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Contents

Monthly Volume 14 Number 3 March 19, 2024

EDITORIAL

334 Potential use of large language models for mitigating students' problematic social media use: ChatGPT as an example

Liu XQ, Zhang ZR

342 How inflammation influences psychiatric disease

Ferat-Osorio E, Maldonado-García JL, Pavón L

REVIEW

350 Digital psychiatry in low-and-middle-income countries: New developments and the way forward

Chakrabarti S

MINIREVIEWS

362 Navigating the intersection of psychiatry and ophthalmology: A comprehensive review of depression and anxiety management in glaucoma patients

Ramesh PV, Morya AK, Azad A, Pannerselvam P, Devadas AK, Gopalakrishnan ST, Ramesh SV, Aradhya AK

ORIGINAL ARTICLE

Case Control Study

370 Brain protective effect of dexmedetomidine *vs* propofol for sedation during prolonged mechanical ventilation in non-brain injured patients

Yuan HX, Zhang LN, Li G, Qiao L

380 Evaluating serum CXCL12, sCD22, Lp-PLA2 levels and ratios as biomarkers for diagnosis of Alzheimer's disease

Liu ZL, Hua FF, Qu L, Yan N, Zhang HF

Retrospective Study

388 Analysis of risk factors of suicidal ideation in adolescent patients with depression and construction of prediction model

Zhou JC, Cao Y, Xu XY, Xian ZP

398 Deliberate self-harm among pediatric psychiatric inpatients in China: A single-center retrospective study

Jiang XZ, Li HH, Yu ZZ, Wang C

Observational Study

409 Mediating role of social support in dysphoria, despondency, and quality of life in patients undergoing maintenance hemodialysis

Zhou X, Jiang H, Zhou YP, Wang XY, Ren HY, Tian XF, Zhang QQ

World Journal of Psychiatry

Monthly Volume 14 Number 3 March 19, 2024

Contents

421 Causal relationship between feelings and cognitive decline: An univariable and multivariable Mendelian randomization study

Liu J, Liu L, Hu YX, Li JH, Zou X, Zhang HY, Fan L

Randomized Controlled Trial

434 Optimization of nursing interventions for postoperative mental status recovery in patients with cerebral hemorrhage

Tang JL, Yang WW, Yang XY

Basic Study

445 KAT7/HMGN1 signaling epigenetically induces tyrosine phosphorylation-regulated kinase 1A expression to ameliorate insulin resistance in Alzheimer's disease

Lu QS, Ma L, Jiang WJ, Wang XB, Lu M

META-ANALYSIS

456 Vulnerable brain regions in adolescent major depressive disorder: A resting-state functional magnetic resonance imaging activation likelihood estimation meta-analysis

Ding H, Zhang Q, Shu YP, Tian B, Peng J, Hou YZ, Wu G, Lin LY, Li JL

SCIENTOMETRICS

467 Psychological interventions for depression in children and adolescents: A bibliometric analysis

Wang N, Kong JQ, Bai N, Zhang HY, Yin M

World Journal of Psychiatry

Monthly Volume 14 Number 3 March 19, 2024

Contents

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EDITORIAL

Potential use of large language models for mitigating students' problematic social media use: ChatGPT as an example

Xin-Qiao Liu, Zi-Ru Zhang

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Abstract

The problematic use of social media has numerous negative impacts on individuals' daily lives, interpersonal relationships, physical and mental health, and more. Currently, there are few methods and tools to alleviate problematic social media, and their potential is yet to be fully realized. Emerging large language models (LLMs) are becoming increasingly popular for providing information and assistance to people and are being applied in many aspects of life. In mitigating problematic social media use, LLMs such as ChatGPT can play a positive role by serving as conversational partners and outlets for users, providing personalized information and resources, monitoring and intervening in problematic social media use, and more. In this process, we should recognize both the enormous potential and endless possibilities of LLMs such as ChatGPT, leveraging their advantages to better address problematic social media use, while also acknowledging the limitations and potential pitfalls of ChatGPT technology, such as errors, limitations in issue resolution, privacy and security concerns, and potential overreliance. When we leverage the advantages of LLMs to address issues in social media usage, we must adopt a cautious and ethical approach, being vigilant of the potential adverse effects that LLMs may have in addressing problematic social media use to better harness technology to serve individuals and society.

Key Words: Problematic use of social media; Social media; Large language models; ChatGPT; Chatbots

Core Tip: Large language models (LLMs) such as ChatGPT have opened a new chapter in the field of intelligent dialog and human history. Through the use of LLMs, better solutions can be provided for problematic social media use, thus mitigating issues associated with its use. In addition to enhancing technological improvements and improving the objectivity and rationality of large language generation results, it is imperative for society, individuals, and various other parties to collectively establish a favorable environment for the application of artificial intelligence.

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INTRODUCTION

Social media is ubiquitous in people's daily lives and plays an increasingly significant role. According to statistical data, as of October 2023, the number of global social media users had reached 4.95 billion, accounting for 61.7% of the global population, and the number of social media users continues to grow at an accelerating pace[1]. The latest data indicate that 90% of internet users use social media every month; a typical social media user is active on or visits an average of six to seven social platforms monthly, spending an average of 2 h and 24 min on social media daily. People spend approximately 15% of their waking hours using social media[1]. Social media has facilitated communication and contact between people, helping them maintain social relationships and obtain social support. Research has shown that using social media contributes to an increase in positive self-views, such as narcissism and self-esteem[2]. As people's time and intensity of mobile social media use have increased, certain disadvantages have gradually become more prominent[3]. The negative effects of individual social media use are often referred to as "problematic social media use". Currently, there are two main perspectives on the nature of this concept. One view is that it is a nonpathological problematic use[4] associated with mild to moderate psychological and physiological symptoms (*e.g.*, anxiety, depression). Another view is that it should be considered a pathological addiction[5], which explains the difficulty in controlling behavior[6] and that social media overuse can have similar negative psychological and physiological consequences similar to other addictive behaviors[7]. To enhance the comprehensiveness of the argument, this article incorporates both views.

Problematic social media use can have adverse effects on individuals' work and study, family relationships and social interactions, as well as health and well-being[8]. Previous studies have shown that users with higher social media use volume and frequency are more likely to experience sleep disturbances[9], increased anxiety levels and depressive tendencies[10], which harm both the physical and psychological health of users[11,12]. Research has also shown that internet usage time has a bidirectional impact on depression symptoms and attention deficit hyperactivity disorder, with this risk being particularly severe in patients with poor previous mental health conditions[13]. During the coronavirus disease 2019 (COVID-19) pandemic, due to home isolation and social distancing requirements, individuals' anxiety levels and overall societal experiences of negative emotions increased[14]. In this situation, the use of social media increased exponentially[15], particularly on platforms such as TikTok, Pinterest, Reddit, Facebook, Snapchat, Instagram, LinkedIn, and Twitter[16]. The growth range of active social media users during the pandemic was between 8% and 38%[17]. The increased use of social media during the COVID-19 pandemic led to lifestyle changes, such as reduced physical activity, more frequent sleep problems, and higher substance use levels. To some extent, social media serves as a tool for addressing anxiety and negative emotions[18], but at the same time, COVID-19-related information overload, with much of the information being sensationalized or even incorrect, exacerbated people's anxiety and fear, thereby reducing their sense of well-being[19].

Based on various theories, several methods have been applied to alleviate problematic social media use. Currently, cognitive-behavioral therapy has been widely used in addiction research related to pathological internet overuse[20]. It is one of the most widely used psychotherapies[21], and its main focus has been on patients' irrational cognitive problems. Changes in patients' views and attitudes toward the already used people or toward changing psychological problems [22], such as cognitive restructuring and technical support, have been used to help students realize the negative consequences of their addiction to social media and the potential benefits of reducing social media usage[23]. For children and adolescents, family-based interventions help address internet addiction[24]. On the one hand, it is necessary to improve communication, enhance the quality of parent-child relationships, and help adolescents perceive social support and regulate emotions. On the other hand, it is important to teach family members to monitor internet use to prevent and address teenage internet addiction[25]. There is also some preliminary evidence that group-based face-to-face interaction, multimodal counseling, and motivational interviewing are effective at alleviating internet addiction[26]. There is relatively limited research on alleviating problematic social media use, and specific related measures are rather limited. Therefore, there is still a need to further explore the potential of technology and tools in this regard.

Large language models (LLMs) are deep learning models trained on a large amount of text data (with parameters reaching billions), which are capable of generating natural language text or understanding the meaning of text and subsequently performing natural language processing tasks such as text classification, question answering, and dialog [27]. Computational linguistic research indicates that LLMs can significantly outperform other Natural Language Processing algorithms[28]. To enhance the ability of natural language understanding, researchers have introduced the

Transformer architecture[29], which can better represent semantic information at a deeper level for deep learning. The Transformer architecture has become the foundation of LLMs, and a variety of architectures and pathways have been built based on the Transformer[30]. LLMs are expected to serve as foundational models for solving various tasks and are considered important approaches for achieving artificial general intelligence. One of the typical applications of LLMs, such as ChatGPT, is an AI chatbot based on OpenAI's GPT (Generative Pre-trained Transformer), which has been trained on a large amount of text data, including books, news articles, websites, and Wikipedia, to generate human-like text[31]. ChatGPT exhibits flexible performance in natural language processing, outperforming other models[32]. In recent years, ChatGPT has received much attention in a variety of areas, including mental health services[33]. ChatGPT has great potential for addressing problematic social media use, such as providing information and resources through integration with search engines and providing real-time monitoring and intervention in problematic social media use through integration with social media.

LLMS CAN ALLEVIATE PROBLEMATIC SOCIAL MEDIA USE: THE CASE OF CHATGPT

Serve as an anonymous channel for communication and venting

Users can share their confusion, challenges, and anxieties about social media use with ChatGPT, which can provide emotional support and advice to help users cope with problematic social media use.

Individuals may be restricted by certain real-life factors, such as time and space, leading to insufficient communication and venting with others in daily life. ChatGPT can compensate for the lack of communication and provide 24-hour online support and companionship for users[34]; however, as ChatGPT does not think or form judgments on its own, people may be more willing to disclose information to a chatbot than to real human communication partners, thereby changing the nature and outcomes of disclosure[35]. Thus, ChatGPT can help people with problematic social media use by compensating for the limitations of real-world conditions while also acting as an anonymous communication object to enhance the objectivity and efficiency of chats.

Research indicates that when adolescents do not experience emotional responses, sufficient care and attention at home, do not receive appropriate supervision and monitoring or are unable to engage in open communication, they may use social media more frequently[25]. In this scenario, ChatGPT can act as a means of communicating and venting by engaging in conversations with users in a friendly manner, thereby reducing issues resulting from inadequate communication on social media. Chatbots and conversational agents have been used for more than half a century, and research indicates their potential in addressing mental health concerns[36], with well-known examples including ELIZA, ALICE, and SmarterChild[37]. Compared to previous chatbots, the ChatGPT chatbot has evolved from being static database-driven to a blend of real-time learning and evolutionary algorithms and has learned new responses and contexts based on real-time interactions with humans[38]. ChatGPT understands and learns from the users' language and internal thinking, ultimately generating well-focused, logical, and organized responses.

Personalized information and resources can be provided to help resolve problems

The advancement of technology and the widespread use of the internet have made it easier for all demographic groups to access health information[39]. Currently, an increasing number of online users are using chatbots and other artificial intelligence systems to obtain information and assistance[40]. When individuals encounter problematic social media usage, they can seek relevant information and resources by querying the internet or consulting chatbots to help them understand and resolve the issue. On the one hand, ChatGPT can respond to various queries and generate responses using internet resources, providing users with the required information and resources. Internet search engines such as Google's Bard and Microsoft's Bing have already integrated conversational artificial intelligence chatbots, such as ChatGPT, to enhance search efficiency by summarizing relevant content for users[41].

On the other hand, due to the high heterogeneity of each user, ChatGPT can capture various keywords during interactions to provide personalized information and resources, catering to the individualized needs of users. This personalized support can focus on the user's specific circumstances, such as demographic characteristics (gender, age, race, *etc*.), personal experiences, environmental conditions, and potential causes of problematic social media usage, and can provide tailored information and resources accordingly. These include: (1) Curricular information and resources focused on cognitive-behavioral skill enhancement[42], such as the harm of problematic social media use and the benefits that may result from improvement[23]; (2) a problematic social media screening and evaluation tool[43], which can be used for self-monitoring and assessment; and (3) the design of an Internet-based intervention program[42] to help users regulate their own state and solve problems. This information and resources can help users identify and improve problematic social media use.

Real-time monitoring and intervention of problematic social media usage behavior

ChatGPT can analyze users' activity characteristics and perform data analysis during their use of social media. It can monitor the content and quality of what users browse on social media, as well as the duration, time periods, and frequency of their social media usage, to assess the reasonableness of their social media usage and promptly identify problematic usage. By analyzing the posts users make on social media, ChatGPT can detect potential problematic social media usage based on the language used in these posts.

Social media posts primarily consist of textual language and, to a certain extent, reflect individuals' mental health status, serving as a potential source of information about their thoughts and feelings about their own condition[44]. Through natural language processing, ChatGPT identifies users' emotions and feelings during social media usage and

monitors the negative effects of social media usage on users. Additionally, in conjunction with websites or mobile applications, when problematic social media usage is detected, ChatGPT can provide real-time feedback to users and intervene with content (such as relevant mental health educational texts, videos, interactive tools) and actions. For example, with appropriate programming, ChatGPT can send specific messages to customers when it detects that a user has been watching a video for too long by inserting a public service video with the participation of a celebrity that the user is familiar with, *etc*., which may improve customer compliance[45]. It also encourages them to bring positive changes to their daily lives and address possible barriers, such as encouraging users to relax their eyesight, exercise, and spend more time with their loved ones and friends[45]. It can also inform clients of stress coping strategies, dietary recommendations, physical activity based on current conditions and user preferences, and routines[45]. This content and these actions can intervene in problematic social media usage to some extent.

POTENTIAL RISK

There are limitations to mitigating problematic social media use

Due to the potential for errors in ChatGPT operations, it cannot be guaranteed that all the generated results are reasonable when applying ChatGPT to mitigate users' problematic social media usage.

First, ChatGPT may operate based on erroneous data. The data that ChatGPT learns from are sourced from the public internet, including but not limited to webpages, books, social media, and conversational data. Due to the vast amount of data and the limitations in current filtering technologies, ChatGPT often replicates text without reliably citing original sources or authors, leading to the inclusion of biased and erroneous content in the dataset.

Second, ChatGPT operates with "hallucinations", which is considered a significant issue in LLMs[46]. Many researchers have noted that ChatGPT sometimes presents fluent and convincing sentences that contain factual inaccuracies, false statements, and erroneous data[47], a phenomenon referred to as "hallucinations". Users with problematic social media usage tendencies are more likely to belong to a group with limited access to information sources. Without the ability to discern errors, they may be misled by false information and inappropriate recommendations when using ChatGPT, which is detrimental to improving problematic social media usage. Finally, in reality, there is still a "digital divide" and a "knowledge divide" between urban and rural areas, and the accessibility of large language modeling technologies and services is unevenly distributed. As a result, the benefits of ChatGPT do not reach all individuals in a balanced way[38], and there is bias in addressing problematic social media use.

There is bias in alleviating problematic social media usage

ChatGPT cannot grasp the nuances of a user's life history and current situation, which may be the root of mental health issues[48].

First, ChatGPT is unable to comprehend many complex factors that impact users, such as socioeconomic status, education, cultural influences, and family dynamics, all of which can have profound effects on a person's mental state. Additionally, the benefits of ChatGPT cannot equally reach all individuals. Research has shown that the richness of ChatGPT language responses and the comprehensibility of writing in some languages are significantly inferior to those in English[49]. This suggests that languages that have not been fully researched may be left out of the ChatGPT revolution. Therefore, people in different language environments may not achieve the same effectiveness in using ChatGPT to address problematic social media usage.

This may cause privacy and security issues for users

Using ChatGPT requires providing a large amount of data, such as users' account information, user content, communication information, and social media information[50]. The initial purpose of collecting data is to serve users, but this process may lead to privacy violations, the illegal use of personal information, and the leakage of state secrets. This not only causes trouble for the users themselves but also impacts a broader range of social groups and areas, sometimes leading to immeasurable losses. OpenAI's regulation of the handling of personal information depends entirely on the privacy laws of different countries[50], and while OpenAI claims to be compliant with the GDPR and other relevant laws, these measures may not fully address the privacy concerns of individuals with respect to ChatGPT[51].

Users' overreliance on ChatGPT may lead to another extreme

The interactions generated by chatbots such as ChatGPT are more similar to real human interactions, which may lead people to rely on them excessively[52], resulting in unsafe and irrational usage. Users may become overly reliant on chatbots, as they can access them 24/7 with just a click, potentially exacerbating addictive behavior[48]. Research has shown that autonomy is directly correlated with positive treatment outcomes and is common in effective treatment interventions[53,54] and that enhancing autonomy is important for reducing problematic social media use. Overcommunication with ChatGPT may lead individuals to reduce their communication and interaction with peers. If users perceive ChatGPT as a more important communication entity than real people, prioritizing interactions with machines over human interactions could lead them to become increasingly detached from real society, resulting in negative impacts[55]. With ChatGPT, people can directly access needed knowledge without autonomy, thereby inhibiting their ability to exercise critical thinking and to evaluate and analyze comprehensive information[56], which is detrimental to their psychological well-being.

The definition of rights and responsibilities for using ChatGPT is still vague. These rights and responsibilities include awareness of the limitations and biases of ChatGPT and that OpenAI, as the developer, is responsible for ensuring that the ChatGPT algorithms are autonomous and beneficial to the users[57]. The impact on people cannot be measured by something tangible; the use of ChatGPT is at one's own risk[58], and once the harm is done, the consequences are on the users themselves and cannot be remedied by something tangible.

DISCUSSION

The era of deep integration between artificial intelligence and human life has arrived. While there is great hope for artificial intelligence to address problematic social media usage, developing accurate algorithms alone cannot solve these issues. The future development of large language models in mitigating problematic social media use is worthy of discussion.

First, addressing the ethical issues and societal impacts of LLMs such as ChatGPT is vital. This requires society as a whole to establish a common understanding and strive to create a positive environment for the use of ChatGPT. On the one hand, guidelines for the use and application of content-generating AI tools such as ChatGPT need to be formulated to establish clear legal boundaries. On the other hand, education and outreach should be provided to ensure that managers and users understand the guidelines, help users enhance their digital literacy, strengthen their rational judgment capabilities, and help them grasp the appropriate methods for using the technology in a responsible and informed manner, reducing potential harm.

Second, in the technical realm, it is essential to continue to strengthen research and development efforts. Developers need to improve the training of ChatGPT to enhance the objectivity and rationality of the results it generates. In addition, OpenAI applies human feedback reinforcement learning techniques to unsupervised and fine-tuned GPT models to maintain objectivity in judging whether the results align more with human performance, further optimizing the parameter weighting in the GPT model and thereby generating more rational results. There is also a need to strengthen the professional skills and ethical training of AI trainers and improve the overall professional environment to ensure that human factors do not exacerbate biases or ethical issues and to improve the accuracy and reduce the biases of these LLMs. Adherence to relevant data protection laws and regulations is necessary to ensure that user privacy is protected at every stage of data collection, storage, analysis, use, and sharing. The results of LLM operations need to be assessed, and errors need to be corrected promptly. There is a continuous need to establish and refine benchmarks for evaluating the performance of ChatGPT with various users or groups to promptly detect and eliminate any adverse effects in its operation.

Finally, there is a need for additional professional and targeted development in the area of problematic social media usage. The current practice of using artificial intelligence to address problematic social media usage largely focuses on fundamental conversation, counseling, and monitoring functions with limited targeting. Due to limited research on problematic social media use, there are knowledge gaps in defining, identifying, and understanding the psychobiological mechanisms behind problematic social media use[59], and future research should attempt to fill these gaps using standardized methods. Therefore, further specialized development is necessary, focusing on the characteristics and factors influencing problematic social media usage, understanding user characteristics, and developing a standardized methodology for detecting and classifying problematic use of social media into problematic use intensity levels/stages [59] in order to more effectively address these issues. In the introduction of ChatGPT, the uniqueness of problematic social media usage and its users should be considered to avoid exacerbating problems while resolving problematic social media usage. The role of professional medical intervention should not be overlooked or avoided simply because of ChatGPT's capabilities. Given the shortcomings of ChatGPT in complex psychological, emotional, and sociocultural aspects, it is important to integrate human therapists and others to work in conjunction with ChatGPT to leverage their combined strengths in alleviating problematic social media usage.

CONCLUSION

Large language models can serve as an anonymous channel for communication and venting, provide personalized information and resources to help resolve the problem, and provide real-time monitoring and intervention of problematic social media usage behavior. Limitations, bias, privacy issues, and overreliance represent potential risks of large language models in mitigating problematic social media use. When LLMs such as ChatGPT are used to address problematic social media usage, it is crucial to have a full understanding of the technology's strengths and weaknesses and to strive to minimize its negative impact.

FOOTNOTES

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EDITORIAL

How inflammation influences psychiatric disease

Eduardo Ferat-Osorio, José Luis Maldonado-García, Lenin Pavón

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Abstract

Recent studies highlight the strong correlation between infectious diseases and the development of neuropsychiatric disorders. In this editorial, we comment on the article "Anti-infective therapy durations predict psychological stress and laparoscopic surgery quality in pelvic abscess patients" by Zhang *et al*, published in the recent issue of the *World Journal of Psychiatry* 2023; 13 (11): 903-911. Our discussion highlighted the potential consequences of anxiety, depression, and psychosis, which are all linked to bacterial, fungal, and viral infections, which are relevant to the impact of inflammation on the sequelae in mental health as those we are observing after the coronavirus disease 2019 pandemic. We focus specifically on the immune mechanisms triggered by inflammation, the primary contributor to psychiatric complications. Importantly, pathophysiological mechanisms such as organ damage, post-injury inflammation, and infection-induced endocrine alterations, including hypocortisolism or autoantibody formation, significantly contribute to the development of chronic low-grade inflammation, promoting the emergence or development of psychiatric alterations in susceptible individuals. As inflammation can have long-term effects on patients, a multidisciplinary treatment plan can avoid complications and debilitating health issues, and it is crucial to recognize and address the mental health implications.

Key Words: Inflammation; infection; Depression; Pelvic inflammatory disease; Psychiatric complication

Core Tip: In recent years there has been increasing evidence that infectious diseases increase the risk of developing psychiatric disorders due to acute or chronic inflammation. This manuscript offers a detailed summary and discussion that will provide valuable insights on the mechanisms behind psychiatric complications observed in infectious conditions as a commentary to the article "Anti-infective therapy durations predict psychological stress and laparoscopic surgery quality in pelvic abscess patients".

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has made it clearer that infectious diseases can cause psychiatric complications. These complications may occur during an infection or, in either case, afterward as a result of the inflammatory response[1]. Although psychiatric symptoms have been commonly associated with systemic (*e.g.*, sepsis) and central nervous system infections (*e.g.*, viral encephalitis or toxoplasmosis)[2], they may occur even without a brain infection[3]. The advances in understanding sepsis's molecular pathophysiology play a crucial role in implementing therapeutic actions, leading to increased patient survival. Nonetheless, the mortality rate is still considerably high, and there are many challenges because of the global burden of sepsis[4,5]. Even though pathophysiology mainly refers to alterations caused by the microorganisms, the host's inflammatory response may contribute to prolonged immune dysfunction, leading to immunosuppression, persistent inflammation, and catabolism[6]. The early phase of sepsis involves organ failure and lasts one to two weeks; this constitutes the pro-inflammatory phase, which is followed by the compensatory (anti-inflammatory) phase. If the anti-inflammatory phase fails to reach homeostasis, a low-grade or cronic persistent inflammatory state can develop. A more severe problem is that patients who survive the first phase experience increasing symptoms at 2 to 3 months. One possible reason for this condition is the advanced intensive care unit care that continues to keep elderly and comorbid patients despite ongoing immunological and metabolic issues[7,8]. Non-encephalic systemic infections can affect the central nervous system, resulting in neurological symptoms such as altered consciousness, disorientation, cognitive deficits, seizures, and coma. Sepsis-associated encephalopathy is a condition that affects the brain, and it can occur in up to 70% of patients with sepsis[9]. Furthermore, it can be acute or chronic[10]. The etiology of sepsis-associated encephalopathy can be caused by almost any systemic infection, including those in the respiratory, urinary, gastrointestinal, biliary (such as cholangitis), and genital tract.

IMMUNE RESPONSE IN PELVIC INFLAMMATORY DISEASE

Pelvic inflammatory disease (PID) is less frequent but also critical. PID is an infection that occurs in the upper female genital tract and primarily affects sexually active young women. Although the actual incidence and prevalence of PID are unknown, data from 2013 suggest that 4.4% of sexually active women report a history of PID. Typically, PID is caused by a sexually transmitted infection by *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, but it can also be caused by *Mycoplasma genitalium* and *Actinomyces* species. Microorganisms present in the gastrointestinal or respiratory tract may also play a role in the development of PID (*E. coli*, *B. fragilis*, *Pepto-streptococcus spp*, *Haemophilus influenzae*). Clinical manifestations may range from mild to severe and require in-hospital management using parenteral antibiotics. Antibiotic treatment can prove efficacious in 34% to 88%. Interventional approaches may provide the definitive treatment for those who do not improve with medical therapy. Interventional radiology (percutaneous drain with drains placed) or laparoscopy are options to treat PID complications like tubo-ovarian abscess (TOA). In this case, it is important to begin the treatment early for optimal results (48 h to 72 h). TOA occurs when pus accumulates in the fallopian tubes and ovaries, leading to inflammation and severe pain. Unfortunately, around 25% to 30% of women with TOA will require surgical drainage to relieve the symptoms. Untreated PID in women with TOA can lead to long-term consequences such as chronic pain (29%), infertility (18%), or ectopic pregnancy (0.6%)[11].

PID presents itself in two scenarios. In the first one, the acute form of the condition can be managed conservatively, but if it does not respond to treatment, it may result in an abscess. If left untreated, this abscess can lead to serious complications such as sepsis, septic shock, and death. The molecular pathophysiology of this condition begins with the host recognizing of the offending agent. Recognition of pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRRs) present in immune cells like neutrophils, monocytes, and dendritic cells can activate signaling cascades that induce the transcription of inflammatory mediators in response to microorganisms. Subsequently, mediators act locally, either in a paracrine or autocrine way[12].

The second scenario of the PID is the chronic form. It has been observed that some women may have mild symptoms or lower suspicion levels, which can lead to the possibility of missing out on identifying an inflammatory-infectious problem from a gynecological perspective. In these cases, chronic infection may result in the previously mentioned sequelae. Infertility due to recurrent or chronic infections seems to be associated with cell death by pyroptosis[13]. This type of cellular death is linked to inflammasome activation, which leads to caspase-1 activation following the recognition of PAMPs and damage associated molecular patterns by different PRRs (intracellular and extracellular, depending on the microorganism). Caspase-1 activation, in turn, triggers a protein called gasdermin D, inducing the formation of pores in the host cell's membrane, and releasing intracellular content that can act as alarmins (*e.g.*, high mobility group box 1 proteins or HMGB1). Caspase-1 also facilitates the cleavage of Pro-IL-1 and Pro-IL-18, releasing them into the extracellular space as IL-1β and IL-18[14]. In the case of PID, there is a process of endometritis that may be associated with pyroptosis[15].

According to several reports, HMGB1-mediated macrophage pyroptosis is involved in the molecular pathophysiology of chronic endometritis[16]. HMGB1 is an intranuclear protein that can be released due to cellular damage associated with multiple causes, sterile inflammation, or infectious processes[17,18]. In the extracellular environment, HMGB1 acts as an alarmin, binds to its receptor RAGE, and subsequently induces pyroptosis, amplifying the inflammatory response following the release of IL-1 and IL-18[19].

Related to central nervous system disorders induced by infectious processes mentioned earlier, HMGB1, through binding with MD-2, is known to promote NLRP3-induced neuroinflammation, resulting in cognitive impairment in cases of sepsis-associated encephalopathy in murine models[20]. In the manuscript of Zhang *et al*[21] "Anti-infective therapy durations predict psychological stress and laparoscopic surgery quality in pelvic abscess patients", serum levels of inflammatory mediators like HMGB1 or pro- and anti-inflammatory cytokines have not been determined. Knowing the concentrations of these proteins could provide insights into cognitive impairments in the group of patients with PID who exhibited neurological symptoms. Psychiatric symptoms may occur without neurological symptoms, as in some cases of viral encephalitis[3]. Psychosis or mood symptoms may feature as a component of the clinical presentation secondary to brucellosis or toxoplasmosis[22]. Late-onset neuropsychiatric complications, such as subacute sclerosing panencephalitis caused by measles, have been reported years after acute infection[23]. Some studies suggest that viral infections like influenza virus or HSV-1 may increase the risk of developing schizophrenia and psychosis, indicating a possible link between psychiatric disorders and infectious diseases[24]. Furthermore, psychiatric symptoms can also be reactivated because of chronic, complicated, and severe infections, such as HIV, that can cause an individual to experience depression, anxiety, or adjustment disorders[25].

HOW INFECTIONS CAUSE INFLAMMATION AND PSYCHIATRIC COMPLICATIONS

Stress plays a crucial role in the development of major depressive disorder (MDD), particularly stress in early life and chronic stress in susceptible individuals[26]. Stress response is modulated by the hypothalamus-pituitary-adrenal (HPA) axis, which connects the nervous and endocrine systems and is formed by the hypothalamus and pituitary and adrenal glands[27]. A stressor, such as an infection, activates the HPA axis and promotes the release of corticotropin hormone release by the hypothalamus, which stimulates the pituitary gland to release corticotropin (ACTH), which enables the adrenal glands to release cortisol and catecholamines to trigger the flight or fight response[28]. Chronic stress affects hippocampus functions, and it has been reported that cortisol is an important mediator. Consequently, if the stress lasts longer, chronic stress can generate changes in the hippocampus, ranging from modification of plasticity to neurotoxicity and neuronal death[29,30]. As a result, chronic stress can induce glucocorticoid resistance[31], which is characterized by alterations in glucocorticoid receptor (GR) function, changes in GR expression, alterations in glucocorticoid bioavailability through modification of serum protein binding, deficiencies in HPA axis feedback and immune system inhibition[32,33]. In chronic stress conditions, MDD patients have higher levels of circulating glucocorticoids compared to healthy individuals. They may coexist with elevated concentrations of proinflammatory cytokines such as IL-1β, tumour necrosis factor alpha (TNF-α), and IL-6[34-36]. The simultaneous presence of elevated levels of glucocorticoids and cytokines creates a complex interaction between the immune system and the HPA axis, a paradoxical phenomenon characterized by chronic inflammation[37,38].

METABOLIC CHANGES INDUCED BY INFLAMMATION AND ITS IMPACT ON PSYCHIATRIC COMPLICATIONS

In systemic or chronic inflammatory diseases (*e.g.*, chronic infections), it has been reported that circulating proinflammatory cytokines stimulate the brain and cause anxiety, anhedonia, fatigue, and sleep disturbances. In addition, sickness behavior characterized by the presence of a febrile response, anorexia, lack of motivation, social deprivation, and reduced movement is also present[39-41]. One of the first associations of cytokines with neuropsychiatric complications was observed in hepatitis C treatment with interferon-alpha (IFN-α); the presence of depressive symptoms and even suicidal ideation was observed in patients receiving IFN-α treatment[42,43].

Proinflammatory cytokines produced in the brain can stimulate the brain through different pathways: (1) Stimulating receptors in the blood-brain barrier (BBB) and producing metabolites in the brain; (2) accessing the brain through the circumventricular organs; (3) being carried through transporters in the BBB; and (4) through stimulation of afferent fibers

of the vagus nerve[44,45].

As previously described, peripheral proinflammatory cytokines stimulate the brain and generate a neuroinflammatory response caused by the activation of neurons, microglia, and astrocytes[46]. Proinflammatory cytokines induce changes in the metabolism of tryptophan, a precursor of serotonin in both the periphery and the brain, thereby increasing inflammation and decreasing serotonin production[47]. One of the mechanisms involved in this metabolic pathway change is the activation of indolamine 2,3-dioxygenase in macrophages and microglia cells, whereby tryptophan is metabolized in the kynurenine pathway; it causes a decrease in serotonin levels and an increase in kynurenine in the body and brain[40,48]. Moreover, peripheral kynurenine crosses the BBB and is metabolized in activated astrocytes and microglia by kynurenine aminotransferase II (KAT II)[49]. The kynurenine metabolism generates quinolinic acid and induces a decrease in dopamine and glutamate production and blockade of α7nAChR cholinergic receptors; these changes are associated with cognitive dysfunction[49,50]. Similarly, activated microglia metabolize kynurenine through the enzymes kynurenine 3-monooxygenase and 3-hydroxyanthranilicoxygenase, which generate metabolites such as kynurenic acid, which stimulates NMDA receptors and causes lipid peroxidation, oxidative stress, excitotoxicity, and neurodegeneration [49,50]. In addition, chronic stress decreases the function of the serotonergic system, characterized by increased SERT and p11 expression in peripheral blood mononuclear cells[51].

On the other hand, inflammation causes oxidative stress, which reduces the production of tetrahydrobiopterin (BH), a necessary cofactor for synthesizing serotonin, dopamine, and norepinephrine. As a result, inflammation leads to a deficiency in the production of monoamines[49,52]. All metabolic changes together are related to the development of disease behavior in patients with systemic inflammatory responses caused by injury or infection, and these symptoms remit as soon as the inflammation is resolved[39].

As mentioned above, inflammation decreases dopamine and serotonin synthesis in the brain and periphery. Inflammation associated with infection has different sources, including antigen persistence, hypocortisolism or HPA axis dysfunction, chronic organ dysfunction or worsening of pre-existent dysfunction, persistent tissue or end-organ damage, and persistent cytokine release, among others[1,53,54].

The immune system usually resolves pathogens that cause acute infections. Still, ample evidence indicates that some pathogens can cause persistent and sometimes lifelong infections[55]. Some bacteria that cause chronic infections are phylogenetically diverse[55]. However, they share common characteristics that allow a prolonged period of colonization and share strategies to evade elimination by the immune system, thus causing chronic intracellular infections[56]. An example is brucellosis and typhoid fever, which are characterized by a long incubation period leading to a regular, sometimes lifelong illness, which is debilitating and can cause severe clinical manifestations[57]. Recently, our group has characterized the neurochemical, hormonal, and inflammatory alterations present in a murine model of brucellosis and behavioral alterations. We have reported that brucellosis infection induces decreased motivation and physical performance, as well as increased hopelessness and anxiety. These findings are complemented by a decrease in dopamine and serotonin in the hippocampus and frontal cortex and elevated levels of IL-6, IFN-γ, and TNF-α in serum[58]. Subsequently, we observed that administration of imipramine in mice infected with *Brucella abortus 2308* causes an improvement in hopelessness, anxiety, physical performance, and motivation even though the infection has not been entirely eliminated[59].

Chronic infections have a significant impact on public health due to the use of resources for the long-term treatment of patients. In addition, chronic infections can lead to disability as they can cause the development of psychiatric illnesses like depression or anxiety. These illnesses can significantly impact the patient's ability to generate economic resources to support their families, ultimately resulting in a substantial socioeconomic burden on countries affected by such infections [57].

OTHER IMMUNOLOGICAL MECHANISMS INDUCING PSYCHIATRIC COMPLICATIONS

Solid evidence shows that some infections can induce hypocortisolism due to adrenal insufficiency[60]. Bacterial infections such as *Mycobacterium tuberculosis*, *Pseudomonas aeruginosa*, Group A *Streptococcus*, or *Haemophilus influenzae* can cause hypocortisolism[60]. Similarly, viral agents such as HIV and cytomegalovirus, and fungal infections by *Pneumocystis carinii*, *Coccidioides immitis*, *Cryptococcus neoformans*, and *Histoplasma capsulatum* can induce adrenal insufficiency which results in hypocortisolism[60]. Low circulating cortisol levels observed in hypocortisolism have been associated with a chronic inflammatory state; this is explained by the inhibition of the proinflammatory cytokines production in leukocytes such as macrophages and lymphocytes induced by cortisol[61,62]. In this way, the generation of autoantibodies against ACTH has been observed during coronavirus infections, and it has been proposed that this mechanism is the cause of the post-infection hypocortisolism observed in patients[63,64]. Furthermore, in the case of COVID-19, hypocortisolism has been proposed as one of the mechanisms associated with the development of chronic inflammation and long-COVID[53].

Another mechanism of damage associated with infections that induce chronic inflammation is target organ damage or worsening of pre-existing damage[65]. Infections that induce chronic inflammation also have been found to cause a mechanism of damage known as target organ damage or the exacerbation of pre-existing damage; for example, in post-COVID-19 patients, it has been observed that damage to the pancreas can occur and induce hyperglycemia due to a deficit in insulin production; such increased hyperglycemia may lead to chronic low-grade inflammation[1,53]. Another example can be observed in patients who have recovered from sepsis. These patients may experience chronic immunosuppression and inflammation due to changes in T lymphocytes and hematopoiesis. They may also suffer from complications arising from damage to their kidneys, heart, or endothelium[66,67].

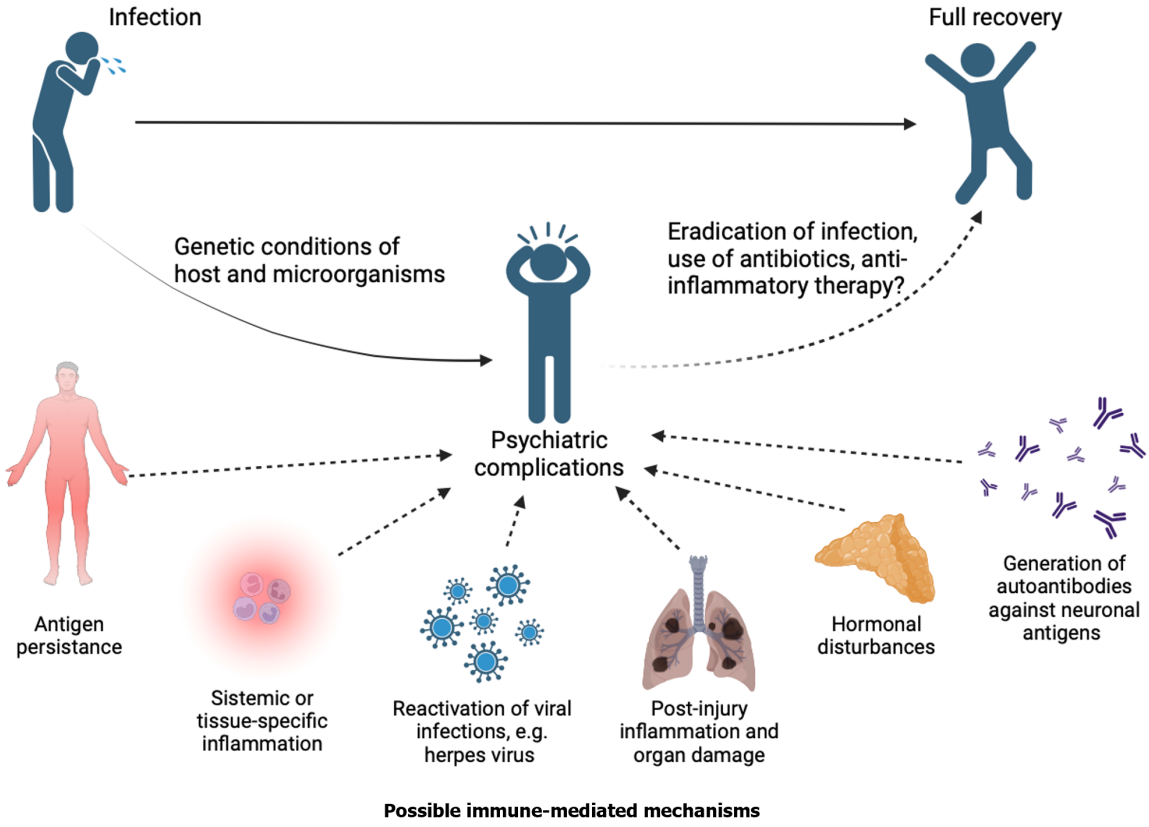

Figure 1 Possible mechanisms by which infections cause psychiatric complications.

Finally, it has been observed that antibodies produced during an infection can trigger neuropsychiatric complications due to a cross-reaction in which antibodies recognize pathogen antigens but may also recognize self-antigens[68,69]. It has been proposed that genetic factors of the host and infectious agent influence the development of these complications [70]. Cross-reacting antibodies can directly recognize neuronal antigens, as in streptococcal infections, and trigger neuropsychiatric symptoms[71]; however, antibodies can cross-react against cortisol, as in the case of coronavirus infections, and thus inhibit the regulation of inflammation and generate neuropsychiatric complications secondary to chronic inflammation[64]. Figure 1 summarizes the proposed mechanisms by which infections may cause psychiatric disorders.

CONCLUSION

Even after injury or infection has been resolved, persistent inflammatory parameters may continue to affect body levels of inflammatory, hormonal, and neurochemical molecules. In some individuals, exposure to stressors like surgery or infections can contribute to the development of psychiatric disorders, such as anxiety and depression, due to chronic stress. It can also exacerbate pre-existing psychiatric conditions. Clinicians must take into account infection-associated factors such as microorganisms, host, and treatment characteristics when treating patients. These factors may lead to the development of psychiatric complications, so it is imperative to offer more holistic therapeutic options that consider the primary problem and its psychiatric complications. Further investigation is crucial for future studies to understand better the mechanisms by which infection causes psychiatric complications.

FOOTNOTES

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REVIEW

Digital psychiatry in low-and-middle-income countries: New developments and the way forward

Subho Chakrabarti

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Abstract

Low- and middle-income countries (LMICs) bear the greater share of the global mental health burden but are ill-equipped to deal with it because of severe resource constraints leading to a large treatment gap. The remote provision of mental health services by digital means can effectively augment conventional services in LMICs to reduce the treatment gap. Digital psychiatry in LMICs has always lagged behind high-income countries, but there have been encouraging developments in the last decade. There is increasing research on the efficacy of digital psychiatric interventions. However, the evidence is not adequate to conclude that digital psychiatric interventions are invariably effective in LMICs. A striking development has been the rise in mobile and smartphone ownership in LMICs, which has driven the increasing use of mobile technologies to deliver mental health services. An innovative use of mobile technologies has been to optimize task-shifting, which involves delivering mental healthcare services in community settings using non-specialist health professionals. Emerging evidence from LMICs shows that it is possible to use digital tools to train non-specialist workers effectively and ensure that the psychosocial interventions they deliver are efficacious. Despite these promising developments, many barriers such as service costs, underdeveloped infrastructure, lack of trained professionals, and significant disparities in access to digital services impede the progress of digital psychiatry in LMICs. To overcome these barriers, digital psychiatric services in LMICs should address contextual factors influencing the delivery of digital services, ensure collaboration between different stakeholders, and focus on reducing the digital divide.

Key Words: Digital psychiatry; Low-and middle-income countries; Developments; Mental health

Core Tip: Given the substantial mental health burden and treatment gap in low- and middle-income countries (LMICs), there is a pressing need to implement digital psychiatric services to augment conventional mental healthcare. LMICs have traditionally lagged in this area, but there have been some encouraging developments recently. They include the increasing evidence of the efficacy of digital psychiatric interventions and the growing use of mobile technologies to provide mental health services and optimize task-shifting. However, there are many gaps in the delivery of digital psychiatric services, which need to be overcome by efficiently organizing these services to improve mental healthcare in LMICs.

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INTRODUCTION

The remote provision of mental health services using digital technology, or digital psychiatry has been evolving constantly since its inception in the late 1950s[1,2]. Advances in technology over this period have driven this evolution and have influenced the nomenclature, types, and ever-expanding uses of digital psychiatric services.

Digital psychiatry subsumes several terms used to describe the remote delivery of mental healthcare. It includes telepsychiatry, which refers to videoconferencing-based, live, synchronous, and interactive communication between providers and users, and asynchronous modes of storing and forwarding data[3]. The primary purpose of telepsychiatry is to deliver specialist psychiatric care to remote and underserved areas. Tele-mental health expands the scope of digital services to include a wide range of clinical and non-clinical mental health services delivered by specialist and non-specialist professionals[4]. Electronic health (eHealth or e-mental health) includes all digital technologies to support healthcare delivery and health-related activities[5]. Mobile health (mHealth) is a subset of eHealth that uses mobile and wireless devices to deliver healthcare services[5]. The fundamental elements of digital psychiatry, the provision of mental health services from a distance using some form of digital technology to improve mental health, have remained the same despite the use of different terms over the years[4,5-7]. Currently, digital psychiatry encompasses a range of older (telephones and computers), current (internet and mobile technologies), and emerging technologies (virtual reality, social media, wearables, and advanced computing). Technological advances have also expanded the uses of digital psychiatric services from improving access to specialist care to supporting primary-care teams and undertaking public health activities[6-10]. New forms of service delivery such as low-intensity interventions[11], hybrid or blended care[12,13], and stepped care[12] have also been introduced.

The rapidly increasing global access to digital technologies has led to a proliferation of digital mental health services worldwide. Sixty-eight percent of the world's population were unique mobile subscribers and 97% were covered by mobile networks in 2023[14-16]. About 85% of the world's population owned smartphones. Internet access stood at 67% and 60% of the people were using social media[14-16]. The global surveys of digital health carried out by the World Health Organization (WHO) since 2005 have noted a steady growth in the different types of digital services[4,17-19]. For example, telepsychiatric services increased from 24% to 34% of all the member states from 2009-2016. The 2016 report found a global increase in the number of mHealth and internet-based programmes, emerging data on the health uses of social media and advanced computing, increased adoption of national telemedicine policies, and efforts to evaluate digital health services in many countries.

