically photosensitive retinal ganglion cells to a previously unrecognized thalamic region, named perihabenular nucleus[22]. The SCN can also be stimulated by BLT to enhance spatial memory[23]. BLT is known to improve nighttime sleep. A quality night's sleep can be rejuvenating and enhance the patient's ability to concentration during the daytime. Although BLT was reported to

Figure 1 Twin beds removable bright light therapy apparatus. Front, back, and detail view.

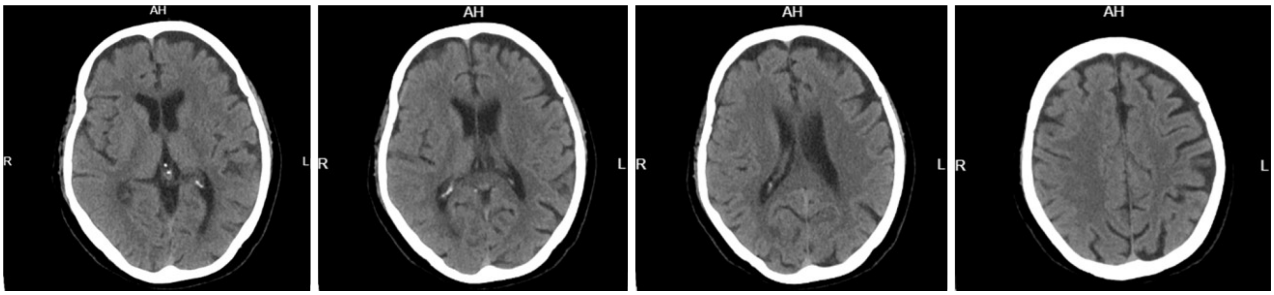

Figure 2 Head computed tomography. The cerebral hemispheres are symmetrical. The brain volume is reduced, and the sulci are deepened and widened. The ventricular system and sulcal fissure are widened. The midline structures are centered.

enhance spatial memory, whether it can improve memory to recall immediate events and become more oriented in time and space for those with reduced volitional activity and lack of self-awareness need to be studied in future.

BLT can also have positive effects on delirium and sundowning syndrome[24]. Circadian-related disorders and alterations in sleep-wake patterns are common complaints in elderly individuals, especially those diagnosed with AD [25]. Light is the main stimulus of the circadian melatoninergic system; therefore, patients with AD should be encouraged to walk outdoors in natural light. The strength and limitation of BLT: Although very few patients reported transient side effects including headaches and eyestrain during the course of the BLT, it was still an effectiveness non-invasive therapy for clinical application. Comparing to medication, BLT is suitable for patients with comorbid conditions, such as hypertension, diabetes mellitus, or a history of stroke, and reduces the physical burden of drug interactions on older adults with multiple health issues. Combined pharmacological and non-pharmacological measures could be adopted in elderly patients before considering multiple pharmacological measures.

CONCLUSION

This case report suggested that BLT can have a positive effect on sleep quality in elderly patients with AD and can be used as an effective and safe non-pharmacological treatment.

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FOOTNOTES

Author contributions: Zou CJ and Hu J participated in patient management and follow-up and collected patient information; Mei X searched the literature for the case description and wrote the first draft of manuscript; Zhou DS and Zheng CY revised the first draft and prepared the final manuscript; and all authors are actively involved in all steps of the contribution.

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LETTER TO THE EDITOR

Heart abnormality associates with a wide spectrum of psychiatric disorders: Evidence from Mendelian randomization analyses