Finally, in the last seven decades, digital psychiatry has shown great potential in improving access, empowering users, and providing high-quality care at a reasonable cost in different settings for different patient populations[2,3,17,19]. Compelling evidence suggests that digital psychiatric interventions are comparable to conventional in-person treatments on a range of outcomes including diagnostic and neuropsychological assessments, feasibility and acceptability of treatment, treatment efficacy, improving quality of life and socio-occupational functioning, and promoting treatment alliances, and treatment engagement[6,20-23]. Internet and videoconferencing-based interventions constitute the bulk of the evidence[21-23] and have replaced phone and computer-delivered interventions[21,24]. The evidence base for mHealth interventions is growing, but convincing evidence for their efficacy is still lacking[25]. Research on social media, virtual reality, and big data analytics is scarce[9,19]. The current consensus appears to be that despite the favourable evidence, firm conclusions about the efficacy of digital psychiatric interventions will require more research. The small number of high-quality and large-scale trials and a great degree of variability in the results from different trials contribute to this uncertainty. Moreover, there are significant gaps in the literature on digital psychiatric services regarding the range of disorders evaluated, utility in different patient populations, unequivocal evidence of cost-effectiveness, and the scarcity of large-scale implementation trials[8,9,21-23]. Last but not least, most of the evidence on digital psychiatry comes from high-income countries (HICs), and there is a considerable gap between the evidence base for the efficacy of digital psychiatric interventions in HICs and low- and middle-income countries (LMICs)[26].

THE STATE OF MENTAL HEALTH IN LMICs AND THE ROLE OF DIGITAL PSYCHIATRIC SERVICES

Currently, over 85% of the people in the world live in LMICs[27]. Apart from poverty, these countries face other challenges such as overpopulation, demographic instability and migrations, poor social and living conditions, environmental degradation and climate change, political instability or armed conflicts, growing unemployment, illiteracy, crime, undernutrition, and hunger. These adversities contribute to the enormous burden of physical and mental disorders in LMICs, which is made worse by the limited access to treatment[28].

Consequently, LMICs have to contend with more than their fair share of the mental health problems that exist globally [28-32]. Estimates show that more than 75% to 80% of the mentally ill in the world live in LMICs. At the same time, these countries have limited capacity to cope with this burden because of a lack of mental healthcare professionals, facilities, services, and funding. Moreover, these scarce resources are distributed unevenly and are least accessible to the poor and marginalized people from remote and rural areas. The situation is made worse by the lack of awareness and culturally-derived negative perceptions about mental illnesses, stigmatization of the mentally ill, and discrimination against them. All these factors culminate in a large gap between those who require mental health treatment and those who can get access to adequate treatment[30,32-34]. Estimates suggest that only about 5%-15% of the people in need of treatment can receive it. The lack of adequate treatment leads to further distress and disability for the mentally ill, greater social and economic burden for their families, increased healthcare costs, and increased burden on society because of loss of productivity. Several measures have been suggested to deal with this treatment gap[26,29,30,32,35]. They include prioritizing mental healthcare, increasing governmental involvement and funding, integrating mental health services with general medical services in primary-care settings, developing community-based facilities for mental healthcare, and training non-specialist workers to provide care. However, these measures have proved insufficient in reducing the mental health burden because of many barriers that have prevented their large-scale implementation. Digital psychiatric services can overcome some of these barriers and effectively augment traditional mental health services. Therefore, using digital tools to improve access, reduce stigma, provide mental health care, and train, support, and supervise non-specialist workers has been recommended as a key strategy to bridge the treatment gap in LMICs[19,29,30,35].

THE CURRENT STATUS OF DIGITAL PSYCHIATRIC SERVICES IN LMICs

Digital psychiatric services offer LMICs a unique opportunity to expand their mental health services and meet the demand for mental health treatment in these countries[36-40]. Digital psychiatry provides patients from remote, rural, and underserved areas access to high-quality, evidence-based treatment available in specialist centres. Digital psychiatric services have the added advantage of overcoming the barriers of distance, costs, treatment delays, stigma, and non-adherence.

The focus of digital psychiatry in HICs has been to shift care from hospitals to the community and patients' homes[17]. In contrast, the task of digital psychiatric services in the LMICs has traditionally been to link patients in underserved areas to healthcare providers at more centrally located sites. Although digital psychiatry has successfully fulfilled this role, LMICs have generally lagged behind HICs in the delivery of digital services because of several factors impeding their progress. The major hurdles have been the costs of digital services and the lack of funding, poorly developed technological infrastructure and lack of technological progress, scarcity of trained workers, and insufficient data on the efficacy of digital psychiatric interventions. Nevertheless, there have been encouraging developments in the last decade or so. The most striking development has been the rapid expansion of the information and communication sectors, which has increased the availability of many more digital devices. Mobile phone ownership has grown the fastest. About 90% of the people in the LMICs have a mobile phone, which is similar to the rates of ownership in HICs. Smartphones make up more than 60% of these phones. However, only about 29%-60% have access to the internet, which is much lower than the internet penetration in HICs[10,15,27,41]. The WHO surveys have also shown that the number of digital psychiatric programmes, particularly internet and mobile-based services has increased[17-19]. Governments have shown greater commitment and many more countries have national policies and guidelines. The use of emerging technologies for mental healthcare such as social media and advanced computing is also on the rise. The evidence for the efficacy of digital psychiatric interventions in LMIC settings has grown[37,38,40]. Moreover, innovations such as the digitalization of task-shifting are being used[9,26,36]. Finally, digital psychiatric interventions, particularly videoconferencing-based telepsychiatry were widely used during the coronavirus disease 2019, which has led to a revival of interest in this mode of service delivery[42].

RECENT DEVELOPMENTS IN DIGITAL PSYCHIATRIC SERVICES IN LMICs

The efficacy of digital psychiatric interventions in LMICs

A relatively recent development in the field of digital psychiatry has been the increase in research on the efficacy of digital psychiatric interventions conducted in LMICs. A literature search with the Reference Citation Analysis tool revealed 13 systematic reviews including two meta-analyses published since 2015. These reviews have shown that research on these interventions has increased over the last 5-10 years[38,40,43-45]. Most of this research has been conducted in South America and Asia. Studies from Africa and the Middle East are relatively scarce. China, Brazil, and India are the countries with the highest number of studies[37,44,46-48]. Although videoconferencing-based telepsy-

chiatry, telephone, and computer-delivered treatments are still used[38,44,45,47,48], there has been a clear shift to mobile and internet-delivered digital interventions[37,40,43,44,46]. Common mental disorders such as depression and anxiety are the most frequently studied conditions[37,38,40,43,46]. These disorders are also commonly examined in HICs reflecting their high prevalence and burden[21-23,40]. A systematic review also found support for internet-based interventions in preventing depression[49]. Other conditions examined include substance use disorders[37,40,43,47,48]. A recent systematic review[44] that focused exclusively on digital interventions in substance use disorders, identified 39 studies most of which were randomized-controlled trials (RCTs). Fewer studies have focused on psychotic disorders. A narrative review of patients with psychosis identified seven studies, three of which were from China[50]. A systematic review from China, which included 39 studies also found that studies of psychotic disorders were more common than those of depression, anxiety, and substance use disorders[45]. The authors attributed this to the increased emphasis on managing severe mental illnesses in the Chinese healthcare system. There are very few studies of other disorders such as post-traumatic stress disorder, dementia, intellectual disability, and self-harm[38,40,43,45,48]. Expectedly, the most common outcome examined was the feasibility and acceptability of delivering digital interventions, which was satisfactory in almost all the studies[37,38,40,48,49]. These studies included patients with depression[37,38,40,48,49], anxiety[45,47,48], substance use[37,40,44,47,48], psychosis[37,40,45,50], and other disorders. The feasibility and acceptability of digital interventions were found in studies from South American countries[47,51], China[45], and India[52]. Digital interventions were safe with minimal adverse effects[43,45,46]. Many studies reported high levels of patient and clinician satisfaction [38,40,51,52]. Treatment efficacy was the other commonly studied outcome, and the majority of studies reported that digital interventions were efficacious in reducing symptoms of all psychiatric disorders[37,38,40,44,48]. Two meta-analyses reported effect sizes of 0.60 for all disorders, 0.61 for depressive, and 0.73 for anxiety symptoms for digital interventions compared to waiting list controls, usual treatment, or other active treatments[43,46]. The number needed to treat was three[43]. The effect sizes were larger in comparisons of digital interventions with minimal or no treatment[43]. The effect sizes were greater among adults than children, patients who were moderately ill, and those receiving internet or mobile-based psychological interventions[46]. Thus, digital interventions were modestly effective in reducing symptoms, a result that was no different from the meta-analytic studies from HICs. Several reviews also reported improvement in treatment engagement and treatment adherence with digital interventions[37,40,44,47,50]. Some of the reviews found that digital interventions improved functioning and the quality of life[37,40,45,51]. The evidence for other outcomes such as the accuracy of diagnostic assessments, preventing relapse or enhancing recovery, improving coping, and reducing the risk of self-harm was limited[37,38,40]. In contrast to these positive outcomes, certain studies reported that digital interventions did not reduce symptoms or increase patients' acceptability[37,40,51,53]. Moreover, all reviews concluded that despite the relatively high proportion of RCTs, the methodological quality of the evidence was inadequate to determine whether digital psychiatric interventions were efficacious in the setting of LMICs. Methodological shortcomings included the small number of studies, small sample sizes, the predominant focus on adult patients, methodological variability and heterogeneity across studies, relative lack of high-quality studies, the possibility of selection or publication bias, the short-term nature of studies, the poor attention to cultural considerations, and the lack of data on the cost-effectiveness of digital interventions[37,40,44,45,48].

Choosing the most appropriate form of digital psychiatric services for LMICs

The choice of the most effective form of digital psychiatric service based on the current evidence from LMICs is difficult. Older technologies such as telephone and computer-based services are widely used[39], and the evidence indicates that these forms of service delivery are effective in LMIC settings[37,43-45,48]. Videoconferencing-based telepsychiatry is another frequently used and effective form of service delivery in LMICs[37,38,47]. Although it is the oldest form of digital psychiatric services, the availability of inexpensive equipment and free internet-based platforms have ensured its continued use. Synchronous videoconferencing can improve access to specialist care, but its public health utility is limited because it cannot compensate for the workforce shortage in LMICs[37]. Asynchronous telepsychiatry can be a more efficient and cost-effective alternative, but the evidence for its efficacy in LMICs is scarce[17,19,37,39]. Internet and mobile-based psychiatric services can extend the reach of digital psychiatric services in LMICs more efficiently. More than half of the digital intervention studies from LMICs involve internet or mobile services[40,43,45-47]. Thus, there is considerable evidence for their efficacy and effectiveness. These interventions can potentially reduce treatment costs and the reliance on specialist care while expanding the capacity of the mental health workforce to deliver treatment[36,47]. Internet-based programmes depend on reliable network connectivity and high levels of digital skills among users[26,37,49]. The disparities in internet access, inadequate network connectivity, and poor digital literacy among users in LMICs can limit the effectiveness of internet-based services. Mobile technologies are less reliant on the internet because of the options of voice calls, text messaging, and other offline uses[54-56]. The rapidly increasing mobile ownership and the use of mHealth interventions for psychiatric disorders suggest that mobile-based services will probably become the digital psychiatric service of choice in LMICs. Emerging technologies such as social media, virtual reality, and advanced computing could be the other options for the future but there is limited data on their use and effectiveness at present[9,40,45,48].

The increasing use of mobile technologies for psychiatric disorders in LMICs

The rising ownership of mobile phones and expanding cellular networks have driven the growing use of mobile technologies to deliver mental health services in LMICs. Reviews of mobile mental health from LMICs have shown that mHealth technologies are primarily used for public health activities and supporting mental healthcare delivery by primary-care workers[44,45,54-56]. Public health functions include data collection, disease surveillance and prevention, health monitoring, health awareness and health promotion, and use in disaster situations. Mobile mental health services include detection and diagnosis, treatment, psychosocial interventions, symptom monitoring, information and support,

facilitating treatment adherence, and emergency psychiatric care. Mobile technologies are used to train, supervise, monitor, and support primary-care workers in delivering mental healthcare. Mobile phones can improve access to mental health services, reduce stigma through educational campaigns, and augment other digital psychiatric interventions. Such functions are not unique to mHealth technologies but their advantage derives from their ubiquity, mobility, and novelty of certain features such as text messages or applications (apps)[54]. Although voice calls remain popular, text messages, apps, and web-based interventions are the most common mental health uses of mobile phones in LMICs[44,55]. Studies from HICs have shown that mobile phones, smartphones, and apps-based interventions are feasible, acceptable, and modestly effective in reducing symptoms in different psychiatric disorders[25,57-60]. In contrast, studies from LMICs have usually examined the feasibility, acceptability, and occasionally the affordability of mHealth interventions. While these outcomes are positive, the evidence for the efficacy of mHealth interventions is limited, inconsistent, and methodologically inadequate[44,45,54,55,61]. However, studies of all but a few medical disorders from LMICs reveal a similar lack of evidence for the efficacy of mobile-based interventions[10,55,62,63]. Moreover, the evidence for the efficacy of mHealth interventions for psychiatric disorders is lacking even in HICs[25].

The role of digital psychiatric interventions in task-shifting in LMICs

One of the innovative uses of digital psychiatry, particularly in LMICs has been the use of digital technologies to optimize task-shifting[63]. Task-shifting or task-sharing refers to the utilization of non-specialist health professionals such as doctors, community health workers, lay health workers, midwives, or nurses for delivering mental healthcare services in primary-care or community settings[9,26]. LMICs are unable to ensure optimal delivery of mental healthcare services because they lack adequate numbers of trained professionals, infrastructure, funding, and appropriate policies[64]. Moreover, workforce shortages are one of the main contributors to the treatment gap in LMICs[26]. By delegating clinical responsibilities to non-specialist workers, task-shifting ensures the optimum use of limited human resources. Task-shifting improves the efficiency of the mental healthcare system and the effectiveness of interventions delivered by non-specialist workers. The essential purpose of task-shifting is the delivery of evidence-based, low-intensity psychological treatments by trained non-specialist professionals. Low-intensity psychological treatments are simpler interventions that are easily taught and require less frequent contact with patients[36]. Another essential requirement for task-shifting and increasing the capacity of the non-specialist workforce is the integration of mental health services with mainstream health services at the primary-care level[26,64]. The principal components of task shifting involve training workers to deliver care, supporting these workers while they provide care, monitoring and supervising their performance, ensuring proper communication between providers and the workers, and implementing measures to improve motivation and retention of the workers. Mobile or internet-based services can aid all these components of task-shifting equally or even more efficiently than conventional mental health services[65-69]. There is convincing evidence to support the effectiveness of task-shifting and the delivery of evidence-based psychosocial interventions by non-specialist professionals as a part of traditional mental health services[70-73]. Reviews of digital psychiatric interventions from LMICs have also found that mobile or internet-based technologies are equally useful in supporting task-shifting and the delivery of low-intensity psychological interventions by non-specialist workers[6,9,26,36,40]. In the meta-analysis by Fu *et al*[43], the efficacy of low-intensity digital psychosocial interventions was greater than similar interventions delivered by non-specialist workers in person. More recently, there have been several RCTs from LMICs showing that mobile-delivered psychosocial interventions are effective in reducing symptoms, promoting remission, improving adherence and functioning, and saving costs in common mental disorders and schizophrenia[74-77]. Other RCTs have shown that mobile technologies are effective in training non-specialist workers to ensure optimal use of the task-shifting approach[78-80]. The details of these RCTs are included in the accompanying table. Despite this impressive evidence, the use of digital technologies to support task-shifting for mental health uses has many shortcomings. These include methodological inadequacies of the evidence, conflicting data on cost-effectiveness, and the lack of large-scale trials on implementing these technologies[9,26,39,54,55]. However, the digitalization of task-shifting appears to be a promising approach for reducing the mental health treatment gap in LMICs, and future research that focuses on cost-effectiveness and implementation will further enhance the role of digital technologies in task-shifting in these countries (Table 1).

Digital psychiatry in LMICs during and after the coronavirus disease 2019

The coronavirus disease 2019 pandemic significantly impacted global digital psychiatric services. There was a rise in mental health problems and psychiatric disorders worldwide[81,82], although there are conflicting reports about the increased prevalence of psychological symptoms in the general population[83]. Nevertheless, the pandemic severely disrupted conventional mental health services and affected the continuity of psychiatric care[82]. The impact was greater in LMICs than in HICs because of the pre-existing deficiencies in their mental healthcare systems[64,82]. The global response to disruption in mental health services was to switch to digital psychiatric services[82,84-86]. According to a WHO survey, around 70% of the countries adopted some form of digital intervention, either telephone support or videoconferencing during the pandemic to replace in-person consultations[87]. Half of the countries achieved the transition to digital care by the first year of the pandemic[86]. The increased global uptake of digital psychiatric services followed the relaxation of regulations and the adoption of policies promoting digital interventions in these countries[82,84-86]. Most countries set up helplines to provide information about infection control and psychosocial support for the general population, patients with psychiatric disorders, and frontline health workers[64,82,87]. A common approach used in LMICs was training healthcare workers in psychosocial skills. Several organizations and countries developed guidelines for the use of digital psychiatric treatments. Digital interventions for task-shifting or digital delivery of low-intensity psychosocial treatments were adopted only by a few countries. Digital interventions used during the pandemic were effective and appeared to improve treatment adherence[84]. The change to digital modes of mental healthcare was feasible and acceptable to most patients, families, and mental health professionals[84,85]. However, there were significant

Table 1 Randomized-controlled trials of digitally-based task-shifting from low- and middle-income countries

Ref.	Details	Interventions	Findings
Chibanda *et al*[74], 2016	Cluster RCT with 6 months follow-up of common mental disorders from a primary-care setting in Zimbabwe (*n* = 573)	Culturally adapted problem-solving therapy with education and support delivered by lay health workers versus standard care with education and support. Mobile phones were used to deliver text messages or make calls to reinforce the intervention	The intervention group had fewer symptoms and lower risk of depression
Xu *et al* [75], 2019	RCT of patients with schizophrenia from rural community settings in China (*n* = 278)	Lay health worker delivered mobile text messages for medication reminders, health education, relapse prevention, and contact with primary healthcare versus non-specialists delivering and monitoring medications at home	The intervention group was more effective in in improving medication adherence, reducing relapses and re-hospitalizations
Gureje *et al*[76], 2019	Cluster RCT with 12 months follow-up of antenatal women with major depression from primary maternal care clinics in Nigeria (*n* = 686)	Interventions delivered by primary maternal care providers. Low-intensity treatment consisting of basic psychosocial treatment according to the mhGAP intervention guide versus high-intensity treatment consisting of a minimum of 8 weekly problem-solving therapy sessions. Mobile phones were used to deliver text messages or make calls to monitor, support, engage patients. Specialist supervision and consultation was conducted by mobile phones	No difference between high- or low-intensity treatments in remission of depression, infant outcomes, cost, and adverse events at 6 months postpartum. High-intensity treatment was more effective for severe depression
Gureje *et al*[77], 2019	Cluster RCT with 12 months follow-up of patients with moderate to severe depression from primary care clinics in Nigeria (*n* = 1035)	Primary healthcare worker delivered culturally adapted structured psychological intervention consisting of behavioural activation and problem-solving therapy for a minimum of 8 sessions, stepped up, if necessary, versus simple psychosocial interventions for depression. Providers were trained, supervised, and monitored by mobile phone contact	The proportion of patients with remitted depression in the 2 groups was similar at 12 months. Enhanced usual care using the mhGAP intervention guide provides a simple and affordable solution for the treatment of depression in primary-care
Rahman *et al*[78], 2019	Single-blind, non-inferiority RCT of technology assisted training of community health workers in delivering an evidence-based, low-intensity psychological intervention for depression (THP) from rural Pakistan (*n* = 80)	The Technology-Assisted Cascaded Training and Supervision system used a tablet-based application to provide standardized training to lay workers using a cascaded training model where a specialist in THP trained non-specialist workers who in turn trained the lay worker. Community health workers were supervised using net-based platforms. Digital training was compared with conventional in-person training	There were no significant differences in digitally-based versus in-person training in the competence of community health workers on the Enhancing Assessment of Common Therapeutic factors scale immediately following the training and at 3 months after completion of training
Muke *et al* [79], 2020	Pilot RCT of the feasibility and acceptability of a digital programme for training non-specialist health workers to deliver a brief psychological treatment for depression (THP) from a primary-care setting in India (*n* = 42)	Digital training was based on the digitized version of the manual for THP. It was hosted on an online learning platform that was accessible by smartphones. Non-specialist workers received technical support during training. Participants were also provided remote weekly support by research assistants through phone calls in the digital training with remote support group. The 2 digital training groups were compared with conventional in-person training of non-specialist health workers	Completion of training was highest in the digital training with remote support group. The competency of the workers improved following training with no significant differences between the 3 groups. Greater improvement in competency was observed in the digital training with remote support group and the in-person group compared to the digital training group
Nirisha *et al*[80], 2023	RCT of hybrid training of lay health workers to screen and refer people with mental health problems from a primary-care setting in India (*n* = 75)	Hybrid training consisted 1 in-person and 7 online sessions. Online learning was based on the Project ECHO (Extension of Community Health care Outcome) adapted for Indian settings. Lay workers used smartphones to access the online platform. Supervision of workers was carried out by the research team through phone calls. Digital training was compared with 1 d of in-person training	The digital training group was better at identifying alcohol use and common mental disorders, whereas the in-person group was better at identifying severe mental illnesses. Scores on knowledge, attitude, and practice did not differ between the 2 groups over time

LMICs: Low- and middle-income countries; mhGAP: World Health Organization Mental Health Gap Action Programme; RCT: Randomized-controlled trial; THP: Thinking Healthy Programme, an evidence-based psychological intervention for depression.

differences between HICs and LMICs in the adoption of digital services. While more than 80% of HICs digitalized their mental health services by 2020, less than 50% of LMICs had shifted to digital psychiatric services[42,87,88]. The contribution of middle-income countries to the global digitalization of mental health services was minimal, while there was hardly any data from low-income countries[85,86,88]. Most of the studies from middle-income countries were from China or India. These were usually descriptive reports of the development of guidelines, virtualization of psychiatric outpatient services, implementation of online interventions, and uncontrolled studies of digital interventions for different psychiatric disorders[88-92]. Lastly, it is uncertain whether the renewed interest in digital psychiatry has persisted after the pandemic. There are conflicting reports about the increased acceptance and use of digital services globally or in HICs [93-95], but there is practically no data from the LMICs.

Other developments

One of the uses of digital psychiatric interventions is to reduce the stigma associated with mental illness and its treatment

[9,37,53]. Some studies have found that internet or mobile interventions effectively reduce stigma among patients from LMICs[36,44,54,56]. A recent review has cited examples of digital health programmes such as mass media campaigns, mHealth-based community interventions, and online interventions that can reduce stigma through education and contact with those suffering from mental illness[96]. Finally, social media, virtual reality, and emerging technologies such as big data analytics and machine learning are also being explored for their potential usefulness in managing mental health problems in LMICs[9,19,45].

CHALLENGES FACING DIGITAL PSYCHIATRIC SERVICES IN LMICs

Despite the promising developments in digital psychiatry in LMICs, there are many barriers to its adoption in these countries. The WHO surveys and other reviews have shown that the principal barriers impeding the progress of digital health across the world are the costs and funding of programmes, technological and infrastructural deficiencies, unawareness, lack of technical expertise, concerns about privacy, confidentiality, and adequate treatment alliances, cultural impediments, lack of regulatory policies and guidelines, competing health-system priorities, and the lack of demand for digital health services[17-19,97,98]. The major hurdles in HICs include legal issues concerning privacy, confidentiality, and safety, lack of priority for digital services, and the lack of demand for them. In contrast, the chief concerns in LMICs relate to the costs of services, under-developed infrastructure, lack of awareness about digital services, lack of technical expertise and trained professionals, cultural barriers, and negative attitudes among providers[17,18,99-101]. The costs related to digital health programmes include the initial costs of infrastructure, training providers, and operational and maintenance costs[99,101]. These are higher in LMICs and there are fewer opportunities to recover these costs because insufficient funding prevents the large-scale and sustained implementation of digital services[68,99]. Policy-makers are also unlikely to invest in these programmes because of inconsistent data on cost-effectiveness[17]. Lastly, the costs of the device or service might be too high for many users[44]. The main technological and infrastructural obstacles include poor network connectivity, lack of internet access, and lack of basic infrastructure such as electricity supply[26,47,99-101] These barriers are more likely to affect the internet than mobile-based services and could be a factor in the preference for mHealth interventions in LMICs[37,68,99]. The lack of trained personnel arises from the perennial shortage of healthcare workers in LMICs, unawareness and unfamiliarity with technology, negative attitudes, and resistance to change among providers[9,17,68,100,101]. Cultural hindrances include language barriers[6,95,102], cultural beliefs and attitudes among patients and families[39,54,100], the impact of culture on treatment relationships[54], and the cultural appropriateness of digital interventions[44,99]. Finally, the rapid advances in technology and its increasing reach have highlighted the significant disparities in access to and use of digital devices. This digital divide exists between countries, regions, and people[103]. In general, digital access is poorer in LMICs compared to HICs, but there is also great variability between the LMICs[17-19]. In LMICs, rural and remote regions are underserved compared to the urban areas[37,44,68,101,103]. However, inequitable access most commonly affects the users of technology, where the digital divide reflects the existing social inequities[104,105]. Consequently, women, the elderly, persons with low literacy, and the socioeconomically deprived, ethnic, and marginal populations have the least access[9,43,104-106] and limited digital literacy[6,44,50,54,100]. The greatest paradox of digital psychiatry is that those with the greatest need and those most likely to benefit from such services are least likely to have access to them.

CONCLUSION

This summary suggests that there is reason for optimism about the progress made in digital psychiatric services in LMICs over the last decade. Nevertheless, further efforts are needed to improve the organization and implementation of these services in LMICs[17,54,65,107,108]. Several factors influence the success or failure of digital services including users' needs, implementation readiness, and stakeholder involvement. Determining the needs of the patients, families, and the wider community and the socio-economic and cultural factors that shape these needs is essential in planning digital services for the targeted population[65,106]. Digital psychiatric services should be in keeping with the prevalent infrastructural, technological, and human resources. The needs of the users and the availability of resources have a role in the design and content of digital psychiatric interventions. A participatory approach soliciting the users' views improves the acceptability and usefulness of the interventions[9,37,50]. Digital interventions should have proven efficacy in LMIC settings before implementation. Thus, there is a need for methodologically adequate and more nuanced research on clinically meaningful outcomes in different patient populations and the cost-effectiveness of interventions[9,26,37,40,43]. A central consideration for such research should be the ability to implement digital interventions on a larger scale. Consequently, factors other than the efficacy of digital services such as operational capacity, funding, and the ability to integrate with mainstream psychiatric services have to be evaluated[45,93,107]. Collaboration between different stakeholders including the government, non-governmental organizations, private enterprises, providers, and users is essential for implementing and sustaining digital psychiatric services[17,107,108]. Regulation of digital services is necessary to maintain their standards of care. Regular monitoring, evaluation, and timely upgrades are also essential to maintain the quality of the services[17,93]. Apart from commercial considerations, focusing on the social benefits of digital services and innovative approaches to reduce the digital divide deserve equal consideration[9,17,37]. Lastly, while the wider and efficient deployment of digital psychiatric services is necessary, digitalization cannot be the sole option for reducing the mental health treatment gap in LMICs[17,99]. Rather, digital and traditional psychiatric services, general health services, and social welfare services all have to act in concert by enabling and facilitating each other.

FOOTNOTES

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MINIREVIEWS

Navigating the intersection of psychiatry and ophthalmology: A comprehensive review of depression and anxiety management in glaucoma patients

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Abstract

Glaucoma, a prevalent and debilitating eye disease, has long been associated with vision impairment and blindness. However, recent research has shed light on the often-underestimated psychological dimensions of this condition. Anxiety and depression, two pervasive psychiatric comorbidities, have been increasingly recognized among glaucoma patients. This comprehensive review aims to explore the intricate relationship between psychiatry and ophthalmology, in the context of managing depression and anxiety in glaucoma patients. By meticulously examining peer-reviewed literature, we synthesize current knowledge on the prevalence, risk factors, and underlying mechanisms of anxiety and depression in glaucoma. The evidence reveals that glaucoma patients face an elevated risk of experiencing these mood disorders. Factors such as progressive vision loss, complex medication regimens, and the fear of further visual deterioration contribute to their vulnerability. Moreover, we delve into the bidirectional relationship between glaucoma and mood disorders, shedding light on the complex interplay between ocular and emotional health. Our review investigates

the implications of anxiety and depression on glaucoma management, including their potential impact on treatment adherence, disease progression, and overall quality of life. We also explore the neurobiological pathways linking glaucoma and mood disorders, providing a foundation for future research and potential therapeutic interventions. In conclusion, recognizing the psychological burden carried by glaucoma patients is essential for holistic and patient-centered care. This review underscores the pressing need for integrated approaches that bring together ophthalmological and psychiatric expertise to optimize the well-being of individuals facing the challenges of glaucoma. By addressing anxiety and depression in glaucoma care, healthcare providers can enhance the overall quality of life for these patients, ultimately leading to improved outcomes and a brighter future for those affected by this condition. This review offers valuable insight for healthcare practitioners and researchers, providing a concise overview of key topics and research in the field of managing depression and anxiety in glaucoma patients.

Key Words: Glaucoma; Psychiatry; Depression; Anxiety; Risk factors; Bidirectional relationship

Core Tip: This literature review underscores the evolving perspective on glaucoma, traditionally viewed solely as an ocular ailment. It delves into the intricate interplay between glaucoma and mental health, shedding light on the psychological toll exacted by the relentless progression of vision loss. The bidirectional relationship between glaucoma, anxiety, and depression is explored, accentuating factors like progressive vision decline and medication intricacies. Emphasizing holistic patient care, the core recommendation advocates for collaborative efforts between ophthalmologists and psychiatrists to address depression and anxiety, recognizing their impact on treatment adherence, disease trajectory, and the overall well-being of individuals grappling with glaucoma.

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INTRODUCTION

Glaucoma, traditionally perceived as a progressively debilitating ocular pathology, not only encroaches upon visual acuity (VA) but also casts a profound impact on the psychological fabric of affected individuals. The relentless progression of vision loss, coupled with the constant awareness of a potentially irreversible condition, places an immense psychological burden on patients. Recent research signifies a pivotal shift from the exclusive focus on its physical aspects to a more nuanced understanding of the psychological dimensions associated with the condition. This literature review explores the intersection of psychiatry and ophthalmology, dissecting the complexities of managing depression and anxiety in glaucoma patients. We analyze prevalence, risk factors, and mechanisms underlying mood disorders in glaucoma, unveiling the complex relationship between the conditions. Contributing factors, such as progressive vision loss and medication complexity, heighten susceptibility to mood disorders. The review explores the impact of anxiety and depression on treatment adherence, disease progression, and overall quality of life in glaucoma patients. Emphasizing holistic care, we advocate for integrated strategies involving both ophthalmologists and psychiatrists to enhance patient-centered care and quality of life.

LITERATURE REVIEW

A thorough search of the PubMed database was conducted, encompassing literature published from January 2000 to August 2023. The search utilized keywords such as "glaucoma", "depression", "anxiety", "glaucoma and depression", and "glaucoma and anxiety". The selected studies included reviews, cross-sectional, case-control, prospective, and retrospective studies, with the primary focus on investigating the correlation between glaucoma and anxiety/depression and identifying potential risk factors. To maintain stringency, case reports and meta-analyses were excluded from consideration. Only studies written in English were included in the evaluation process. The retrieved articles underwent a careful manual review to eliminate duplicates, resulting in the selection 55 articles from the screened abstracts (Table 1).

Table 1 Summary of 8 selected studies on glaucoma and anxiety/depression association

Ref.	Region	Study design	No. of patient	Results	Key findings
Mabuchi *et al*[3], 2008	Japan	Case control study	230 POAG patients; 230 controls	Prevalence of anxiety: 13.0% (P = 0.030); depression: 10.9% (P = 0.026)	POAG was related to anxiety and depression
Wang *et al* [7], 2012	United States	Cross sectional study	453 glaucoma patients	10.9% prevalence of depression among self-reported glaucoma patients	Visual function parameters were associated with depression
Zhou *et al* [9], 2013	China	Cross sectional study	506 glaucoma patients	Prevalence of anxiety: 22.92%; depression: 16.40%	High anxiety and depression rates exist among Chinese glaucoma patients
Chen *et al* [5], 2017	Taiwan	Case control study	15865 glaucoma patients; 77014 controls	SSRI use linked to increased glaucoma risk (OR: 1.39, 95%CI: 1.29-1.50)	SSRIs use associated with glaucoma
Chen *et al* [4], 2018	Taiwan	Cohort study	8777 glaucoma patients; 35108 controls	In 11 yr follow up period, incidence of depression: Glaucoma group = 5.9% depression, control group = 3.2%	Patients with glaucoma are at significantly greater risk of developing depression
Berchuck *et al*[10], 2021	United States	Cohort study	3259 glaucoma suspects; 28% (911 cases) diagnosed with glaucoma during follow-up	Prevalence of anxiety: 32%; depression: 33%	Prior anxiety or anxiety with depression history raises the risk of developing glaucoma in glaucoma suspects
Shin *et al* [6], 2021	Korea	Case control study	251 eyes with POAG	Anxiety linked to disc hemorrhage, peak IOP, and RNFL thinning rate (P = 0.017, P = 0.046, P = 0.026); depression tied to visual field mean deviation and heart rate variability (P = 0.003, P = 0.006)	Anxiety increase the risk of glaucoma progression and they are also associated with IOP profile and disc hemorrhage
Dayal *et al* [8], 2022	India	Cross sectional study	200 patients	Mean HADS-anxiety = 4.5 (SD = 3.4); HADS-depression = 4.1 (SD = 3.8)	Visual loss in glaucoma correlates with anxiety and depression symptoms, regardless of disease duration

POAG: Primary open-angle glaucoma; HADS: Hospital Anxiety and Depression Scale-Anxiety; SSRI: Selective serotonin reuptake inhibitors; IOP: Intraocular pressure; 95%CI: 95% confidence interval; OR: Odds ratio.

PREVALENCE AND RISK FACTORS OF ANXIETY AND DEPRESSION IN GLAUCOMA

Glaucoma, characterized by the progressive loss of retinal ganglion cells (RGCs), is an optic neuropathy with no current effective treatment to control the ganglion cell degeneration[1,2]. The management of glaucoma focuses on the proactive prevention of its progression, rendering it a chronic medical condition that necessitates lifelong care. The literature review reveals compelling evidence of a statistically significant association between glaucoma and elevated levels of anxiety and depression[3-10]. Owing to the lack of symptoms, the persisting nature of the debilitation, nature, and the looming possibility of blindness, glaucoma frequently places a psychological weight on individuals[11,12]. Individuals diagnosed with glaucoma are at an elevated risk of developing depression, a correlation substantiated by various studies. Notably, Studies from Taiwan, Japan, and Singapore collectively revealed a significant association between glaucoma and depression. In Taiwan, a retrospective cohort study involving 8777 glaucoma patients and 35108 controls showed a significantly higher hazard of depression (P < 0.0001)[4]. In a Japanese case-control study demonstrated elevated rates of anxiety (13.0%, P = 0.030) and depression (10.9%, P = 0.026) among 230 primary open-angle glaucoma (POAG) patients [3]. Meanwhile, in Singapore, a cross-sectional study with 15,865 glaucoma cases and 77014 controls highlighted that individuals receiving Selective Serotonin Reuptake Inhibitors had a greater risk of glaucoma incidence [odds ratio (OR): 1.39; 95% confidence interval (95%CI): 1.29-1.50][5].

In a study involving 6760 participants aged 40 years and older within the National Health and Nutrition Examination Survey, those diagnosed with glaucoma exhibited a higher prevalence of depression (10.9%, SEM: 2.20%) compared to those without glaucoma (6.9%, SEM: 0.62%). The association remained significant after adjusting for demographic factors but lost significance when considering self-reported general health[7].

Shin *et al*[6], in their retrospective case-control study spanning 2 years and involving 251 eyes diagnosed with open-angle glaucoma, observed a significant incidence of anxiety and depression in affected individuals. Similarly, Zhou *et al* [9] found high rates of anxiety and depression in Chinese glaucoma patients, with the prevalence of anxiety and depression being 22.92% and 16.40%, respectively.

Amidst the body of research on this subject, the presence of some conflicting results from studies conducted across diverse global regions introduced a layer of intricacy to the overall understanding of the subject. European cohort study published by Rezapour *et al*[13], involving 293 participants, revealed no significant association between self-reported glaucoma and depression or anxiety. The prevalence rates for depression (6.6%) and anxiety (5.3%) among individuals with glaucoma were comparable to those without glaucoma (7.7% and 6.6%). Adjusted odds ratios indicated no link

between self-reported glaucoma and depression (OR: 1.10, P = 0.80) or anxiety (OR: 1.48, P = 0.35)[13]. This lack of association persisted even after adjusting for various factors, including socio-demographic variables and health parameters. Consistent with these findings, in both the Australian study by Eramudugolla *et al*[14] and the Beijing Eye Study conducted by Jonas *et al*[15], there was no evidence supporting elevated rates of depressive or anxiety symptoms associated with self-reported glaucoma. Cumurcu *et al*[16] found a correlation between pseudoexfoliative glaucoma (PXG) and depressive symptoms using assessments like the Diagnostic and Statistical Manual of Mental Disorders-IV interview, Hamilton Depression Rating Scale, Hamilton Anxiety Rating Scale, Mini Mental State Examination, and Montgomery-Asberg Depression Rating Scale. However, they noted no significant difference in anxiety levels among PXG, POAG, and control groups. In a study performed on the Israeli population, Weiss *et al*[17] discovered a depression rate in glaucoma patients similar to that of the general Israeli population, and despite depression itself not being directly linked to non-compliance, a positive correlation was observed between the severity of depression and the level of non-compliance in these patients (P = 0.04).

The mental health burden in glaucoma patients are influenced by various factors, including the perpetual fear of potential blindness, financial strain, and disruption to daily activities[18,19]. Insightful studies have explored nuanced risk factors for depression in glaucoma patients, such as accelerated progression of visual impairment, advanced disease stages, female gender, substance abuse, and, in some cases, advanced age[4,20]. Younger age was found to be a significant risk factor for anxiety, irrespective of demographic and clinical variables, as indicated by a study that uncovered significant negative relationships between age and the Hospital Anxiety and Depression Scale-Anxiety (HADS-A) subscore both with (b = -0.046, P = 0.0008) and without (b = -0.043, P = 0.0022) adjusting for these factors; furthermore, older age and increasing glaucoma severity were identified as risk factors for depression in glaucoma patients[21]. In contrast, an extensive study conducted in North Carolina discovered that advanced age did not elevate the likelihood of depression[18]. Onwubiko *et al*[22] identified high rates of anxiety (44.0%) and depression (41.8%) among glaucoma patients in Enugu, Nigeria, with key contributing factors being reduced VA and also, blindness. Poor treatment adherence in glaucoma patients was associated with heightened anxiety, negatively affecting therapeutic outcomes[23]. According to the studies by Mabuchi *et al*[3] and Chen *et al*[4], the use of eye drops and the number of anti-glaucoma medications were not identified as significant risk factors for depression; furthermore, the use of topical β-blockers for glaucoma, showed no significant correlation with depression. The nature and strength of this association seemed to vary across different populations, types of glaucoma, and even treatment modalities for depression/anxiety.

THE BIDIRECTIONAL RELATIONSHIP: EXPLORING THE UNDERLYING LINK BETWEEN ANXIETY, DEPRESSION, AND GLAUCOMA

The intricate relationship between glaucoma and anxiety/depression is marked by an interplay of psychological and physiological factors. The diagnosis of chronic diseases can trigger anxiety and depression due to functional limitations, social isolation, relationship loss, guilt, and future uncertainties, while simultaneously, studies suggest that anxiety and depression can either precipitate or worsen chronic conditions[13,24-26]. The progressive vision loss and intricate medication regimens inherent in glaucoma contribute to a heightened vulnerability to mood disorders. Fear of visual deterioration becomes a continual concern. Numerous studies emphasize on the impact of glaucoma on elevating the risk of anxiety and depression[7,13,18,19]. Additionally, alternative research suggested a reciprocal relationship, revealing that a history of anxiety or depression may increase the likelihood of developing glaucoma in individuals identified as glaucoma suspects[6,10]. In a study by Skalicky *et al*[27], a growing incidence of depression was observed as the severity of glaucoma increased. Similarly, Yochim *et al*[28] established a significant correlation between cognitive impairment, memory deficits, and mild-to-moderate depressive symptoms in a cohort of glaucoma patients. After adjusting for age, they noted that 20% of participants manifested memory impairment, while 22% exhibited compromised executive functioning, and 12.2% of individuals displayed mild-to-moderate depressive symptoms.

The interconnection between glaucoma, anxiety, and depression encompasses intricate neurobiological links that affect not only mental health but also the pathophysiological processes that influence the development and progression of this ocular condition. Studies suggest that the degeneration of retinal tissue in glaucoma is linked to an increased risk of depression and sleep disturbances[18,21,29,30]. This association may stem from disruption in the central light input and the psychological challenges posed by the chronic and progressive nature of the condition, along with the impending threat of vision loss. Glaucoma's impact on RGCs, their axons, and accompanying glial cells leads to distinct structural alterations in the optic disc and retinal nerve fiber layer (RNFL)[31]. The severity of the condition is directly correlated with a reduction in RNFL thickness[32]. The analysis of the optic nerve head (ONH) and RNFL through optical coherence tomography (OCT) is crucial for early glaucoma detection. By combining OCT with perimetry, which assesses the visual field sensitivity, clinicians can obtain a comprehensive understanding of both structural and functional aspects of the visual system. The integration of structural and functional assessments enhances the sensitivity and specificity of glaucoma diagnosis, allowing for earlier intervention and management. RNFL thickness, in particular, serves as a superior indicator compared to ONH measurements. This reflects the function of RGCs and allows for more effective monitoring of disease progression[33]. Agorastos *et al*[29] in their study, found that visual field defects (VFD) in glaucoma are pivotal predictors for depressive symptoms, trait anxiety, and sleep disturbances, with a higher prevalence of these symptoms in severe VFD cases compared to those with minor or no VFD. The research showed that patients with severe VFD faced a significantly increased risk of achieving clinically significant psychometric scores for depression (OR: 4.0; 95%CI: 1.17-13.60), trait anxiety (OR: 6.1; 95%CI: 1.35-27.10), and sleep disturbance (OR: 4.2; 95%CI: 1.36-13.30). Ayaki *et al*[30] demonstrated that sleep disorders in glaucoma patients are associated with visual field loss and mood status, but not

significantly linked to structural damage in RGCs. Additionally, Shin *et al*[6] investigated the relationship between anxiety and RNFL thinning in glaucoma patients, uncovering a significant connection with the high anxiety group exhibiting an accelerated rate of RNFL decline ($P = 0.026$), while no notable differences in visual field progression rates were observed between individuals with low and high anxiety or depression within the study cohort.

Intraocular pressure (IOP) is widely acknowledged as the foremost modifiable factor influencing onset or progression of glaucoma. Psychological stress has been documented to increase IOP, and this effect is mediated through the cortisol hormone, which is associated with the hypothalamic-pituitary-adrenal axis[34,35]. The autonomic nervous system (ANS) functions in regulating blood flow and IOP. The emotional responses of anxiety and depression is believed to originate in the amygdala and trigger the release of neurotransmitters and can adversely impact the ANS, stimulating multiple organs. The ANS plays a crucial role in maintaining biological balance by regulating blood flow and IOP; it is also important in the development or progression of glaucoma[36-39]. Frequent emotional fluctuations and persistent anxiety reactions can disrupt the equilibrium in the ANS, potentially exacerbating the risk of glaucoma or contributing to its progression[40]. Recognizing and addressing these multifaceted aspects, including the potential neurobiological links, is crucial for providing comprehensive support to individuals hustling through the complexities of living with glaucoma.

INTEGRATED APPROACHES TO GLAUCOMA CARE: IMPLICATIONS ON MANAGEMENT

The intersection of psychological factors, specifically anxiety and depression, with glaucoma management is integral to understanding and improving patient outcomes. The impact of these psychological elements permeates various facets of the disease trajectory, with treatment adherence serving as a focal point. Anxiety and depression may instigate hesitation, making it difficult to adhere to medication and follow-up appointments, thereby compromising the necessary steps to impede disease progression[41]. This compromised adherence becomes a gateway to exacerbated glaucomatous damage, ultimately leading to an unfavorable prognosis[42]. This progression significantly impacts the patient's overall quality of life. Detecting glaucoma in its early stages is crucial in clinical care to maintain visual function and quality of life[43,44]. Research findings indicate that simply being aware of one's glaucoma, even in the absence of visual field damage, may have a detrimental effect on the individual's quality of life[45].

The loss of peripheral visual function in glaucoma patients has cascading impact on daily activities, ranging from driving limitations, increased incidents of bumping into objects, slower walking, and a higher risk of falls. There is also a major jolt on activities like reading, which becomes evident primarily in cases of severe field damage. Although overall physical activity may not show significant difference, substantial reduction is noted with greater visual field loss[46-49]. A study by Sesar *et al*[50] asserts the negative impact of disease progression and predisposing socio-demographic factors on the quality of life in glaucoma patients. Notably, male individuals aged 50 to 69 exhibited the highest Glaucoma Health-Related Quality of Life (GHRQL), followed by those consistently using anti-glaucoma therapy and then those without glaucoma progression. These distinctions were found to be statistically significant ($P < 0.05$) based on responses to two self-administered questionnaires assessing GHRQL[50]. Ajith *et al*[51] also found elevated rates of depression (35.81%) and anxiety (25.0%) among glaucoma patients in their study, comprising 148 subjects with glaucoma and 150 subjects without glaucoma, emphasizing the need for screening protocols using Patient Health Questionnaire, the Generalized Anxiety Disorder scales. They further advocated that the lack of ophthalmic risk factors associated with depression and anxiety accentuated the significance of psychological assessment and collaborative intervention with a psychiatrist. Social isolation, stemming from difficulties in communication and participation, adds to the emotional burden. Slota *et al*[52] stressed the importance of proactive medication concern addressal in glaucoma patients with lower health literacy, in order to enhance adherence, given by their potential reluctance to communicate issues regarding medication side effects and administration. Incorporating psychological support for severe glaucoma patients with reduced vision can enhance communication and treatment adherence[22]. Musa *et al*[53] pointed out the impact of socioeconomic barriers on glaucoma care, urging attention to factors like companionship, transportation, insurance, education, and telemedicine for improved outcomes. Additionally, addressing the stigma associated with vision loss and mental health issues, the constraint of time during medical appointments, limited access to mental health services, and the need for effective coping strategies further complicate the provision of comprehensive care. Birhan *et al*[54] conducted a cross-sectional study involving 423 glaucoma patients, revealing that 50.1% (95%CI: 45.1%-54.5%) of the surveyed individuals employed maladaptive coping strategies, potentially exacerbating mental health challenges. Conversely, Zhou *et al*[55] found a connection between improved mental health regulation and better self-management behavior in glaucoma patients in China. These studies highlight integrating coping strategy care into glaucoma treatment, to encourage positive approaches towards fostering improved overall patient well-being. To effectively address these challenges, a patient-centered approach is essential, incorporating educational initiatives that cover both the ocular and emotional aspects of glaucoma. However, recognizing the emotional toll of vision loss, the coordination of interdisciplinary collaboration among ophthalmologists, psychologists, and other healthcare professionals is crucial to ensure optimal visual outcomes while safeguarding mental and emotional well-being in the face of this challenging ocular condition.

CONCLUSION

The evidence synthesized from peer-reviewed literature reiterates the heightened susceptibility of glaucoma patients to mood disorders, attributed to factors such as progressive vision loss, complex medication regimens, and the relentless

fear of visual deterioration. The bidirectional interplay between glaucoma and mood disorders, elucidated in this review, highlights the complex dynamics between ocular and emotional health. The impact of anxiety and depression on critical aspects of glaucoma care, including treatment adherence, disease progression, and overall quality of life, has been thoroughly investigated. Recognizing the psychological burden in glaucoma patients has been emphasized to be crucial for holistic and patient-centered care. Conflicting results from studies conducted across diverse global regions introduce complexity to the understanding of the subject, urging the need for further research. Future studies should aim to standardize methodologies, explore cultural and regional differences, and delve deeper into the underlying mechanisms and risk factors associated with anxiety and depression in glaucoma patients.

In conclusion, this review serves as a foundation for ongoing research endeavours to optimize the management of depression and anxiety in individuals with glaucoma. By addressing the psychological aspects of glaucoma care, healthcare providers can strive to enhance patient-centered approaches and contribute to improved outcomes for those grappling with this debilitating condition.

FOOTNOTES

Author contributions: Ramesh PV and Morya AK played big roles they helped plan and carry out the study, and carefully looked at the results; Azad A took the lead in designing the study and writing the manuscript; Pannerselvam P had a key role in coming up with the study's main ideas and adding helpful suggestions; Ramesh SV made sure the data we used was reliable; Devadas AK, Gopalakrishnan ST, and Aradhya AK provided valuable expertise in reviewing and editing the manuscript; and all authors have carefully reviewed and given their approval for the final manuscript.

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ORIGINAL ARTICLE

Case Control Study

Brain protective effect of dexmedetomidine *vs* propofol for sedation during prolonged mechanical ventilation in non-brain injured patients

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Abstract

BACKGROUND

Dexmedetomidine and propofol are two sedatives used for long-term sedation. It remains unclear whether dexmedetomidine provides superior cerebral protection for patients undergoing long-term mechanical ventilation.

AIM

To compare the neuroprotective effects of dexmedetomidine and propofol for sedation during prolonged mechanical ventilation in patients without brain injury.

METHODS

Patients who underwent mechanical ventilation for > 72 h were randomly assigned to receive sedation with dexmedetomidine or propofol. The Richmond Agitation and Sedation Scale (RASS) was used to evaluate sedation effects, with a target range of -3 to 0. The primary outcomes were serum levels of S100-β and neuron-specific enolase (NSE) every 24 h. The secondary outcomes were remifentanil dosage, the proportion of patients requiring rescue sedation, and the time and frequency of RASS scores within the target range.

RESULTS

A total of 52 and 63 patients were allocated to the dexmedetomidine group and propofol group, respectively. Baseline data were comparable between groups. No significant differences were identified between groups within the median duration of study drug infusion [52.0 (IQR: 36.0-73.5) h *vs* 53.0 (IQR: 37.0-72.0) h, *P* = 0.958], the median dose of remifentanil [4.5 (IQR: 4.0-5.0) μg/kg/h *vs* 4.6 (IQR:

4.0-5.0) μg/kg/h, P = 0.395], the median percentage of time in the target RASS range without rescue sedation [85.6% (IQR: 65.8%-96.6%) *vs* 86.7% (IQR: 72.3%-95.3), P = 0.592], and the median frequency within the target RASS range without rescue sedation [72.2% (60.8%-91.7%) *vs* 73.3% (60.0%-100.0%), P = 0.880]. The proportion of patients in the dexmedetomidine group who required rescue sedation was higher than in the propofol group with statistical significance (69.2% *vs* 50.8%, P = 0.045). Serum S100-β and NSE levels in the propofol group were higher than in the dexmedetomidine group with statistical significance during the first six and five days of mechanical ventilation, respectively (all P < 0.05).

CONCLUSION

Dexmedetomidine demonstrated stronger protective effects on the brain compared to propofol for long-term mechanical ventilation in patients without brain injury.

Key Words: Dexmedetomidine; Propofol; Sedation; Prolonged mechanical ventilation; Brain protective

Core Tip: In this study, we designed a single center, prospective, randomized controlled study to compare the brain protective effect of dexmedetomidine *vs* propofol for sedation during prolonged mechanical ventilation in non-brain injured patients.

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INTRODUCTION

Patients who require intensive care may experience a strong stress response due to their own serious illness, leading to long-term negative emotions such as anxiety and irritability. In addition, most of these patients also necessitate mechanical ventilation, which can readily result in conflict between the individual and the machine, thereby affecting the efficacy of mechanical ventilation[1,2]. Analgesic and sedative therapies can alleviate pain, anxiety, and restlessness in patients, reduce oxygen consumption, reduce stress reactions, playing a crucial role in intensive care unit (ICU) treatment [3]. However, long-term sedation may cause serious adverse reactions, including extended mechanical ventilation, impaired cognitive function, coma, and post-traumatic stress disorder. These outcomes are closely related to the choice of sedation regimen.

Dexmedetomidine and propofol are two sedatives used for long-term sedation[4]. Dexmedetomidine, an adrenergic receptor agonist, possesses analgesic, sedative, and inhibitory effects on sympathetic nervous activity[5,6], contributing to enhanced patient safety and comfort during long-term sedation[5,6]. Previous studies have demonstrated that compared to propofol or midazolam, dexmedetomidine can reduce the incidence of coma and delirium, as well as decrease mechanical ventilation time in ICU patients[6,7]. A multicenter randomized controlled trial from Europe revea-led that in ICU patients undergoing long-term mechanical ventilation, dexmedetomidine is non-inferior to midazolam or propofol in maintaining mild to moderate sedation, while also shortening the duration of mechanical ventilation and improving patients' ability to communicate pain[4]. Additionally, several clinical trials[8,9] and animal studies[10,11] have confirmed the brain-protective effects of dexmedetomidine. Nevertheless, it remains unclear whether dexmedetomidine provides superior cerebral protection for patients undergoing long-term mechanical ventilation.

In this study, we designed a single-center, prospective, randomized controlled study to compare the brain-protective effects of dexmedetomidine versus propofol for sedation during prolonged mechanical ventilation in non-brain-injured patients.

MATERIALS AND METHODS

Patients and ethical statement

This single-center, prospective, randomized controlled study was approved by the Ethics Committee of Peking University International Hospital (Approval No. 2021-KY-0037-01). Patients or their legal representatives signed an agreement to voluntarily participate in the present study.

The inclusion criteria of patients included: (1) Age ≥ 18 years and ≤ 75 years; (2) mechanical ventilation time ≥ 72 h and sedation time ≥ 24 h; and (3) patients without brain injuries.

Exclusion criteria: (1) Body mass index (BMI) < 18 kg/m^2 or > 30 kg/m^2; (2) acute severe neurological disorders; (3) brain injury, including head trauma, cerebral hemorrhage, cerebral infarction, and neurosurgery; and (4) acute hepatitis or serious hepatic dysfunction (Child-Pugh class C); (5) chronic kidney disease with glomerular filtration rate < 60 mL/min/1.73 m^2; (6) alcohol consumption or drug addiction; (7) myasthenia gravis, pregnancy or lactation, study drug allergies, or contraindications; and (8) patients with malignant tumors.

Randomization and intervention

Eligible patients received sedative drugs by doctors who were blind to the research details. The patients were unaware of the sedative medications administered as well.

All patients received analgesia at a dosage ranging from 4.0 to 9.0 μg/kg/h. Patients in the dexmedetomidine group received dexmedetomidine hydrochloride injection (0.1-1.2 μg/kg/h) (H20183219, Yangzijiang Pharmaceutical Group Co., Ltd, China) for sedation, while patients in the propofol group were given propofol medium long chain fat emulsion injection (0.3-4.0 mg/kg/h) (HJ20150655, Beijing Feisenyuskabi Pharmaceutical Co., Ltd, China) for sedation.

Primary outcome

Serum S100-β and neuron-specific enolase (NSE) levels were measured to assess brain function. Briefly, venous blood was collected every 24 h during mechanical ventilation, followed by centrifugation (1000 × g, room temperature, 10 min) to separate the serum. The central laboratory detects serum S100-β and NSE levels using enzyme-linked immunosorbent assay.

Secondary outcomes

The secondary outcomes included the remifentanil dosage, the proportion of patients receiving rescue sedation, and the time and frequency of Richmond Agitation Sedation Scale (RASS) within the target range. Briefly, patients eventually included in the analysis recorded the dose of remifentanil used during the study. If a patient's RASS score was above the target range (-3 to 0) and required rescue sedation, the patient was recorded as requiring rescue sedation. RASS scores were assessed every 4 h prior to any administration of rescue therapy.

Statistical analysis

Due to a lack of assumptions, sample size estimation was not conducted in this study. Data were collected using an Excel table and analyzed by SPSS 25.0 (IBM, United States). Continuous data were presented as median and interquartile range (IQR). Differences between groups were compared utilizing Student's *t*-test or the Mann-Whitney *U* test, based on the results of the Kolmogorov-Smirnov test. Count data were expressed as percentages (%), and differences between groups were compared utilizing the chi-square test or Fisher's exact test. Statistical significance was set at $P < 0.05$.

RESULTS

Demographics and diagnostic results at baseline

We screened 3047 ICU patients and ultimately included 115 patients in the final analysis: 52 in the dexmedetomidine group and 63 in the propofol group (Figure 1). Their median age was 61.0 years (IQR: 54.00-65.00), with 69 male patients (60.0%) and a median BMI of 21.32 kg/m^2 (IQR: 19.35-22.98). No significant differences were observed in the baseline clinical characteristics between groups, such as the SAPS II score, the main reason for ICU admission, infection at ICU admission, SOFA score of organs (including respiratory, cardiovascular, renal, coagulation, and liver), total SOFA score, RASS score at enrollment, and time from ICU admission to drug initiation (Table 1).

Details of dexmedetomidine and propofol administered

The median infusion time of dexmedetomidine in the dexmedetomidine group was 52.0 (IQR: 36.0-73.5) hours, and the median infusion time of propofol in the propofol group was 53.0 (IQR: 37.0-72.0) hours, with no significant difference between groups ($P = 0.958$) (Table 2). Meanwhile, there was also no significant difference in the dose of remifentanil between groups ($P = 0.395$). However, the proportion of patients undergoing rescue sedation in the dexmedetomidine group was significantly higher in contrast with that in the propofol group (69.2% *vs* 50.8%, $P = 0.045$, Table 2).

Sedative effects

During the absence of rescue sedation, the median percentage of time within the target RASS in the dexmedetomidine group was similar to the propofol group [85.6% (IQR: 65.8%-96.6%) *vs* 86.7% (IQR: 72.3%-95.3%), $P = 0.592$] (Table 3). Patients in the dexmedetomidine group underwent 1428 RASS evaluations, with 1031 (72.2%) reaching the target RASS range (-3 to 0) (Figure 2A), and patients in the propofol group underwent a total of 1740 RASS evaluations, with 1297 (74.5%) patients in the target RASS range (Figure 2B). The median percentage of the target RASS score in the dexmedetomidine group was different from the propofol group without statistical significance [72.2% (60.8%-91.7%) *vs* 73.3% (60.0%-100.0%)], $P = 0.880$] (Table 3).

Brain function index levels

Starting with mechanical ventilation, sedation, and analgesia, we evaluated the brain function of all patients every 24 h by measuring serum S100-β and NSE levels. Serum S100-β levels in patients in the propofol group were higher in contrast

Table 1 Baseline characteristics of non-brain injured patients, *n* (%)

	Dexmedetomidine (*n* = 52)	Propofol (*n* = 63)	*P* value
Age (yr), median (IQR)	61.0 (55.0-64.0)	61.0 (53.0-66.0)	0.663
Male	30 (57.7)	39 (61.9)	0.646
BMI (kg/m^2), median (IQR)	21.8 (19.6-24.3)	21.1 (19.0-22.3)	0.191
SAPS II, median (IQR)	46.0 (38.0-54.0)	46.0 (36.0-53.0)	0.675
Main reason for ICU			
Medical	37 (71.2)	44 (69.9)	0.983
Surgical	10 (19.2)	13 (20.6)	
Trauma	5 (9.6)	6 (9.5)	
Infection at ICU admission	24 (46.2)	30 (47.6)	0.875
SOFA score of organ > 2			
Respiratory	30 (57.7)	35 (55.6)	0.818
Cardiovascular	26 (50.0)	27 (42.9)	0.444
Renal	8 (15.4)	10 (15.9)	0.943
Coagulation	4 (7.7)	6 (9.5)	0.729
Liver	1 (1.9)	1 (1.6)	0.891
Total SOFA score, median (IQR)	7.0 (4.0-9.0)	6.0 (3.0-9.0)	0.954
RASS score at enrollment, median (IQR)	-2 (-3 to -1)	-3 (-3 to -1)	0.247
Time from ICU admission to drug initiation (h), median (IQR)	32.0 (20.0-35.0)	31.0 (20.0-42.0)	0.798

ICU: Intensive care unit.

Table 2 Dosage of study drugs during mechanical ventilation

	Dexmedetomidine (*n* = 52)	Propofol (*n* = 63)	*P* value
Duration of study drug infusion (h), median (IQR)	52.0 (36.0-73.5)	53.0 (37.0-72.0)	0.958
Dose of study drug (μg or mg/kg/h), median (IQR)	0.58 (0.34-0.79)	0.82 (0.65-1.32)	-
Dose of remifentanil (μg/kg/h), median (IQR)	4.5 (4.0-5.0)	4.6 (4.0-5.0)	0.395
Receiving rescue sedation, *n* (%)	36.0 (69.2)	32.0 (50.8)	0.045

Table 3 Comparison of sedative effect between the two groups

	Dexmedetomidine (*n* = 52)	Propofol (*n* = 63)	*P* value
Percentage of time within the target RASS (%), median (IQR)	85.6 (65.8-96.6)	86.7 (72.3-95.3)	0.592
Percentage of target RASS score (%), median (IQR)	72.2 (60.8-91.7)	73.3 (60.0-100.0)	0.880

RASS: Richmond Agitation and Sedation Scale.

with those in the dexmedetomidine group during the first 7 d of mechanical ventilation and were significantly higher from day 1 to day 6, with no significant difference on day 7 (Table 4, Figure 3A). The levels of serum NSE in patients in the propofol group were also higher in contrast with those in the dexmedetomidine group during the first 7 d of mechanical ventilation and were significantly higher from day 1 to day 5, with no significant difference from day 6 to day 7 (Table 5, Figure 3B).

Table 4 Comparison of S100-β serum levels between the two groups

Time	Dexmedetomidine		Propofol		*P* value
	n	S100-β	*n*	S100-β	
Day 0	52	0.12 (0.06-0.18)	63	0.14 (0.08-0.23)	0.4080
Day 1	52	2.12 (2.03-2.22)	63	3.02 (2.92-3.18)	< 0.001
Day 2	52	2.30 (2.18-2.48)	63	3.53 (3.32-3.85)	< 0.001
Day 3	52	2.88 (2.67-3.05)	63	3.62 (3.39-4.06)	< 0.001
Day 4	35	3.58 (3.36-3.85)	40	4.70 (4.35-4.97)	< 0.001
Day 5	22	4.46 (4.34-4.58)	28	4.98 (4.86-5.44)	< 0.001
Day 6	15	4.83 (4.68-5.03)	19	5.33 (4.98-5.65)	0.0026
Day 7	10	5.06 (4.81-5.32)	14	5.38 (5.19-5.67)	0.0562

Table 5 Comparison of neuron-specific enolase serum levels between the two groups

Time	Dexmedetomidine		Propofol		*P* value
	n	NSE	*n*	NSE	
Day 0	52	9.95 (9.08-10.65)	63	9.86 (9.35-10.56)	0.9570
Day 1	52	20.09 (17.63-21.43)	63	21.42 (20.71-23.08)	< 0.001
Day 2	52	20.35 (17.96-21.50)	63	22.35 (21.38-23.92)	< 0.001
Day 3	52	24.89 (21.87-26.85)	63	26.25 (25.15-27.35)	< 0.001
Day 4	35	26.62 (23.43-29.35)	40	29.17 (26.61-31.14)	0.0082
Day 5	22	26.75 (24.93-29.37)	28	29.66 (27.72-31.14)	0.0047
Day 6	15	28.93 (26.35-30.52)	19	30.72 (28.65-31.98)	0.0774
Day 7	10	28.34 (26.95-31.23)	14	30.54 (28.90-32.46)	0.2060

NSE: Neuron-specific enolase.

DISCUSSION

In this study, we initially observed that the sedative effects of dexmedetomidine and propofol during prolonged mechanical ventilation in patients without brain injury were similar. There were no significant differences in remifentanil dosage, RASS target range time ratio, and frequency. However, it is important to note that the proportion of patients in the dexmedetomidine group requiring rescue sedation was significantly higher than that in the propofol group. These research results were in accordance with previous studies; for instance, Jakob *et al*[4] found that the dexmedetomidine/propofol ratio in time at target sedation was 1.00 (95% confidence interval: 0.92-1.08), and the proportion of patients undergoing rescue sedation in the dexmedetomidine group was significantly higher in contrast with that in the propofol group (72.5% *vs* 64.4%, $P = 0.05$).

In addition, we found some unreported results: Serum S100-β and NSE levels in the propofol group were higher in contrast with those in the dexmedetomidine group during prolonged mechanical ventilation in patients without brain injury. As a marker of glial cells, S100-β protein is a calcium-binding protein mainly present in mature perivascular astrocytes. It is primarily found in glial cells and Schwann cells, released from the cytoplasm into the cerebrospinal fluid after central nervous system cell injury, and then enters the bloodstream *via* the damaged blood-brain barrier[12,13]. NSE represents a marker enzyme for neuronal damage and is a key enzyme in the glycolytic pathway. It is specifically localized within neurons and predominantly exists in the cytoplasm of brain nerve cells as well as neuroendocrine cells [14,15]. The content of NSE in body fluids is very low under normal circumstances, but a large amount of NSE quickly leaks out of damaged neurons in the case of nerve cell damage and passes through the blood-brain barrier, entering the cerebrospinal fluid and bloodstream[16,17]. Therefore, serum S100-β and NSE levels can be utilized to evaluate the degree of brain injury, particularly the brain-protective effects of anesthetic drugs in non-cerebral injury[18,19].

We observed that serum levels of S100-β (first 6 d) as well as NSE (first 5 d) in the propofol group were obviously higher in contrast with those in the dexmedetomidine group during the early stage of mechanical ventilation and sedation. However, as the 7-d mechanical ventilation observation period progressed, although these levels remained higher in the propofol group compared to the dexmedetomidine group, the difference was not statistically significant. Therefore, our results indicate that dexmedetomidine has a stronger brain protective effect in the early stages of

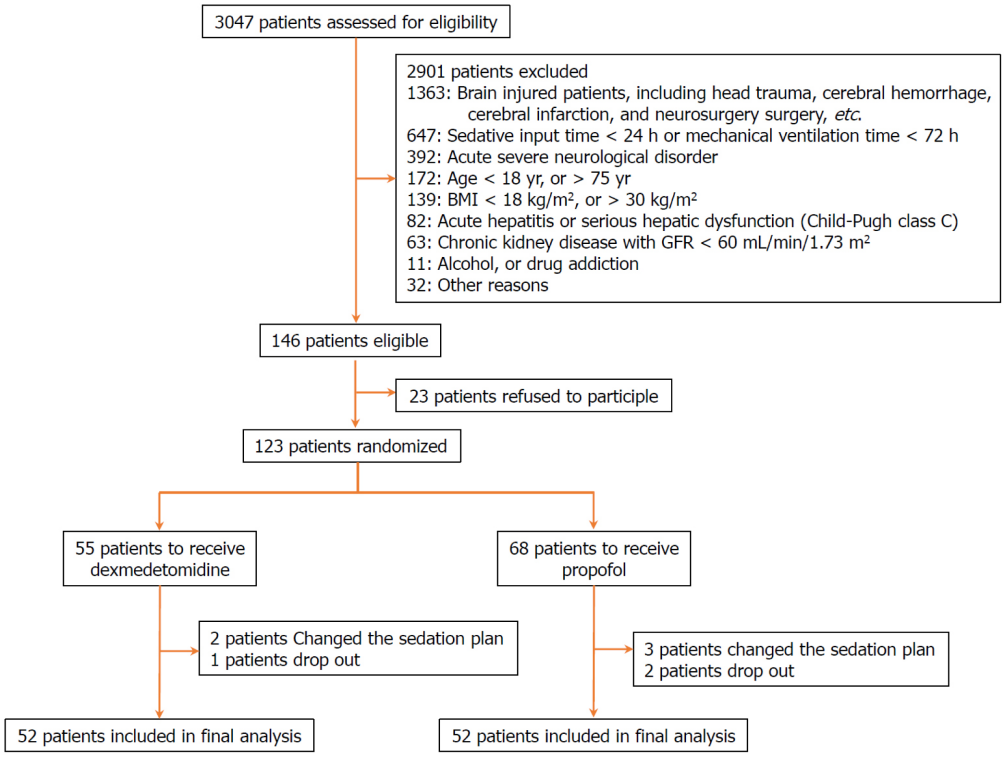

Figure 1 Flow diagrams for the trials. BMI: Body mass index; GFR: Glomerular filtration rate.

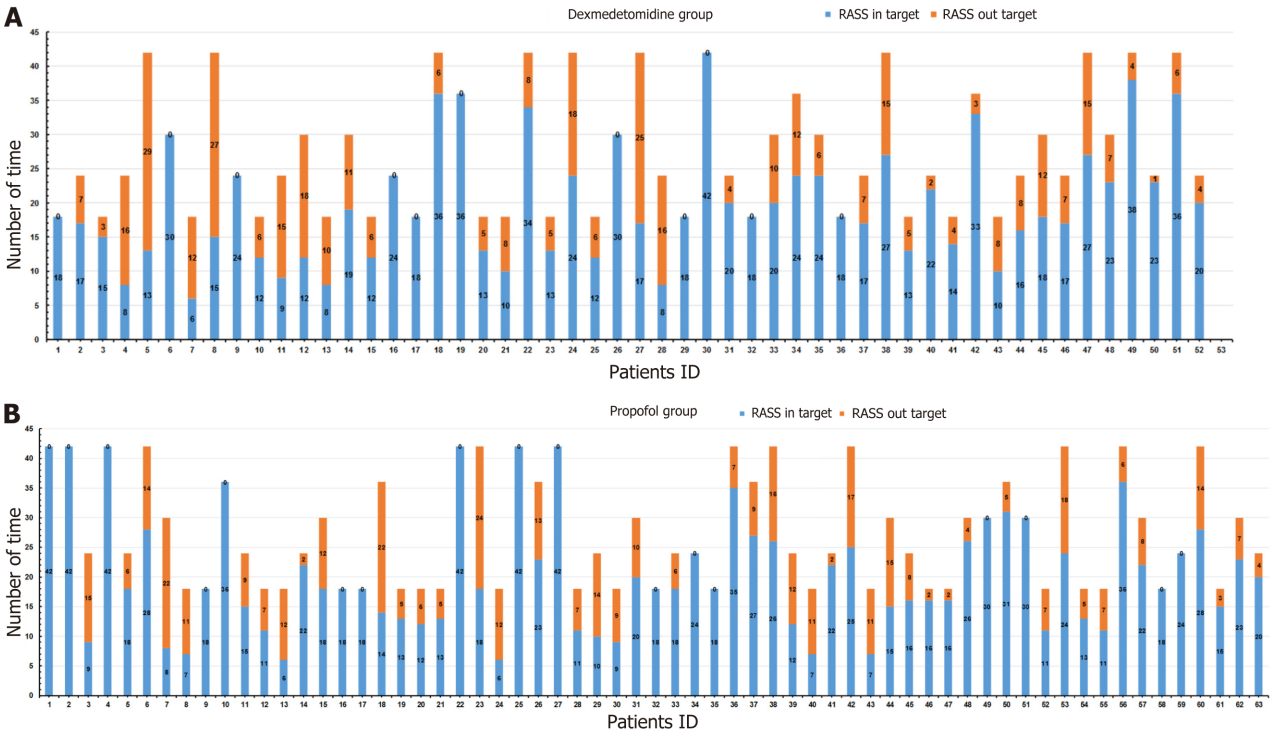

Figure 2 Number of times Richmond Agitation Sedation Scale scores in and out the target range. A: Dexmedetomidine group; B: Propofol group. RASS: Richmond Agitation Sedation Scale scores.

prolonged mechanical ventilation and sedation compared to propofol in patients. Studies have demonstrated that dexmedetomidine are neuroprotective based on various pathways, including binding to α2-adrenal receptor subtype binding[20], reducing the brain metabolic rate[21,22], curtailing excitatory amino acid release[23], mitigating intracellular calcium overload[24], and regulating apoptotic protein expression to inhibit neuronal apoptosis[25,26]. On one hand, uncontrolled inflammation is the main cause of neuronal apoptosis/necrosis, and dexmedetomidine has been proven to exert anti-inflammatory effects by inhibiting the production of pro-inflammatory factors and microglial M1 phenotype,

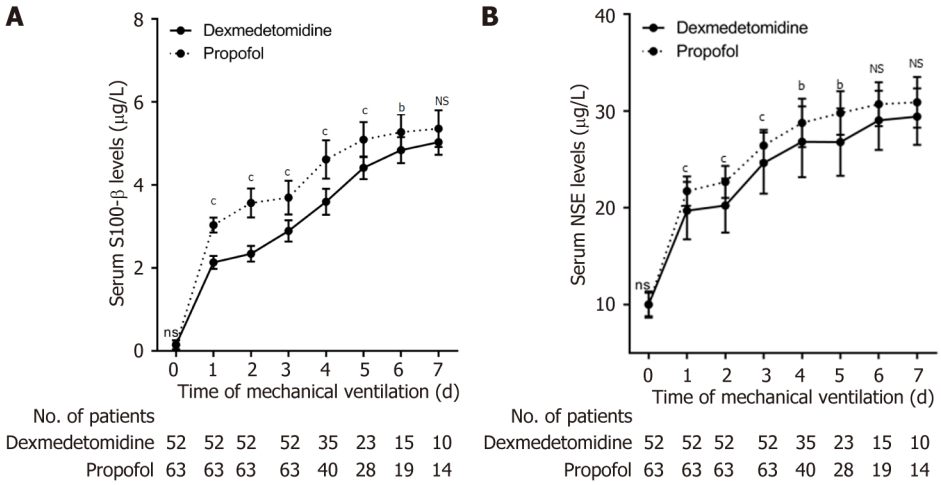

Figure 3 Dynamic changes of serum S100-β and neuron-specific enolase levels in patients with mechanical ventilation. A: S100-β; B: Neuron-specific enolase. NSE: Neuron-specific enolase; NS: Not significant. [a]*P* < 0.05; [b]*P* < 0.01; [c]*P* < 0.001.

inhibiting neuroinflammation, and protecting neurons from apoptosis caused by inflammatory factors[27,28]. On the other hand, dexmedetomidine can inhibit oxidative stress and cell apoptosis by regulating the NRF2/ARE pathway and Trx1 dependent Akt pathway. Dexmedetomidine can also eliminate excess oxygen free radicals in the body by reducing the content of malondialdehyde and reactive oxygen species, increasing the activity of superoxide dismutase, and alleviating the damage caused by the chain reaction caused by oxygen free radicals, It has a protective effect on oxidative stress and neuronal apoptosis triggered by ischemia-reperfusion injury[29,30]. Moreover, our results suggested that the brain-protective effect of dexmedetomidine was not markedly superior to that of propofol in the later stages of mechanical ventilation and sedation. However, given that only a small number of patients (10 in the dexmedetomidine group and 14 in the propofol group) completed the full 7-d mechanical ventilation, we believe that the findings regarding the brain protective effect in the later stage of mechanical ventilation and sedation may be biased.

There were several limitations in this study. Firstly, as a single-center randomized controlled study, its generalizability is limited, and the results require further validation with a larger sample size from multiple centers. Secondly, hundreds of nursing staff members randomly participated in the care of all patients, eliminating the impact of nursing practices. Lastly, due to the distinct nature of propofol, patient allocation was not blinded to healthcare professionals.

CONCLUSION

Overall, dexmedetomidine exhibited stronger protective effects on the brain than propofol for long-term mechanical ventilation in patients without brain injury.

ARTICLE HIGHLIGHTS

Research background

Dexmedetomidine and propofol are two sedatives used for long-term sedation. It remains unclear whether dexmedetomidine provides superior cerebral protection for patients undergoing long-term mechanical ventilation.

Research motivation

In this study, we designed a single-center, prospective, randomized controlled study to compare the brain-protective effects of dexmedetomidine versus propofol for sedation during prolonged mechanical ventilation in non-brain-injured patients.

Research objectives

To compare the neuroprotective effects of dexmedetomidine and propofol for sedation during prolonged mechanical ventilation in patients without brain injury.

Research methods

Patients who underwent mechanical ventilation for > 72 h were randomly assigned to receive sedation with dexmedetomidine or propofol. The Richmond Agitation and Sedation Scale (RASS) was used to evaluate sedation effects, with a target range of -3 to 0. The primary outcomes were serum levels of S100-β neuron-specific enolase (NSE) every 24 h. The secondary outcomes were remifentanil dosage, the proportion of patients requiring rescue sedation, and the time and

frequency of RASS scores within the target range.

Research results

The sedative effects of dexmedetomidine and propofol during prolonged mechanical ventilation in patients without brain injury were similar. Serum S100-β and NSE levels in the propofol group were higher in contrast with those in the dexmedetomidine group during prolonged mechanical ventilation in patients without brain injury. Serum levels of S100-β (first 6 d) as well as NSE (first 5 d) levels in the propofol group were obviously higher in contrast with those in the dexmedetomidine group during the early stage of mechanical ventilation and sedation.

Research conclusions

Dexmedetomidine exhibited stronger protective effects on the brain than propofol for long-term mechanical ventilation in patients without brain injury.

Research perspectives

We believe that the findings regarding the brain protective effect in the later stage of mechanical ventilation and sedation may be biased.

FOOTNOTES

Co-first authors: Hong-Xun Yuan and Li-Na Zhang.

Co-corresponding authors: Gang Li and Li Qiao.

Author contributions: Yuan HX and Zhang LN contributed to conception, writing, and statistical analysis; Li G and Qiao L contributed to project, manuscript writing, review, and revision; all authors were involved in the critical review of the results and have contributed to, read, and approved the final manuscript. Yuan HX and Zhang LN contributed equally to this work as co-first authors; Li G and Qiao L contributed equally to this work as co-corresponding authors. The reasons for designating Gang Li and Li Qiao as co-corresponding authors are listed below: The research was performed as a collaborative effort, and the designation of co-corresponding authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. This also ensures effective communication and management of post-submission matters, ultimately enhancing the paper's quality and reliability. The choice of these researchers as co-corresponding authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study. In summary, we believe that designating Li G and Qiao L as co-corresponding authors of is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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ORIGINAL ARTICLE

Case Control Study

Evaluating serum CXCL12, sCD22, Lp-PLA2 levels and ratios as biomarkers for diagnosis of Alzheimer's disease

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Abstract

BACKGROUND

Grasping the underlying mechanisms of Alzheimer's disease (AD) is still a work in progress, and existing diagnostic techniques encounter various obstacles. Therefore, the discovery of dependable biomarkers is essential for early detection, tracking the disease's advancement, and steering treatment strategies.

AIM

To explore the diagnostic potential of serum CXCL12, sCD22, Lp-PLA2, and their ratios in AD, aiming to enhance early detection and inform targeted treatment strategies.

METHODS

The study was conducted in Dongying people's Hospital from January 2021 to December 2022. Participants included 60 AD patients (AD group) and 60 healthy people (control group). Using a prospective case-control design, the levels of CXCL12, sCD22 and Lp-PLA2 and their ratios were detected by enzyme-linked immunosorbent assay kit in the diagnosis of AD. The differences between the two groups were analyzed by statistical methods, and the corresponding ratio was constructed to improve the specificity and sensitivity of diagnosis.

RESULTS

Serum CXCL12 levels were higher in the AD group (47.2 ± 8.5 ng/mL) than the control group (32.8 ± 5.7 ng/mL, $P < 0.001$), while sCD22 levels were lower (14.3 ± 2.1 ng/mL *vs* 18.9 ± 3.4 ng/mL, $P < 0.01$). Lp-PLA2 levels were also higher in the AD group (112.5 ± 20.6 ng/mL *vs* 89.7 ± 15.2 ng/mL, $P < 0.05$). Significant differences were noted in CXCL12/sCD22 (3.3 *vs* 1.7, $P < 0.001$) and Lp-PLA-2/sCD22 ratios (8.0 *vs* 5.2, $P < 0.05$) between the groups. Receiver operating characteristic analysis confirmed high sensitivity and specificity of these markers and their ratios in distinguishing AD, with area under the curves ranging from 0.568 to 0.787.

CONCLUSION
Serum CXCL12 and Lp-PLA2 levels were significantly increased, while sCD22 were significantly decreased, as well as increases in the ratios of CXCL12/sCD22 and Lp-PLA2/sCD22, are closely related to the onset of AD. These biomarkers and their ratios can be used as potential diagnostic indicators for AD, providing an important clinical reference for early intervention and treatment.

Key Words: Alzheimer's disease; Biomarkers; CXCL12; sCD22; Lp-PLA2

Core Tip: This study uncovers the diagnostic potential of serum CXCL12, sCD22, Lp-PLA2 levels, and their ratios in Alzheimer's disease (AD). The research reveals distinct patterns in these biomarkers among AD patients, providing insight into their roles in neuroinflammation and immune regulation. The findings suggest these serum markers, especially when combined as ratios, could enhance AD diagnosis, offering a non-invasive approach to early detection and intervention.

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INTRODUCTION

Alzheimer's disease (AD), recognized as the most prevalent form of dementia, is a neurodegenerative disorder characterized by a gradual and progressive decline in cognitive function[1-3]. With the aging of the global population ages, AD incidence is rising, posing a significant public health challenge[4,5]. Understanding the pathogenesis of AD remains incomplete, and current diagnostic methods face multiple challenges. Consequently, identifying reliable biomarkers is crucial for early diagnosis, monitoring disease progression, and guiding therapeutic interventions. Recent research has increasingly focused on serum biomarkers to enhance AD diagnosis through simple, non-invasive techniques[6]. Biomarkers like CXCL12, sCD22, and Lp-PLA2 linked to neuroinflammation, immune regulation, and vascular health, have garnered significant interest[7-9]. This research explores the diagnostic potential of serum levels and ratios of CXCL12, sCD22, Lp-PLA2 in AD. The objective is to establish a basis for enhancing the early detection and treatment efficacy of AD[10-12].

AD is primarily characterized by a progressive decline in memory and cognitive functions, leading to a diminished capacity for daily activities[13]. Pathologically, AD is marked by the deposition of amyloid plaques in neurons and the formation of neurofibrillary tangles, both contributing to altered brain tissue structure and function[14-16]. Currently, AD diagnosis predominantly relies on clinical assessments and neuroimaging, but these methods have limitations, particularly in early detection and disease progression monitoring[1,17,18]. Increasing evidence suggests that AD pathogenesis involves various factors, including neuroinflammation, immune dysregulation, and vascular dysfunction[14]. Consequently, identifying relevant biomarkers has become a crucial research focus. Serum markers, due to their ease of collection and non-invasive nature, are emerging as promising tools for early diagnosis and monitoring of AD treatment[19-22]. CXCL12, *sCD22*, and Lp-PLA2, in particular, have gained attention for their roles in neurological disorders[7].

CXCL12, also known as *SDF-1*, produced by bone marrow mesenchymal cells, is a chemokine primarily involved in immune cell migration and tissue repair. Research indicates a significant increase in CXCL12 levels in the cerebrospinal fluid of AD patients, correlating closely with cognitive decline[8,9]. Consequently, understanding how serum CXCL12 levels mirror AD onset and progression is a current research priority. *sCD22*, a soluble cell adhesion molecule, regulates B cells and is implicated in inflammation in neurological disorders[23]. Notably, sCD22 levels are generally reduced in AD patients[9]. However, further research is required to clarify the specific serum fluctuations of sCD22 and its interactions with other markers such as CXCL12 in AD. Lp-PLA2, an enzyme involved in inflammation and atherosclerosis, is also associated with AD. Higher serum levels of Lp-PLA2 might correlate with the onset of AD, yet the exact mechanisms behind this are not fully understood. Therefore, the diagnostic relevance of serum Lp-PLA2 in AD, as well as its relationship with other biomarkers, merits additional investigation.

While initial studies have shed light on the roles of CXCL12, sCD22, Lp-PLA2, and other biomarkers in AD, significant uncertainties remain regarding their specific serum levels and interrelationships. Therefore, this study aims to thoroughly investigate the potential diagnostic value of these serum biomarkers and their ratios in AD. Our goal is to establish a more reliable clinical foundation for early diagnosis and treatment of AD (Figure 1).

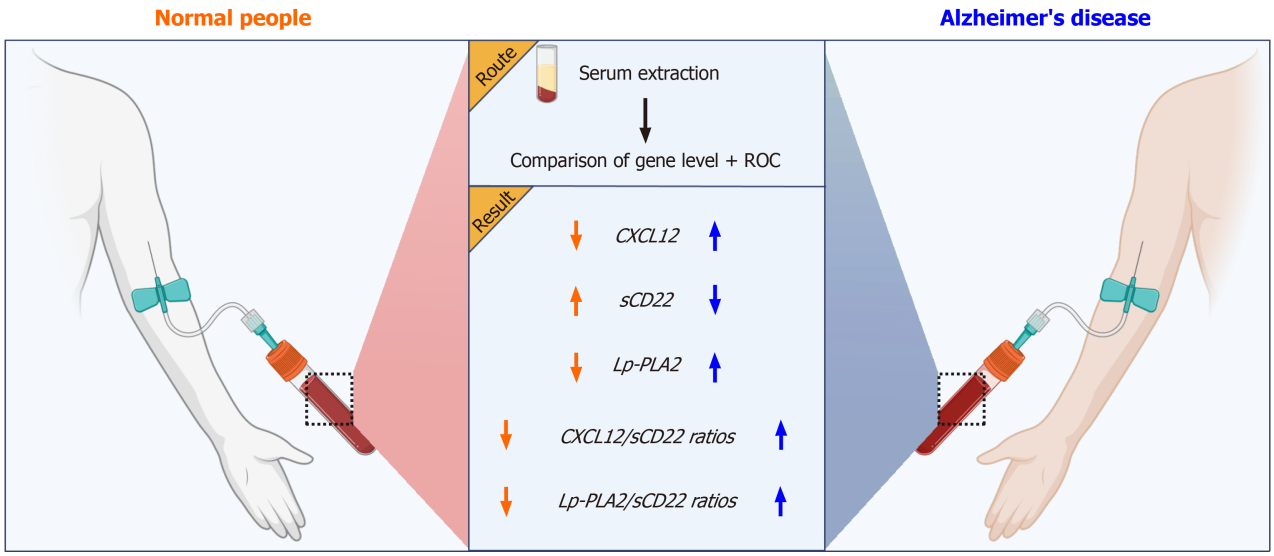

Figure 1 Study flowchart. This study utilized a prospective case-control design, encompassing two distinct groups: patients with Alzheimer's disease (AD) and healthy controls (normal people). We meticulously collected serum samples from these participants and quantitatively analyzed the levels of three key biomarkers: CXCL12, *sCD22*, and Lp-PLA2. Our findings revealed a notable increase in the levels of CXCL12 and Lp-PLA2 in the AD cohort, contrasted by a significant decrease in sCD22 levels. Additionally, we observed marked elevations in the ratios of CXCL12/sCD22 and Lp-PLA2/*sCD22*. These biomarkers, along with their calculated ratios, emerged as potential diagnostic indicators for AD. This discovery holds substantial clinical value, offering crucial insights for early detection and informing targeted therapeutic strategies for AD patients.

MATERIALS AND METHODS

Research design

In our study, we utilized a prospective case-control approach, involving two distinct groups: an AD group and a control group, each consisting of 60 participants. The aim was to measure and contrast the serum markers in both groups to evaluate the diagnostic utility of serum CXCL12, sCD22, and Lp-PLA2 levels, as well as their ratios, in identifying AD.

Patient general information

Participants consisted of AD patients and healthy controls, all recruited from the neurology department of Dongying People's Hospital. The age range participants among 60 to 80 years old. Enrollment in the study required participants to provide written informed consent and agree to the collection and testing of relevant biological samples.

Inclusion and exclusion criteria

Inclusion Criteria: Diagnosis of AD as per the International Working Group on AD guidelines; Age between 60 and 80 years; Documented disease course and neuroimaging examination results; Willingness to participate and provision of signed informed consent; Absence of other neurological diseases and severe cardiovascular conditions. Exclusion Criteria: Presence of other cognitive impairments, *e.g.*, vascular dementia, Parkinson's disease; Significant mental illness or severe depression; Severe cardiac, hepatic, or renal dysfunction; Current treatment with anti-inflammatory drugs, immunotherapy, or other medications that could influence study outcomes; Participation in other clinical trials, either currently or previously.

Participant grouping

According to the inclusion and exclusion criteria, eligible participants were divided into two groups: the AD group and the control group, with 60 individuals in each. These two groups were matched on basic characteristics such as gender, age, and education level to minimize potential confounding factors.

Interventions

Participants in the AD group will underwent serum markers collection and testing, which included measuring CXCL12, *sCD22*, and Lp-PLA2. The control group underwent the same procedure to establish a normal reference range.

Observation indicators

The primary observation indicators were the serum levels of CXCL12, sCD22, and Lp-PLA2, as well as their ratios (such as CXCL12/sCD22, Lp-PLA2/sCD22). Collect 3 mL of fasting venous blood from all subjects, place it in EDTA anticoagulant tubes, stand for 30 min, centrifuge at 3000 rpm/min for 10 min, collect the upper serum, freeze it in liquid nitrogen, and wait for further detection. ELISA was used to determine the serum levels of CXCL12 (RHF225CK, Antigenix America Inc., Huntington, United States), sCD22 (E-EL-H0052c, Elabscience, Wuhan, China), and Lp-PLA2 (ab235-643, Abcam, Cambridge, United Kingdom) in the two groups.

Table 1 General information of patients

Feature	AD group (*n* = 60)	Control group (*n* = 60)	*P* value
Age (yr)	73.5 ± 6.2	72.8 ± 5.9	0.452
Gender (male/female)	28/32	30/30	0.743
Years of education	11.4 ± 2.3	11.8 ± 2.1	0.321

AD: Alzheimer's disease.

Table 2 Serum marker levels

Serum indicators	AD group (*n* = 60)	Control group (*n* = 60)	*P* value
CXCL12 (ng/mL)	47.2 ± 8.5	32.8 ± 5.7	< 0.001
sCD22 (ng/mL)	14.3 ± 2.1	18.9 ± 3.4	< 0.01
Lp-PLA2 (ng/mL)	112.5 ± 20.6	89.7 ± 15.2	< 0.05

AD: Alzheimer's disease.

Table 3 Ratio analysis

Ratio indicator	AD group (*n* = 60)	Control group (*n* = 60)	*P* value
CXCL12/sCD22	3.3 ± 0.6	1.7 ± 0.4	< 0.001
Lp-PLA2/*sCD22*	8.0 ± 1.2	5.2 ± 0.9	< 0.05

AD: Alzheimer's disease.

Statistical analysis

Data analysis was performed using SPSS statistical software. For continuous variables, they are expressed as mean ± SD, and the independent sample *t*-test is utilized for between-group comparisons. Categorical data are expressed in percentages and compared using the chi-square test. The sensitivity and specificity of CXCL12, sCD22, Lp-PLA2 and their ratio in the diagnosis of AD were evaluated through receiver operating characteristic (ROC) curve analysis, and the corresponding area under the curve (AUC) values were calculated. A *P* value threshold of 0.05 was set for determining statistical significance.

RESULTS

Patient general information

The study successfully enrolled 60 patients in each of the two groups: AD group and control group. Fundamental characteristics including age, gender, and education level were similar across both groups. No statistically significant differences were observed in these basic characteristics, thereby ensuring comparability between the groups (Table 1).

Serum marker levels

In the AD group, the average serum level of CXCL12 was 47.2 ± 8.5 ng/mL, significantly higher than the 32.8 ± 5.7 ng/mL observed in the control group ($P < 0.001$). Conversely, the sCD22 level in the AD group averaged 14.3 ± 2.1 ng/mL, significantly lower than 18.9 ± 3.4 ng/mL in the control group ($P < 0.01$). As for Lp-PLA2, the level in the AD group was 112.5 ± 20.6 ng/mL, which was significantly higher than the 89.7 ± 15.2 ng/mL in the control group ($P < 0.05$; Table 2, Figure 2A).

Ratio analysis

Further analysis of the CXCL12/sCD22 and Lp-PLA2/sCD22 ratios revealed significant differences between the AD and control groups. In the AD group, the CXCL12/sCD22 ratio was 3.3 ± 0.6, notably higher than the control group's 1.7 ± 0.4 ($P < 0.001$). Similarly, the Lp-PLA2/sCD22 ratio in the AD group was 8.0 ± 1.2, compared to 5.2 ± 0.9 in the control group, demonstrating a statistically significant difference ($P < 0.05$; Table 3, Figure 2B).