Xue-Shi Chen, Zi-Yan Song, Xuan-Long Chen, Yi-Ming Bo, Li-Liang Li

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Abstract

Psychiatric disorders and heart abnormality are closely interconnected. Previous knowledge has been well-established that psychiatric disorders can lead to increased cardiovascular morbidity and even sudden cardiac death. Conversely, whether heart abnormality contributes to psychiatric disorders remains rarely studied. The work by Zhang *et al* pointed out that chronic heart failure had effects on the anxiety and depression (AD) severity, and indices including left ventricular ejection fraction, N-terminal pro-brain natriuretic peptide and interleukin-6 were independent risk factors for AD severity. In addition to the aforementioned AD, we herein find that heart failure might additionally impact the development of autism spectrum disorder and post-traumatic stress disorder (albeit $P > 0.05$), and significantly protects against the presence of attention deficit hyperactivity disorder (ADHD), [odds ratio (OR) = 0.61, $P = 0.0071$] by using a Mendelian randomization analysis. Bradycardia is also a protective factor for ADHD (OR = 0.61, $P = 0.0095$), whereas hypertrophic cardiomyopathy is a mild risk factor for schizophrenia (OR = 1.02, $P = 0.032$). These data suggest a wide spectrum of psychiatric disorders secondary to heart abnormality, and we highlight more psychiatric care that should be paid to patients with heart abnormality.

Key Words: Psychiatric disorders; Schizophrenia; Heart abnormality; Heart failure; Mendelian randomization analyses

Core Tip: Numerous studies have reported the effects of psychiatric disorders on heart dysfunction. Little attention has been paid to the effects of heart abnormality on psychiatric status. We highlight that in addition to the impact on anxiety and depression, heart failure might further contribute to increased risks of autism spectrum disorder and post-traumatic stress disorder, and protects from the development of attention deficit hyperactivity disorder (ADHD). Furthermore, bradycardia is a protective factor for ADHD, and hypertrophic cardiomyopathy may significantly contribute to the presence of schizophrenia. Heart abnormality is associated with a wide spectrum of psychiatric disorders.

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TO THE EDITOR

We read with interest the recent article by Zhang *et al*[1]. This paper demonstrates that heart disease influences the development of psychiatric disorders [anxiety and depression (AD)] through the humoral circulation approach. Myocardial markers and inflammatory factors such as left ventricular ejection fraction, N-terminal pro-Brain natriuretic peptide and interleukin-6 can predict the AD severity in patients with chronic heart failure. This study suggests that cardiac dysfunction may contribute to psychiatric disorders.

In recent years, an increasing amount of evidence has underscored the heart dysfunction in patients with psychiatric disorders (summarized in Table 1)[2-8]. For example, researchers found that depression[2], attention deficit hyperactivity disorder (ADHD)[3] and post-traumatic stress disorder (PTSD)[4] were associated with increased risks of cardiovascular disease. Similarly, a recent report[5], as well as our study[6], have found a significantly higher rate of sudden cardiac death in patients with schizophrenia. Activation of dopaminergic neurons linked to psychiatric disorders enhances cardiac remodeling following acute myocardial infarction[9]. The impact of these psychiatric disorders on cardiac function stems from genetic variations, modulation of neurocircuitry and the cardiotoxicity of anti-psychotropic medications[3,10].

On the other hand, little attention has been paid to the impact of heart abnormality on psychiatric status. In addition to the aforementioned study[1], a pioneering study found that a faster heart rate can cause an increase in anxiety through activation of the insula cortex[11], shedding light on the potential role that normal heart function plays in maintaining mental health. Whether heart abnormality has any impact on other psychiatric disorders beyond AD, however, remains to be evaluated. Herein, using a Mendelian randomization analysis, we further assessed whether there is a causal relationship between genetic variation in heart phenotypes and the development of psychiatric disorders. Single nucleotide polymorphism data from genome-wide association study were extracted for exposure factors (heart abnormality) including atrial fibrillation, bradycardia, congestive heart failure, PR intervals, dilated cardiomyopathy, and hypertrophic cardiomyopathy, and for outcome factors (psychiatric disorder) encompassing anorexia nervosa, ADHD, autism disorders, bipolar disorder, PTSD, and schizophrenia (Figure 1). The results showed that heart failure might also contribute to the development of autism spectrum disorder [odds ratio (OR) = 1.1695, P = 0.3797] and PTSD (OR = 1.1725, P = 0.3358), albeit differences not reaching a statistical significance. Interestingly, heart failure (OR = 0.61, P = 0.0095) and bradycardia (OR = 0.61, P = 0.0071) are observed to significantly protect against the presence of ADHD. Hypertrophic cardiomyopathy, however, is observed to significantly contribute to the presence of schizophrenia (OR = 1.02, P = 0.032). These results extend the content of the original study[1] and illustrate the important regulatory role of heart abnormality in mental health.