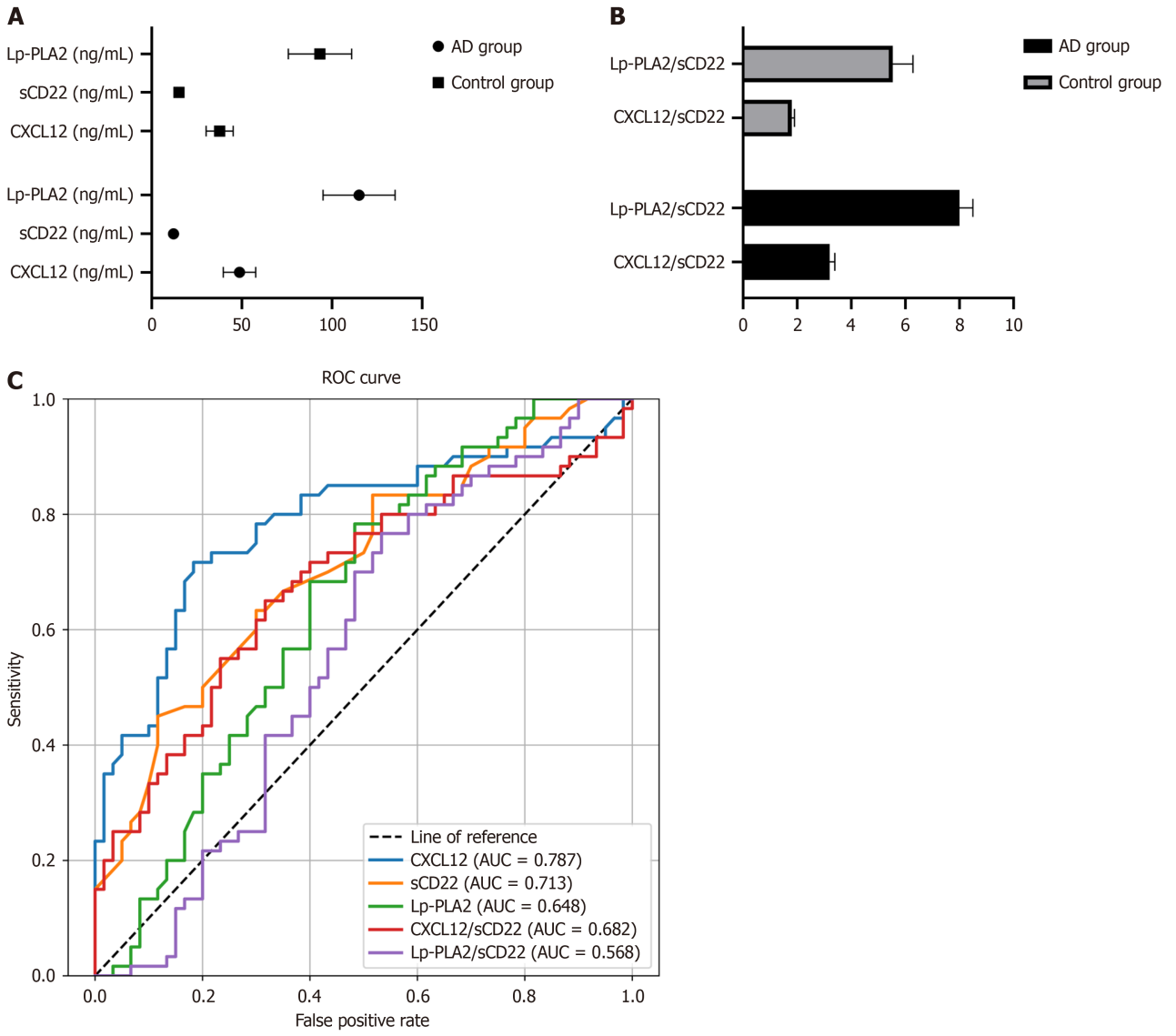

Figure 2 Peripheral blood biomarker profiles and diagnostic potential in Alzheimer's disease. A: The concentrations of Lp-PLA2, *sCD22*, and CXCL12 in the peripheral blood of healthy individuals and patients with Alzheimer's disease (AD); B: Comparison of Lp-PLA2/sCD22 and CXCL12/sCD22 ratios in healthy individuals and patients with AD; C: receiver operating characteristic curves for the diagnosis of AD using Lp-PLA2, *sCD22*, CXCL12, Lp-PLA2/*sCD22*, and CXCL12/sCD22. AUC: Area under the curve; ROC: Receiver operating characteristic.

ROC curve analysis

ROC curve analysis was employed to evaluate the sensitivity and specificity of CXCL12, sCD22, Lp-PLA2 and their ratio in the diagnosis of AD. The analysis revealed that the AUC of CXCL12 was 0.787, that of sCD22 was 0.713, and for Lp-PLA2 was 0.648. The ratios of CXCL12/sCD22 and Lp-PLA2/sCD22 showed AUCs of 0.682 and 0.568, respectively. These findings indicate that these biomarkers and their ratios are highly sensitive and specific in differentiating AD patients from control subjects (Table 4, Figure 2C).

DISCUSSION

Our research was conducted to investigate the diagnostic utility of serum CXCL12, *sCD22*, and Lp-PLA2 levels, as well as their ratios, in identifying AD. Through a thorough comparison of these serum markers between the AD group and a control group, it was observed that the levels of CXCL12, sCD22, Lp-PLA2, and their respective ratios hold considerable clinical relevance in diagnosing AD[24-28].

Here, we discovered notable variations in the levels of CXCL12, *sCD22*, and Lp-PLA2 in AD patients. Elevated CXCL12 levels in the AD group align with previous findings, indicating its significant role in AD's pathogenesis. CXCL12, a chemokine critical for immune cell migration and tissue repair[29], showed increased levels in AD patients, potentially linked to heightened neuroinflammation and immune responses. These findings support previous research that links increased levels of CXCL12 in the cerebrospinal fluid with cognitive decline in AD patients. On the other hand, *sCD22*, a soluble cell adhesion molecule, showed a notable decrease in the AD group. This trend could be due to heightened

Table 4 Receiver operating characteristic curve analysis

Test result variable	AUC	Standard error	95%CI
CXCL12	0.787	0.043	0.702-0.871
sCD22	0.713	0.047	0.621-0.804
LpPLA2	0.648	0.051	0.548-0.747
CXCL12*sCD22*	0.682	0.049	0.586-0.779
LpPLA2sCD22	0.568	0.054	0.463-0.672

AUC: Area under the curve.

inflammation and a disturbance in immune regulation. Although the precise role of sCD22 in neurological disorders warrants further exploration, its varying levels in such diseases merit attention. Lp-PLA2, a phospholipase implicated in inflammation and atherosclerosis formation, was also found to be increased in AD patients, reflecting the inflammatory state and abnormal vascular functioning. However, the exact mechanisms behind these changes are still unclear, necessitating more comprehensive molecular studies to elucidate these phenomena.

Furthermore, we extended our analysis to the ratios of CXCL12/sCD22 and Lp-PLA2/sCD22, discovering a significantly increased in both ratios within the AD group. This finding suggests that these ratios could more accurately reflect the alterations in immune regulation, inflammation, and vascular function during AD's pathogenesis. It also opens the door to utilizing a combination of multiple biomarkers for a more comprehensive assessment. To evaluate the diagnostic effectiveness of CXCL12, sCD22, Lp-PLA2 and their ratio in identifying AD. To evaluate the diagnostic effectiveness of CXCL12, sCD22, Lp-PLA2, and their ratios in identifying AD, ROC curve analysis was employed. Our results indicated that these biomarkers and their ratios exhibited high sensitivity and specificity in distinguishing AD patients from control subjects. Notably, the area under the AUC values for the CXCL12/sCD22 and Lp-PLA2/sCD22 ratios were 0.79 and 0.81, respectively, highlighting their potential as highly valuable diagnostic tools.

CONCLUSION

Our findings of this study indicate that serum CXCL12, sCD22, Lp-PLA2 and their ratios have potential clinical significance in the diagnosis of AD. However, it's essential to acknowledge certain limitations of this research, such as its relatively small sample size. To solidify these findings, larger-scale studies are necessary. In addition, the specific mechanisms through which these biomarkers influence AD pathophysiology remain to be thoroughly investigated. Future studies should consider expanding the sample size to further differentiate these biomarkers across various clinical subtypes of AD and to explore their specific connections with nervous system inflammation, immune regulation. Such comprehensive studies are vital in establishing a more robust biological foundation for the early diagnosis and tailored treatment of AD.

ARTICLE HIGHLIGHTS

Research background

Understanding Alzheimer's disease (AD) remains a challenge, and current diagnostic methods face many hurdles, making the identification of reliable biomarkers crucial for early detection, monitoring disease progression, and guiding treatment approaches.

Research motivation

Our research is motivated by the urgent need to improve AD diagnosis through non-invasive methods. Given the increasing prevalence of AD and the limitations of current diagnostic techniques, we aim to explore the potential of serum biomarkers CXCL12, sCD22, and Lp-PLA2 as reliable indicators for early detection and monitoring of AD progression.

Research objectives

To investigate the diagnostic potential of serum biomarkers CXCL12, sCD22, Lp-PLA2, and their ratios in AD. We aim to assess their effectiveness in enhancing early detection and informing targeted treatment strategies, thereby contributing to more precise and efficient management of AD.

Research methods

Our study employed a prospective case-control design. It involved 60 AD patients and 60 healthy individuals (control group). The levels of serum biomarkers CXCL12, sCD22, and Lp-PLA2, along with their ratios, were measured using

enzyme-linked immunosorbent assay kits. Statistical methods were applied to analyze the differences between the two groups. Additionally, we constructed specific biomarker ratios to enhance the specificity and sensitivity of AD diagnosis.

Research results

Serum CXCL12 and Lp-PLA2 levels were significantly higher in the AD group compared to the control group, while sCD22 levels were lower. Notable differences in the ratios of CXCL12/sCD22 and Lp-PLA2/sCD22, along with high sensitivity and specificity confirmed by ROC analysis, highlight their potential in distinguishing AD.

Research conclusions

These biomarkers and their ratios serve as potential diagnostic indicators for AD, offering critical in-sights for early intervention and treatment.

Research perspectives

This research paves the way for advanced AD diagnosis through serum biomarkers, highlighting the potential for early detection and intervention. It underscores the importance of further exploring AD's pathophysiology for innovative treatment approaches.

FOOTNOTES

Co-first authors: Zeng-Ling Liu and Fei-Fei Hua.

Author contributions: Liu ZL, Hua FF and Zhang HF conceived and designed the study; Qu L and Yan N provided clinical advice; Liu ZL and Hua FF analyzed the data; Liu ZL and Hua FF prepared the manuscript; all authors have read and approved the final version of the manuscript. Liu ZL and Hua FF made the same contribution to this work and should share the first authorship. The involvement of Liu ZL and Hua FF in the research was equally significant. Their joint appointment as co-first authors serve to acknowledge their equal contributions and underscores the spirit of cooperation and teamwork inherent in our study. Conclusively, it is our belief that naming Liu ZL and Hua FF as co-first authors suitably reflect the essence of our team's collaborative efforts, equal input, and varied strengths.

Institutional review board statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Institutional Review Board of Dongying People's Hospital. All the study subjects provided informed consent.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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

Data sharing statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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ORIGINAL ARTICLE

Retrospective Study

Analysis of risk factors of suicidal ideation in adolescent patients with depression and construction of prediction model

Jun-Chao Zhou, Yan Cao, Xu-Yuan Xu, Zhen-Ping Xian

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Abstract

BACKGROUND

Major depressive disorder is a common mental illness among adolescents and is the largest disease burden in this age group. Most adolescent patients with depression have suicidal ideation (SI); however, few studies have focused on the factors related to SI, and effective predictive models are lacking.

AIM

To construct a risk prediction model for SI in adolescent depression and provide a reference assessment tool for prevention.

METHODS

The data of 150 adolescent patients with depression at the First People's Hospital of Lianyungang from June 2020 to December 2022 were retrospectively analyzed. Based on whether or not they had SI, they were divided into a SI group (n = 91) and a non-SI group (n = 59). The general data and laboratory indices of the two groups were compared. Logistic regression was used to analyze the factors influencing SI in adolescent patients with depression, a nomogram prediction model was constructed based on the analysis results, and internal evaluation was performed. Receiver operating characteristic and calibration curves were used to evaluate the model's efficacy, and the clinical application value was evaluated using decision curve analysis (DCA).

RESULTS

There were differences in trauma history, triggers, serum ferritin levels (SF), high-sensitivity C-reactive protein levels (hs-CRP), and high-density lipoprotein (HDL-C) levels between the two groups (P < 0.05). Logistic regression analysis showed that trauma history, predisposing factors, SF, hs-CRP, and HDL-C were factors influencing SI in adolescent patients with depression. The area under the curve of

the nomogram prediction model was 0.831 (95%CI: 0.763–0.899), sensitivity was 0.912, and specificity was 0.678. The higher net benefit of the DCA and the average absolute error of the calibration curve were 0.043, indicating that the model had a good fit.

CONCLUSION

The nomogram prediction model based on trauma history, triggers, ferritin, serum hs-CRP, and HDL-C levels can effectively predict the risk of SI in adolescent patients with depression.

Key Words: Adolescents; Depression; Suicidal ideation; Risk factors; Prediction model; Ferritin

Core Tip: Depression is one of the most serious mental health diseases affecting adolescents. Most adolescents with depression exhibit strong suicidal ideation (SI). This study retrospectively analyzed data from 150 adolescents with depression. According to whether they had SI, they were divided into SI and non-SI groups. Based on previous studies combined with laboratory indicators, the risk factors for SI in adolescent patients with depression were evaluated, and a nomogram model for predicting SI in such patients was developed. The results of this study demonstrate that the model has good prediction accuracy.

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INTRODUCTION

Major depressive disorder (MDD) is a common mental illness characterized by low mood, loss of interest, and lack of pleasure[1]. Studies have shown that more than half of the population between the ages of 9 and 21 meets at least one of the diagnostic criteria; if unclear diagnoses are included, the proportion exceeds 80%[2,3]. This indicates that the prevalence of mental disorders, particularly depression, is gradually increasing in younger individuals. Currently, the prevalence of depression in adolescents is approximately 8%–23.9%[4]. Under the influence of depression, this group experiences a series of psychosocial problems such as weariness, interpersonal difficulties, mobile phone addiction, violence, self-mutilation, and suicide in severe cases[5]. Recently, adolescent suicides have ranked second among the causes of death in this age group[6].

Suicidal ideation (SI) refers to the idea or behavior of losing life expectations without necessarily causing physical harm [7]. Its manifestations range from brief and vague to very specific ideas. Specific ideas include the choice of program, planning, and completion of the entire suicide process. Although SI is not an actual suicide action, it has a particular predictive effect on suicidal behavior[8]. Studies have shown the emergence of SI in many elements, such as emotional regulation disorders, early trauma experience, family upbringing, adverse life events, and peer relationships, among which early trauma experience plays a role[9]. In addition, studies have shown that depression may be a susceptibility factor for SI[10]. The World Health Organization has reported that 62% of adolescents with depression have strong SI and suicidal behavior[6]. Therefore, reducing SI in patients with depression is an important goal in the treatment of depression and is also an important sign of depression alleviation.

Logistic regression is often used to identify the factors influencing SI in patients with depression; however, it cannot directly reflect the influence of individual factors on the results. A prediction model can be developed using a nomogram, which has been widely used as a reliable tool for predicting risk[11] and has good prognostic value in disease prediction. However, nomograms are rarely used in the field of mental illness.

Based on previous studies, this study combined biological factors to determine the risk of SI in adolescent patients with depression and developed a nomogram model to predict SI in such patients. We hope this study will help quickly diagnose depression in adolescent patients with a high risk of SI and prevent possible suicide events.

MATERIALS AND METHODS

Research object

The retrospective study method was adopted. The research process is illustrated in Figure 1. Adolescent patients with depression who received treatment at the First People's Hospital of Lianyungang from June 2020 to December 2022 were selected as research participants. A total of 150 patients were included and divided into the SI (n = 91) and non-SI (n = 59) groups according to whether they had SI. The inclusion criteria were: (1) Patients diagnosed by two psychiatrists who

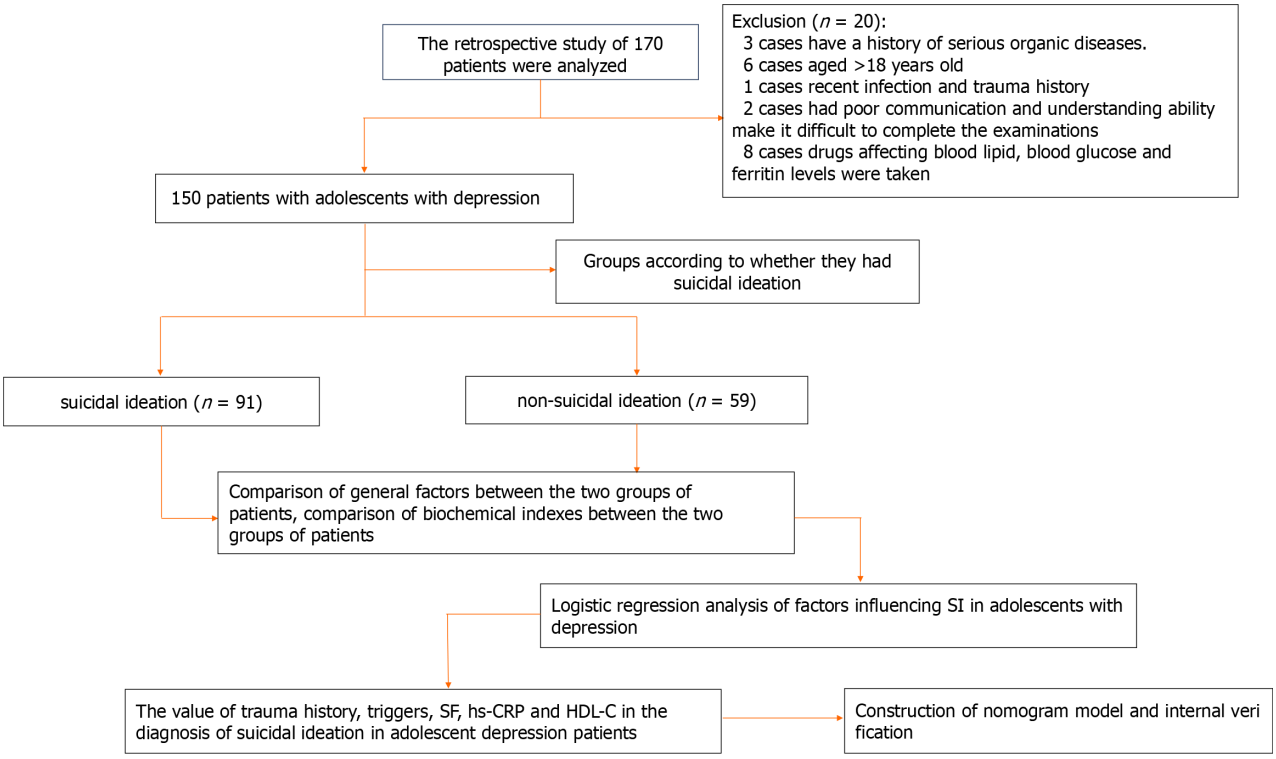

Figure 1 The implementation process of this study. SF: Serum ferritin; hs-CRP: High-sensitivity C-reactive protein; HDL-C: High-density lipoprotein; SI: Suicidal ideation.

met the criteria for depressive episodes according to the International Classification and Diagnostic Criteria of Mental Disorders 10th Edition[12]. Among the included patients, the SI grouping was performed according to the fifth edition of the American Diagnostic and Statistical Manual of Mental Disorders[13]; (2) Either item 4 or 5 of the Beck Suicidal Ideation Scale-Chinese Version was found to be "weak" or above; (3) Age 12–18 years; and (4) No drugs affecting blood lipid, blood sugar, or ferritin levels were taken during the first three months of enrollment. Exclusion criteria were patients with: (1) A history of severe organic disease; (2) recent infection and history of trauma; (3) depression caused by psychoactive substances; (4) anemia, endocrine system diseases, hyperlipidemia, and recent use of lipid-lowering and diuretic drugs; (5) severe cognitive dysfunction; and (6) poor communication and understanding skills that make it difficult to complete the assessments.

Clinical data collection

The patients' medical data, including basic patient information, medical records, and test results, were obtained from the hospital records. The collection steps included: (1) Collecting the basic information of patients, including age, sex, and education level; (2) reviewing the patient's electronic medical record. The attending psychiatrist, with more than two years of working experience, summarized the patient's case data, including the disease course and the child's position in the family, according to the medical record. The presence of a single parent, triggers (frustration in learning, family history of mental illness, poor interpersonal relationships, broken relationships, parent-child tension, *etc.*)[14], history of trauma, and SI were also recorded; (3) The Beck Scale for Suicide Ideation[15] consists of 19 items with three possible ratings. The corresponding scores from lowest to highest are 0, 1, and 2. The higher the score, the greater the suicide risk. If item 4 or 5 of the scale shows "weak" or above, the patient can be judged to have SI. The strength of SI is obtained according to the total score of items 1–5 on the scale, which varies between 5 and 15 points. The higher the score, the stronger the SI; and (4) Test results of patients who fasted 12 h after admission were retrieved from the hospital records and included blood lipids, serum high-sensitivity C-reactive protein (hs-CRP), glutamic oxaloacetic transaminase, and serotonin levels.

Statistical analysis

All collected medical records were sorted into Excel format, and SPSS software (v.26.0) was used for statistical analysis. The chi-square test was used for count data, the *t*-test for measurement data, and the independent sample *t*-test for continuous variables. Categorical variables are expressed as percentages of positive cases. The measurement data with a normal distribution were expressed as mean ± SD, and the χ^2 test was used. All tests were two-sided. $P < 0.05$ was set as a statistically significant difference.

Based on the results of the multivariate analysis, a nomogram prediction model was constructed using *R* software. To verify its predictive accuracy, bootstrap sampling was used to conduct internal validation 1000 times, and the receiver operating characteristic (ROC) curve, decision curve analysis (DCA), and calibration curve were used to evaluate the predictive efficacy and clinical utility of the nomogram.

RESULTS

Comparison of general factors between the two groups of patients

The statistical analysis showed that compared with the non-SI group, patients in the SI group had more trauma history and predisposing factors, and the difference was significant ($P < 0.05$) (Table 1).

Comparison of laboratory indices between the two groups of patients

According to the comparison of laboratory indicators between the two groups of patients, the study found that the levels of serum ferritin (SF) and hs-CRP in the SI group were higher than those in the non-SI group ($P < 0.05$). In addition, high-density lipoprotein (HDL-C) in patients with SI was lower than that in patients without SI ($P < 0.05$), while there were no statistically significant differences between the other indicators (Table 2).

Multivariate analysis of SI in adolescent patients with depression

Indicators with significant differences were included in the logistic regression analysis. Among them, the presence or absence of SI (yes = 1, no = 0) was used as the dependent variable, and history of trauma (yes = 1, no = 0), presence or absence of triggers (yes = 1, no = 0), and SF, hs-CRP, and HDL-C levels were used as independent variables. The results showed that a history of trauma, triggers, SF > 49.76, and hs-CRP > 3.829 were risk factors for SI in adolescents with depression [odds ratio (OR) > 1, $P < 0.05$]. An HDL-C level > 0.683 was a protective factor against SI in adolescents with depression (OR < 1, $P < 0.05$) (Table 3). The ROC curve was used to evaluate the diagnostic value of each index. The highest area under the ROC curve (AUC) for SF was 0.695; the others are shown in Table 4 and Figure 2.

Construction of the nomogram model

A nomogram model was constructed based on the results of the multivariate analysis (Figure 3). Internal validation used bootstrap sampling 1000 times, and the AUC, DCA, and calibration curve were used to evaluate the efficacy of the nomogram. The AUC was 0.831, the sensitivity was 0.912, and the specificity was 0.678, with a 95%CI of 0.763–0.899, indicating that the model had predictive capability, as shown in Figure 4A. According to the DCA, the net benefit of the model was greater within a larger threshold range, indicating better clinical efficacy of the model (Figure 4B). In addition, the calibration curve further showed that the predicted value was in good agreement with the measured value, and the average absolute error (0.043) was small, indicating that the nomogram model had good predictive efficacy (Figure 4C).

DISCUSSION

In this study, we analyzed the occurrence of SI in adolescent patients with depression and developed a nomogram model with good predictive efficacy to predict SI risk.

In this study, 60.67% (91/150) of adolescent patients with depression had SI, which is consistent with a previous study [16]. In our study, female patients showed higher SI than male patients, consistent with the results of domestic and foreign studies[17,18]. This may be related to the hormone levels of female patients. The proportion of patients with SI with a history of trauma was significantly higher than that in the control group, suggesting that childhood trauma is a risk factor[19]. In addition, the study also found that a higher proportion of patients with various triggers had SI than those without triggers, indicating that triggers play a role in SI in adolescent patients with depression[20].

Ferritin is an important marker of inflammation and oxidative stress. It is also a unique protein that stores iron and is often used to assess the level of iron stored in the body. Studies have shown that the mechanism underlying increased SF levels in patients with depression is mainly an oxidative stress reaction caused by increased ferritin[21]. Oxidative stress is directly related to the pathogenesis of depression, indicating that ferritin can indirectly affect the occurrence and development of depressive symptoms by triggering an oxidative stress response. In this study, the SI group had significantly higher SF levels than the non-SI group, suggesting that SF levels are associated with depression.

Furthermore, according to previous studies, elevated serum hs-CRP levels can oversecrete inflammatory cytokines, causing dysfunction of the 5-hydroxytryptamine and noradrenaline systems, thereby inducing depressive symptoms[22]. According to the study of Tabaeizadeh *et al*[23], there is a correlation between hs-CRP levels and depression in adolescent girls. Our study found that adolescents with depression and SI had higher hs-CRP levels. These results indicate that hs-CRP levels are associated with depression. In recent years, an increasing number of studies on the relationship between HDL-C and depression accompanied by suicidal thoughts have shown that patients with depression have a unique lipid metabolism profile compared to those without depression[24]. Our study showed that the HDL-C level in adolescent patients with depression and SI was lower than that in the non-SI group, which is consistent with previous studies. For example, Maes *et al*[25] showed that serum HDL-C levels in patients with depression and SI were low. This suggests that HDL-C may be a biological marker of MDD accompanied by SI. Simultaneously, it provides a new therapeutic target for treating depression and depressive symptoms, especially in patients with depression and SI, by regulating lipid levels through various mechanisms[26,27].

Based on the related risk factors for SI in adolescent patients with depression, we developed a risk prediction model and conducted internal validation. The calibration curve suggests good consistency between the values predicted by the model and measured values, and the DCA suggests that the net benefit of the model is better when the threshold is above 20%, indicating that the model has high clinical practicability. These results indicate that the model has good predictive efficacy. To the best of our knowledge, this is the first nomogram model that includes sociological factors and laboratory

Table 1 Comparison of general information between the two groups, *n* (%)

Characteristic	SI group (*n* = 91)	Non-SI group (*n* = 59)	t/χ^2 value	*P* value
Sex				
Male	25 (27.47)	20 (33.90)	0.704	0.402
Women	66 (72.53)	39 (66.10)		
Age	14.165 ± 0.793	14.220 ± 0.789	0.186	0.157
Trauma history				
Yes	39 (42.86)	8 (13.56)	14.28	0.001
No	52 (57.14)	51 (86.44)		
Only child				
Yes	60 (65.93)	40 (67.80)	0.056	0.813
No	31 (34.07)	19 (32.20)		
Single parent				
Yes	19 (20.88)	11 (18.64)	0.112	0.738
No	72 (79.12)	48 (81.36)		
First-episode				
Yes	66 (72.53)	46 (77.97)	0.560	0.454
No	25 (27.47)	13 (22.03)		
Are there triggers				
Yes	42 (46.15)	23 (38.98)	13.328	0.039
No	49 (53.85)	36 (61.02)		
Ethnic groups				
Han nationality	82 (90.11)	53 (89.83)	0.003	0.956
Ethnic minorities	9 (9.89)	6 (10.17)		
Educational level				
High school and above	39 (42.86)	21 (35.59)	0.787	0.375
Junior high school and below	52 (57.14)	38 (64.41)		
Religious belief				
Yes	3 (3.30)	4 (6.78)	0.976	0.323
No	88 (96.70)	55 (93.22)		
Residential area				
City	61 (67.03)	36 (61.02)	0.567	0.451
Rural	30 (32.97)	23 (38.98)		
Economic situation				
Poor	15 (16.48)	8 (13.56)	0.284	0.868
Medium	55 (60.44)	36 (61.02)		
Better	21 (23.08)	15 (25.42)		
Father's education level				
Junior high school and below	65 (71.43)	42 (71.19)	0.001	0.974
High school and above	26 (28.57)	17 (28.81)		
Mother's educational level				
Junior high school and below	63 (69.23)	43 (72.88)	0.230	0.631

High school and above	28 (30.77)	16 (27.12)

SI: Suicidal ideation.

Table 2 Comparison of biochemical indices between the two groups

Index	SI group	Non-SI group	*t* value	*P* value
SF (μg/L)	71.010 ± 13.278	58.422 ± 17.842	-4.945	0.015
Folic acid (mmol/L)	4.350 ± 0.139	4.436 ± 0.172	11.864	0.053
Vitamin D_3 (mg/L)	12.773 ± 0.836	13.200 ± 0.846	4.366	0.054
hs-CRP (mg/L)	4.115 ± 1.497	3.423 ± 1.012	-3.115	0.020
UA (mmol/L)	335.989 ± 16.667	330.924 ± 16.875	-1.809	0.861
TG (mmol/L)	1.073 ± 0.103	1.061 ± 0.105	-0.656	0.794
TC (mmol/L)	3.737 ± 0.048	3.737 ± 0.047	-0.023	0.949
HDL-C (mmol/L)	1.039 ± 0.210	1.174 ± 0.282	3.351	0.009
LDL-C (mmol/L)	2.079 ± 0.055	2.076 ± 0.061	-0.313	0.411
TP (g/L)	76.312 ± 1.088	75.951 ± 1.230	-1.881	0.062
ALB (g/L)	47.230 ± 0.916	46.716 ± 1.088	-3.549	0.081
TBIL (μmol/L)	14.964 ± 0.218	14.820 ± 0.203	-4.045	0.121
AST (U/L)	42.325 ± 0.543	41.897 ± 0.501	-4.852	0.089
TSH (mmol/L)	150.080 ± 1.180	149.890 ± 1.109	0.986	0.326
T_3 (pmol/L)	1.519 ± 0.292	1.514 ± 0.246	-0.124	0.902
T_4 [M(Q)pmol/L]	86.850 ± 18.366	87.285 ± 19.229	0.139	0.889
FT_3 (pmol/L)	4.317 ± 0.501	4.250 ± 0.437	1.913	0.050
FT_4 (pmol/L)	11.339 ± 1.965	11.244 ± 2.040	-0.284	0.777

SI: Suicidal ideation; SF: Serum ferritin; hs-CRP: High-sensitivity C-reactive protein; UA: Uric acid; TG: Triglyceride; TC: Total cholesterol; HDL-C: high-density lipoprotein; LDL-C: Low-density lipoprotein; TP: Total protein; ALB: Albumin; TBIL: Total bilirubin; AST: Aspartate transaminase; TSH: Thyroid-stimulating hormone; T_3: Triiodothyronine; T_4: Thyroxine; FT_3: Free T_3; FT_4: Free T_4.

Table 3 Multivariate analysis of suicidal ideation in adolescents with depression

Independent variable	B	SE	Wald	*P* value	OR	95%CI
Trauma history	1.106	0.519	4.552	0.033	3.023	1.094–8.354
Triggers	1.311	0.461	8.107	0.004	3.711	1.505–9.153
SF (μg/L)	0.051	0.014	12.598	0.000	1.052	1.023–1.082
hs-CRP (mg/L)	0.453	0.172	6.927	0.008	1.573	1.123–2.205
HDL-C (mmol/L)	-2.104	0.852	6.095	0.014	0.122	0.023–0.648
FT_3 (pmol/L)	-1.217	0.502	5.886	0.078	0.296	0.111–0.791
Constant	-2.293	1.609	2.031	0.154	0.101	-

OR: Odds ratio; SF: Serum ferritin; hs-CRP: High-sensitivity C-reactive protein; HDL-C: High-density lipoprotein; FT_3: Free triiodothyronine.

indicators to predict SI in patients with depression. This can help implement early clinical measures to reduce suicide mortality in adolescent patients with depression.

This study has some limitations. First, the participants were adolescents with depression. This is a relatively special group, as they are in a period of growth and development; therefore, fluctuations in hormone levels can significantly affect the results. Second, the dietary habits and nutritional status of patients were not considered. This may affect the

Table 4 Diagnostic value of receiver operating characteristic curve evaluation index

Independent variable	Cutoff	AUC	Sensitivity	Specificity	Youden index	*P* value	95%CI
Trauma history	-	0.647	0.429	0.864	0.293	0.002	0.558–0.734
Triggers	-	0.651	0.538	0.763	0.301	0.002	0.562–0.740
SF (μg/L)	49.76	0.695	0.989	0.322	0.311	0.000	0.607–0.783
hs-CRP (mg/L)	3.829	0.643	0.593	0.712	0.305	0.003	0.556–0.731
HDL-C (mmol/L)	0.683	0.656	0.967	0.068	0.035	0.001	0.250–0.439

AUC: Area under the receiver operating characteristic curve; SF: Serum ferritin; hs-CRP: High-sensitivity C-reactive protein; HDL-C: High-density lipoprotein.

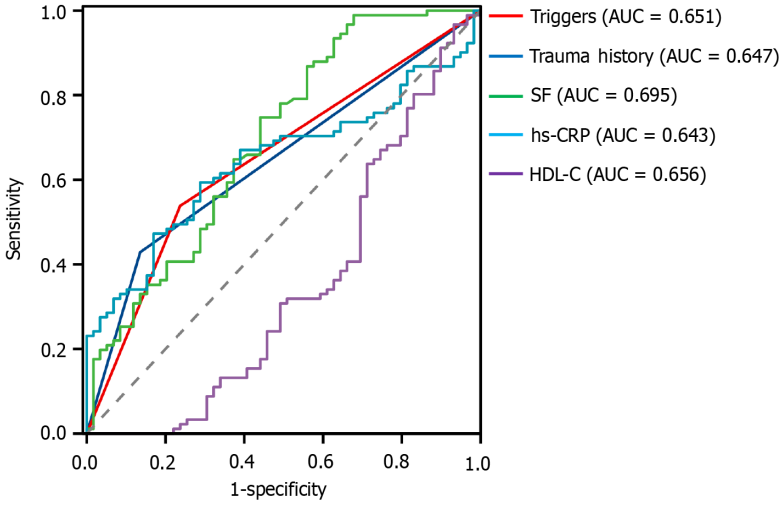

Figure 2 The diagnostic value of the receiver operating characteristic curve evaluation index. AUC: Area under the receiver operating characteristic curve; SF: Serum ferritin; hs-CRP: High-sensitivity C-reactive protein; HDL-C: High-density lipoprotein.

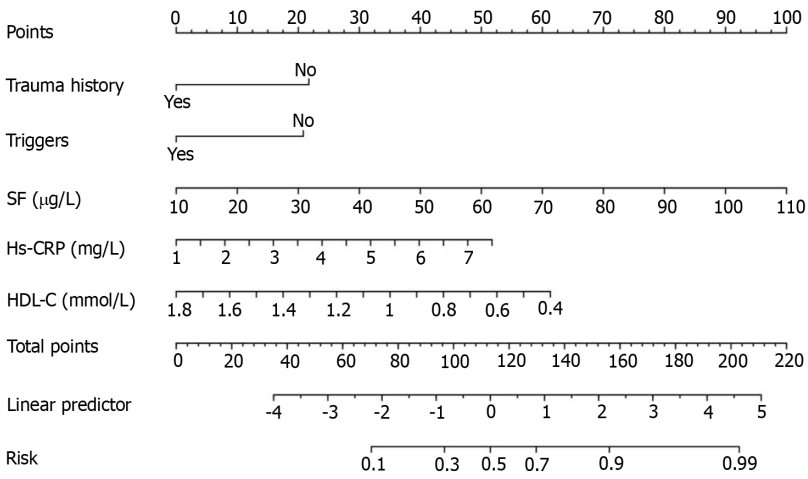

Figure 3 Nomogram for predicting suicidal ideation in adolescents with depression. For an individual patient, each variable corresponds to a single point at the top of the nomogram (Points). The total points were the sum of all single points and are indicated in the second line from the bottom (Total Points), and each total point corresponds to a probability of suicidal ideation. SF: Serum ferritin; hs-CRP: High-sensitivity C-reactive protein; HDL-C: High-density lipoprotein.

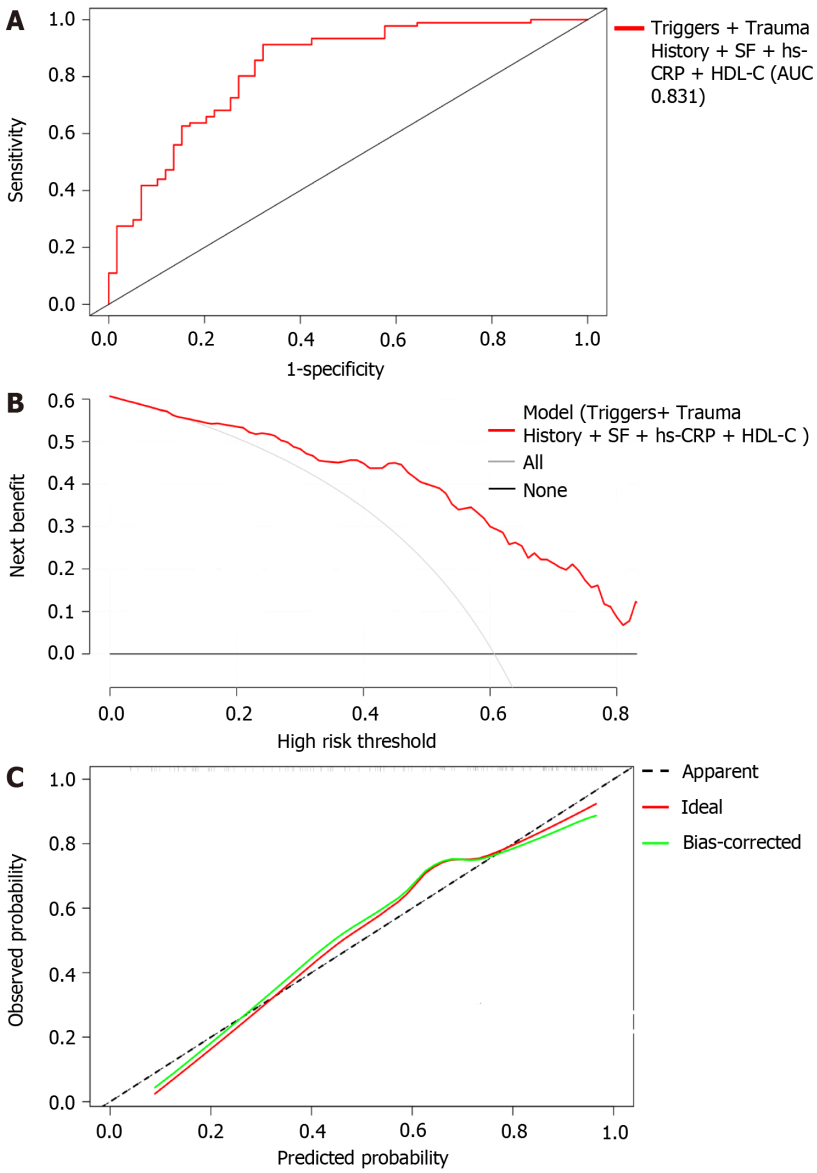

Figure 4 The nomogram of suicidal ideation in internal validation. A: Receiver operating characteristic of the nomogram for predicting the probability of suicidal ideation (SI); B: Density curve analysis of the nomogram for predicting the probability of SI; C: Calibration curve of the nomogram for predicting the probability of SI. AUC: Area under the receiver operating characteristic curve; SF: Serum ferritin; hs-CRP: High-sensitivity C-reactive protein; HDL-C: High-density lipoprotein; DCA: Density curve analysis; SI: Suicidal ideation.

levels of iron, hs-CRP, and HDL-C in the body, which may have caused bias in the study results. Further external validation is required in future studies. Finally, the insufficient sample size may have affected the validity of the nomogram model.

CONCLUSION

In conclusion, this study found that trauma history, predisposing factors, ferritin level, hs-CRP level, and HDL-C level may be early factors influencing SI in adolescent patients with depression. The nomogram model can effectively predict the occurrence of SI in adolescent patients with depression, which can help to quickly diagnose adolescent patients with depression at high risk of SI to prevent suicidal events.

ARTICLE HIGHLIGHTS

Research background

Depression is one of the most severe diseases affecting the mental health of adolescents. Most adolescents with

depression have suicidal ideation (SI). However, few studies have focused on the factors related to SI, and there is a lack of effective predictive models.

Research motivation

This study determined the factors influencing SI in adolescent patients with depression and construct a risk prediction model to provide a theoretical basis for prevention and intervention.

Research objectives

This study aimed to construct a risk prediction model for SI in adolescents with depression and provide an assessment tool for early screening.

Research methods

Based on a retrospective analysis of social factors and laboratory indicators of 150 adolescent patients with depression and SI, this study constructed and internally validated a risk prediction model.

Research results

Studies have shown that trauma history, predisposing factors, and serum ferritin levels (SF), high-sensitivity C-reactive protein levels (hs-CRP), and high-density lipoprotein (HDL-C) levels influence SI in adolescents with depression. The AUC of the nomogram prediction model was 0.831 (95%CI: 0.763–0.899), the sensitivity was 0.912, and the specificity was 0.678. The high net benefit of the DCA and the average absolute error of the calibration curve were 0.043, indicating that the model had a good fit.

Research conclusions

The nomogram model based on trauma history, predisposing factors, SF, hs-CRP levels, and HDL-C levels can effectively predict the occurrence of SI in adolescents with depression, which can help in implementing early clinical measures to reduce suicide mortality in adolescents with depression.

Research perspectives

According to the general data and laboratory indicators of adolescents with depression, we identified risk factors for SI and used them to develop an effective predictive model for quick detection.

FOOTNOTES

Author contributions: Zhou JC designed and performed the study and wrote the paper; Xian ZP designed the study and supervised the report; Cao Y and Xu XY organized the data and provided clinical advice. All authors were involved in the critical review of the results and contributed to, read, and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of the First People's Hospital of Lianyungang (Approval No. KY-20230926001-01).

Informed consent statement: The Ethics Committee granted an exemption from obtaining informed consent.

Conflict-of-interest statement: The authors declare no conflict of interest.

Data sharing statement: Data used in this study can be obtained from the corresponding author.

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Retrospective Study

Deliberate self-harm among pediatric psychiatric inpatients in China: A single-center retrospective study

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Abstract

BACKGROUND

For children and adolescents, deliberate self-harm (DSH) is becoming a mental health problem of concern. Despite several studies on the prevalence and factors of DSH in the world, there is little information on DSH among children and adolescents in China. This study explores the prevalence, types, associated risk factors and tendency of DSH in pediatric psychiatric inpatients in China.

AIM

To understand the situation of DSH among hospitalized children and adolescents and its related factors.

METHODS

In this study, we retrospectively studied 1414 hospitalized children and adolescents with mental illness at Xiamen Mental Health Center from 2014 to 2019, extracted the demographic and clinical data of all patients, and analyzed clinical

risk factors of DSH.

RESULTS

A total of 239 (16.90%) patients engaged in at least one type of DSH in our study. Cutting (n = 115, 48.12%) was the most common type of DSH. Females (n = 171, 71.55%) were more likely to engage in DSH than males (n = 68, 28.45%). DSH was positively associated with depressive disorders [OR = 3.845 (2.196-6.732); P < 0.01], female [OR = 2.536 (1.815-3.542); P < 0.01], parental marital status [OR = 5.387 (2.254-12.875); P < 0.01] and negative family history of psychiatric illness [OR = 7.767 (2.952-20.433); P < 0.01], but not with occupation, substance use and history of physical abuse.

CONCLUSION

Our findings suggest that for patients with depression, females, an abnormal marriage of parents, and no history of mental illness, attention should be paid to the occurrence of DSH.

Key Words: Deliberate self-harm; Children; Adolescent; Psychiatric inpatients; Retrospective study

Core Tip: Deliberate self-harm (DSH) is a serious global problem in children and adolescents. Studies have proved that DSH is related to many factors. This study collected a total of 1414 hospitalized case records of children and adolescents under the age of 18 from 2014 to 2019. According to the study, 16.9% of hospitalized children and adolescents had at least one kind of DSH which was associated with gender, depression, parents' marital status and so on. This suggests that we can deal with DSH in children and adolescents from the aspects of relevant influencing factors.

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INTRODUCTION

Deliberate self-harm (DSH) is an all-embracing term for self-injurious behavior, which can range from the absence of suicidal ideation (the aim is to relieve anxiety, tension and so on) to attempted suicide[1]. In other words, DSH is an act of intentionally harming oneself, regardless of type and real intention (both suicidal and non-suicidal). But with or without suicidal intention, DSH may cause death[2]. Studies have shown that suicide is the second leading cause of death among people aged 15 to 29 around the world[3]. And DSH has attracted much attention as a strong predictor of future suicide attempts[4].

The high incidence of DSH has made it a global public health concern[5]. A previous study found that the lifetime prevalence rate of DSH was 13.7%, and the incidence rate in Western countries was higher than in non-Western countries [5]. Furthermore, the lifetime and annual prevalence of DSH in Asia was the highest among non-western countries[5]. A study in Japan reported that the annual prevalence rate of DSH was 8.4%[6]. In Singapore, two published studies showed that the DSH rates of adolescent psychiatric outpatients were 23.6% and 23.1%, respectively[7,8]. In addition, a study in Hong Kong, China found that about 23.5% of eighth graders had engaged in DSH in the past 12 months[9], but less current relevant study exists in Mainland China related to DSH among juveniles.

Typical behaviors of DSH usually include cutting (with a knife or razor), hitting, burning, scratching, biting or excessively rubbing the skin, and the ultimate goal is to cause themselves to get hurt[10]. Most of the children and adolescents who exhibit DSH behavior, in reality, do not intend to commit suicide but rather channel their negative emotional states such as anxiety and depression[9]. Maybe sometimes they engage in DSH as a way to punish themself, generate excitement and get the attention of others. Although children and adolescents engage in DSH without suicidal thoughts, this kind of act may lead to death[11]. Moreover, self-harm behavior is easy to have a negative impact on teenagers and imitate each other[8]. People with self-harm behavior have a higher rate of suicide[12], so early identification of DSH influencing factors and intervention may prevent patients from potential suicidal behavior[7]. The study found that interpersonal relationship problems, environmental stress and academic pressure seem to be related factors for DSH among young people in Asia[13]. All of the above factors may contribute to depression, anxiety, conduct disorders and other mental disorders in young people with DSH[14]. And depression, in particular, has been found to be the most common diagnosis among teenagers with DSH[15]. Furthermore, studies from non-western countries have found that there were gender differences in DSH among adolescents, and the prevalence of girls was higher than that of boys, which was consistent with reports in Western countries[7,9,12,13]. In a word, depression, gender, age, social contact or engaged in DSH seem to be the main risk factors for the occurrence of DSH in children and adolescents[16]. At the same time, marginal personality traits or disorders are also a factor that cannot be ignored in the occurrence of DSH behavior[17].

Although there are many studies on DSH around the world, there are few studies on DSH among children and adolescents in hospitalized psychiatric patients in China. In addition, there are few studies in the world to analyze the development trend of DSH in children and adolescents in recent years. So, using a sample of children and adolescent psychiatric inpatients in China, the follow-up study described the prevalence, factors, as well as tendency and different types of DSH behaviors engaged. We investigated primary diagnosis in the prevalence of DSH and explored whether gender, age, substance use, census registration, occupation, parental marital status, family history of psychiatric illness, and history of physical abuse were predictive of DSH. This study expands existing knowledge about the clinical phenomenology in China and allows us to observe the trends of DSH over time.

MATERIALS AND METHODS

Participants and procedures

A retrospective study was conducted on inpatients with mental illness among children and adolescents in Xiamen Xianyue Hospital, Xiamen Mental Health Center in Fujian, China. Xianyue hospital is a Grade III level A hospital of psychiatric hospital in China, which take on important tasks of medical treatments, teaching and scientific research in Fujian Province and its surrounding provinces and cities, and receive psychiatric patients from all over the country. With the help of the hospital information department, we obtained information of 1414 inpatients under the age of 18 between January 2014 to December 2019. This study was approved by the Ethics Committee of Xiamen Xianyue Hospital (Xiamen, China) and all methods were performed in accordance with the relevant guidelines and regulations. According to the purpose of our study, two professional psychiatrists designed a standardized data collection table to collect basic demographic data and clinical characteristics of patient. And Epidata3.1 was used to record, manage and check the data.

Demographic and clinical characteristics (*e.g.*, age, gender, family history, parental marital status, bad habits) were collected in the clinical history. In order to avoid the error caused by subjective judgment of researchers, statistics were made only based on the records of cases. DSH was defined as the deliberate destruction of one's own body tissue, with or without suicidal intent in this article. Parents were defined as biological parents, and the abnormal marriages of the parents include separation, divorce, remarriage and orphans. The patient's bad habits include smoking, alcohol use, substance dependence and gambling. The data needed to be collected but not recorded in detail in the case is recorded as unknown. In the sample, there were more than 20 main diagnosis types, and some of them had a small proportion or only a few cases in the total sample size, which increased the interference factors of statistical analysis. So on the premise of not affecting the analysis results, these main diagnoses were divided into five groups, and the grouping was as follows: Depression, bipolar diosder, schizophrenia and other primary psychiatric disorder (*e.g.*, schizoaffective disorder, delusional disorder, acute and transient psychotic disorder), neurodevelopmental disorder (*e.g.*, autism, attention deficit hyperactive disorder, tic disorder), other diseases (*e.g.*, anxiety disorder, obsessive-compulsive disorder and organic psychosis). All patients were diagnosed according to ICD-10.

Statistical analysis

The data were analyzed by IBM SPSS Statistics 22.0 software. First of all, descriptive statistics were used to analyze basic demographic data and clinical variables. Then chi-square test and Fisher's exact test were used to compare the demographic and clinical variables between the DSH group and the non-DSH group, and the candidate risk factors for DSH were screened. Finally, multiple Logistic regression analysis was used to further analyze the statistically significant risk factors to test the correlation between the variables and DSH. Inputting variables into the model in turn, selecting the model that is most suitable for hybrid variable control, and identifying the optimal risk factors. We considered P value less than 0.05 to be statistically significant.

RESULTS

The demographics and clinical characteristics

The socio-demographic and clinical characteristics of all samples are shown in Table 1. As shown in Table 1, the number of hospitalized children and adolescents increased year by year from 2014 to 2019. Among the children and adolescents with DSH, female accounted for 71.55%, diagnosed with depression accounted for 63.18%, and 79.50% were students. Most patients with DSH lived with their biological parents (92.05%) and 95.82% had a negative family history of psychiatric illness. Only 1.67% patients who emerged in DSH behavior had a history of physical abuse.

Analysis of risk factors related to DSH

Table 2 analyzes the risk factors of DSH by chi-square test or fisher's accurate test. The results showed that DSH behavior was significantly associated with main diagnosis ($P < 0.01$), gender ($P < 0.01$), occupation ($P < 0.01$), marital status of parents ($P = 0.02$), family history of psychiatric illness ($P < 0.01$) and history of physical abuse ($P < 0.01$). We found no association between DSH and age ($P = 0.0137$), census registration ($P = 0.405$) and bad habits ($P = 0.184$).

Further analysis of risk factors related to DSH

Logical regression analysis is performed based on the results shown in Table 3. Multiple regression analysis revealed four factors related to DSH: Depressive disorders [OR = 3.845 (2.196-6.732); $P < 0.01$], female gender [OR = 2.536 (1.815-3.542);

Table 1 Sample demographic and clinical characteristics (*n* = 1414)

Characteristic	*n* (%)
Year	
2014	135 (9.55)
2015	150 (10.61)
2016	184 (13.01)
2017	208 (14.71)
2018	315 (22.28)
2019	422 (29.84)
Main diagnosis	
Depression	427 (30.20)
Bipolar disorder	188 (13.30)
Schizophrenia or other primary psychotic disorder	366 (25.88)
Neurodevelopmental disorder	275 (19.45)
Others	158 (11.17)
Gender	
Male	721 (50.99)
Female	693 (49.01)
Age (yr)	
≤ 12	144 (10.18)
13-18	1270 (89.82)
Census registration	
Rural	890 (62.94)
City	524 (37.06)
Occupation	
Student	970 (68.60)
Employed	17 (1.20)
Not working or studying	427 (30.20)
Marital status of parents	
Normal	1354 (95.76)
Abnormal	60 (4.24)
Family history of psychiatric illness	
Positive	172 (12.16)
Negative	1215 (85.93)
Unknown	27 (1.91)
Substance use	
Yes	26 (1.84)
No	1388 (98.16)
History of physical abuse	
Yes	9 (0.64)
No	1384 (97.88)
Unknown	21 (1.49)
DSH	

Yes	239 (16.90)
No	1175 (83.10)
Types of DSH	
Cutting	115 (48.12)
Scratching	14 (5.86)
Hitting	36 (15.06)
Puncturing	4 (1.67)
Swallow medications	3 (1.26)
Refusing foods	16 (6.69)
Biting	9 (3.77)
Multiple ways	21 (8.79)
Others	6 (2.51)
Unknown	15 (6.28)

DSH: Deliberate self-harm.

$P < 0.01$], parental marital status [OR = 5.387 (2.254-12.875); $P < 0.01$] and negative family history of psychiatric illness [OR = 7.767 (2.952-20.433); $P < 0.01$], but not with occupation, substance use. There were no statistically significant differences in age, census registration, and history of physical abuse among patients with or without DSH.

The trend of DSH from 2014 to 2019

Finally, it is worth emphasizing that from 2014 to 2019, the number of patients in the inpatient department of children and adolescents showed a trend of gradual increase, and the number of inpatients reached a six-year high in 2019. At the same time, the proportion of patients with DSH behavior basically showed an upward trend, although there was a fluctuation in the ratio from 2015 to 2016 (Figure 1).

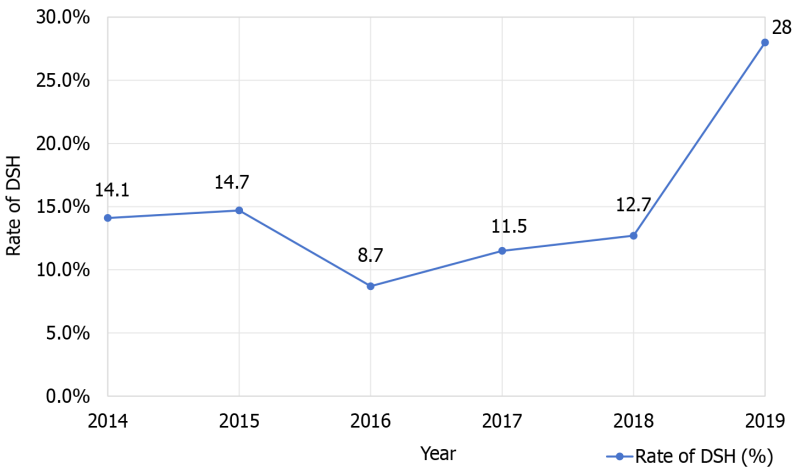

Figure 1 Rate of deliberate self-harm from 2014 to 2019. DSH: Deliberate self-harm.

DISCUSSION

DSH can cause irreparable damage to the body and even cause accidental death. It is undeniable that people who have committed DSH have a higher risk and tendency to commit suicide[12,18]. Compared with adults, children and adolescents are at high risk of DSH behavior, and they are more vulnerable to imitating DSH to cope with challenges or to obtain a sense of identity from their peer group[19,20]. The primary purpose of this study was to verify the previous research results and further improve the research content. This research studied the DSH behavior among inpatient children and adolescents in China from 2014 to 2019, and explored the influencing factors, incidence and development trend of DSH. This will help to improve the cognition of DSH behavior, understand the vulnerable group of DSH, comprehend the psychology of patients involved in self-harm, then design targeted preventive measures and intervention means for DSH and its related risk factors.

Table 2 Risk factors of children and adolescents psychiatric in patients with and without deliberate self-harm (*n* = 1414)

Factors	No. of patients (%)		χ^2/Z	*P* value
	With DSH	Without DSH		
Main diseases			157.308	< 0.001
Depression	151 (35.36)	276 (64.64)		
Bipolar disorder	4 (2.13)	184 (97.87)		
Schizophrenia or other primary psychotic disorder	33 (9.02)	333 (90.98)		
Neurodevelopmental disorder	34 (12.36)	241 (87.64)		
Others	17 (10.76)	141 (89.24)		
Gender			58.463	< 0.001
Male	68 (9.43)	653 (90.57)		
Female	171 (24.68)	522 (75.32)		
Age (yr)			2.212	0.137
≤12	18 (12.50)	126 (87.50)		
13-18	221 (17.40)	1049 (82.60)		
Census registration			-	0.405[1]
Rural	151 (16.97)	739 (83.03)		
City	88 (16.79)	436 (83.21)		
Occupation			16.193	< 0.001
Student	190 (19.59)	780 (80.41)		
Employed	1 (5.88)	16 (94.12)		
Not working or studying	48 (11.24)	379 (88.76)		
Marital status of parents			9.725	0.002
Normal	220 (16.25)	1134 (83.76)		
Abnormal	19 (31.67)	41 (68.33)		
Family history of psychiatric illness			27.310	< 0.001
Positive	5 (2.91)	167 (97.09)		
Negative	229 (18.85)	986 (81.15)		
Unknown	5 (18.52)	22 (81.48)		
Substance use			-	0.184[1]
Yes	7 (26.92)	19 (73.08)		
No	232 (16.71)	1156 (83.29)		
History of physical abuse			-	0.033[1]
Yes	4 (44.44)	5 (55.56)		
No	234 (16.91)	1150 (83.09)		
Unknown	1 (4.76)	20 (95.24)		

[1]Fisher's exact test.
DSH: Deliberate self-harm.

Among the 1,414 samples in this study, DSH patients accounted for 16.9%, which was lower than the previous study in Singapore and western countries[8,11,21]. The difference in ratio may due to the way of obtaining the sample and the amount of sample size. After all, patients with DSH usually go to the out-patient clinic first, and then decide whether to be hospitalized for further treatment after evaluation. So, in theory, there will be more outpatients than inpatients. In our study, the samples were all from inpatients while the previous research samples were from outpatients, communities or schools, which may be the main reason for the difference. But there is not much difference in the research method and

Table 3 Multivariate logistic regression analysis of deliberate self-harm behavior

Factors	*P* value	OR (95%CI)
Main diseases		
Depression	< 0.001	3.845 (2.196-6.732)
Schizophrenia or other primary psychotic disorder	0.356	0.738 (0.387-1.407)
Bipolar disorder	0.004	0.188 (0.060-0.589)
Neurodevelopmental disorder	0.453	1.283 (0.669-2.460)
Others		1.000
Gender		
Male		1.000
Female	< 0.001	2.536 (1.815-3.542)
Occupation		
Student	0.091	1.398 (0.948-2.063)
Employed	0.847	1.233 (0.146-10.389)
Not working or studying		1.000
Marital status of parents		
Normal		1.000
Abnormal	< 0.001	5.387 (2.254-12.875)
Family history of psychiatric illness		
Yes		1.000
No	< 0.001	7.767 (2.952-20.433)
Unknown	< 0.001	54.444 (5.758-514.780)
History of physical abuse		
No		1.000
Yes	0.088	5.296 (0.783-35.846)
Unknown	0.005	0.020 (0.001-0.312)

content in essence.

Our results are consistent with those of previous studies, suggesting that patients with depression are more likely to conduct DSH behavior[8,11]. It also confirms the findings of some countries in the West and Asia that depression is a high risk factor for DSH[22]. The associations between DSH and gender factors reflected the results of previously published researches[11,23,24], that is, women are more likely to participate in DSH. Our research found that female were about 2.5 times more likely to engage in DSH than males. It suggests that DSH has a stronger association with female. The gender differences in the prevalence of depression and DSH behavior reflect the different responses and coping styles of male and women in the face of emotional distress[8]. As we all know, males are more likely to take external measures to tackle challenges when they run into trouble and setback, while women are more likely to choose internal coping styles of self-suppression, such as self-harm. There is a strong correlation between anxiety and DSH in most studies, but the number of patients who were mainly diagnosed as anxiety disorder in this study was relatively small, so anxiety disorder was not regarded as a separate factor.

In a study conducted in Singapore, no relationship was found between parents' marital status and the occurrence of DSH, and it was speculated that the DSH behavior might be related to family function and quality[11]. Different from the research of Singapore, the occurrence of DSH was associated with the marital status of the parents in this paper. We found the incidence of DSH among children and adolescents whose parents are in normal marriages is lower than that of their parents in abnormal marriages. It is well known that poor family structure (*i.e.*, not living with both biological parents and not having married parents) is commonly associated with depression[25,26], so it's not hard to explain why children from abnormally married families are more likely to conduct DSH behavior. Therefore, parents are advised to manage their own marriages as well as possible to give their children a complete family. The other difference in our study, children and adolescents with no family history of psychiatric illness have a higher incidence of DSH, which is completely different from previous studies. There is a possible explanation: under the influence of traditional Chinese cultural values and beliefs, Chinese people generally believe that “Mianzi” is very important. “Mianzi” represents the social class and dignity of the Chinese social stratum[27]. Unfortunately, the diagnosis of mental illness can cause the “loss of face” to patients and their families. for the sake of preserving the "face", patients and their families are more likely

to conceal the family history of psychiatric illness[28]. Our findings indicated that it is necessary to improve parents' awareness of their children's mental health and enhance their ability to judge abnormal emotion or behavior so as to identify their children's abnormalities timely and accurately and prevent the occurrence of DSH as far as possible.

There was no correlation between DSH and substance uses (*i.e.*, smoking, alcohol use, substance dependence and gambling) in our study, which is different from some studies[8,11,29]. Three possible reasons are as follows. First, children and adolescents are a special group, so they have less chance to develop bad habits during the school year. Next, the patients may deliberately conceal his true information for some reason. Last, under the influence of Chinese traditional culture, females are not allowed to develop substance uses such as smoking and drinking. And DSH behaviors mostly occur in women, which may lead to a low incidence of substance uses in our sample. Therefore, the correlation between DSH occurrence and substance uses cannot be verified. We also studied the relationship between DSH with the age. One researches have shown that the ages between 13 and 18 are the peak of the beginning and end of self-harm, and most studies about DSH mainly focus on adolescents between 12 and 18 years old[30]. But in our study, all children and adolescents under 18 years old were included. And the results showed that there was no statistical significance in the DSH behavior of children under 12 years old and adolescents between 13 and 18 years old, indicating that children and adolescents are equally likely to participate in DSH, and children are also a group that cannot be ignored.

Physical abuse has been proved to be one of the main risk factors for the occurrence of DSH, which has also been verified in a number of literatures[31]. But, the history of physical abuse has not been confirmed to be related to the DSH behavior in this study. Abuse has traditionally been understood as the physical or/and psychological or/and sexual harm inflicted on the victim by others[32,33], without defining the problem whether the victim has a self-abuse. The DSH shown in this study is a kind of self-abuse behavior, and the relationship between DSH and being abused is not clear at present. Therefore, the correlation between DSH and abuse cannot be explained. But a 2013 systematic review on the relationship between maltreatment and adolescent suicidal behavior suggested that abuse, whether sexual or physical, or emotional abuse and neglect, was associated with suicidal ideation and suicide attempts in children and adolescents[34]. A recent study showed the same conclusion: Child maltreatment in the form of emotional abuse may be distinguishing characteristics of female patients with DSH in psychiatric settings[35]. Therefore, it should be theoretically concluded that DSH is associated with physical abuse, but no such correlation was found in this study. There are two possible reasons: First, due to the Chinese people's "Mianzi", as mentioned above, "Mianzi" is very important in the eyes of Chinese people, and some private or difficult things are reluctant to reveal to others[27]. Secondly, for children and adolescents, they may think that things have already happened, it is useless to say, and it is such a private thing (which is also what we often hear children and adolescents express in clinical work). In summary, this study may not reach the same conclusion as before.

The incidence of DSH generally presented an upward trend from 2014 to 2019. However, the DSH ratio decreased from 2015 to 2016, which may be due to the staff adjustment of hospital department and hospitalization standard readjustment of the child and adolescent psychiatric department in Xianyue Hospital in 2015. But the overall upward trend especially from 2016 to 2019 indicate that the physical and mental health of children and adolescents are facing more and more serious challenges.

CONCLUSION

Important evidence-based findings of Chinese children and adolescents with mental illness were obtained: The positive associations between DSH and female gender, depressive disorders, abnormal parental marital status and negative family history of psychiatric illness suggest that it may be helpful to refine interventions in order to target these factors. In other words, the occurrence of DSH should be controlled from the source. Because children are most exposed to the parents and teachers, families and schools need to pay as much attention as possible to help these special groups actively prevent the occurrence of DSH and take intervention measures to better promote the psychological and physical recovery of children with DSH. At present, many psychiatric hospitals have carried out individual or/and group treatment for children and adolescents who implement DSH, which is considered a better intervention means. At the same time, regular lectures and educations for parents and school teachers on children's physical and mental health are important for the prevention, detection and intervention of DSH behavior. The combination of individual, family, school, hospital and social support is particularly vital in managing children's DSH behavior. Especially within the family and school, recognized as the primary ecological environments for children and adolescents, family education and school education play pivotal roles in fostering the healthy growth of children. Family caregivers should ensure children receive ample emotional support and values, paying close attention to their psychological upbringing. Meanwhile, schools need to create a healthy and joyful learning environment, with a focus on each student's mental health. Strengthening the management of bullying and peer discrimination within schools is also essential. Child and adolescent self-harm has become a public health problem in Asia and even around the world. This study is helpful for us to understand the current situation and trend of DSH behavior in Chinese children and adolescents. However, this is far from enough; we still need to continue in-depth research, expand our understanding of the relationship between DSH and its related risk factors, and improve relevant interventions to help troubled children get rid of the harm to themselves as soon as possible. However, simply paying attention to the severity, treatment options, and intervention effect of DSH cannot improve the current status of DSH, and minimizing the risk factors associated with DSH, such as depression, is the most important goal at present. Furthermore, it has been decades since the relevant research on DSH, but whether these studies can really attract the attention of the family, society, and the country is still something to look forward to.

ARTICLE HIGHLIGHTS

Research background

Deliberate self-harm (DSH) in children and adolescents is a serious challenge. Many foreign studies have explored the characteristics and factors of DSH in children and adolescents, but there are few large-scale epidemiological investigations and studies on DSH in China.

Research motivation

The focus of this study is to explore the characteristics and factors related to DSH in children and adolescents from 2014 to 2019 before the epidemic, which can help us explore ways and measures to prevent DSH in children and adolescents.

Research objectives

The purpose of this study was to explore the risk factors associated with DSH.

Research methods

A retrospective study was conducted on 1414 children and adolescents with mental illness who were hospitalized at Xiamen Mental Health Center from 2014 to 2019. chi-square test and Fisher's exact test were used to compare the demographic and clinical variables between the DSH group and the non-DSH group, and the candidate risk factors for DSH were screened. Then, multiple logistic regression analysis was used to analyze the statistically significant risk factors further to test the correlation between the variables and DSH. Inputting variables into the model, in turn, selecting the most suitable model for hybrid variable control and identifying the optimal risk factors.

Research results

A total of 239 (16.90%) patients engaged in at least one type of DSH in our study. Cutting was the most common type of DSH. Females were more likely to engage in DSH than males. DSH was positively associated with depressive disorders, female, parental marital status and negative family history of psychiatric illness, but not with occupation, substance use and history of physical abuse.

Research conclusions

The occurrence of DSH should be noted for patients with depression, women, parents with marital abnormalities, and no history of mental illness.

Research perspectives

Future research should further explore the characteristics and influencing factors of DSH in children and adolescents, including outpatient and hospitalization, and carry out multi-center studies.

FOOTNOTES

Co-first authors: Xing-Zhi Jiang and Huan-Huan Li.

Co-corresponding authors: Chen Wang and Zhen-Zhen Yu.

Author contributions: Jiang XZ contributed to the study conception and design, drafting manuscript, data analysis and interpretation, critical revision of article for important intellectual content; Li HH contributed to the critical revision of article for important intellectual content; Yu ZZ contributed to the study conception and design, critical revision of article for important intellectual content; Wang C contributed to the study conception and design, drafting manuscript, critical revision of article for important intellectual content. Jiang XZ and Li HH contributed equally to this work as co-first authors. The reasons for designating Jiang XZ and Li HH as co-first authors authors are threefold. First, the research was performed as a collaborative effort, and the designation of co-corresponding authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. This also ensures effective communication and management of post-submission matters, ultimately enhancing the paper's quality and reliability. Second, the overall research team encompassed authors with a variety of expertise and skills from different fields, and the designation of co-first authors best reflects this diversity. This also promotes the most comprehensive and in-depth examination of the research topic, ultimately enriching readers' understanding by offering various expert perspectives. Third, Jiang XZ and Li HH contributed efforts of equal substance throughout the research process. The choice of these researchers as co-first authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study. In summary, we believe that designating Jiang XZ and Li HH as co-first authors of is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity. Wang C and Yu ZZ contributed equally to this work as co-corresponding authors. The reasons for designating Wang C and Yu ZZ as co-corresponding authors are threefold. First, the research was performed as a collaborative effort, and the designation of co-corresponding authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. This also ensures effective communication and management of post-submission matters, ultimately enhancing the paper's quality and reliability. Second, the overall research team encompassed authors with a variety of expertise and skills from different fields, and the designation of co-corresponding authors best reflects this diversity. This also promotes the most comprehensive and in-depth examination of the research topic, ultimately enriching readers' understanding by offering various expert perspectives. Third, Wang C and Yu ZZ contributed efforts of equal substance throughout the research process. The choice of these researchers as co-corresponding authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study. In summary, we believe that

designating Wang C and Yu ZZ as co-corresponding authors of is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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ORIGINAL ARTICLE

Observational Study

Mediating role of social support in dysphoria, despondency, and quality of life in patients undergoing maintenance hemodialysis

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Abstract

BACKGROUND

Dysphoria and despondency are prevalent psychological issues in patients undergoing Maintenance Hemodialysis (MHD) that significantly affect their quality of life (QOL). High levels of social support can significantly improve the physical and mental well-being of patients undergoing MHD. Currently, there is limited research on how social support mediates the relationship between dysphoria, despondency, and overall QOL in patients undergoing MHD. It is imperative to investigate this mediating effect to mitigate dysphoria and despondency in patients undergoing MHD, ultimately enhancing their overall QOL.

AIM

To investigate the mediating role of social support in relationships between dysphoria, despondency, and QOL among patients undergoing MHD.

METHODS

Participants comprised 289 patients undergoing MHD, who were selected using a random sampling approach. The Social Support Rating Scale, Self-Rating Anxiety Scale, Self-Rating Depression Scale, and QOL Scale were administered. Correlation analysis was performed to examine the associations between social support, dysphoria, despondency, and QOL in patients undergoing MHD. To

assess the mediating impact of social support on dysphoria, despondency, and QOL in patients undergoing MHD, a bootstrap method was applied.

RESULTS

Significant correlations among social support, dysphoria, despondency, and quality in patients undergoing MHD were observed (all $P < 0.01$). Dysphoria and despondency negatively correlated with social support and QOL ($P < 0.01$). Dysphoria and despondency had negative predictive impacts on the QOL of patients undergoing MHD ($P < 0.05$). The direct effect of dysphoria on QOL was statistically significant ($P < 0.05$). Social support mediated the relationship between dysphoria and QOL, and this mediating effect was significant ($P < 0.05$). Similarly, the direct effect of despondency on QOL was significant ($P < 0.05$). Moreover, social support played a mediating role between despondency and QOL, with a significant mediating effect ($P < 0.05$).

CONCLUSION

These findings suggest that social support plays a significant mediating role in the relationship between dysphoria, despondency, and QOL in patients undergoing MHD.

Key Words: Maintenance hemodialysis; Social support; Dysphoria; Despondency; Quality of life; Mediating effect

Core Tip: Dysphoria and despondency are prevalent negative emotional experiences in patients undergoing maintenance hemodialysis (MHD), significantly affecting both prognosis and overall quality of life (QOL). Enhancing social support can improve the QOL of patients undergoing MHD. This study surveyed 289 patients undergoing MHD using questionnaires to examine the mediating role of social support in the relationship between dysphoria, despondency, and QOL. The findings contribute to the development of a theoretical foundation for psychological interventions in patients undergoing MHD, ultimately aiming to effectively alleviate dysphoria and despondency and subsequently enhance their overall QOL.

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INTRODUCTION

Maintenance Hemodialysis (MHD) is an enduring and often lifelong therapy for patients with end-stage kidney disease. This treatment is known for its lengthy and demanding process, which frequently results in a range of psychological challenges for patients[1]. Numerous studies have demonstrated a high prevalence of psychological disorders in patients undergoing MHD, with dysphoria and despondency being particularly prevalent[2]. These psychological issues have a significant impact on the physical and mental well-being of patients and can diminish their sense of hope for survival. Social support refers to the emotional and material assistance individuals receive from their social relationships, including family members, friends, significant others, and various organizations[3]. Strong social support has been shown to positively affect a patient's quality of life (QOL). Research has consistently revealed negative associations among social support, dysphoria, and despondency, highlighting the role of social support in reducing the risk of these psychological problems[4,5]. Additionally, social support is positively correlated with QOL, with improved social support leading to enhanced QOL[6]. Despite the existing body of research on dysphoria, despondency, social support, and QOL in patients undergoing MHD[7-10], few studies have investigated the underlying mechanisms through which social support influences dysphoria, despondency, and QOL in these patients. This study aimed to explore the intricate relationships between social support and dysphoria, despondency, and QOL in patients undergoing MHD. Furthermore, this study aimed to investigate the mediating role of social support in the relationship between dysphoria, despondency, and QOL among these patients. The ultimate goal of this study was to provide a theoretical foundation for clinical healthcare professionals to deliver targeted treatments and comprehensive care for individuals undergoing MHD.

MATERIALS AND METHODS

Subjects

Between January and December 2022, a random sampling method was employed to select patients undergoing MHD from the hemodialysis center of the People's Hospital of Xinjiang Uygur Autonomous Region for participation in a questionnaire survey. The demographic information of patients is shown in Table 1. All patients included in this study

Table 1 Demographic information of patients undergoing Maintenance Hemodialysis

Variables	Categories	Number, *n* (%)
Sex	Male	158 (54.67)
	Female	131 (45.33)
Age	< 45 yr	39 (13.50)
	45-60 yr	128 (44.29)
	> 60 yr	122 (42.21)
Education	Below high school	164 (56.75)
	High school and above	125 (43.25)
Marital status	Married	242 (83.74)
	Single (unmarried, divorced, widowed)	47 (16.26)
Monthly income	< 3000 yuan	55 (19.03)
	3000-5000 yuan	129 (44.64)
	> 5000 yuan	105 (36.33)
Medical insurance status	Medical insurance/social insurance	212 (73.36)
	Self-payment	77 (26.64)

were of biological sex. Inclusion criteria were as follows: (1) Age ≥ 18 years; (2) undergoing regular hemodialysis for a minimum of three months; (3) conscious and free from communication disorders; and (4) willing to participate in the survey. Exclusion criteria included: (1) The presence of a mental disorder or cognitive impairment; (2) experiencing acute infections, acute heart failure, or other severe organ dysfunction; and (3) inability to complete the questionnaire.

Research tools

Social support rating scale: The Social support rating scale version developed by Xiao *et al*[11] was utilized in this study. This scale comprises ten items categorized into three dimensions: Subjective support (items 1, 3-5), objective support (items 2, 6-7), and the utilization of social support (items 8-10). Items 1-4 and 8-10 were single-choice questions. A 4-point Likert scoring method was employed, with items 1-4 scored individually. Item 5 offered five options (A-E). Each option was assigned a score from 1 to 4 ("none" = 1 point, "very little" = 2 points, "general" = 3 points, and "full support" = 4 points). For items 6-7, selecting "no source" was scored as 0, while choosing "the following sources" resulted in points being calculated based on the number of sources selected. The scores for the 10 items were summed to calculate the scale's total score, which ranged from 12 to 66. These scores were divided into three levels: A total score of ≤ 22 indicated a low level of support, a total score of 23-44 denoted a medium level of support, and a total score of 45-66 signified a high level of support. A higher score indicated greater availability of social support. The Cronbach's α coefficient for this scale was 0.808.

Self-rating anxiety scale: The dysphoria scale developed by Zhang *et al*[12] was used in this study. The scale consisted of 20 items scored on a 4-point scale. The total raw score was calculated by adding the scores of the 20 Self-rating anxiety scale (SAS) items. The integer part of this total score, when multiplied by 1.25, yielded the standard score. A cut-off value of 50 points was used to assess dysphoria, with scores below 50 indicating the absence of dysphoria, scores between 50-59 indicating mild dysphoria, scores between 60-69 indicating moderate dysphoria, and scores equal to or greater than 70 indicating severe dysphoria. The Cronbach's α coefficient for this scale was 0.855.

Self-rating depression scale: The 2-item despondency scale developed by Xu *et al*[13] was used. Each item was scored on a 4-point scale. The total raw score was calculated by summing the scores of the 20 Self-rating depression scale (SDS) items, and the integer part of this total score, when multiplied by 1.25, yielded the standard score. A cutoff value of 53 was used to assess despondency, with scores less than 53 indicating the absence of despondency, scores between 53-62 indicating mild despondency, scores between 63-72 indicating moderate despondency, and scores greater than 72 indicating severe despondency. The Cronbach's α coefficient for this scale was 0.8.

QOL scale (SF-36): The SF-36 scale, developed by the Boston Health Research Institute and the Chinese version by Zhejiang University[14], was used. This scale consisted of 36 items distributed across 8 dimensions: Physical Functioning (PF), Role Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role Emotional (RE), and Mental Health (MH). The original scores for each dimension were computed using the summated rating method and converted into a hundred-mark system (0-100)[15]. QOL was assessed based on the overall scores of the physical component summary (PCS) and mental component summary (MCS), with scores for both domains converted into hundred-mark scores[16]. The overall PCS and MCS scores were calculated based on the scores from each dimension: PCS = PF + RP + BP + GH and MCS = VT + SF + RE + MH. The Cronbach's α coefficient for this scale was 0.869.

Data collection

A questionnaire survey was conducted to collect the data. Before the survey, approval was obtained from the relevant hospital authorities, and the research's purpose, significance, and ethical aspects were explained to the participants. Informed consent was obtained from all the participants. The distribution and collection of questionnaires were managed by the research investigators. A consistent set of instructions was used in the survey questionnaire to ensure uniformity in the data collection process. Upon completion of the questionnaires, the participants were collected onsite to ensure the responses' authenticity, validity, and completeness. In total, 300 questionnaires were distributed, with 289 valid questionnaires successfully collected, for a recovery rate of 96.33%.

Statistical analysis

SPSS statistical software (version 26.0) was used for data analysis, and the significance level was set at $P < 0.05$. The scores obtained from each scale were described using the interquartile range, and the count data were presented as n (%). Nonparametric and correlation tests were used to analyze the data. The mediating effect was assessed using PROCES.

RESULTS

Analysis of social support

The total social support scores obtained from the 289 patients undergoing MHD ranged from 13 to 60, indicating a moderate overall level of support. Of the participants, 63 (20.80%) were categorized as having a low level of support, 128 (44.29%) as having a medium level of support, and 98 (33.91%) as having a high level of support (Table 2). Based on the different levels of social support, patients undergoing MHD were grouped into three categories: Low, medium, and high levels of support. Subsequently, the levels of dysphoria, despondency, and QOL were analyzed for each group.

Effects of social support on dysphoria

The SAS scores of the 289 patients undergoing MHD had a score of 52 (42, 65), indicating an overall level of mild dysphoria. Among them, 115 (39.79 %) patients did not exhibit dysphoria, 73 (25.26%) had mild dysphoria, 54 (18.69%) had moderate dysphoria, and 47 (16.26%) had severe dysphoria (Table 3). Significant differences were observed in the SAS scores among the low, medium, and high levels of support ($P < 0.05$). Additionally, significant differences were noted in pairwise comparisons among the low, medium, and high support levels ($P < 0.05$; Figure 1A).

Effects of social support on despondency

The median SDS score of the 289 patients had a score of 55 (45, 67), indicating an overall level of mild despondency. Among them, 132 (45.67%) did not experience despondency, 63 (21.80%) had mild despondency, 44 (15.23%) had moderate despondency, and 50 (17.30%) experienced severe despondency (Table 4). Significant differences were observed in the SDS scores between the low, medium, and high support levels ($P < 0.05$). Additionally, significant differences were noted in pairwise comparisons among the low, medium, and high support levels ($P < 0.05$; Figure 1B).

Effects of social support on QOL

Among the 289 patients undergoing MHD, the QOL (PCS) score had a value of 105.11 (80.70, 126.64). Similarly, the QOL (MCS) score had a value of 111.64 (84.74, 130.18; Table 5). Significant differences were noted in the scores of all eight dimensions as well as in QOL (PCS) and QOL (MCS) among the low, medium, and high levels of support ($P < 0.05$). Moreover, significant differences were observed in pairwise comparisons among the low, medium, and high support levels ($P < 0.05$; Table 6).

Correlation analysis among social support, dysphoria, despondency, and QOL

Social support was positively correlated with both QOL (PCS and MCS) ($P < 0.01$). Dysphoria showed a positive correlation with despondency ($P < 0.01$). Dysphoria and despondency were negatively correlated with QOL (PCS and MCS) and social support ($P < 0.01$; Table 7).

Mediating effect of social support among QOL, dysphoria, and despondency

Dysphoria: In the first step, the regression coefficient was examined when dysphoria was considered the independent variable, and PCS and MCS were the dependent variables. Second, the regression coefficient was analyzed with dysphoria as the independent variable and social support as the dependent variable. In the third step, a regression equation was constructed, involving both dysphoria and social support as independent variables and PCS and MCS as dependent variables. The results revealed that dysphoria had a negative predictive effect on PCS and MCS (β = -0.869, β = -0.823, $P < 0.05$). Furthermore, dysphoria negatively predicted social support (β = -0.450, $P < 0.05$). The impact of dysphoria on PCS and MCS decreased when accounting for the presence of social support (β of PCS from -0.869 to -0.267, β of MCS from -0.823 to -0.329, $P < 0.05$). This suggests that social support partially mediated the relationship between dysphoria and QOL (PCS and MCS) in patients undergoing MHD (Table 8).

Despondency: In the first step, the regression coefficient was assessed with despondency as the independent variable and PCS and MCS as the dependent variables. Second, the regression coefficient was investigated with despondency as the independent variable and social support as the dependent variable. In the third step, a regression equation was

Table 2 Various scores of social support in patients undergoing Maintenance Hemodialysis

Items	Number, *n* (%)	Score range (points)	Score (points)
Subjective support	289 (100.00)	8-32	19 (12, 26)
Objective support	289 (100.00)	1-22	9 (5, 16)
The utilization of social support	289 (100.00)	3-12	7 (5, 10)
Total score	289 (100.00)	13-60	39 (24.5, 46)
Low level of support	63 (20.80)	14-22	20 (18, 21)
High levels of support	128 (44.29)	23-44	37 (30, 41)
High levels of support	98 (33.91)	45-60	49 (46, 53)

Table 3 Dysphoria scores and levels in patients undergoing Maintenance Hemodialysis

	Number, *n* (%)	Score (points)
Standard score	289 (100.00)	52 (42, 65)
No dysphoria	115 (39.79)	41 (35, 43)
Mild dysphoria	73 (25.26)	53 (51, 56)
Moderate dysphoria	54 (18.69)	65 (62, 66)
Severe dysphoria	47 (16.26)	77 (74, 86)

Table 4 Despondency scores and levels in patients undergoing Maintenance Hemodialysis

	Number, *n* (%)	Score (points)
Standard score	289 (100.00)	55 (45, 67)
No despondency	132 (45.67)	43 (37, 48)
Mild despondency	63 (21.80)	57 (56, 61)
Moderate despondency	44 (15.23)	67 (64, 70.5)
Severe despondency	50 (17.30)	81 (77, 87)

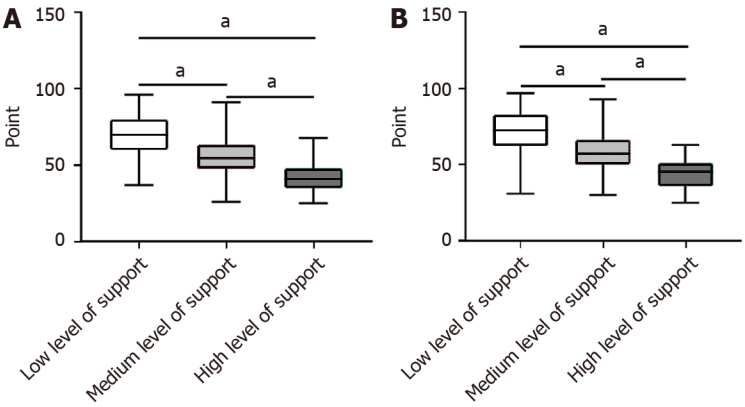

Figure 1 Analysis in patients undergoing Maintenance Hemodialysis with different levels of social support. A: Analysis of Self-rating anxiety scale scores in patients undergoing Maintenance Hemodialysis (MHD) with different levels of social support; B: Analysis of Self-rating depression scale scores in patients undergoing MHD with different levels of social support. Note: $^{a}P < 0.05$.

Table 5 Quality of life scores of patients undergoing Maintenance Hemodialysis

	Score (points)
PF	55 (25, 80)
RP	50 (25, 75)
BP	62.5 (46, 87.5)
GH	62 (40, 82)
VT	60 (40, 80)
SF	64 (44, 84)
RE	66.67 (44.44, 88.89)
MH	66.67 (0, 100)
Quality of life (PCS)	105.11 (80.70, 126.64)
Quality of life (MCS)	111.64 (84.74, 130.18)

PF: Physical functioning; RP: Role physical; BP: Bodily pain; GH: General health; VT: Vitality; SF: Social functioning; RE: Role emotional; MH: Mental health; PCS: Physical component summary; MCS: Mental component summary.

Table 6 Analysis of differences in quality-of-life scores of patients undergoing Maintenance Hemodialysis with different levels of social support

	Low level of support	Medium level of support	High level of support	H	*P* value
Physical functioning	10 (5, 20)	50 (30, 70)	85 (73.75, 91.25)	169.696	< 0.001
Role physical	0 (0, 25)	50 (25, 75)	75 (75, 100)	135.561	< 0.001
Bodily pain	49.5 (33.5, 58.5)	58.5 (37.5, 69.5)	94 (81.5, 100)	109.892	< 0.001
General health	25 (20, 35)	57 (45, 67)	87 (75, 92)	180.510	< 0.001
Vitality	30 (20, 40)	57.5 (46.25, 70)	85 (73.75, 91.25)	164.913	< 0.001
Mental health	32 (20, 40)	64 (52, 76)	92 (76, 96)	170.850	< 0.001
Social functioning	22.22 (11.11, 22.22)	55.56 (44.44, 75)	88.89 (77.785, 100)	173.945	< 0.001
Role emotional	0 (0, 33.33)	66.67 (0, 100)	66.67 (66.67, 100)	57.644	< 0.001
Quality of life (PCS)	73.17 (60.73, 73.17)	99.04 (83.29, 113.28)	129.76 (121.32, 140.17)	177.620	< 0.001
Quality of life (MCS)	73.72 (64.62, 87.28)	106.86 (88.02, 127.40)	129.16 (116, 138.81)	115.293	< 0.001

PCS: Physical component summary; MCS: Mental component summary.

established involving both despondency and social support as independent variables and PCS and MCS as dependent variables. The findings indicated that despondency had a negative predictive effect on PCS and MCS (β = -0.896, β = -0.717, $P < 0.05$). Additionally, despondency negatively predicted social support (β = -0.412, $P < 0.05$). Importantly, the influence of despondency on PCS and MCS decreased when considering the presence of social support (β of PCS from -0.896 to -0.372, β of MCS from -0.717 to -0.232, $P < 0.05$). This implies that social support played a partial mediating role in the relationship between despondency and QOL (PCS and MCS) in patients undergoing MHD (Table 9).

Mediating effect of social support on dysphoria, despondency, and QOL

To further assess the mediating effect of social support on dysphoria, despondency, and QOL in patients undergoing MHD, a bootstrap method was employed. The bootstrap 95%CI was analyzed but did not include 0.

Dysphoria: The direct effects of dysphoria on PCS and MCS were statistically significant ($P < 0.05$), accounting for 30.61% and 40.10% of the total effect value, respectively. The mediating effect of social support on dysphoria, PCS, and MCS was significant ($P < 0.05$), accounting for 69.39% and 59.90% of the total effect value, respectively.

Despondency: The direct effects of despondency on PCS and MCS were statistically significant ($P < 0.05$), accounting for 41.52% and 32.36% of the total effect value, respectively. The mediating effect of social support on despondency, PCS, and MCS was significant ($P < 0.05$), accounting for 50.48% and 67.64% of the total effect value, respectively (Table 10 and

Table 7 Correlation analysis of social support, dysphoria, despondency, and quality of life in patients undergoing Maintenance Hemodialysis

	Social support	Dysphoria	Despondency	Quality of life (PCS)	Quality of life (MCS)
Social support	1.000				
Dysphoria	-0.584[b]	1.000			
Despondency	-0.549[b]	0.435[b]	1.000		
Quality of life (PCS)	0.718[b]	-0.502[b]	-0.540[b]	1.000	
Quality of life (MCS)	0.600[b]	-0.454[b]	-0.404[b]	0.206[b]	1.000

[b]$P < 0.01$ (two-tailed).
PCS: Physical component summary; MCS: Mental component summary.

Table 8 The effect of dysphoria on quality of life and the mediating effect of social support

Model path	Standard regression equation	β	SE	*t*	*P* value
Step 1	Y_1 = -0.869A	-0.869	0.087	-9.963	< 0.001
Step 2	M = -0.450A	-0.450	0.038	-11.998	< 0.001
Step 3	Y_1 = -0.267A + 1.340M	-0.267	0.088	-3.046	0.003
		1.340	0.113	11.902	< 0.001
Step 1	Y_2 = -0.823A	-0.823	0.090	-9.190	< 0.001
Step 2	M = -0.450A	-0.450	0.038	-11.998	< 0.001
Step 3	Y_2 = -0.329A + 1.098M	-0.329	0.098	-3.371	< 0.001
		1.098	0.126	8.752	< 0.001

Note: Y_1 = Quality of life (physical component summary), Y_2 = Quality of life (mental component summary), M = Social support, and A = Dysphoria.

Table 9 The effect of despondency on quality of life and the mediating effect of social support

Model path	Standard regression equation	β	SE	*t*	*P* value
Step 1	Y_1 = -0.896B	-0.896	0.084	-10.709	< 0.001
Step 2	M = -0.412B	-0.412	0.038	-10.891	< 0.001
Step 3	Y_1 = -0.372B + 1.274M	-0.372	0.082	-4564	< 0.001
		1.274	0.107	11.888	< 0.001
Step 1	Y_2 = -0.717B	-0.717	0.090	-7.945	< 0.001
Step 2	M = -0.412B	-0.412	0.038	-10.891	< 0.001
Step 3	Y_2 = -0.232B + 1.178M	-0.232	0.093	-2.483	0.014
		1.178	0.123	9.590	< 0.001

Note: Y_1 = Quality of life (physical component summary); Y_2 = Quality of life (mental component summary); M = Social support; B = Despondency.

Figure 2).