CONCLUSION

In summary, there is a close interplay between heart abnormality and mental health. Numerous studies have underscored the impact of psychiatric disorders on heart dysfunction, while less is known on whether heart abnormality influences psychiatric status. The study by Zhang *et al*[1] have confirmed that heart failure is indeed associated with the AD severity from a humoral cycle perspective, and our Mendelian randomization analysis further extends this conclusion from a genetic standpoint. The results indicate that heart failure might also contribute to the development of autism spectrum disorder and PTSD; heart failure and bradycardia are independent protective factors for ADHD. Hypertrophic cardiomyopathy is a significant risk factor for schizophrenia. Collectively, these data suggest a wide spectrum of psychiatric disorders following heart abnormality. Early screening and monitoring of psychiatric symptoms should be conducted in patients with heart abnormality especially heart failure and hypertrophic cardiomyopathy.

Table 1 Cardiovascular symptoms in patients with psychiatric disorders

Primary psychiatric disorder	Secondary cardiovascular symptom	Ref.
Depression	Cardiovascular disease and mortality	Rajan *et al*[2]
ADHD	Hypertension and arterial disease	Zhang *et al*[3]
PTSD	Coronary artery disease	Walczewska *et al*[4]
Schizophrenia	Sudden cardiac death	Dimsdale[5]; Wang *et al*[6]
Autism	High heart rate	Klusek *et al*[7]
Bipolar disorder	Heart failure	Chen *et al*[8]

ADHD: Attention deficit hyperactivity disorder; PTSD: Post-traumatic stress disorder.

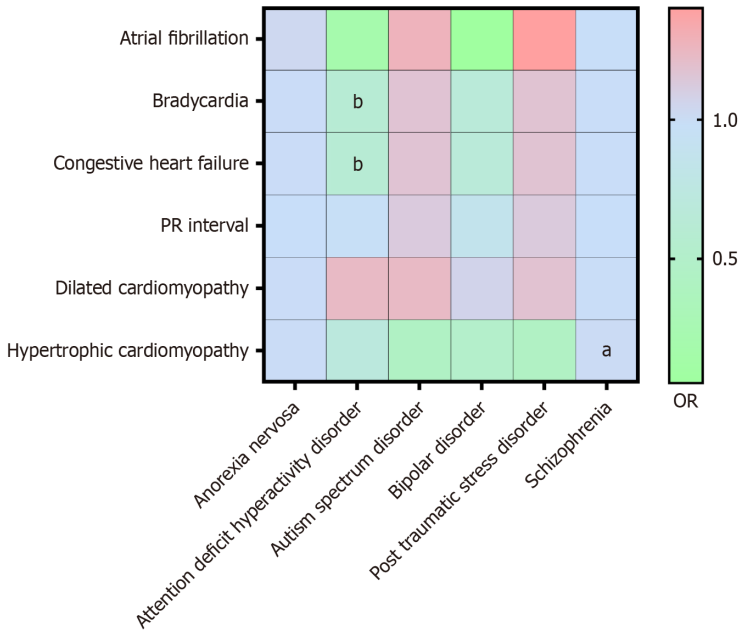

Figure 1 A Mendelian randomization analysis of heart abnormality (exposure factor, longitudinal axis) to psychiatric disorders (outcome, horizontal axis). The odds ratio (OR) is represented by color code, with OR values greater than 1 shown in red, less than 1 shown in green, and close to 1 shown in blue. OR values become greater from the bottom to the top of the color bar. Statistical significance is indicated by the letter, while the absence of letters indicates no statistical significance. [a]*P* < 0.05. [b]*P* < 0.01. OR: Odds ratio.

FOOTNOTES

Author contributions: Chen XS and Song ZY contributed equally to this study; Chen XS gathered literatures, drew the figure and drafted the manuscript; Song ZY gathered literatures and conducted data analysis; Chen XL and Bo YM designed the table; Li LL conceived the original idea and edited the manuscript; All authors participated fully in this work, taking public responsibility for its content, and provided final approval of the version that was submitted.

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