DISCUSSION

The buffer effect model of social support posits that when individuals encounter stressors, social support can mitigate the negative impact of these stressors on individuals[17]. In the context of long-term hemodialysis treatment, as time progresses and the disease advances, patients often experience significant psychological and financial burdens, leading to

Table 10 Results of the mediation effect test

	The path		Coeff	SE	LLCI	ULCI	Relative effect Size (%)
Dysphoria	Direct effect	Dysphoria → Quality of life (PCS)	-0.266	0.088	-0.439	-0.094	30.61
	Indirect effect	Dysphoria → Social support → Quality of life (PCS)	-0.603	0.064	-0.731	-0.482	69.39
	Total effect		-0.869	0.087	-1.041	-0.698	
Dysphoria	Direct effect	Dysphoria → Quality of life (MCS)	-0.330	0.098	-0.521	-0.137	40.10
	Indirect effect	Dysphoria → Social support → Quality of life (MCS)	-0.493	0.071	-0.644	-0.366	59.90
	Total effect		-0.823	0.090	-0.999	-0.647	
Despondency	Direct effect	Despondency → Quality of life (PCS)	-0.372	0.082	-0.533	-0.212	41.52
	Indirect effect	Despondency → Social support → Quality of life (PCS)	-0.524	0.063	-0.659	-0.412	50.48
	Total effect		-0.896	0.084	-1.061	-0.732	
Despondency	Direct effect	Despondency → Quality of life (MCS)	-0.232	0.093	-0.416	-0.048	32.36
	Indirect effect	Despondency → Social support → Quality of life (MCS)	-0.485	0.065	-0.620	-0.367	67.64
	Total effect		-0.717	0.090	-0.894	-0.539	

LLCI: Lower limit of 95%CI; ULCI: Upper limit of 95%CI; PCS: Physical component summary; MCS: Mental component summary.

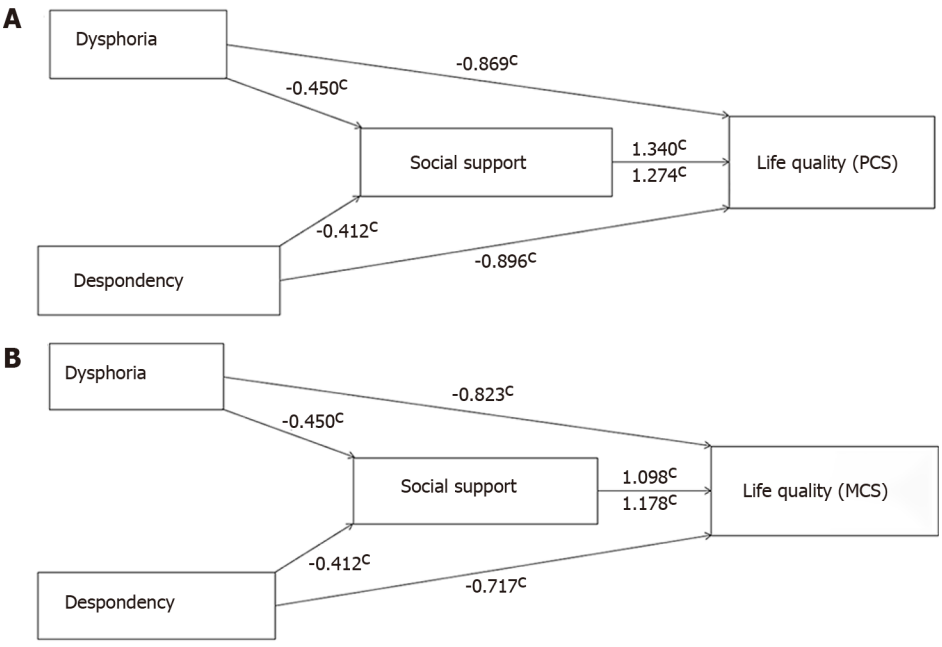

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Figure 2 Mediating effect model. A: Mediating effect model of physical component summary; B: Mediating effect model of mental component summary. Note: *c* *P* < 0.001. PCS: Physical component summary; MCS: Mental component summary.

feelings of despondency and dysphoria. These emotional struggles can have a profound impact on the patient's QOL for patients[18]. This study focused on patients undergoing MHD at our hospital's blood dialysis center using a questionnaire-based investigation. We aimed to explore the relationship among social support, dysphoria, despondency, and QOL in these patients. Through correlation analysis, we constructed a mediating effect model to delve deeper into the role of social support in mediating the effects of dysphoria and despondency on QOL in patients undergoing MHD. Our findings provide valuable insights into targeted interventions to improve the QOL of these patients.

The results of this study revealed the following: (1) Among the 289 patients undergoing MHD included in the study, the incidences of dysphoria and despondency were 60.21% and 54.33%, respectively. Comparatively, Ye *et al*[19] reported an incidence rate of 36.89% for dysphoria (68.93% for despondency), whereas Meng *et al*[20] reported an incidence rate of 25.9% for dysphoria (55.1% for despondency). These variations in research results may be attributed to differences in the assessment scales used for patients undergoing MHD, regional economic development, educational level, living environment, and sample size. However, dysphoria and despondency are prevalent in patients undergoing MHD; (2)

This study found a positive correlation between social support and QOL. Higher levels of social support were associated with a better QOL, which is consistent with the findings of Alexopoulou *et al*[21]. Social support encompasses the assistance provided by various social relationships. The psychological well-being of patients undergoing MHD is often influenced by the support they receive from their families and social environments. Social support plays a crucial role in helping patients effectively cope with various pressures and challenges[22]. Medical staff should pay close attention to the social support levels of patients undergoing MHD and collaborate with their families to provide assistance and support tailored to their individual needs, ultimately enhancing the quality of patients undergoing MHD; (3) This study found positive correlations between dysphoria and despondency and negative correlations between dysphoria, despondency, social support, and QOL. These findings are consistent with those reported by Al-Nashri and Almutary [23], Hoang *et al*[24], and Ma *et al*[1]. Our findings indicated that deeper dysphoria was associated with deeper despondency. Furthermore, increased levels of dysphoria and despondency are linked to lower levels of social support and diminished QOL. This relationship can be partially explained by the social isolation that may result from hemodialysis, which requires patients undergoing MHD to spend extended periods (3-4 h) in dialysis rooms at least twice a week. Psychological challenges, particularly dysphoria and despondency, often go unnoticed and can gradually affect physical and MH. Moreover, long-term dysphoria and despondency can lead to reduced social engagement and overall life satisfaction, negatively impacting quality[25]. To address this issue, medical staff should recognize that low social support may contribute to dysphoria and despondency in patients undergoing MHD. Intervention strategies can be developed to strengthen these patients' social networks, encourage them to express their feelings, and address their psychological needs, thereby helping them cope with the emotional burden of their condition; and (4) This study revealed that social support mediated the relationship between dysphoria, despondency, and QOL. With increased social support, the adverse effects of dysphoria and despondency on QOL were mitigated, consistent with the findings of Shang *et al*[26] and Shukri *et al*[27]. Dysphoria and despondency not only directly influence the QOL of patients undergoing MHD but also indirectly affect it by shaping their level of social support. This implies that enhancing social support levels can improve the QOL of patients undergoing MHD who experience dysphoria and despondency. This improvement may be attributed to the encouragement and strength that patients on MHD derive from various forms of social support, thereby enabling them to cope better with life challenges and significantly enhancing their MH and overall QOL[28]. In clinical practice, it is advisable to develop tailored, individualized psychological intervention measures aimed at improving social support levels, boosting the confidence of patients undergoing MHD in managing their condition, and ultimately working toward the goal of enhancing their overall QOL.

This study had some limitations: (1) This study employed a cross-sectional design, and the participants were exclusively patients undergoing MHD at our hospital's hemodialysis center. This single-source sample with a relatively small size could potentially limit the generalizability of the findings. Future research should consider conducting multicenter studies to enhance the representativeness of the results[29]; and (2) The research outcomes were based solely on data from patients in our hospital, which may not fully capture the experiences of all patients undergoing MHD in the broader region. To gain a more comprehensive understanding, future research should incorporate longitudinal studies that track the dynamics of social support, dysphoria, despondency, and life patients undergoing MHD.

CONCLUSION

This study revealed that dysphoria and despondency had a direct negative impact on the QOL of patients undergoing MHD. Additionally, social support plays a mediating role in the relationship between dysphoria, despondency, and QOL among patients undergoing MHD. Thus, enhancing the level of social support provided to patients on MHD can help mitigate the occurrence of dysphoria and despondency, ultimately leading to an improved QOL for these patients. These findings provide valuable insights for clinical staff and offer a theoretical basis for the implementation of targeted treatment and nursing care for patients undergoing MHD.

ARTICLE HIGHLIGHTS

Research background

Patients undergoing Maintenance Hemodialysis (MHD) frequently experience dysphoria and despondency during extended dialysis treatment. These psychological difficulties can lead to alterations in daily routines, a decline in physical capabilities, a loss of social roles and status, and a profound influence on physical and mental well-being, along with overall quality of life (QOL). Consequently, enhancing their QOL is of the utmost importance.

Research motivation

Dysphoria and despondency can significantly diminish the QOL of patients undergoing MHD, whereas strong social support can enhance it. This study investigated the role of social support as a mediator between dysphoria, despondency, and QOL in patients undergoing MHD. This study aimed to establish a theoretical foundation for psychological interventions among patients undergoing MHD, enabling the implementation of effective strategies to boost social support levels and enhance their overall QOL.

Research objectives

The primary objective of this study was to investigate the influence of social support on dysphoria, despondency, and QOL in patients undergoing MHD. Additionally, it aimed to assess the mediating role of social support by constructing a mediating effect model that incorporated social support, dysphoria, despondency, and QOL. The ultimate goal was to enhance the level of social support for patients undergoing MHD, thereby mitigating the effects of dysphoria and despondency and ultimately improving their overall QOL.

Research methods

This cross-sectional study included 289 patients from our hospital. The Social support rating scale, Self-rating anxiety scale, Self-rating depression scale, and Life quality scale were used to collect data. Correlation analysis was used to examine the associations between social support, dysphoria, despondency, and the QOL in patients undergoing MHD. Furthermore, the bootstrap method was employed to assess the mediating effect of social support on the relationships among dysphoria, despondency, and QOL in these patients.

Research results

The study revealed several key findings: (1) Social support was positively correlated with QOL and negatively correlated with dysphoria and despondency; (2) Dysphoria and despondency had a negative impact on the QOL of patients undergoing maintenance hemodialysis; (3) The negative impact of dysphoria and despondency on QOL decreased in the presence of social support; and (4) Social support played a significant mediating role in the relationship between dysphoria, despondency, and QOL. These findings provide valuable insights for healthcare professionals and offer a basis for the targeted treatment and improved care of patients undergoing MHD.

Research conclusions

This study demonstrated that social support plays a mediating role in the relationship between dysphoria, despondency, and QOL in patients undergoing MHD. This study addressed the gap in the understanding of how social support influences the interplay between dysphoria, despondency, and QOL in patients undergoing MHD, providing a valuable theoretical foundation for future studies in this area.

Research perspectives

Future research in this area should consider expanding the sample size and incorporating multi-regional samples to gain a more comprehensive understanding of the relationships among social support, dysphoria, despondency, and QOL in patients undergoing MHD. Additionally, longitudinal studies could provide valuable insights into the evolution of these factors over time in patients undergoing MHD.

FOOTNOTES

Author contributions: Zhou X designed and performed the research and wrote the paper; Zhou YP designed the research and supervised the report; Wang XY and Hong J designed the research and contributed to the analysis; Ren HY and Tian XF designed the research and provided clinical advice; Zhang QQ designed the research and supervised the report; All authors approved the final manuscript.

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ORIGINAL ARTICLE

Observational Study

Causal relationship between feelings and cognitive decline: An univariable and multivariable Mendelian randomization study

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Abstract

BACKGROUND

While the impact of depression on cognition is well-documented, the relationship between feelings and cognition has received limited attention.

AIM

To explore the potential association between feelings and cognition with a two-sample Mendelian randomization (MR) analysis.

METHODS

Our analysis utilized genome-wide association data on various feelings (fed-up feelings, n = 453071; worrier/anxious feelings, n = 450765; guilty feelings, n = 450704; nervous feelings, n = 450700; sensitivity/hurt feelings, n = 449419; miserableness, n = 454982; loneliness/isolation, n = 455364; happiness, n = 152348) in the European population and their impact on cognitive functions (intelligence, n = 269867). Conducting a univariable MR (UVMR) analysis to assess the relationship between feelings and cognition. In this analysis, we applied the inverse variance weighting (IVW), weighted median, and MR Egger methods. Additionally, we performed sensitivity analysis (leave-one-out analysis), assessed heterogeneity

(using MR-PRESSO and Cochran's *Q* test), and conducted multiple validity test (employing MR-Egger regression). Subsequently, a multivariable MR (MVMR) analysis was employed to examine the impact of feelings on cognition. IVW served as the primary method in the multivariable analysis, complemented by median-based and MR-Egger methods.

RESULTS

In this study, UVMR indicated that sensitivity/hurt feelings may have a negative causal effect on cognition (OR = 0.63, 95%CI: 0.43-0.92, *P* = 0.017). After adjustment of other feelings using MVMR, a direct adverse causal effect on cognition was observed (OR_{MVMR} = 0.39, 95%CI: 0.17-0.90, P_{MVMR} = 0.027). While a potential increased risk of cognitive decline was observed for fed-up feelings in the UVMR analysis (OR_{UVMR} = 0.64, 95%CI: 0.42-0.97, P_{UVMR} = 0.037), this effect disappeared after adjusting for other feelings (OR_{MVMR} = 1.42, 95%CI: 0.43-4.74, P_{MVMR} = 0.569). These findings were generally consistent across MV-IVW, median-based, and MR-Egger analyses. MR-Egger regression revealed pleiotropy in the impact of worrier/anxious feelings on cognition, presenting a challenge in identifying the effect. Notably, this study did not demonstrate any significant impact of guilty feelings, nervous feelings, miserableness, or loneliness/isolation on cognition. Due to a limited number of instrumental variables for happiness, this study was unable to analyze the relationship between happiness and cognition.

CONCLUSION

This MR study finds that sensitivity/hurt feelings are associated with cognitive decline, while the link between worrier/anxious feelings and cognition remains inconclusive. Insufficient evidence supports direct associations between happiness, guilty feelings, nervous feelings, miserableness, loneliness/isolation, and cognition.

Key Words: Mendelian randomization analysis; Feelings; Cognition; Intelligence

Core Tip: Our two-sample Mendelian randomization analysis investigated the relationship between various emotions and cognitive function in the European population. We found compelling genetic evidence suggesting that sensitivity/hurt feelings may have a negative causal effect on cognition, even after adjusting for other emotional factors. In contrast, the causal link between worrier/anxious feelings and cognition remains inconclusive due to pleiotropy. Additionally, we did not find significant associations between happiness, guilty feelings, nervous feelings, miserableness, loneliness/isolation, and cognitive decline. This study sheds light on the complex interplay between emotions and cognition, highlighting the importance of sensitivity/hurt feelings in cognitive health.

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INTRODUCTION

Intelligence encompasses a spectrum of cognitive functions, including reasoning, planning, problem-solving, abstract thinking, experiential learning, and the comprehension of intricate concepts[1]. Intelligence or cognition can be assessed by a variety of neurocognitive tests[2,3]. Given the expanding elderly population, cognitive health has become a paramount concern. Mild cognitive impairment (MCI) and dementia represent discrete stages of cognitive decline. MCI prevalence varies, ranging from 4% to 19% among individuals aged 65 and older[4-6]. Globally, around 50 million individuals live with dementia, and this number is expected to reach 152 million by 2050[7]. MCI serves as an intermediary stage between healthy cognitive aging and early-stage dementia. Individuals with MCI, also known as those with cognitive impairment without dementia, maintain their functional daily activities. However, they report objective cognitive deficits, either self-reported or observed by their relatives[8,9]. While some individuals with MCI may revert to a state of healthy cognition, a substantial proportion (22%) progress to dementia within a span of 3 to 10 years[10]. Both modifiable risk factors, including factors like smoking, diabetes, and depression, as well as non-modifiable factors like age, can contribute to cognitive decline[11]. Furthermore, neuropsychiatric symptoms frequently accompany cognitive decline, with their severity often escalating alongside cognitive impairment[11,12].

Feelings represent psychological experiences linked to physiological states, aiding in adaptation to changes in bodily conditions, and enabling effective responses in complex scenarios[13]. Several critical health conditions, such as depression, substance addiction, and intractable pain, center on disturbances in feelings. Numerous neuropsychiatric disorders exhibit marked deficits in both cognitive and emotional domains. These included Alzheimer's disease, autism, and schizophrenia. The central challenge in comprehending these disorders revolves around unraveling the intricate interplay

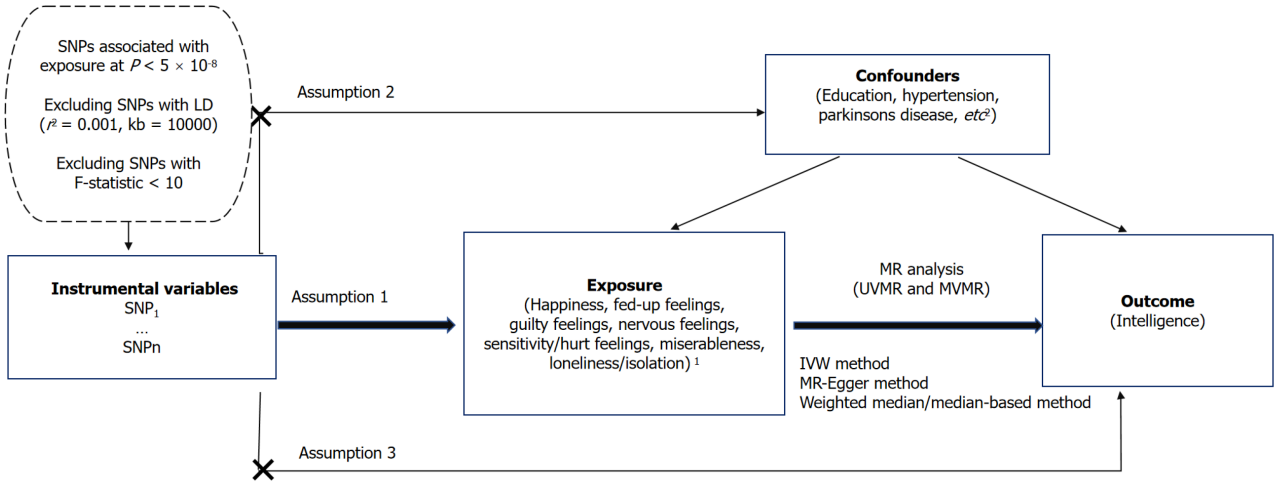

Figure 1 Study design overview. [1]Worrier/anxious feelings was excluded because of potential pleiotropy. [2]Hearing difficulty, diabetes, high cholesterol, body mass index, smoking, alcohol intake, coronary artery disease, progressive supranuclear palsy, neuroticism, depressive symptoms or depression, schizophrenia, multiple sclerosis, autism, bipolar disorder, progressive supranuclear palsy, epilepsy, Alzheimers disease, spinal injury. SNPs: Single-nucleotide polymorphisms; LD: Linkage disequilibrium; MR: Mendelian randomization; IVW: Inverse-variance weighted; UVMR: Univariable Mendelian randomization; MVMR: Multivariable Mendelian randomization.

between cognitive and emotional processes in both normal and pathological contexts[14]. Currently, the precise influence of feelings on cognition remains a subject of ongoing investigation.

Mendelian randomization (MR), an innovative tool for evaluating causal relationships between exposure factors and outcomes, employs genetic variants as instrumental variables[15]. MR essentially functions as a natural randomized controlled trial, built on the assumption that genetic variant alleles associated with exposure are randomly distributed. Consequently, MR methodology serves to mitigate common pitfalls associated with confounding and reverse causation often encountered in observational studies[16]. In this study, we conduct a two-sample MR analysis to delve into the causal relationship between feelings and cognitive function.

MATERIALS AND METHODS

Study design

The study design overview is depicted in Figure 1. To comprehensively assess the causal role of feelings in cognition, we initially conducted univariable MR (UVMR) analyses. Subsequent multivariable MR (MVMR) analyses, considering the genetic interrelationships among these feelings, were conducted to examine their independent effects. All MR analyses followed a two-sample approach. To ensure unbiased causal assessments, the MR study must satisfy three key assumptions: (1) The genetic variants are highly associated with exposures; (2) genetic variants are not associated with potential confounders; and (3) genetic variants influencing the outcome exclusively through the exposure pathway. Our MR analyses relied on publicly available Genome-Wide Association Study (GWAS) data, obviating the need for additional approvals or informed consent.

Data source

Intelligence: The summary-level data on intelligence were derived from a GWAS meta-analysis involving 14 independent epidemiological cohorts of European ancestry[17]. These cohorts assessed intelligence through a range of neurocognitive tests, including mathematical reasoning, verbal fluency, digit span, immediate and delayed recall tests, among others. In most of these 14 cohorts, intelligence was treated as a continuous variable, quantified by cognitive test scores. However, in the high IQ/health and retirement study, which differed from the other cohorts, individuals were categorized as either high-IQ or unselected, rather than being assessed with a specific intelligence score. Comprehensive GWAS information related to intelligence is available on the public GWAS website, with the ID ebi-a-GCST006250 (https://gwas.mrcieu.ac.uk/).

Feelings: GWAS information pertaining to feelings can be accessed on the website (https://gwas.mrcieu.ac.uk/), with the following identifiers: Happiness (ID: ukb-b-4062), fed-up feelings (ID: ukb-b-19809), worrier/anxious feelings (ID: ukb-b-6519), guilty feelings (ID: ukb-b-10169), nervous feelings (ID: ukb-b-20544), sensitivity/hurt feelings (ID: ukb-b-9981), miserableness (ID: ukb-b-18994), and loneliness/isolation (ID: ukb-b-8476). It is worth noting that, except for Happiness, which is classified as categorical ordered, the remaining feelings are represented as binary variables. These variables were derived from GWAS pipeline using phesant-derived variables from UK Biobank (Table 1).

Selection of genetic instruments

Single-nucleotide polymorphisms: We selected valid instrumental variables (IVs) according to the following criteria: (1) Single-nucleotide polymorphisms (SNPs) were required to exhibit strong associations with the exposure and possess significant P values of $< 5 \times 10^{-8}$; (2) To evaluate linkage disequilibrium (LD) between the selected SNPs, we utilized a clumping process ($r^2 = 0.001$, clumping distance = 10000 kb); (3) We employed PhenoScanner (http://www.phenoscanner.medschl.cam.ac.uk/) to assess whether the selected SNPs were associated with other traits at genome-wide significance levels, thereby eliminating genetic variants associated with the outcome and potential confounders; and (4) For SNPs to be considered meaningful, a minor allele frequency threshold of 0.01 was set, and the F-test statistic was employed to quantify the strength of IVs, with a threshold of $F > 10$ for MR analyses. All SNPs were harmonized for the exposure and the outcome by alleles to ensure alignment of allele effects. In cases where a specific IV could not be matched in the outcome dataset, proxy SNPs with high LD ($r^2 > 0.8$) were identified for inclusion.

Statistical analysis

All statistical analyses were conducted using the following R software packages: TwoSampleMR (version 0.5.6), MendelianRandomization (version 0.9.0), and MRPRESSO (version 1.0), implemented in R software version 4.2.2. Statistical significance was defined by a P value < 0.05.

For the UVMR analysis, we employed three distinct methods: inverse-variance weighted (IVW), weighted median, and MR-Egger approaches[18-20]. The primary analysis, using IVW, was conducted to investigate the causal relationship between feelings and intelligence. We assessed heterogeneity among IVs through Cochran's Q test. In cases where no evidence of heterogeneity was observed, we utilized fixed-effect IVW models; otherwise, random-effect IVW models were applied[18]. To assess horizontal pleiotropy, we examined the intercept of MR-Egger regression and conducted MR-PRESSO analysis[20,21]. We also employed a leave-one-out analysis to assess whether the results were significantly influenced by any specific SNP. In the UVMR, we carried out a total of seven MR analyses, applying a Bonferroni-corrected threshold of $P < 0.007$ (0.05/7). Associations with P values ranging from ≥ 0.007 to < 0.05 were considered suggestive associations.

Considering potential correlations among feelings that may impact intelligence, we conducted a MVMR analysis to assess the independent causal influence of feelings on cognition[22,23]. In this analysis, we employed three different MVMR methods: MR-IVW, the MR-Egger method, and the median-based method.

RESULTS

SNP selection

Following the removal of SNPs exhibiting LD, the feelings-related SNPs obtained from GWAS in Supplementary Table 1. The final selection of independent SNPs, meticulously excluding any confounding factors, is thoughtfully presented in Supplementary Table 2. Notably, the F-statistics associated with the included SNPs in this study all exceeded the threshold of 10. However, when it comes to the analysis of Happiness, it is worth mentioning that only one instrumental variable (IV), namely rs685031, met the criteria with a P value $< 5 \times 10^{-8}$, an $r^2 = 0.001$, and kb = 10000, rendering the analysis considerably challenging. Furthermore, the excluded confounding factors in this study encompassed a wide array of variables, including education, hearing impairment, diabetes, hypertension, high cholesterol, body mass index, smoking, alcohol intake, coronary artery disease, as well as an assortment of neuropsychiatric disorders, such as progressive supranuclear palsy, neuroticism, depressive symptoms or depression, schizophrenia, Parkinson's disease, multiple sclerosis, autism, bipolar disorder, epilepsy, Alzheimer's disease, and spinal cord injuries.

UVMR analysis of the causal relationship between feelings and cognitive function

The results from the IVW-mre (multiplicative random effects) method suggested that fed-up feelings have a potential effect on cognitive function, with an OR of 0.64 (95%CI: 0.42-0.97; $P = 0.037$). Similarly, sensitivity/hurt feelings showed an OR of 0.63 (95%CI: 0.43-0.92; $P = 0.017$), as detailed in Figure 2. Conversely, feelings such as guilty feelings, miserableness, loneliness/isolation, and nervous feelings showed no significant impact on cognitive function (Figure 2). These findings were corroborated by other MR analysis methods. Sensitivity analysis revealed heterogeneity in the analysis of these feelings and intelligence (Table 2). Consequently, we employed a multiplicative random-effects inverse-variance weighted method in this study. Intercepts from MR-Egger regression and MR-PRESSO analyses indicated directional pleiotropy in the relationship between worrier/anxious feelings and cognitive function. Importantly, no outliers were identified in the analysis of sensitivity/hurt feelings (Table 2). Leave-one-out analysis demonstrated that the effects of fed-up feelings and sensitivity/hurt feelings on cognitive function were not driven by a single SNP. Scatter plots, forest plots, and leave-one-out plots that illustrate the analysis of sensitivity/hurt feelings and fed-up feelings can be found in the Supplementary Figures 1-6.

Multivariable MR analysis of the causal relationship between feelings and cognitive function

Worrier/anxious feelings were excluded from the multivariable MR analysis due to pleiotropy concerns. Eventually, we included a total of 36 SNPs in the multivariable MR analysis. The intercept derived from the MR-Egger regression indicated no evidence of pleiotropy in the multivariable MR (MVMR) analysis. However, the heterogeneity test revealed the presence of heterogeneity (Supplementary Table 3).

Table 1 Detailed information on data sources

Trait	*n*	Case	Control	ID	Cohort(s)	Population
Intelligence	269867			ebi-a-GCST006250	Meta-analysis of 14 cohorts	European
Happiness	152348			ukb-b-4062	UK Biobank	European
Fed-up feelings	453071	184258	268813	ukb-b-19809	UK Biobank	European
Worrier/anxious feelings	450765	255812	194953	ukb-b-6519	UK Biobank	European
Guilty feelings	450704	129383	321321	ukb-b-10169	UK Biobank	European
Nervous feelings	450700	106635	344065	ukb-b-20544	UK Biobank	European
Sensitivity/hurt feelings	449419	249799	199620	ukb-b-9981	UK Biobank	European
Miserableness	454982	195435	259547	ukb-b-18994	UK Biobank	European
Loneliness, isolation	455364	82436	372928	ukb-b-8476	UK Biobank	European

Table 2 Sensitivity analysis of feelings and cognition

Risk factors	Pleiotropy test			Heterogeneity test	
	Intercept	*P* value[1]	*P* value[2] (distortion)	Cochran's Q	*P* Value
Fed-up feelings	0.007	0.428	0.387	61.73	< 0.001
Worrier/anxious feelings	0.026	0.018	0.012	87.97	< 0.001
Guilty feelings	0.0003	0.761	0.257	47.46	< 0.001
Nervous feelings	-0.006	0.242	0.317	46.51	< 0.001
Sensitivity/hurt feelings	-0.002	0.816	NA	23.06	0.017
Miserableness	0.018	0.246	0.553	28.44	< 0.001
Loneliness, isolation	0.003	0.946	NA	14.31	< 0.001

[1]*P* values assessing pleiotropy were obtained using the MR-Egger test, and a *P* value < 0.05 suggests a potential pleiotropic effect.
[2]*P* values for distortion were obtained through the MR-PRESSO test, where a *P* value < 0.05 indicates a significant distinction between estimates before and after removing outliers. Notably, the distortion test *P* value was not applicable for loneliness/isolation and sensitivity/hurt feelings analysis.

Even with adjustments for other feelings, sensitivity/hurt feelings still showed a negative direct effect on cognitive function (OR_{IVW} = 0.39, 95%CI: 0.17-0.90, P_{IVW} = 0.027). Both MR-Egger and median-based analyses were consistent with the results obtained from IVW method. On the other hand, Fed-up feelings, along with other factors, showed no significant association with cognitive function in the multivariable MR analysis (Figure 3).

DISCUSSION

In this study, our examination of the influence of feelings on cognitive function revealed genetic evidence that links sensitivity/hurt feelings with cognitive decline. However, after accounting for the genetic effects of other feelings in the MVMR analysis, the direct causal effect of Fed-up feelings did not persist. Furthermore, our findings show no associations between various feelings - happiness, guilty, nervous, miserableness, and loneliness/isolation - and cognitive function.

It is well-documented that the upper brainstem and hypothalamus serve as the structural basis for generating feelings, while the cerebral cortex facilitates complex cognitive processes such as memory, language, reasoning, and imagination [24,25]. These cognitive processes enhance emotional states, aiding the body's adaptation to changes. Feelings are vital in understanding shifts in bodily states due to environmental changes and in applying this knowledge to predict future situations, thereby enhancing behavioral adaptability. Feelings lay the foundation for establishing higher levels of cognition and consciousness[13].

Hurt feelings, also known as social pain, often arise in unfavorable circumstances and intertwine closely with cognitive functionslike perception, judgment, expectations, and beliefs[26,27]. The perception of hurt feelings and high sensitivity to rejection have been shown to predict more verbal aggression but less physical aggression[28]. Researchers have proposed the "interactive influence model of emotion and cognition", which suggests that feelings can override cognition, influencing decision-making from the bottom-up, particularly in emotion exaggeration context[29]. Using the MR approach, our study strengthened the evidence for a causal effect of hurt feelings on cognitive decline.

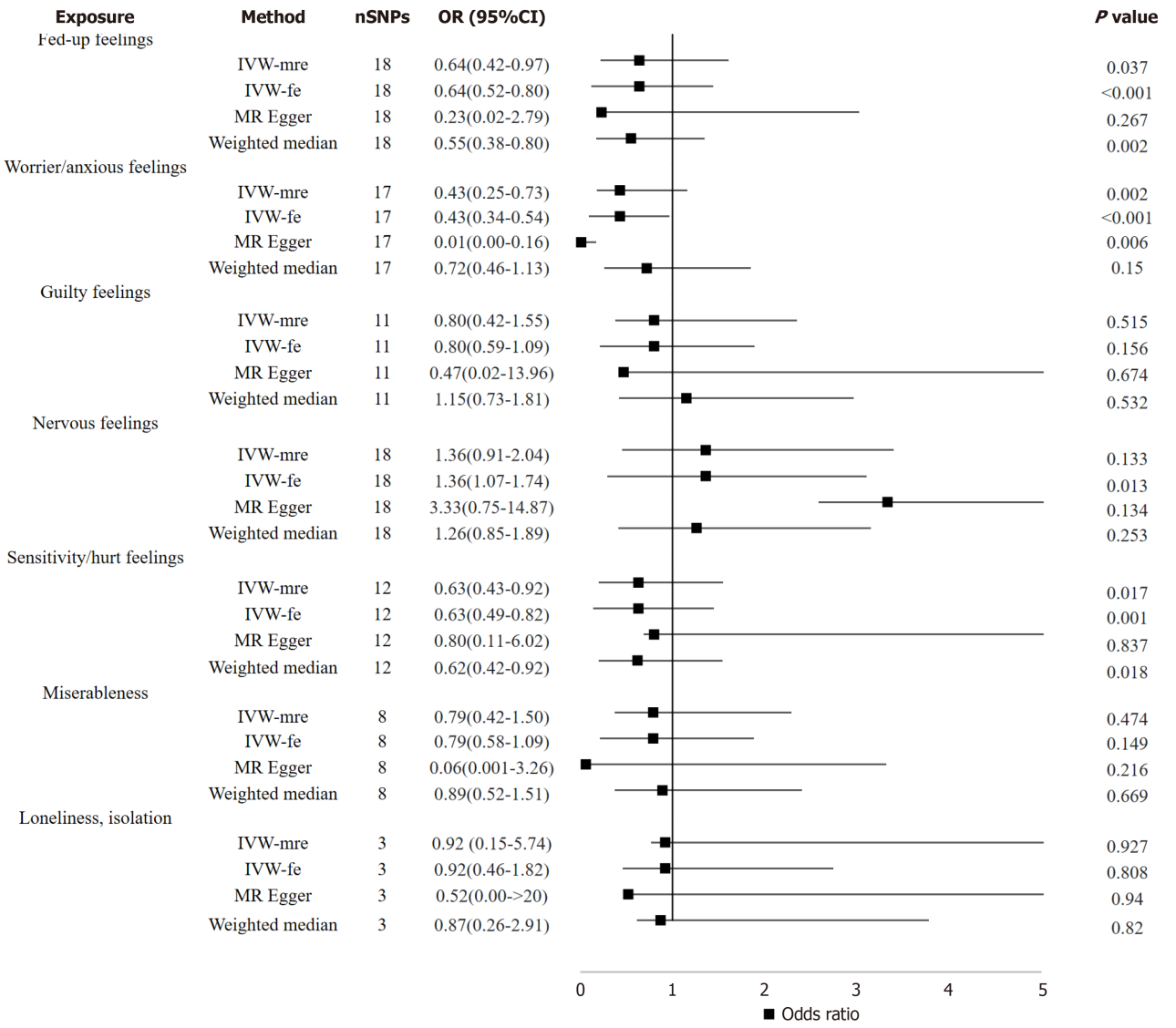

Figure 2 Univariable Mendelian randomization analysis of the impact of feelings on cognitive function. SNPs: Single-nucleotide polymorphisms; IVW: Inverse variance weighting; MR: Mendelian Randomization; mre: Multiplicative random effects; fe: Fixed effects.

Loneliness is a psychological condition resulting from a disconnect between an individual's desired and actual social relations, leading to the negative experience of feeling alone or socially isolated, even in the presence of family or friends [30]. Research has indicated that loneliness and depression are distinct, with loneliness increasing the risk of depression [31,32]. Loneliness is also a risk factor for cognitive decline and Alzheimer's disease progression[33]. Social isolation, on the other hand, relates to the structural aspects of one's social network. An observational study revealed that social isolation was independently associated with a 1.26-fold increased risk of dementia over an average follow-up period of 11.7 years, while the fully adjusted hazard ratio for dementia specifically associated with loneliness was 1.04[34]. However, due to insufficient instrumental variables, this study could not conclusively explore a causal relationship between loneliness/isolation and cognition, highlighting the need for further investigation.

Guilt feelings emergewhen a person feel responsible perceives responsibility for a negative outcome impacting others [35]. Guilt is often viewed as a detrimental emotion that should be avoided, yet it is also associated with a desire to improve subsequent performance, apologize, and rectify misdeeds. Guilt feelings can influence interpersonal decision-making[36]. However, our study did not find any impact of guilt on cognition.

Furthermore, there is limited research on the cognitive implications of miserableness, nervous feelings, and fed-up feelings. Our univariate MR research initially suggested that fed-up feelings might lead to decreased cognition. However, after adjusting for various factors, we observed no significant impact on cognition.

Study limitations

Data generalizability: Since this study's data were sourced exclusively from European populations, the generalizability of the findings to other ethnic groups may be limited.

Pleiotropy challenges: Completely eliminating pleiotropy in MR analysis is challenging, and horizontal pleiotropy can notably affect the stability of MR results. In this study, univariate MR research indicates that worrier/anxious feelings

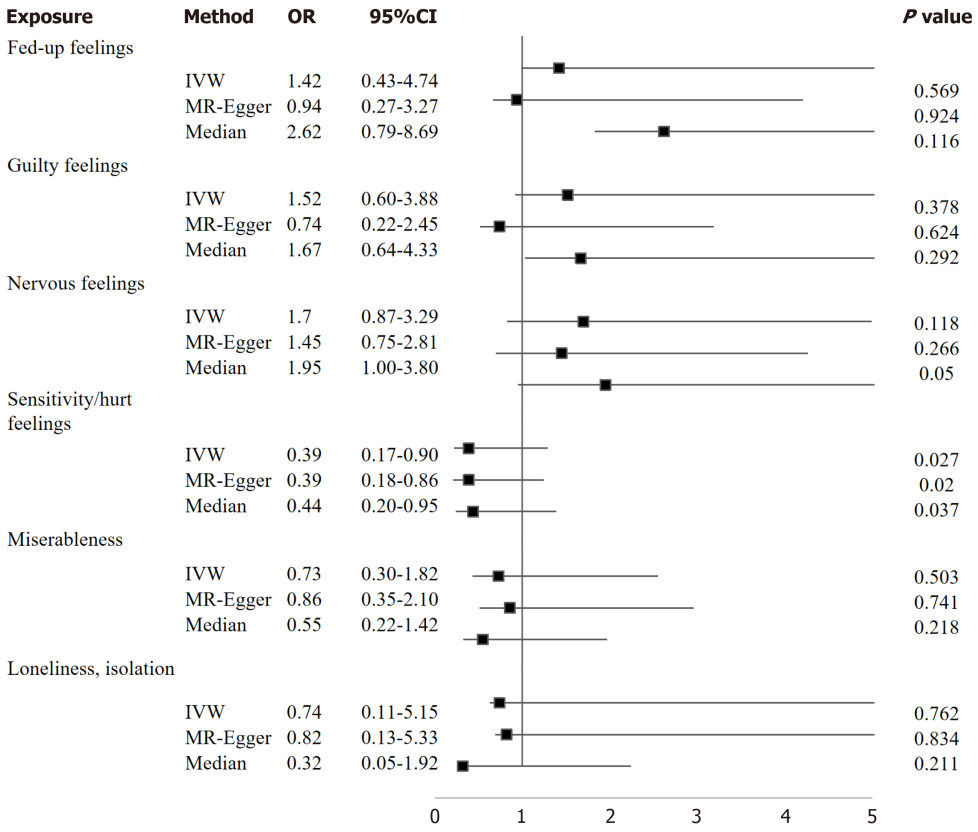

Figure 3 Multivariable Mendelian randomization analysis of the impact of feelings on cognitive function. IVW: Inverse variance weighting; MR: Mendelian Randomization.

may influence cognition. However, their effects appear to be pleiotropic. Consequently, it is not possible to conclusively assert that worrier/anxious feelings directly affect cognition, warranting further investigation.

CONCLUSION

These MR findings provide causal evidence linking sensitivity/hurt feelings with cognitive decline. However, the causal relationship between worrier/anxious feelings and cognition remains inconclusive. Insufficient evidence exists to suggest a direct association of happiness, guilty feelings, nervous feelings, miserableness, and loneliness/isolation with cognition.

ARTICLE HIGHLIGHTS

Research background

The study addresses the escalating concern of cognitive health, particularly in the aging population. With conditions like Mild Cognitive Impairment (MCI) and dementia on the rise, understanding the prevalence, progression, and contributing factors becomes paramount. Globally, millions grapple with cognitive disorders, and the intricate interplay between cognitive decline and neuropsychiatric symptoms poses a significant challenge. The study aims to explore the complex relationship between feelings and cognition, utilizing innovative Mendelian randomization (MR) methodology to assess causal links and overcome common pitfalls associated with observational studies.

Research motivation

The increasing prevalence of cognitive disorders, such as MCI and dementia, poses a critical challenge in understanding the complexities of cognitive decline. With a global aging population, the urgency to address cognitive health issues becomes evident. The study aims to unravel the intricate interplay between cognitive and emotional processes in various health conditions, including neu-ropsychiatric disorders, and to explore the significant impact of feelings on cognitive function. This investigation is motivated by the need to fill gaps in our understanding of the causal relationship between emotions and cognition, utilizing innovative MR methodology to overcome limitations in observational studies and advance future research in this field.

Research objectives

The primary objectives of this study are to comprehensively investigate the prevalence and progression of MCI and dementia in the aging population, identifying modifiable and non-modifiable risk factors contributing to cognitive decline. Additionally, we aim to elucidate the intricate interplay between cognitive and emotional processes in various neuropsychiatric disorders, such as Alzheimer's disease, autism, and schizophrenia. Achieving these objectives will not only enhance our understanding of the causal relationship between emotions and cognition but also provide valuable insights for future research in the field of cognitive health.

Research methods

The study employed a two-sample MR approach, utilizing univariable MR (UVMR) and subsequent multivariable MR (MVMR) analyses to comprehensively assess the causal role of feelings in cognition. Data on intelligence and feelings, sourced from publicly available Genome-Wide Association Study data and the UK Biobank, respectively, underwent meticulous selection of valid instrumental variables (IVs). Statistical analyses using R software packages included UVMR analysis employing IVW, weighted median, and MR-Egger approaches, assessing the causal relationship between feelings and intelligence. The study addressed potential correlations among feelings impacting cognition through seven UVMR analyses with a Bonferroni-corrected threshold and employed MVMR methods to assess the independent causal influence of feelings on cognition, ensuring robust investigation into their intricate relationship.

Research results

Following the meticulous elimination of SNPs in linkage disequilibrium, feelings-related SNPs were carefully chosen, meeting the F-statistics threshold for robust instrumental variables. Notably, the analysis of Happiness faced challenges with only one qualifying IV. In the UVMR analysis, fed-up feelings and sensitivity/hurt feelings showed potential impacts on cognitive function (OR 0.64, 95%CI: 0.42-0.97, P = 0.037 and OR 0.63, 95%CI: 0.43-0.92, P = 0.017, respectively). Other feelings had no significant impact, and robustness was ensured by addressing heterogeneity and pleiotropy concerns. The MVMR analysis, excluding worrier/anxious feelings, utilized 36 SNPs. Despite heterogeneity, sensitivity/hurt feelings exhibited a negative direct effect on cognitive function (ORIVW = 0.39, 95%CI: 0.17-0.90, PIVW = 0.027), with consistent results from MR-Egger and median-based analyses. Conversely, fed-up feelings, when considering other factors, showed no significant association with cognitive function. These findings deepen our understanding of the nuanced relationship between specific feelings and cognitive function, offering insights into potential causal links, while challenges in the analysis of Happiness and remaining heterogeneity indicate avenues for further exploration in future research.

Research conclusions

This study introduces a groundbreaking theory by genetically linking sensitivity/hurt feelings to cognitive decline. Employing MR as a method, the research sheds light on the causal relationships between emotions and cognitive function. Notably, it proposes that while hurt feelings have a potential causal effect on cognitive decline, fed-up feelings do not exhibit a direct causal effect after adjusting for genetic influences.

Research perspectives

Several aspects merit further exploration in future studies. Firstly, regarding the potential impact of feelings of fed-upness on cognitive function, despite the absence of a direct causal effect in this study, it is essential to delve deeper into potential moderating mechanisms or interactions with other emotional factors. Secondly, in relation to the potential association between loneliness, social isolation, and cognitive decline, further research with careful design and diverse samples is necessary to elucidate this relationship due to limitations in the current dataset. Additionally, a more in-depth investigation into the role of anxiety and worry in cognitive function is needed to address questions about their potentially bidirectional effects. Lastly, cross-cultural and cross-ethnic studies will contribute to validating the universality of these findings across different populations, providing a more comprehensive understanding of the relationship between emotions and cognition.

FOOTNOTES

Author contributions: Fan L ensured the overall integrity of the study, defined the intellectual content, participated in the literature search, and reviewed the manuscript; Liu J conducted the research, analyzed the data and drafted the initial manuscript; Liu L, Hu YX, and Zou X provided input and support for the research design; Li JH and Zhang HY offered assistance with statistical analysis; all authors read and approved the final manuscript.

Institutional review board statement: The study used public GWAS statistics and did not collect new human data. Hence, ethical approval was not required by the ethics committee of Chinese PLA General Hospital.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: The authors declare that there are no conflicts of interest associated with this research.

Data sharing statement: The data used in this study were obtained from publicly available genome-wide association studies (GWAS) databases. The summary-level data on intelligence were derived from a GWAS meta-analysis involving 14 independent epidemiological cohorts of European ancestry. The data related to feelings were obtained from separate GWAS datasets. Comprehensive GWAS information can be accessed through the public GWAS website (https://gwas.mrcieu.ac.uk/), with the provided identifiers. These datasets are publicly accessible and can be obtained directly from the GWAS website for research purposes. No additional data were used in this study.

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Optimization of nursing interventions for postoperative mental status recovery in patients with cerebral hemorrhage

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Abstract

BACKGROUND

Hypertensive cerebral hemorrhage (HCH), the most common chronic diseases, has become a topic of global public health discussions.

AIM

To investigate the role of rehabilitative nursing interventions in optimizing the postoperative mental status recovery phase and to provide clinical value for future rehabilitation of patients with HCH.

METHODS

This randomized controlled study included 120 patients with cerebral HCH who were contained to our neurosurgery department between May 2021–May 2023 as the participants. The participants have randomly sampled and grouped into the observation and control groups. The observation group received the rehabilitation nursing model, whereas the control group have given conventional nursing. The conscious state of the patients was assessed at 7, 14, 21, and 30 d postoperatively. After one month of care, sleep quality, anxiety, and depression were compared between the two groups. Patient and family satisfaction were assessed using a nursing care model.

RESULTS

The results showed that the state of consciousness scores of the patients in both groups significantly increased ($P < 0.05$) after surgical treatment. From the 14th day onwards, differences in the state of consciousness scores between the two groups

of patients began to appear ($P < 0.05$). After one month of care, the sleep quality, anxiety state, and depression state of patients were significantly better in the observation group than in the control group ($P < 0.05$). Satisfaction with nursing care was higher in the observation group than in the control group ($P < 0.05$).

CONCLUSION

The rehabilitation nursing model has a more complete system compared to conventional nursing, which can effectively improve the postoperative quality of life of patients with cerebral hemorrhage and improve the efficiency of mental state recovery; however, further analysis and research are needed to provide more scientific evidence.

Key Words: Cerebral hemorrhage; Nursing interventions; Mental status; Optimization; Rehabilitation nursing model; Quality of life

Core Tip: This study provides a theoretical basis for the prognosis of the post-operative care and rehabilitation of patients with a cerebral hemorrhage. Mental health problems in patients with hypertensive cerebral hemorrhage after surgery should be given more attention in the future.

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INTRODUCTION

Cerebral hemorrhage is a severe bleeding in the brain caused by the blood rupture vessels in the brain tissue due to sudden excitement, excessive exercise, and mental work[1]. Its clinical morbidity is very high, with the World Health Organization statistics finding that about 40.4% of patients die in the first month after a cerebral hemorrhage, and many more survivors have irreversible disabilities after successful clinical resuscitation[2]. However, in a previous review study, it was found that the common causes of cerebral hemorrhage are hypertension, cerebrovascular atherosclerosis, and cerebrovascular malformation. Hypertension is responsible for > 80% of all cerebral hemorrhages and is a priority for prevention[3].

In modern society, with the change of the global medical model, the clinical treatment of the patient's disease is not a single requirement, but the pursuit of a full range of needs, from health care prevention-treatment-physical and mental rehabilitation - the pursuit of a better quality of life, but today's medical care model only meets the general needs of the patient, the individual needs of the care, there are still some shortcomings. Most studies have shown that patients with cerebral hemorrhage experience significant changes in their psychological state after surgery, including anxiety, depression, and decreased sleep quality, and that these psychological conditions can lead to dysfunctions in multiple systems[4,5]. Quality of life has been found to be positively correlated with the ability to care for oneself. A good nursing care model can help patients with cerebral hemorrhage have a good prognosis and improve their satisfaction with their care[6].

Recently, studies have domesticated that the addition of psychological intervention in rehabilitation care has a better effect on the psychological recovery of postoperative patients, and psychological intervention care can effectively improve the psychological stress of postoperative patients due to the fear of surgery and the expectation of the recovery effect, but there are fewer studies on the joint psychological intervention care in the rehabilitation care of cerebral hemorrhage patients. Based on the background of the previous studies, we used a randomized controlled study to investigate the optimization of the role of the nursing intervention in the recovery of the mental state of postoperative patients with brain hemorrhage, and to provide a clinical reference for the rehabilitation of patients with cerebral hemorrhage in the future.

MATERIALS AND METHODS

Research participants

Our study population consisted of patients with postoperative hypertensive cerebral hemorrhage (HCH) who were admitted to our surgical department. The admission period was from May 2021 to May 2023, and 120 patients were admitted. Simple random sampling was used to divide the patients into the observation and control groups, with 60 patients per group. The criteria for inclusion in the study were as follows: (1) Patients with cerebral hemorrhage who met

the diagnostic criteria for stroke, as evidenced by computed tomography or magnetic resonance imaging; (2) meet the diagnostic criteria for high blood pressure, which are a systolic blood pressure of ≥ 140 mmHg and a diastolic blood pressure of ≥ 90 mmHg; (3) conscious patients with a neurological deficit score of ≥ 5 points; (4) patients without previous serious mental illness; (5) patients without severe comorbid organ damage; and (6) patients without cognitive dysfunction or psychological disorders.

If any patient has the following conditions, the observation should be terminated and excluded: (1) The observation group cannot successfully complete the whole treatment phase during the intervention for various reasons, and their compliance is poor that they cannot cooperate and comply with the nursing intervention on time; (2) patients in the control group did not comply with the nursing model during the study period; and (3) patients who experienced a sudden accidental life crisis during the period of receiving treatment.

The study was approved by the ethics committee of our hospital prior to the study, and all participants signed an informed consent form.

Research design

This study mainly used randomized controlled trials. Subjects were randomized into observation and control groups. Rehabilitation nursing was added to the routine nursing model to care for patients with cerebral hemorrhage. The control group only used the conventional nursing model.

Rehabilitation nursing model: The researcher formed an observation group with five nurses and one professional rehabilitation therapist who passed training in the undergraduate department; the nurses had more than five years of clinical work experience, bachelor's degree or above, and supervisor nurse or above; the rehabilitation therapist had a professional qualification certificate, postgraduate education or above, and possessed good clinical rehabilitation skills. Patients in the observation group underwent a mental nursing intervention prescription based on the control group, and the intervention prescription was set according to the characteristics of stroke disease staging, which included self-concept aspects in the onset stage; disease-related behavioral aspects and daily life behaviors in the critical stage; disease-related behavioral aspects, daily life behaviors, and self-concept in the acute stage; and disease-related behavioral aspects, daily life behaviors, and self-concept in the stable stage; daily living behavior aspects and self-concept aspects in the stable phase; and disease-related behavior aspects and daily living behavior aspects in the unstable phase.

In the process of intervention, the researcher, to help patients master knowledge of the disease and various rehabilitation techniques and self-care skills, uses the health education board structure chart to carry out individualized health education for patients. The main method is that the researcher carries the health knowledge board structure chart to the patient's bedside, and the patient chooses the boards that interest him according to his needs, carries out one-to-one guidance, and asks his family members or the patient to cooperate with the exercise, to judge whether the patient has mastered the knowledge.

To judge whether the patient has mastered it, the researcher can carry out semi-structured questioning and set up identification cards for knowledge feedback, and the health education of different disease stages follows the patient's individual wishes and needs for health guidance. The intervention was carried out from the day the patient was admitted to the hospital. During the hospital period, the intervention time was concentrated from 10:00 a.m. to 12:00 p.m. and 14:00 p.m. to 18:00 p.m. every day, each time from 30 min to 60 min. After discharge, the intervention time was for WeChat interaction every day from 18:00 p.m. to 20:00 p.m., weekly home visits, and weekly remote video on Saturdays and Sundays. According to the patient's needs, appointment of home visits and guidance was made, and if the patient had serious problems, they were asked to return to the hospital for follow-up at any time. The entire prescription intervention was conducted for eight weeks.

State of consciousness rating Scale

The Glasgow Coma Scale, developed by Teasdale and Jennett in 1974, assesses disorders of consciousness. The items included eye-opening responses (1-4 points), motor responses (1–5 points), and verbal responses (1–6 points). The scale has a maximum score of 15 and a minimum score of 3. The higher the score, the better the state of consciousness. Those with a score lower than 3 are in a deep coma, and a score of 3–6 suggests that the patient has a poor prognosis[7].

Mental status score

Pittsburgh sleep quality index: In 1989, Dr Buysse, a psychiatrist at the University of Pittsburgh, USA, and others developed the Pittsburgh sleep quality index (PSQI). Participants' sleep quality over the past month was assessed using the PSQI. It consists of 19 self-rating items and 5 others review projects, of which the 19th self-rating item and the 5 others review projects do not take part in the scoring process. Only 18 self-evaluation items that participated in scoring are introduced here. Eighteen items have seven components, each of which has a score on a scale of 0-3. The cumulative score for each component is the total PSQI score, with a total score range of 0-21. Each component is summed to produce a PSQI score, which ranges from 0 to 21. The higher the score, the poorer the quality of sleep[8].

Anxiety scale (SAS): The Zung Anxiety Self-Rating Scale, first developed in 1971, is a self-report measure of anxiety used primarily in adults and consists of 20 items on a four-point scale ranging from one to four. These are then multiplied by 1.25 for a standard score. In relation to the national norm, the final classification of the SAS standard is as follows: Total score ≥ 50 has anxiety symptoms, < 50 has no anxiety symptoms. Cronbach's αfor this scale was 0.931[9].

Depression scale (SDS): Developed by Zung in 1965, the SDS is a self-report measure of the severity of depressive symptoms in adults, consisting of 20 items on a four-point Likert scale from one to four (*i.e.*, none to all of them). The total score of the SDS index is the integer portion of the scores of each of the 20 entries added together to obtain the initial

score, and then multiplied by 1.25. Referring to the results of the national norm, the final SDS criteria were: a total score ≥ 53 as having depressive symptoms and < 53 as not having depressive symptoms[10].

Nursing care satisfaction scores

Newcastle Satisfaction with Nursing Scale was used in this study for nursing satisfaction measurement. Several scholars in China have systematically elaborated on the study of satisfaction with inpatient nursing services, and found that the scale is universal, with a total of 19 entries, and adopts the Likert 5-point scale, including very dissatisfied, dissatisfied, overall satisfaction, satisfaction and very satisfaction in terms of "One, two, three, four and five". The higher the score, the greater the satisfaction with care[11].

Statistical analysis

A database was set up and the data was entered using EpiData, after having double-checked. Data were entered after double checking. SPSS 26.0 software was used to analyze the data. Count data were analyzed using the chi-squared test for comparison. Measurement data were expressed as mean ± SD. The two groups before and after the intervention were compared by repeated-measures ANOVA, the two groups were compared by two independent samples *t*-test, and the two groups within the groups were compared by the LSD procedure. Statistical significance was set at $P < 0.05$.

RESULTS

Research participants

This randomized controlled study included 120 patients admitted to our neurosurgery department for cerebral hemorrhage surgery who were randomly divided into observation and control groups. The results showed that there were no significant differences between the patients in the observation group and the control group in terms of age, sex, body mass index, years of education, or site of cerebral hemorrhage ($P > 0.05$) (Table 1).

Consciousness scores of patients

The patients' state of consciousness was regularly assessed after surgery and analyzed and compared between the two groups on 7, 14, 21 d postoperatively. The results showed that the state of consciousness scores of the patients in both groups significantly increased ($P < 0.05$) after surgical treatment. From the 14th day onwards, differences in the state of consciousness scores between the two groups of patients began to appear ($P < 0.05$) (Figure 1).

Mental status score of patients

The patient's psychological state was assessed using indicators, including sleep quality, anxiety, and depression. The results showed that after one month of care, the sleep quality, anxiety, and depression states of patients in the observation group were significantly better than those in the control group ($P < 0.05$) (Table 2).

Nursing care satisfaction scores

Comparison and analysis of the care satisfaction scores of the two groups of patients showed that the care satisfaction scores of the observation group were significantly higher than those of the control group ($P < 0.05$) (Table 3).

DISCUSSION

Cerebral hemorrhage caused by hypertension is usually found in the elderly population, and the latest statistics show that there are about 2 million cases of spontaneous cerebral hemorrhage in China every year, more than half of which accounts for HCH, with a mortality rate of up to 40%–70% and a disability rate of 50%–85%[12]. The results of this randomized controlled study showed that the rehabilitation nursing intervention combined with psychological care was able to significantly reduce the time it took for patients to recover from impaired consciousness in the postoperative period, and that patients in the observation group were in a better psychological state and were more satisfied with the care provided by the nursing staff compared with the control group.

HCH, as the most common chronic disease, has become a topic of global public health discussion because it is a key causative factor of functional disability, cognitive impairment, and dementia in humans. Knowledge of the disease and prevention of patients with HCH has gradually attracted the attention of the public. Due to the large population base in China, there are more patients with cerebral hemorrhage, which places a huge burden on patients, their families, and society, and seriously affects people's standard of living; most patients suffer from neurological sequelae after treatment, cannot return to their daily life before the disease, and have a high degree of dependence, poor self-care ability, and more negative emotions[13,14]. Therefore, solving the psychological and self-care ability problems of HCH patients has become a challenge. Scientific and effective nursing care and active and accurate clinical treatment are the key to improving the prognosis and cure rate of the disease. However, the traditional nursing model has certain limitations in the clinic and cannot fully adapt to patients in different situations, which will ultimately lead to the patient's prognosis not reaching their own expectations, especially in terms of the patient's emotions. Therefore, the introduction of a new model that meets the needs of the modern chronic patient population in clinics will play a crucial role in the recovery and

Table 1 Baseline characteristics of the study patients

Factors	Observation group (*n* = 60)	Control group (*n* = 60)	*P* value
Age (yr)	67.23 ± 0.23	68.11 ± 0.36	0.590
Sex (Male/Female)	45/15	47/13	0.975
Body mass index (kg/m^2)	22.14 ± 0.25	22.03 ± 0.20	0.057
Year of education (yr)	8.0 ± 0.50	7.5 ± 0.50	0.078
Cerebral hemorrhage site			0.612
Lobes of the brain	16	16	
Ventricles	13	12	
Thalamus	25	27	
Brainstem	6	5	

Table 2 Mental status score of patients

Index	Observation group	Control group	*P* value
SDS	45.72 ± 0.92	55.13 ± 2.21	< 0.001
SAS	44.11 ± 1.02	60.92 ± 2.90	< 0.001
PSQI	3.90 ± 0.67	19.02 ± 0.82	< 0.001

SDS: Self-rating depression scale; SAS: Self-rating anxiety scale; PSQI: Pittsburgh sleep quality index.

Table 3 Nursing care satisfaction scores

Group	Satisfaction scores
Observation group	95.20 ± 3.5
Control group	89.90 ± 2.5
t value	11.421
P value	< 0.001

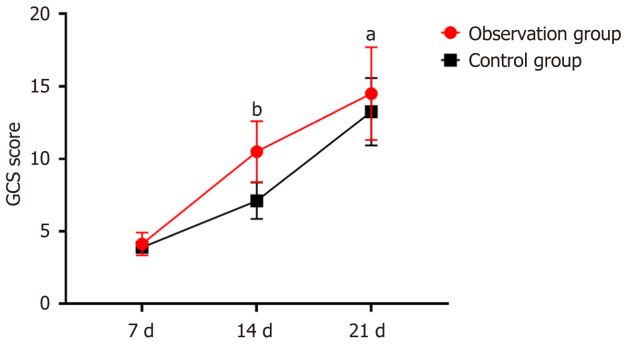

Figure 1 Consciousness scores of patients. $^{a}P < 0.05$, $^{b}P < 0.01$, observation group *vs* control group. GCS: Glasgow Coma Scale.

management of patients with chronic diseases.

Consciousness assessment is of great significance in the postoperative rehabilitation and prognosis of patients with cerebral hemorrhage. Rehabilitation nursing care requires the nursing staff to pay constant attention to the patient's state of consciousness and communicate with the attending physician in a timely manner. Moreover, patients with postoperative cerebral hemorrhage often suffer from pressure injuries, and in the state of coma, nursing staff are required to turn the patient over and massage him/her regularly to avoid pressure injuries and to promote the recovery of consciousness[15,16]. In our study, we showed that the rehabilitative care provided to the patients resulted in a difference in

the state of consciousness scores of the observation group compared to the control group on day 14, and that the state of consciousness scores of the observation group were significantly higher than those of the control group on day 21 ($P < 0.05$). Psychological support is of great importance to the postoperative rehabilitation of patients with cerebral hemorrhage, and early psychological support for patients cerebral hemorrhage to prevent postoperative depressive disorders has shown good results[17]. In the traditional nursing model, the psychological state of patients and their families is often poorly perceived, but in fact, most postoperative patients with cerebral hemorrhage are anxious and depressed due to the fear of the effect of postoperative treatment and the need for bed rest, which leads to a strong stress reaction after surgery [18]. It is important to implement personalized psychological care for patients at this stage. A British study showed that postoperative psychological care for patients with cerebral hemorrhage effectively improved their recovery and reduced the incidence of adverse complications[19]. Similarly, our study showed that postoperative psychological care improved patients' sleep quality and that good sleep quality greatly reduced the development of adverse emotions, and the relationship between sleep quality and anxiety and depression has been demonstrated in a number of previous studies [20]. Furthermore, by assessing anxiety and depression status after treatment, the psychological status of patients in the observation group was found to be significantly better than that of the control group. Although our study used a randomized controlled study to systematically demonstrate the role of nursing interventions in optimizing the mental status of patients with cerebral hemorrhage, our study lacked comprehensiveness, had a short observation period, and did not follow up the patients for a long period of time. In the future, extensive research is needed to demonstrate this.

CONCLUSION

Our study showed that quality nursing interventions have an optimizing effect on the psychological state of patients with cerebral hemorrhage, which can significantly improve the psychological state of patients, promote the recovery of their consciousness, and increase nursing satisfaction and improve the doctor-patient relationship, however, extensive evidence needs to be further researched.

ARTICLE HIGHLIGHTS

Research background

Hypertensive cerebral hemorrhage (HCH), as the most common chronic disease, has become a topic of global public health discussion because it is a key causative factor of functional disability, cognitive impairment, and dementia in humans. Knowledge of the disease and prevention of HCH has gradually attracted the attention of the public.

Research motivation

This study provided information for clinical nursing and improve the prognosis of cerebral hemorrhage.

Research objectives

This study aimed to investigate the role of rehabilitative nursing interventions in optimizing the postoperative mental status recovery phase and to provide clinical value for future rehabilitation of patients with cerebral hemorrhage.

Research methods

This randomized controlled study included 120 patients with cerebral HCH between May 2021–May 2023. The participants have randomly sampled and grouped into the observation and control groups. The observation group received the rehabilitation nursing model, whereas the control group have given conventional nursing. The conscious state of the patients was assessed at 7, 14, 21, and 30 d postoperatively. After one month of care, sleep quality, anxiety, and depression were compared between the two groups. Patient and family satisfaction were assessed using a nursing care model.

Research results

The results showed that the state of consciousness scores of the patients in both groups significantly increased after surgical treatment. From the 14th day onwards, differences in the state of consciousness scores between the two groups of patients began to appear. After one month of care, the sleep quality, anxiety state, and depression state of patients were significantly better in the observation group than in the control group. Satisfaction with nursing care was higher in the observation group than in the control group.

Research conclusions

This study showed that quality nursing interventions have an optimizing effect on the psychological state of patients with cerebral hemorrhage, which can significantly improve the psychological state of patients, promote the recovery of their consciousness, and increase nursing satisfaction and improve the doctor-patient relationship.

Research perspectives

Further analysis and research are needed to provide more scientific evidence.

FOOTNOTES

Co-corresponding authors: Wei-Wei Yang and Xiao-Yang Yang.

Author contributions: Tang JL and Yang WW contributed equally to this work; Tang JL, Yang WW and Yang XY designed the research study; Tang JL, Yang WW and Yang XY performed the research; Tang JL, Yang WW and Yang XY contributed new reagents and analytic tools; Yang WW and Yang XY analyzed the data and wrote the manuscript; All authors have read and approve the final manuscript. Yang WW and Yang XY contributed equally to this work as Co-Corresponding Author. The decision to designate Yang WW and Yang XY as Co-Corresponding Author. is based in three primary reasons. First, the research was performed as a collaborative effort, and the designation of Co-Corresponding Author. accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant manuscript. Designating two Co-Corresponding Author will ensure effective communication and management of post-submission matters, which will enhance the paper's quality and reliability. Second, the research team Co-Corresponding Author with diverse expertise and skills from various fields, and the designation of two Co-Corresponding Author best reflects this diversity. This also promotes the most comprehensive and in-depth examination of the research topic, ultimately enriching readers' understanding by offering various expert perspectives. Third, both Yang WW and Yang XY Made substantial and equal contributions throughout the research process. Selecting these researchers as Co- Corresponding Author. acknowledges and respects their equal contribution and exemplifies the collaborative spirit and teamwork within this study. we believe that designating Yang WW and Yang XY as Co-Corresponding Author. is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

Institutional review board statement: The study was reviewed and approved by the Affiliated Hospital of Nantong University Institutional Review Board.

Clinical trial registration statement: This study is registered at Clinical Trial Center (www.researchregistry.com). The registration identification number is researchregistry9637.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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ORIGINAL ARTICLE

Basic Study

KAT7/HMGN1 signaling epigenetically induces tyrosine phosphorylation-regulated kinase 1A expression to ameliorate insulin resistance in Alzheimer's disease

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Abstract

BACKGROUND

Epidemiological studies have revealed a correlation between Alzheimer's disease (AD) and type 2 diabetes mellitus (T2D). Insulin resistance in the brain is a common feature in patients with T2D and AD. KAT7 is a histone acetyltransferase that participates in the modulation of various genes.

AIM

To determine the effects of KAT7 on insulin patients with AD.

METHODS

APPswe/PS1-dE9 double-transgenic and *db/db* mice were used to mimic AD and diabetes, respectively. An *in vitro* model of AD was established by Aβ stimulation. Insulin resistance was induced by chronic stimulation with high insulin levels. The expression of microtubule-associated protein 2 (MAP2) was assessed using immunofluorescence. The protein levels of MAP2, Aβ, dual-specificity tyrosine phosphorylation-regulated kinase-1A (DYRK1A), IRS-1, p-AKT, total AKT, p-GSK3β, total GSK3β, DYRK1A, and KAT7 were measured *via* western blotting. Accumulation of reactive oxygen species (ROS), malondialdehyde (MDA), and SOD activity was measured to determine cellular oxidative stress. Flow cytometry and CCK-8 assay were performed to evaluate neuronal cell death and proliferation, respectively. Relative RNA levels of KAT7 and DYRK1A were examined using quantitative PCR. A chromatin immunoprecipitation assay was conducted to detect H3K14ac in DYRK1A.

RESULTS
KAT7 expression was suppressed in the AD mice. Overexpression of KAT7 decreased Aβ accumulation and MAP2 expression in AD brains. KAT7 overexpression decreased ROS and MDA levels, elevated SOD activity in brain tissues and neurons, and simultaneously suppressed neuronal apoptosis. KAT7 upregulated levels of p-AKT and p-GSK3β to alleviate insulin resistance, along with elevated expression of DYRK1A. KAT7 depletion suppressed DYRK1A expression and impaired H3K14ac of DYRK1A. HMGN1 overexpression recovered DYRK1A levels and reversed insulin resistance caused by KAT7 depletion.

CONCLUSION
We determined that KAT7 overexpression recovered insulin sensitivity in AD by recruiting HMGN1 to enhance DYRK1A acetylation. Our findings suggest that KAT7 is a novel and promising therapeutic target for the resistance in AD.

Key Words: Alzheimer's disease; Diabetes; Insulin resistance; KAT7; Dual-specificity tyrosine phosphorylation-regulated kinase-1A; HMGN1

Core Tip: Type 2 diabetes mellitus (T2D) is closely associated with neurodegenerative diseases, such as Alzheimer's disease (AD), in which insulin resistance dysfunction plays a critical role. However, the pathological mechanisms underlying diabetes mellitus-related atopic dermatitis remain unclear. Our study demonstrated that the histone acetyltransferase KAT7 ameliorated neuronal death and oxidative stress in AD and restored insulin sensitivity in insulin-resistant neurons by recruiting HMGN1 to enhance the acetylation of the dual-specificity tyrosine phosphorylation-regulated kinase-1A gene, suggesting the promising therapeutic potential of KAT7 in diabetes mellitus-associated AD.

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INTRODUCTION

Alzheimer's disease (AD) is a complicated and prevalent neurodegenerative disease that commonly occurs among older adults globally[1,2]. It is characterized by a progressive decline in cognitive ability and memory loss[3]. The deposition of Aβ-comprised extracellular plaques and neurofibrillary tangles are the main pathological hallmarks of AD[3]. Moreover, most patients with AD have cerebrovascular diseases, including impaired integrity of the blood-brain barrier[4]. An increasing number of epidemiological studies have shown a strong association between AD and type 2 diabetes mellitus (T2D), in which insulin resistance is a common and critical pathological feature[5,6]. However, the pathological mechanisms underlying the association between insulin resistance and AD remain unclear.

Histone acetyltransferases (HATs) are divided into different families according to their structure and sequence homology, including the P300/CBP, MYST, and GCN5 families[7]. The HATs play a central role in transcriptional regulation by catalyzing the transfer of acetyl from acetyl CoA to ε-amino of histone lysine residues[8]. Abnormal HAT function is closely correlated with various diseases, including developmental disorders and cancers[9-11]. HATs of the MYST family are characterized by conserved MYST catalytic domains, which include the KAT5 (TIP60), KAT6A (MOZ and MYST3), KAT6B (MORF and MYST4), KAT7 (HBO1 and MYST), and KAT8 (MOF)[12]. KAT7 acetylates the K14 and K23 on histone H3 by interacting with scaffolding protein BRPF and acetylates K5, K8, and K12 on histone H4 *via* scaffolding protein JADE[13,14]. During tissue development, depletion of KAT7 Leads to significantly decreased H3K14ac levels in erythrocytes of the fetal liver and mouse embryos[15].

Dual-specificity tyrosine phosphorylation-regulated kinase-1A (DYRK1A) is a highly conserved protein kinase that phosphorylates tyrosine and silk/threonine residues on exogenous substrates[16]. DYRK1A catalyzes multiple critical proteins, such as NOTCH, CREB, STAT3, eIF2B, and caspase-9[17]. Transgenic mice with high DYRK1A levels exhibit impaired motor and spatial learning abilities[18]. DYRK1A knockout mice died at the embryonic stage, and heterozygous mice exhibited low survival rates and abnormal neurological behavior[19]. DYRK1A has also been reported to participate in the development of AD, Down syndrome, diabetes, and cancer[20,21].

In this study, we explored the mechanisms underlying insulin resistance in AD and determined that KAT7 epigenetically upregulates the acetylation and expression of DYRK1A to reduce insulin resistance during AD. Our study identified novel therapeutic targets for AD.

MATERIALS AND METHODS

AD mouse model

Eight-month-old APPswe/PS1-dE9 double-transgenic mice were brought from Vital River Laboratory (China). The mice were randomly divided into experimental groups; the KAT7 overexpressing lentivirus (1×10^9 IU/mL) was stereotactically injected (3 μL/min) into the CA1 area of the hippocampus. All experiments were approved by the Animal Ethics Committee of the Qilu Hospital of Shandong University.

Diabetic mouse model

Twelve-week-old *db/db* and control mice were purchased from Vital River Laboratory (China). Brain tissues were collected from these mice, and protein expression was assessed *via* western blotting.

Cell lines

Primary neurons were isolated from mice and maintained in a specific culture medium at 37 °C in a humidified atmosphere containing 5% CO_2[22]. To mimic insulin resistance, the cells were stimulated with culture medium containing insulin (3 μM), no foetal bovine serum, and no B27 for 24 h, followed by insulin deprivation for 30 min. The cells were stimulated with or without insulin (10 nM) for 15 min and collected for subsequent experiments.

Cell transfection

A lentiviral system for KAT7 and HMGN1 overexpression and siRNAs targeting KAT7 (siKAT7) and HMGN1 (siHMGN1) were synthesized by GenePharma (Shanghai, China). Oligonucleotides were transfected into cells using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, United States), following the manufacturer's instructions.

Cell viability and apoptosis

Cell viability was assessed using cell counting kit-8 (CCK-8) (Beyotime, China). Briefly, 5000 cells were seeded in each well of a 96-well plate and incubated for 24 h. Then, 20 μL CCK-8 reagent was added and hatched for another 2 h at 37 °C. Absorbance was measured at 450 nm using a microplate detector (Thermo Fisher Scientific). Apoptosis was assessed *via* flow cytometry using an Annexin V/PI Apoptosis Detection Kit (Beyotime, China).

Immunofluorescence staining

For immunofluorescence staining, brain tissues were fixed and coated with optimal cutting temperature compound, made into 5 μm slices, and then probed with primary antibodies against microtubule-associated protein 2 (MAP2) overnight at 4 °C. The next day, samples were incubated with Alexa Fluor 633-conjugated secondary antibodies (Thermo Fisher Scientific) for 1 h at room temperature. Nuclei were labeled with DAPI (Thermo Fisher Scientific). Five random images were captured using a microscope (Leica, Germany).

Quantitative real-time PCR assay

Brain tissues and cells were homogenized using TRIzol reagent (Thermo Fisher Scientific) to extract total RNA, followed by reverse transcription to cDNA using the First Strand cDNA Synthesis Kit (Thermo Fisher Scientific). Gene expression levels were quantified using the SYBR Green system (Thermo Fisher Scientific). Relative gene expression was normalized to that of GAPDH.

Western blotting

Total protein was obtained from brain tissues and cells using ice-cold RIPA lysis buffer (Thermo, United States) containing protease inhibitors (Sigma, United States). Equal amounts of proteins were separated *via* SDS-PAGE, blotted onto the PVDF membranes (Millipore, United States), blocked with 5% non-fat milk, and then hatched with anti-Aβ, anti-MAP2, anti-KAT7, anti-DYRK1A, anti-AKT, anti-pAKT, anti-GSK3β, and ani-β-actin for one night at 4 °C. The blots were visualized after incubation with secondary antibodies and ECL reagent (Millipore, United States). All the antibodies were purchased from Abcam and used according to the manufacturer's instructions.

Evaluation of reactive oxygen species level

The levels of reactive oxygen species (ROS) were evaluated by staining with 2',7'-dichlorodihydrofluorescein diacetate (Sigma, United States) according to the manufacturer's protocol. Samples were hatched with DCF-DA (25 μM) at 37 °C incubator in dark for 30 min. Relative fluorescence at 485 nm was measured using a microplate detector (Thermo, United States).

Evaluation of oxidative stress

The levels of malondialdehyde (MDA) and superoxide dismutase[23] activity were assessed using MDA and SOD kits (Beyotime, China), according to the manufacturer's instructions.

Chromatin immunoprecipitation assay

The chromatin immunoprecipitation (ChIP) assay was performed using the EZ-ChIP kit (Millipore, United States) according to the manufacturer's instructions. Briefly, neurons were treated with formaldehyde for 10 min to obtain a crosslink between DNA and protein. Chromatin fragments were obtained after sonication of the cell lysates and

incubation with an antibody targeting H3K27me3. The precipitated DNA was evaluated using quantitative PCR.

Statistical analysis

All data are presented as mean ± SD and were analyzed using SPSS software (SPSS, United States). Data comparisons between two groups or among multiple groups were conducted using Student's *t*-test or one-way analysis of variance [24]. Statistical significance was set at $P < 0.05$, significant.

RESULTS

KAT7 expression was correlated with AD and insulin resistance

To determine the role of KAT7 in IR-induced AD, we established an *in vivo* AD model. We observed a notable accumulation of Aβ and decreased expression of MAP2, the biomarker of neuron generation (Figure 1A and B) in brain tissues from AD mice, compared with control mice, which suggested the successful establishment of the AD model. In contrast, we observed decreased KAT7 expression in the AD group (Figure 1A and B). In addition, KAT7 was coordinately overexpressed with IRS-1 and DYPK1A in diabetic mice (*db/db*) compared to that in normal mice (m/m), as shown in Figure 1C. The insulin receptor substrate-1 is an important regulator of insulin homeostasis, and its downregulation promotes insulin resistance[25,26]. Recent studies have indicated that DYPK1A/IRS-1 signaling represses insulin resistance[27]. Hence, we speculate that KAT7 may modulate insulin resistance in AD.

KAT7 alleviated AD-induced neurological damages in vivo

Next, we determined how KAT7 overexpression affected damage and oxidative stress in the brain. As shown in Figure 2A, treatment with KAT7 overexpression vectors led to significant elevation of KAT7 in brain tissues, along with decreased Aβ accumulation, which revered the phenotype of AD brains. KAT7 treatment also enhanced the proportion of MAP2-positive neurons compared to that in AD brains (Figure 2B). Moreover, AD brains exhibited elevated ROS accumulation, enhanced MDA levels, and decreased SOD activity, whereas KAT7 overexpression reversed these effects (Figure 2C-E).

KAT7 alleviated AD-induced neurological damages in vitro

We also adopted an *in vitro* model to assess the effects of KAT7 overexpression on Aβ-induced neuron cell damage. Stimulation with Aβ repressed the expression of KAT7, and transfection with KAT7 vectors enhanced its protein levels in neurons (Figure 3A). Results from flow cytometry and CCK-8 demonstrated suppressed cell viability and increased apoptosis of neurons in the Aβ-stimulated cell model, whereas KAT7 overexpression recovered cell viability and alleviated cell apoptosis (Figure 3B-D). In contrast with the *in vivo* model, KAT7 also alleviated oxidative stress induced by Aβ (Figure 3E-G). These data indicated that KAT7 alleviated AD-induced neuronal cell death and oxidative stress.

KAT7 ameliorated chronic high insulin-induced insulin resistance

Insulin resistance can be caused by the sustained stimulation of high levels of insulin. Here, we first treated neurons with insulin (3 μM) for 24 h to achieve insulin resistance, and treatment with serum-free medium reached a basal status, followed by acute stimulation with 10 nM insulin for 15 min. As shown in Figure 4A-C, acute stimulation by insulin caused an elevated ratio of p-AKT and p-GSK3β in control neurons, indicating insulin sensitivity. In contrast, neurons pre-treated with insulin (3 μM) for 24 h presented no significant alteration of p-AKT and p-GSK3β ratio (Figure 4A-C), indicating the acquired insulin resistance. We also found that IRS-1 expression was decreased by pre-stimulation with insulin and was increased by acute stimulation (Figure 4D), consistent with previously reported findings. Notably, chronic stimulation with insulin caused increased expression of DYRK1A with or without insulin pre-stimulation (Figure 4E). Overexpression of KAT7 upregulated the sensitivity to insulin in both stimulated and basal neurons, manifested by elevated levels of p-AKT and p-GSK3β ratio (Figure 4F). These data suggest that KAT7 ameliorates chronic insulin-induced insulin resistance.

KAT7 epigenetically induced DYRK1A expression and ameliorated insulin resistance via HMGN1

Next, we explored the downstream regulation of KAT7 during insulin resistance in AD. We depleted KAT7 in the neurons and evaluated the expression of DYRK1A. Transfection with siKAT7-3 effectively downregulated KAT7 and DYRK1A levels (Figure 5A and B). ChIP results revealed that the depletion of KAT7 alleviated the acetylation of K14 on histone 3 of DYRK1A (Figure 5C). Moreover, HMGN1 binds to the nucleosome and facilitates H4K14 acetylation[28]. We observed that siHMGN1-3 effectively suppressed HMGN1 and DYRK1A expression in neurons (Figure 5D and E). HMGN1 overexpression reversed both the RNA and protein levels of DYRK1A (Figure 5F and G). We used insulin-resistant neurons to evaluate the function of KAT7/HMGN1/DYRK1A. We observed that p-AKT, p-GSK3β, and IRS-1 expression were decreased by KAT7 knockdown (Figure 6A-D) or HMGN1 (Figure 6E-H), whereas overexpression of DYRK1A reversed this phenomenon. These findings indicate that KAT7 modulates DYRK1A expression by recruiting HMGN1 and ameliorating neuronal insulin resistance *via* DYRK1A/HMGN1 signaling.

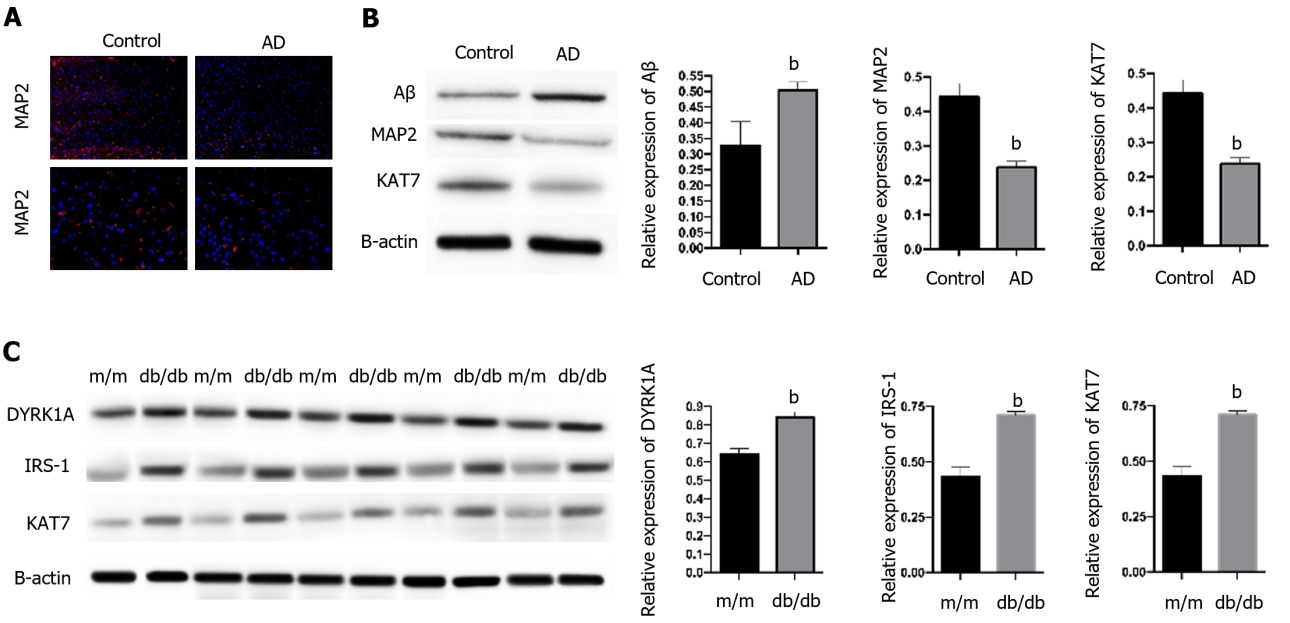

Figure 1 KAT7 expression is correlated with Alzheimer's disease and insulin resistance. A: Immunofluorescence staining of MAP2 in brain tissues form Alzheimer's disease mice and control. Blue, nuclei; Red, MAP2; B: Western blotting assay to evaluate the expression of MAP2, Aβ, and KAT7 in brain tissues. Histogram of relative protein expression in brain tissues form Alzheimer's disease mice and control; C: Western blotting assay to evaluate the expression of dual-specificity tyrosine phosphorylation-regulated kinase-1A, IRS-1, and KAT7 in brain tissues of diabetic mice (*db/db*) and control mice (*m/m*). Histogram of relative protein expression. [b]*P* < 0.01. AD: Alzheimer's disease. DYRK1A: Dual-specificity tyrosine phosphorylation-regulated kinase-1A.

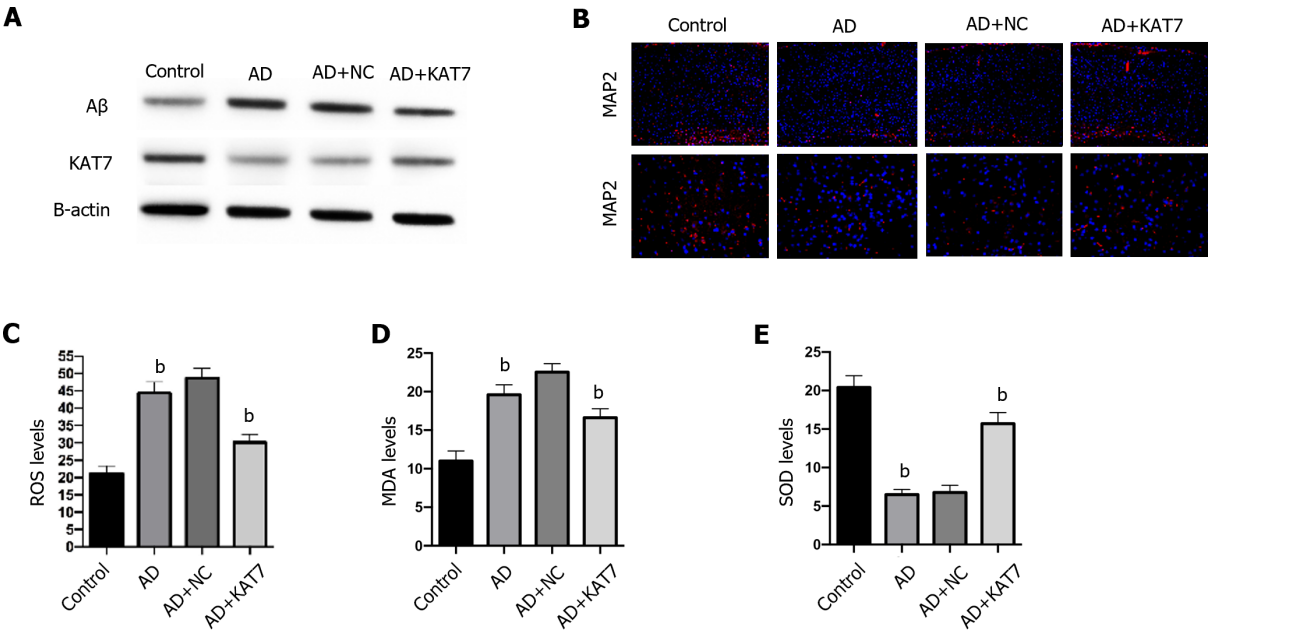

Figure 2 KAT7 alleviated Alzheimer's disease-induced neurological damages *in vivo*. A: Western blotting assay to evaluate the expression of KAT7 and Aβ in brain tissues; B: Immunofluorescence staining of microtubule-associated protein 2 in brain tissues; C: Evaluation of oxidative biomarkers reactive oxygen species in brain tissues; D: Evaluation of oxidative biomarkers malondialdehyde in brain tissues; E: Evaluation of oxidative biomarkers SOD activity in brain tissues. [b] *P* < 0.01. MDA: Malondialdehyde; ROS: Reactive oxygen species; AD: Alzheimer's disease; NC: Negative control; MAP2: Microtubule-associated protein 2.

DISCUSSION

Epidemiological and basic research studies have revealed a correlation between AD and T2D[4,29]. Diabetes is a novel risk factor for AD[5]. However, mechanisms underlying the correlation between AD and T2D remain unclear. Insulin resistance in the brain is a common feature in both T2D and AD[30]. Studies have reported that diabetic mice with cognitive disorders exhibit notable insulin resistance in the brain[31]. Accumulating evidence demonstrates that insulin resistance promotes Tau phosphorylation and Aβ plaques accumulation in AD brains[31]. Here, we established an *in vivo* AD model and determined a notable decrease in KAT7 expression in AD brains compared to control mice. KAT7 overex-

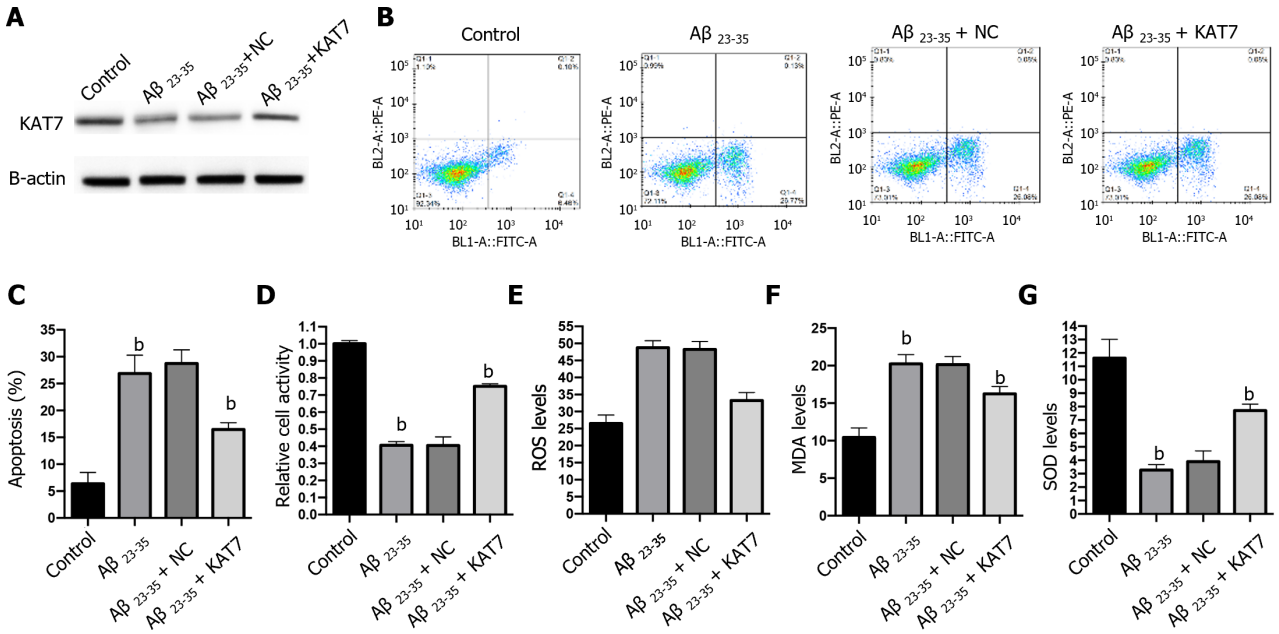

Figure 3 KAT7 alleviated Alzheimer's disease-induced neurological damages *in vitro*. A: Western blotting assay to evaluate the expression of KAT7 in neurons; B: Apoptosis of neurons checked by flow cytometry; C: Histogram of apoptotic cells; D: Cell viability of neurons after stimulation of Aβ with or without KAT7 overexpression was measured by cell counting kit-8 assay; E-G: Evaluation of oxidative biomarkers reactive oxygen species (E), malondialdehyde (F), and SOD activity (G). $^{b}P < 0.01$.

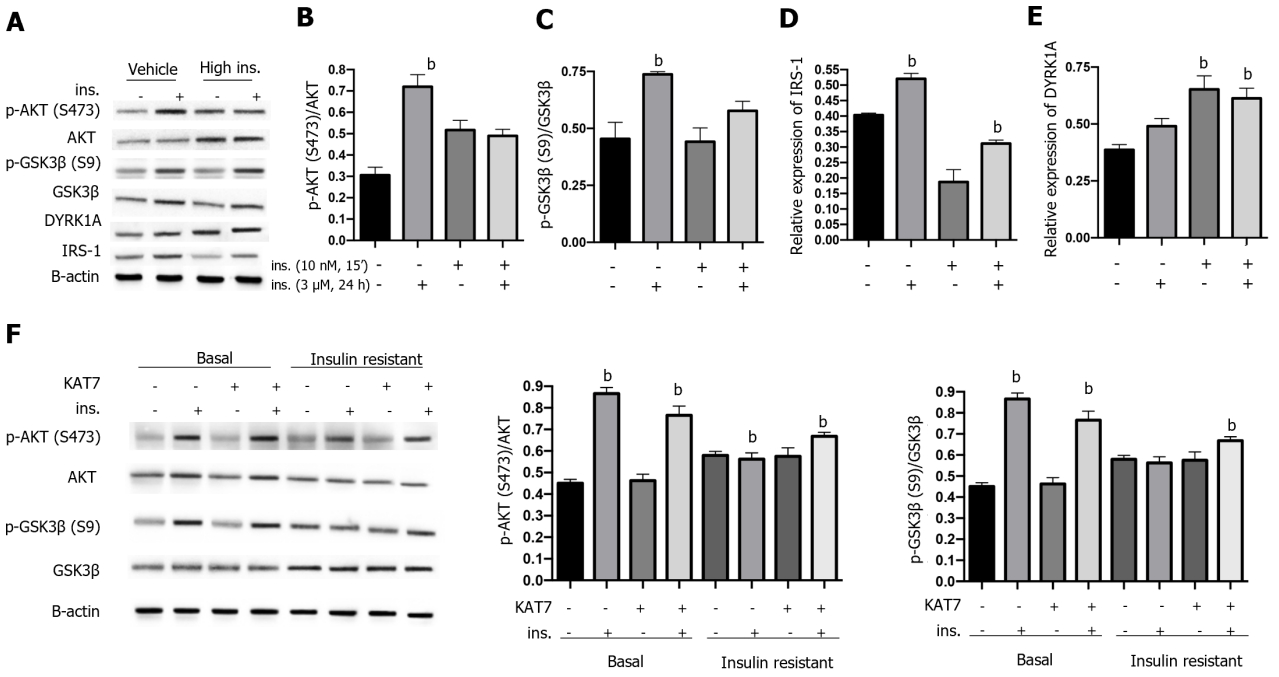

Figure 4 KAT7 ameliorates chronic high insulin-induced insulin resistance. A: The protein levels of p-AKT, total AKT, p-GSK3β, total GSK3β, dual-specificity tyrosine phosphorylation-regulated kinase-1A (DYRK1A), and IRS-1 in neurons were assessed *via* western blotting; B: Histogram to quantify protein expression of pAKT in A; C: Histogram to quantify relative protein expression of p-GSK3β in A; D: Histogram to quantify relative protein expression of IRS-1 in A; E: Histogram to quantify relative protein expression of DYRK1A in A. Vehicle, no pre-stimulation with insulin; High ins, pre-stimulation with insulin (3 μM) for 24 h + indicated restimulation with insulin (10 nM, 15 min); F: Neurons treated the same as in A to establish insulin resistance, along with or without KAT7 overexpression. The protein levels of p-AKT, total AKT, p-GSK3β, and total GSK3β in neurons were assessed *via* western blotting. Histogram to quantify protein expression. $^{b}P < 0.01$. DYRK1A: Dual-specificity tyrosine phosphorylation-regulated kinase-1A.

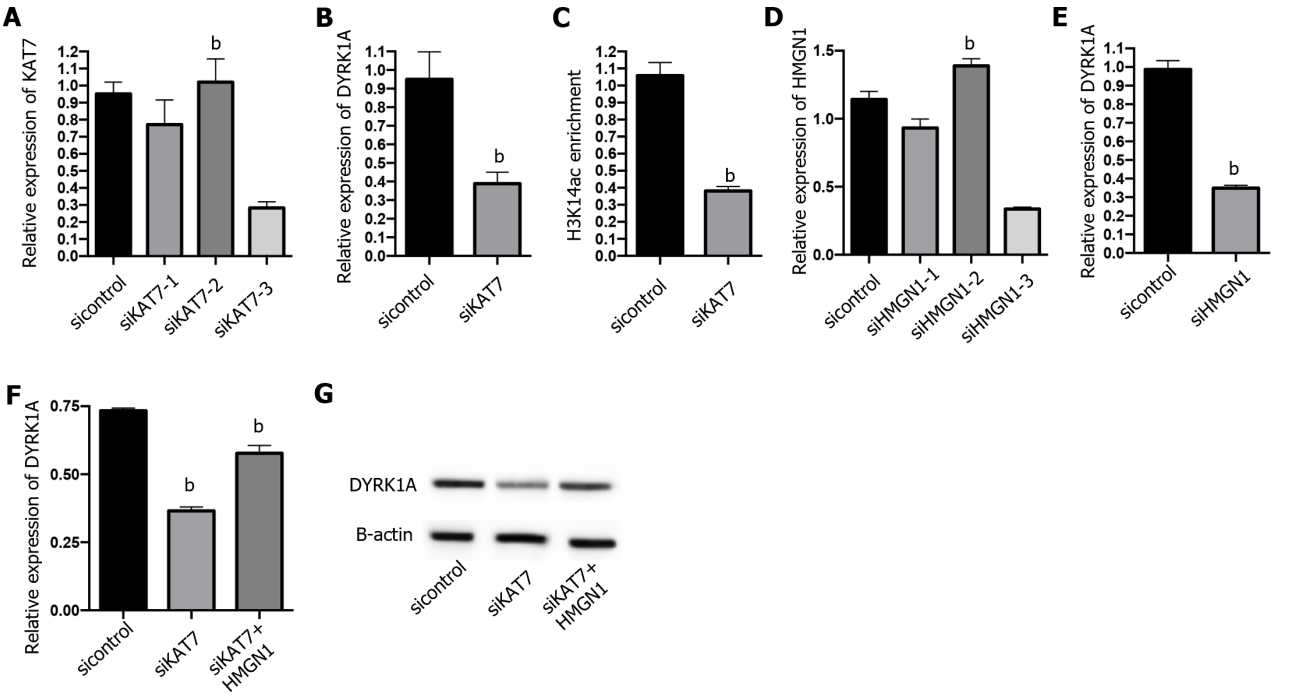

Figure 5 KAT7 epigenetically induces dual-specificity tyrosine phosphorylation-regulated kinase-1A expression. A: RNA level of KAT7 in neurons after transfection of siKAT7-1, siKAT7-2, or siKAT7-3 was measured using qPCR; B: RNA level of dual-specificity tyrosine phosphorylation-regulated kinase-1A (DYRK1A) in neurons after siKAT7-3 transfection was measured using qPCR; C: Chromatin immunoprecipitation assay to measure enrichment of H3K14ac on DYRK1A gene; D: RNA level of HMGN1 in neurons after transfection of siHMGN1-1, siHMGN1-2, or siHMGN1-3 was measured using qPCR; E: RNA level of DYRK1A in neurons after transfection of siHMGN1-3 was measured using qPCR; F and G: RNA and protein levels of DYRK1A in neurons after siKAT7-3 transfection with or without KAT7 overexpression vectors was measured using qPCR. $^{b}P < 0.01$. DYRK1A: Dual-specificity tyrosine phosphorylation-regulated kinase-1A.

pression alleviated the accumulation of Aβ and increased MAP2 positive neurons, simultaneously suppressing oxidative stress and apoptosis of neurons, suggesting the protective function of KAT7 against AD.

DYRK1A is a protein kinase that phosphorylates serine and tyrosine residues of target proteins[18]. It has been reported that the dosage of DYRK1A is critical in the central nervous system during development and aging, and abnormal DYRK1A levels occur in neurodegenerative diseases, such as AD and Parkinson's disease[18]. Previous studies have reported that DYRK1A interacts with IRS-1 *via* serine phosphorylation[27]. In addition, DYRK1A inhibitors have been proposed as potential therapeutic agents for diabetes[32-34]. Consistently, we showed that both DYRK1A and IRS-1 were elevated in the brain tissue of diabetic mice, along with elevated KAT7 expression. IRS-1 is a critical factor that mediates insulin signal transduction, and decreased IRS-1 Levels are a feature of insulin resistance[35]. Studies have revealed that drugs that upregulate IRS-1 expression alleviate insulin resistance[36]. In this study, we established an insulin-resistant neuronal model by chronic stimulation with high levels of insulin. The levels of p-AKT and pGSK3β in established insulin-resistant neurons did not change under insulin stimulation, indicating the successful establishment of the model. Subsequently, we found that overexpression of KAT7 Led to elevated p-AKT and p-GSK3β levels.

KAT7 is a histone acetyltransferase that acetylates the K14 and K23 on histone H3 by interacting with scaffolding protein[13,14]. Here, we evaluated the acetylation of DYRK1A in neurons and determined the decreased enrichment of H3K14ac on DYRK1A upon depletion of KAT7. HMGN1 is a DNA-binding protein[37,38]. A recent study reported that HMGN1 could increase the acetylation H3K14 by enhancing the function of HATs[28]. Hence, we investigated whether KAT7 modulated DYRK1A expression by recruiting HMGN1. As expected, the depletion of HMGN1 downregulated DYRK1A and H3K14ac enrichment in DYRK1A cells. HMGN1 knockdown also recovered the phosphorylation of AKT and GSK3β in insulin-resistant neurons. However, the current study did not identify any direct interactions among KAT7, HMGN1, and DYRK1A. Verification of the KAT7–HMGN1–DYRK1A axis in an *in vivo* model requires further experiments.

CONCLUSION

In summary, we observed decreased KAT7 Levels in AD. Overexpression of KAT7 ameliorates neuronal death and oxidative stress in AD and restores insulin sensitivity in insulin-resistant neurons by recruiting HMGN1 to enhance DYRK1A acetylation. Our findings suggest that KAT7 is a potential therapeutic target for the treatment of insulin resistance in AD.

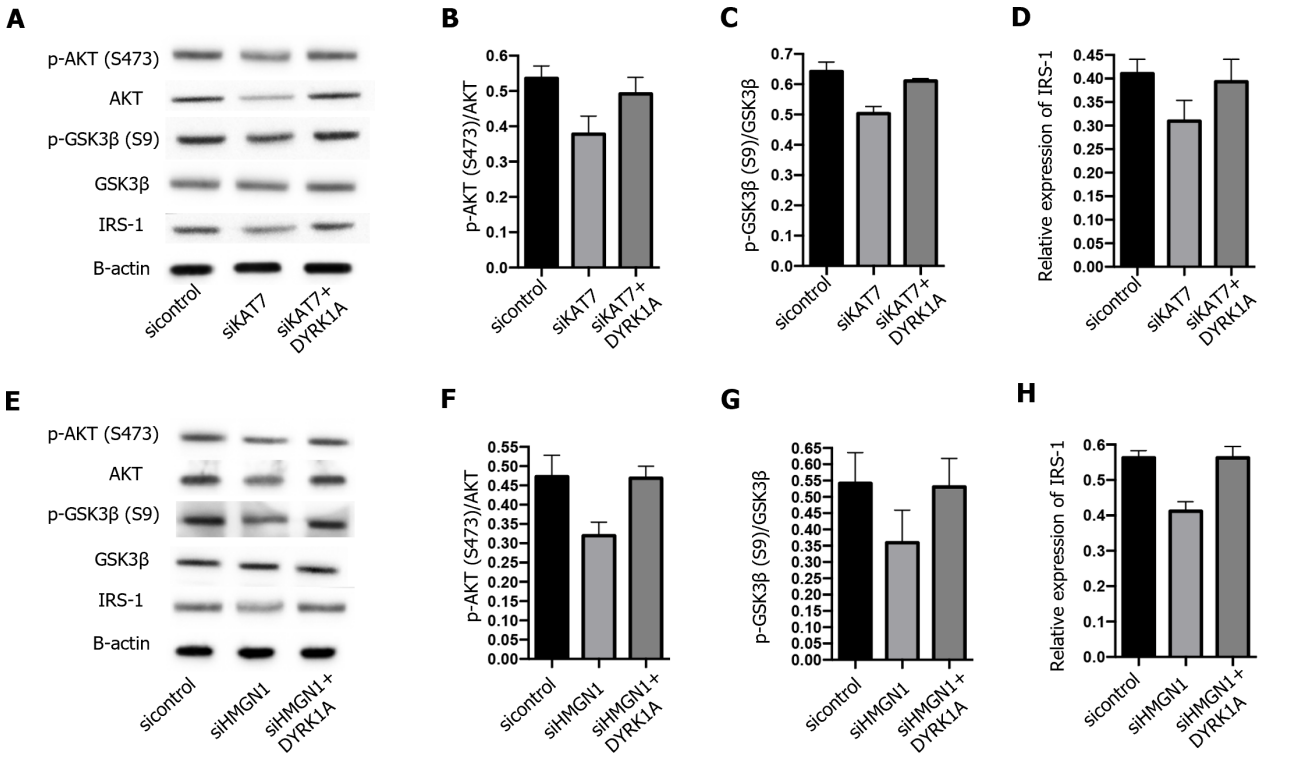

Figure 6 KAT7 epigenetically induces dual-specificity tyrosine phosphorylation-regulated kinase-1A expression in a HMGN1 dependent-manner. The insulin-resistant neurons were transfected with siKAT7 or siHMGN1 with or without dual-specificity tyrosine phosphorylation-regulated kinase-1A (DYRK1A) overexpression. A: The protein levels of p-AKT, total AKT, p-GSK3β, total GSK3β, and IRS-1 in neurons were assessed *via* western blotting; B: Histogram to quantify relative protein expression of pAKT in A; C: Histogram to quantify relative protein expression of pGSK3β in A; D: Histogram to quantify relative protein expression of IRS-1 in A; E: The protein levels of p-AKT, total AKT, p-GSK3β, total GSK3β, and IRS-1 in neurons treated with siHMGN1 and DYRK1A overexpression were assessed *via* western blotting; F: Histogram to quantify relative protein expression of pAKT in B; G: Histogram to quantify relative protein expression of pGSK3β in B; H: Histogram to quantify relative protein expression of IRS-1 in B. DYRK1A: Dual-specificity tyrosine phosphorylation-regulated kinase-1A.

ARTICLE HIGHLIGHTS

Research background

Epidemiological studies increasingly suggest a significant connection between Alzheimer's disease (AD) and type 2 diabetes mellitus, primarily attributed to insulin resistance, a prominent and pivotal pathological characteristic.

Research motivation

The precise pathological mechanisms that underlie the correlation between insulin resistance and AD remain elusive.

Research objectives

This study aims to investigate the impact of KAT7, a histone acetyltransferase involved in regulating multiple genes, on insulin resistance in AD.

Research methods

APPswe/PS1-dE9 transgenic mice were employed to study AD, while *db/db* mice were utilized as a model for diabetes. An *in vitro* AD model was established through Aβ stimulation.

Research results

Overexpression of KAT7 decreased Aβ accumulation, alleviated ferroptosis and apoptosis in brain tissues and neurons. KAT7 epigenetically regulated the expression of DYRK1A *via* recruiting the HMGN1 and activated AKT and GSK3β to alleviate insulin resistance.

Research conclusions

Our study revealed that upregulation of KAT7 restored insulin sensitivity in AD by recruiting HMGN1 to augment acetylation of the *DYRK1A* gene.

Research perspectives

Our findings highlight KAT7 as a novel and promising therapeutic target for addressing insulin resistance in AD.

FOOTNOTES

Author contributions: Lu QS and Lu M designed the study; Lu QS, Ma L, Jiang WJ, and Wang XB performed the experiments; Lu QS and Lu M wrote the manuscript.

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META-ANALYSIS

Vulnerable brain regions in adolescent major depressive disorder: A resting-state functional magnetic resonance imaging activation likelihood estimation meta-analysis

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Abstract

BACKGROUND

Adolescent major depressive disorder (MDD) is a significant mental health concern that often leads to recurrent depression in adulthood. Resting-state functional magnetic resonance imaging (rs-fMRI) offers unique insights into the neural mechanisms underlying this condition. However, despite previous research, the specific vulnerable brain regions affected in adolescent MDD patients have not been fully elucidated.

AIM

To identify consistent vulnerable brain regions in adolescent MDD patients using rs-fMRI and activation likelihood estimation (ALE) meta-analysis.

METHODS

We performed a comprehensive literature search through July 12, 2023, for studies investigating brain functional changes in adolescent MDD patients. We utilized regional homogeneity (ReHo), amplitude of low-frequency fluctuations (ALFF) and fractional ALFF (fALFF) analyses. We compared the regions of aberrant

spontaneous neural activity in adolescents with MDD *vs* healthy controls (HCs) using ALE.

RESULTS

Ten studies (369 adolescent MDD patients and 313 HCs) were included. Combining the ReHo and ALFF/fALFF data, the results revealed that the activity in the right cuneus and left precuneus was lower in the adolescent MDD patients than in the HCs (voxel size: 648 mm^3, $P < 0.05$), and no brain region exhibited increased activity. Based on the ALFF data, we found decreased activity in the right cuneus and left precuneus in adolescent MDD patients (voxel size: 736 mm^3, $P < 0.05$), with no regions exhibiting increased activity.

CONCLUSION

Through ALE meta-analysis, we consistently identified the right cuneus and left precuneus as vulnerable brain regions in adolescent MDD patients, increasing our understanding of the neuropathology of affected adolescents.

Key Words: Major depressive disorder; Resting-state functional magnetic resonance imaging; Adolescent; Activation likelihood estimation; Meta-analysis

Core Tip: Utilizing activation likelihood estimation meta-analysis, this study identified consistently vulnerable brain regions in adolescent major depressive disorder (MDD) patients. The findings of this study revealed distinct neural alterations, specifically decreased activity in the precuneus and cuneus areas, indicating the potential neurobiological underpinnings specific to adolescent MDD. This study offers crucial insights into the unique neural signatures of depression in adolescents, paving the way for targeted interventions and advancing our understanding of adolescent mental health.

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INTRODUCTION

Major depressive disorder (MDD) is a prevailing mental health challenge that disproportionately affects adolescents and has profound clinical and societal implications[1]. MDD typically originates during adolescence with a marked increase in incidence, particularly among females, and a male-to-female ratio of approximately 1:2[2]. In addition, the recurrence rate of adolescent depression is substantial, constituting a pivotal risk factor for suicide and giving rise to severe social consequences[3]. Understanding the intricate neural underpinnings of MDD during this critical developmental phase is imperative for advancing effective therapeutic interventions.

Resting-state functional magnetic resonance imaging (rs-fMRI) has emerged as an indispensable tool in neuroimaging research, offering unparalleled insights into the intrinsic functional architecture of the brain[4]. By assessing spontaneous fluctuations in blood oxygen level-dependent signals during rest, rs-fMRI can reveal intricate patterns of connectivity and activity across distinct brain regions, providing a unique perspective for comprehending the aberrant neurocircuitry implicated in MDD. The analytical techniques for localized spontaneous brain activity in rs-fMRI include regional homogeneity (ReHo), amplitude of low-frequency fluctuations (ALFF), and fractional ALFF (fALFF)[5]. These methods are frequently employed to characterize intrinsic brain activity during rest. ReHo can be used to evaluate the local coherence of rs-fMRI signals, aiding in identifying neural synchronization anomalies; ALFF can directly reflect the changes in the functional activities of the corresponding local brain regions by calculating the ALFF value of each voxel; and fALFF can be used to measure the relative contribution of low-frequency signal power, highlighting aberrant neural activity patterns in MDD[6]. Accordingly, the combination of ReHo, ALFF, and fALFF can more comprehensively reflect the pattern of changes in spontaneous local brain activity in adolescent depression patients. Functional connectivity (FC) indicates the functional correlation between seed sites and surrounding brain regions, which is distinct from the spontaneous neurobrain functional activity reflected by ReHo, ALFF, and fALFF. FC is not a suitable candidate for meta-analysis unless all studies are the same kind of network study[7]. To our knowledge, although many previous studies have used ReHo, ALFF, and fALFF methods and rs-fMRI to explore the changes in spontaneous brain activity in adolescent depression patients[8-17], the results of these studies are inconsistent and are still controversial.

We used neuroimaging activation likelihood estimation (ALE) to analyze the pattern of changes in spontaneous brain activity in adolescents with MDD. ALE aggregates the peak activation coordinates across neuroimaging studies to create spatial probability maps highlighting consistent brain region involvement in specific tasks[18]. Previously, Yuan *et al*[19] used the ALE method to conduct a meta-analysis of MDD patients; however, they did not distinguish age ranges specific to adolescents and may not have captured the consistently vulnerable brain regions in the resting state that may differ

between adolescent depression patients and adults. In this study, we employed ALE analysis to focus exclusively on the integration and assessment of data from abnormal active brain regions reported in prior studies using ReHo and ALFF/fALFF approaches. This analysis enables us to further explore the more consistently impaired brain regions involved in the spontaneous activity of the local brain in adolescent depression patients, with the aim of uncovering the potential neural mechanisms underlying brain injury in these patients.

MATERIALS AND METHODS

Literature search

Study selection was conducted in accordance with the PRISMA 2020 guidelines. This review was registered with PROSPERO (ID: CRD42023371521). A comprehensive literature search in PubMed, Google Scholar, Embase, Web of Science, and CNKI was conducted to identify all fMRI studies published before June 13, 2022. The keywords used for the search included "depression", "major depressive disorder", "adolescent", "regional homogeneity", "amplitude of low-frequency fluctuation", "fractional amplitude of low-frequency fluctuation", "resting", "functional magnetic resonance" and "fMRI". Moreover, we searched the references of several reviews and imported them into the EndNote 20.2 document management tool for filtering.

Study selection

The studies that met the following inclusion criteria were considered for subsequent analysis: (1) MDD diagnosed according to the DSM-5 criteria; (2) inclusion of adolescent participants; (3) whole-brain analysis of differences in brain functional activity between adolescents with MDD and healthy controls (HCs) *via* rs-fMRI; (4) ReHo or ALFF/fALFF analysis methods; and (5) brain regions with differences between adolescents with MDD and HCs presented as Montreal Neurological Institute (MNI) or Talairach three-dimensional peak coordinates (x, y, z).

The studies were excluded if they met at least one of the following criteria: (1) Studies using rs-fMRI methods to assess FC, independent component analysis (ICA), degree centrality, default mode network (DMN), or other networks; (2) studies using voxel-based morphometry (VBM), task-state fMRI (t-fMRI) or cerebral perfusion; (3) meta-analyses, reviews, or case reports; (4) studies with incomplete three-dimensional coordinates (x, y, z); and (5) studies involving subjects other than adolescents with MDD.

Quality assessment

The quality of the included studies was assessed using the Newcastle–Ottawa Quality Assessment Scale (NOS)[20]. The NOS has 3 levels and a total of 8 items: (1) 4 items for subject selection; (2) 1 item for comparability between groups; and (3) 3 items for outcome measurement. The total possible score is 9 points. Studies with a score ≥ 5 points were included in the data analysis.

Data extraction

Two independent reviewers systematically compiled pertinent details from the selected studies. These data included study particulars, such as authors, publication year, and design; participant characteristics, such as sample size, age, and sex; rs-fMRI details, such as the MRI scanner model, field strength, and analysis software/methods used; and differential brain regions between adolescents with MDD and HCs, including quantities and central coordinates of reported discrepancies.

Data processing

ALE meta-analysis was performed using GingerALE 3.0.2 software (www.brainmap.org/ale)[21]. For the ALE meta-analysis, our study was conducted in the MNI standard space. Hence, we utilized the Lancaster transformation in GingerALE 3.0.2 to convert the three-dimensional coordinates of brain regions in the Talairach space to MNI space.

Subsequently, Gaussian function smoothing with a full width at half maximum (FWHM) was performed based on the sample size of each test group. Using the FWHM values, Gaussian functions were simulated on the three-dimensional brain mask of coordinates for a set of aberrantly activated brain regions reported in the study group. This process yielded three-dimensional modeling activation (MA) maps for each study group.

Then, based on the 3D-MA maps, a 3D ALE map was generated from the Gaussian probability distribution of the activated brain regions between different study groups, and the p value of the activation probability of the brain regions was calculated according to the Gaussian model to construct a 3D-*P* value distribution map. Moreover, the statistical test threshold was set by a 3D-*P* value distribution plot. The main parameters were as follows: The cluster-level familywise error correction was set at $P < 0.05$, the threshold permutations were set at $P < 0.001$ with 1000 permutations, and a threshold map (ALE image) was obtained[18]. Finally, Mango software (http://rii.uthscsa.edu/mango/) was used to analyze the resulting ALE images.

Sensitivity analysis

The jackknife sensitivity analysis method was used to assess the reproducibility of the meta-analysis outcomes. In this approach, a single study was systematically excluded from the dataset, and the remaining study data were subjected to ALE meta-analysis using GingerALE 3.0.2 software. This procedure was repeated 7 times, removing one study each time, to verify the consistency of the results after the exclusion of a study and to compare these results with the original

analysis.

RESULTS

Literature search and data extraction

Based on the aforementioned inclusion and exclusion criteria, a total of 420 retrieved articles were screened. There were 97 duplicates, 242 irrelevant studies, 12 reviews, 25 FC studies, 9 DMN studies, 16 t-fMRI studies, 3 VBM studies, and 4 studies without HC groups. Ultimately, 10 studies were included (Figure 1), including 2 ReHo studies, 7 ALFF studies, and 1 fALFF study.

Finally, a total of 369 adolescent depression patients and 313 HCs were retained for the ALE meta-analysis. There were 38 distinct brain areas in total, including 28 ALFF, 7 ReHo, and 3 fALFF regions (Table 1).

Data analysis

ALE meta-analysis results: Incorporating the results of both the ReHo and ALFF/fALFF data analyses, adolescents with depressive disorder exhibited reduced activity in the right cuneus and left precuneus regions compared to HCs (Table 2, Figure 2A). Then, ReHo and ALFF/fALFF ALE meta-analyses were carried out. The ALFF method ALE meta-analysis revealed that adolescent depression patients exhibited decreased activity in the right cuneus and left precuneus regions compared to HCs (Table 2, Figure 2B), but no brain regions with increased activity were found. However, the ALE meta-analyses for the ReHo and fALFF methods indicated no discernible increase or decrease in brain activity in adolescents with depressive disorder compared to HCs.

Sensitivity analysis results: In the sensitivity analysis for decreased activity, the jackknife method indicated that the cuneus and precuneus consistently appeared in 5 out of the 7 dataset combinations (Table 3).

DISCUSSION

In this study, we used an ALE meta-analysis method with rs-fMRI data to explore the brain regions associated with changes in brain activity between adolescents with MDD and HCs. By integrating the findings of previous studies, this ALE meta-analysis revealed brain regions with relatively consistent changes in brain function and activity in adolescents with depression. The results showed that the vulnerable brain regions in adolescent patients with depressive disorder were mainly distributed in the right cuneus and left precuneus regions and revealed the possible neuroimaging mechanism of brain injury in adolescent patients with depression. This convergence of evidence underscores the robustness of our findings. The subsequent jackknife sensitivity and heterogeneity analyses affirmed the reproducibility and reliability of our results, further confirming the validity of the observed differences. Thus, these results could lead to the identification of a potential therapeutic target for the treatment of brain injury in adolescents with MDD.

Brain regions with abnormal spontaneous neural activity in adolescents with MDD

The DMN is a network of interconnected brain regions that are active when an individual is at rest[22], notably including both the precuneus and cuneus[23]. The precuneus plays a key role in executive functions related to visuospatial imagery, episodic memory retrieval, and self-processing operations[24]. However, the cuneus is primarily responsible for processing visual information[25]. Like in other regions within the occipital lobe, the cuneus is essential for the perception and interpretation of visual stimuli, underpinning our ability to recognize and interact with our environment. Abnormal functioning of both the precuneus and cuneus can indicate compromised integrity of the DMN, a phenomenon that is frequently observed in depression[26]. The cuneus, which is a crucial part of the visual recognition network and is situated in the occipital lobe of the brain, has the primary functions of processing visual data, facial perception, emotion, and working memory[27]. Gong *et al*[9] showed that, compared to control individuals, adolescents with MDD had lower ALFF values in the bilateral cuneus. An fMRI reward processing task study demonstrated that adolescents with unremitting depression exhibited less activation in the cuneus than adolescents with remitting depression[28]. Hence, in adolescent MDD patients, interruptions in spontaneous brain activity associated with visual processing could lead to depressive symptoms. This finding is consistent with the abnormal spontaneous neuronal activity discovered in our ALE analysis, namely, a decrease in the spontaneous activity of the right cuneus in adolescents with depression. Additionally, in their fALFF study of sleep disorder depression, Zhu *et al*[29] reported that, compared to those in the normal sleep efficiency depression group, patients in the low sleep efficiency group exhibited a decrease in the fALFF in the right cuneus. Therefore, we speculated that right cuneus dysfunction in the DMN of adolescents with MDD may be related to a decrease in visual-associated brain activity. Recently, Yan *et al*[30] reported that the ReHo values of the bilateral cuneus were lower in MDD patients with functional gastroenterological diseases than in HCs. This finding suggested that gastrointestinal symptoms in MDD patients might be associated with the information analyzing and interpreting functions of the occipital gyrus. Yao *et al*[31] reported ReHo changes in the cuneus in both patients with bipolar depression and patients with unipolar depression. Moreover, Sun *et al*[32] reported that, compared to those in the nontreatment resident depression group, the treatment resident depression group exhibited a decrease in ALFF in the left cuneus. These findings provide a neuroimaging perspective that might help elucidate the consistently vulnerable brain regions in adolescent MDD patients according to local spontaneous brain activity. Moreover, this study could further

Table 1 Characteristics of the included studies

Ref.		Sample size		Age (mean ± SD)		Field strength	Method	Differential brain region	Coordinate	Quality
		Adolescent MDD	HC	Patients	HC					
1	Jiao *et al*[8], 2011	18	18	15.78 ± 1.20	16.20 ± 0.90	3.0T	ALFF	9	MNI	4/1/1
2	Gong *et al* [9], 2014	15	16	15.00 ± 2.00	15.00 ± 2.00	3.0T	ALFF	10	MNI	4/1/1
3	Jiang *et al* [10], 2016	19	24	15.58 ± 1.47	15.71 ± 1.55	3.0T	ReHo	2	MNI	4/1/1
4	Zhu *et al*[11], 2016	27	28	21.67 ± 3.39	21.33 ± 2.4	3.0T	ALFF	2	MNI	4/1/1
5	Hu *et al*[12], 2019	76	44	20.40 ± 3.50	20.30 ± 2.10	3.0T	ALFF	3	MNI	4/1/1
6	Mao *et al* [13], 2020	24	23	17.31 ± 1.34	18.21 ± 1.29	3.0T	ReHo	5	MNI	4/1/1
7	Kang *et al* [14], 2020	30	28	15.00 ± 1.66	15.18 ± 2.04	3.0T	ALFF	1	MNI	4/1/1
8	Yang *et al* [15], 2021	39	39	≤ 21	≤ 21	N/A	fALFF	3	MNI	4/1/1
9	Zhang *et al* [16], 2023	50	39	15.80 ± 1.43	15.82 ± 1.89	3.0T	ALFF	1	MNI	4/1/1
10	Zhou *et al* [17], 2023	71	54	13.97 ± 1.51	14.17 ± 1.48	3.0T	ALFF	2	MNI	4/1/1

MDD: Major depressive disorder; HC: Healthy control; ALFF: Amplitude of low-frequency fluctuations; ReHo: Regional homogeneity; fALFF: Fractional amplitude of low-frequency fluctuations; MNI: Montreal Neurological Institute; N/A: Not available.

Table 2 Activation likelihood estimation meta-analysis results of regions of decreased brain activity in adolescents with major depressive disorder compared to healthy controls

Research methods	Anatomical label BA	Peak MNI coordinate			ALE value	Cluster	Volume (mm^3)
		X	Y	Z			
ReHo and ALFF/fALFF decrease	Right cuneus BA 7	4	-66	40	0.011956828	1	648
	Left precuneus BA 7	-2	-66	40	0.0098253535	1	648
ALFF decrease	Right cuneus BA 7	4	-66	40	0.011956828	1	736
	Left precuneus BA 7	-2	-66	40	0.0098253535	1	736

ALFF: Amplitude of low-frequency fluctuations; ReHo: Regional homogeneity; fALFF: Fractional amplitude of low-frequency fluctuations; MNI: Montreal Neurological Institute; ALE: Activation likelihood estimation; BA: Brodmann area.

elucidate the pathophysiological mechanisms behind depressive symptoms in adolescents with MDD. The precuneus is located within the medial aspect of the parietal lobe, serving as a pivotal nexus in the DMN and playing an indispensable role in various cognitive processes. Functionally, it is closely linked with memory, emotion, and visuospatial executive functions[33]. A task-based fMRI study of adolescents with depression revealed a correlation between activity in the precuneus and the severity of depression, where greater activity in the precuneus was associated with more severe depression. This discovery may be attributed to the rapid neural development period in adolescents with depression, which makes them more sensitive to negative features and thus allows them to access more attentional resources in the precuneus[34]. In addition, Cullen *et al*[35] reported that in adolescent depression patients treated with medication, treatment response was linked to increased amygdala connectivity with the right frontal cortex but reduced amygdala connectivity with the right precuneus and posterior cingulate cortex. Adolescent MDD can be simplistically regarded as an early-onset subtype of the adult disease, given its close association with later recurrences. However, the vulnerable brain regions involved in MDD among adolescents differ from those involved in adults[36]. A study on adolescent depression showed that both anhedonia and depression severity were related to decreased dorsal medial prefrontal cortex resting-state FC with the precuneus[37]. This finding suggested that decreased activity in the precuneus may be associated with adolescent MDD. A previous study compared resting-state FC (rsFC) in the precuneus subregions

Table 3 Jackknife sensitivity analyses

Discarded article	Adolescent MDD < HC	
	CUN_R	PCUN_L
Jiao *et al*[8], 2011	Yes	Yes
Gong *et al*[9], 2014	Yes	Yes
Zhu *et al*[11], 2016	No	No
Hu *et al*[12], 2019	Yes	Yes
Mao *et al*[13], 2020	Yes	Yes
Yang *et al*[15], 2021	Yes	Yes
Zhou *et al*[17], 2023	No	No
Total	5 out of 7	5 out of 7

MDD: Major depressive disorder; HC: Healthy control; CUN: Cuneus; PCUN: Precuneus; R: Right; L: Left.

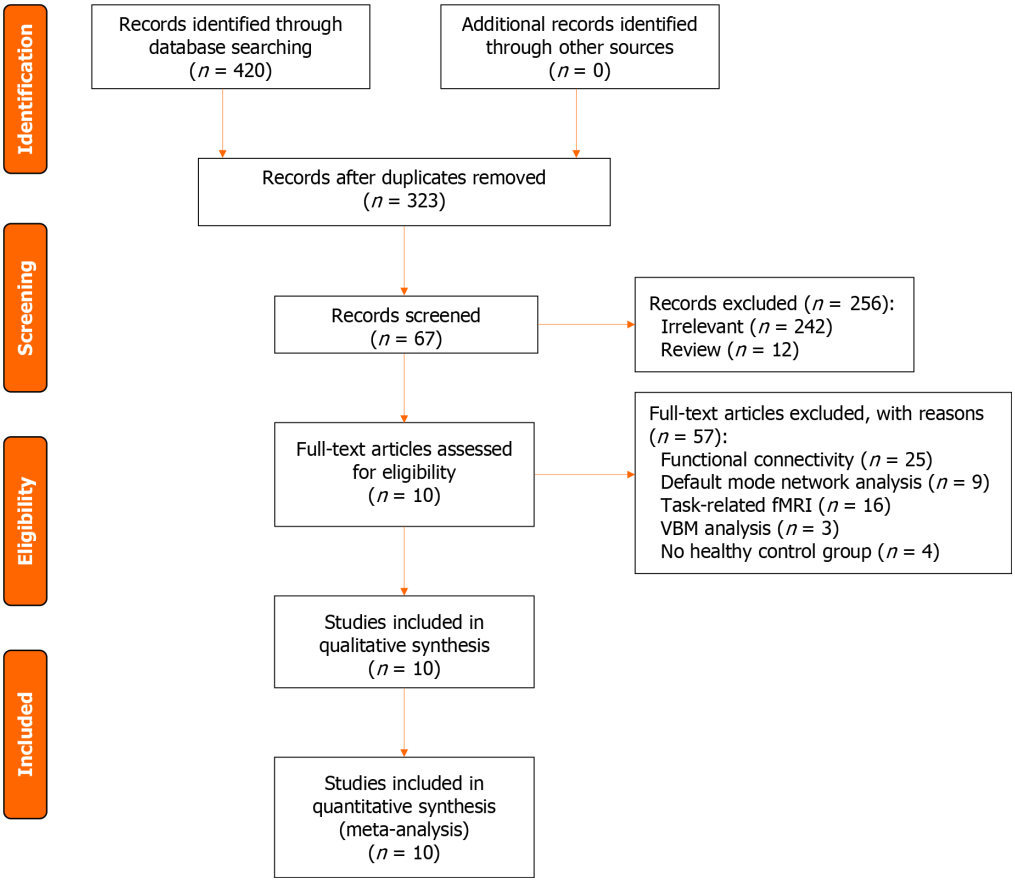

Figure 1 Flow chart of the study selection strategy. VBM: Voxel-based morphometry; fMRI: Functional magnetic resonance imaging.

between adult patients with MDD and HCs and revealed that patients with MDD exhibited increased rsFC between the left precuneus and several brain regions[38]. Our study confirms reduced precuneus activity, a pivotal element in cognitive function, among adolescents with MDD, indicating a potential link to compromised cognitive functions in comparison to their healthy counterparts. These findings may improve our understanding of functional dysconnectivity in adolescents with MDD.

Causes of the lack of brain regions with increased spontaneous neural activity in adolescents with MDD

In this study, we observed a decrease in spontaneous neural activity in the brain regions of adolescents with MDD through integrated ALE meta-analysis or meta-analysis of ALFF alone, and no increased spontaneous neural activity was found. There have been studies reporting elevated spontaneous neural activity, such as those conducted by Kang and

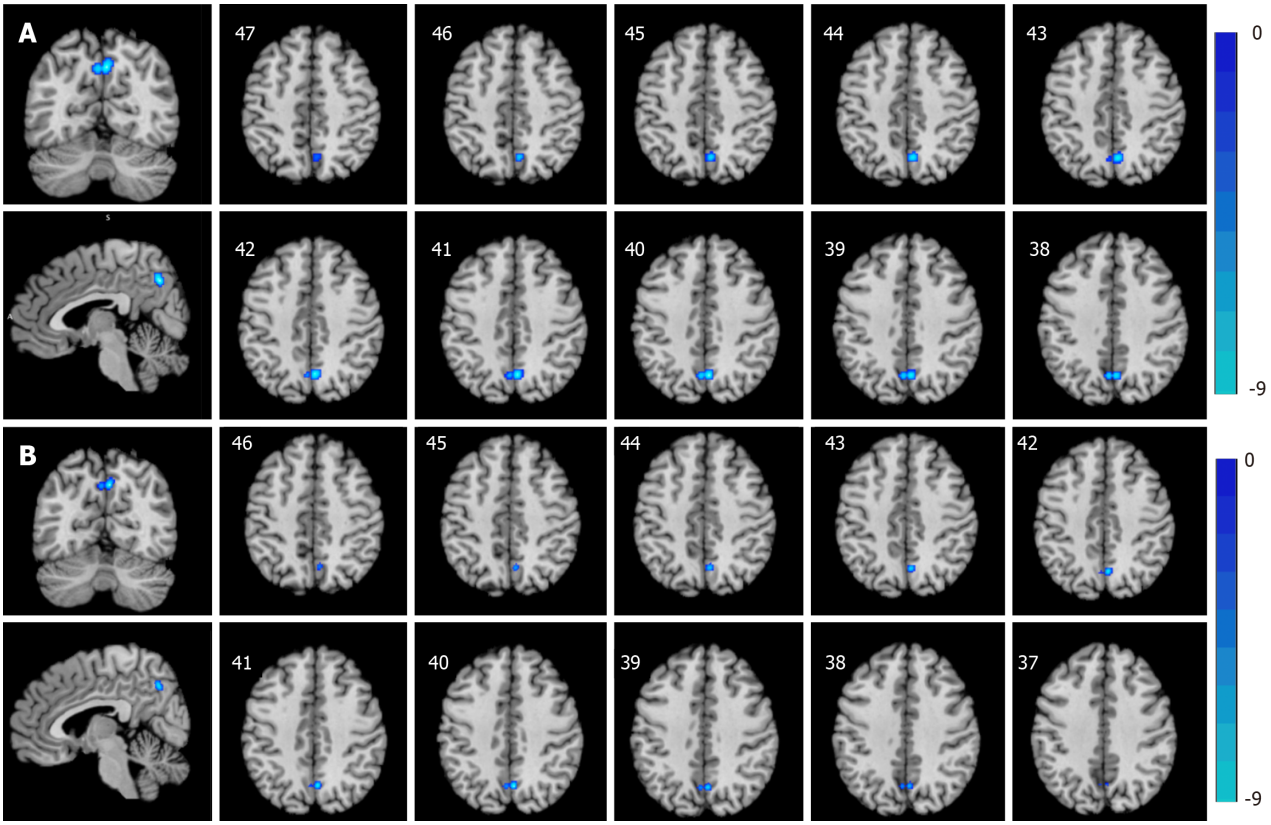

Figure 2 Schematic construction of brain areas with decreased activity in adolescents with major depressive disorder relative to healthy controls (cluster-level FWE correction at *P* < 0.05). A: Regional homogeneity and amplitude of low-frequency fluctuations (ALFF)/fractional ALFF methods; B: The ALFF method.

Kong[14], Jiao *et al*[8], and Zhang *et al*[16], which revealed that certain brain regions in adolescents with MDD exhibited increased ALFF values in comparison to those in the control group during the resting state. Jiang *et al*[10] and Mao *et al*[13] also discovered that ReHo values were greater in adolescent depression patients than in the control group. However, during the ALE meta-analysis process, a limited number of coordinates might preclude reaching the significance threshold. Consequently, although our ALE meta-analysis included 4 ALFF analyses, 2 ReHo analyses, and 1 fALFF analysis with coordinates for enhanced brain regions, comprising 21 peak coordinates of activated brain regions (foci), these activated regions are too scattered to yield results in relatively fixed brain regions. It is important to note that rs-fMRI studies have identified abnormal spontaneous low-frequency brain activity in individuals with various conditions, including adolescents with MDD[39]. However, these studies often reported inconsistent results, which may be related to the small sample sizes and different study methods. Other studies have reported structural and functional abnormalities in the anterior cingulate cortex and other brain regions in adolescents with MDD[40]. Another study revealed shared reductions in FC among the sensorimotor, visual, and auditory networks in adolescents with MDD, as well as increased sensorimotor-subcortical FC[41]. However, these findings were not found in our meta-analysis, possibly due to limitations inherent to the ALE meta-analysis method[42]. ALE meta-analysis, a probabilistic analytical approach, is effective at reducing false positives but may still encounter false negatives, particularly when dealing with a limited number of coordinates or excessively dispersed coordinates. Peak-based meta-analyses in neuroimaging studies, such as those involving adolescents with MDD, rely on summing coordinates from previously published studies rather than original statistical brain maps[43]. This approach may produce less accurate results due to potential confounding factors, such as sex distribution, mean age, symptom severity, illness duration, and scanner field strength. In this study, we concentrated on analyzing ReHo and ALFF/fALFF in adolescent MDD patients, excluding other neuroimaging methods, such as FC, ICA, and DMN, to avoid potential confusion arising from combining different rs-fMRI analysis methods. Considering the inconsistency in rs-fMRI studies and the complexity of potential neurobiological mechanisms in adolescents with MDD, further research in larger sample sizes and using more advanced imaging techniques may help to better understand the changes in spontaneous neural activity in this population.

Limitations and prospects

Although this ALE meta-analysis can properly reflect the changes in spontaneous neural activity in the brains of adolescent patients with MDD, our study has several limitations. First, the ALE meta-analysis does not account for variation between studies or activation intensity, potentially omitting brain regions with low activation intensity[44]. Second, as our analysis exclusively included studies conducted in Asian countries, caution should be exercised in extending these findings to other populations, particularly Caucasians, given the potential cultural and genetic variations that can impact neural patterns. Third, inadequate data in the included studies prevented us from analyzing adolescents'

educational backgrounds and current statuses, potentially overlooking the correlation between educational factors and changes in brain regions linked to depression. Fourth, neuroimaging data can be significantly affected by common artifacts, including respiratory effects and head movements, which can potentially impact outcomes. Finally, given the cross-sectional design of these studies, our meta-analysis could not elucidate any causal association between adolescent MDD and spontaneous brain function alterations, highlighting the need for essential longitudinal research.

CONCLUSION

In conclusion, our ALE meta-analysis revealed consistent vulnerability in the right cuneus and left precuneus among adolescents with MDD in the resting state compared to HCs. These findings may help further the understanding of the neurophysiological mechanisms underlying adolescent MDD and contribute to the development of more targeted interventions.

ARTICLE HIGHLIGHTS

Research background

Major depressive disorder (MDD) significantly impacts adolescents, leading to recurrent depression in adulthood. Despite previous research, the specific vulnerable brain regions affected in adolescent MDD patients have not been fully elucidated. Resting-state functional magnetic resonance imaging (rs-fMRI) offers a unique opportunity to understand the neural mechanisms underlying this condition, focusing on spontaneous brain activity patterns.

Research motivation

Adolescent MDD poses a serious threat to the recurrence of depression in adulthood. By exploring the spontaneous neural activity in the brains of adolescents with MDD, this study not only contributes to a deeper understanding of the neurobiological mechanisms behind adolescent depression but also aims to pave the way for more targeted intervention measures and broader advancements in the field of mental health research.

Research objectives

To address the inconsistencies in existing neuroimaging studies on adolescent MDD, this research aims to identify consistent vulnerable brain regions through an activation likelihood estimation (ALE) meta-analysis of rs-fMRI data. The realized objectives include the integration of diverse studies to unveil specific brain regions with decreased activity in adolescents with MDD. Through the exploration of spontaneous neural activity, this research contributes to establishing critical knowledge for improving mental health outcomes in adolescents.

Research methods

A comprehensive literature search was conducted, encompassing studies up to July 12, 2023, employing regional homogeneity, amplitude of low-frequency fluctuations (ALFF), and fractional ALFF (fALFF) analyses. Ten studies involving 369 adolescent MDD patients and 313 healthy controls (HCs) were included in the meta-analysis. The ALE method was utilized to aggregate peak activation coordinates, creating spatial probability maps and highlighting consistent brain regions with abnormal spontaneous activity.

Research results

The ALE meta-analysis revealed consistently decreased activity in the right cuneus and left precuneus in adolescents with MDD compared to HCs. No brain region exhibited increased activity. This consistent vulnerability in specific brain regions, particularly within the default mode network, sheds light on potential neurobiological mechanisms associated with adolescent MDD.

Research conclusions

This study consistently identifies the right cuneus and left precuneus as vulnerable brain regions in adolescent MDD. The findings contribute to the comprehension of the neurophysiological mechanisms associated with depression in this demographic. By delineating specific brain regions with altered activity, this research lays a foundation for targeted interventions in adolescent MDD. The implications extend to future investigations, offering a nuanced understanding of the neuropathology that can inform advancements in therapeutic approaches and contribute to the broader discourse in mental health research.

Research perspectives

While the study provides crucial insights into the unique neural signatures of depression in adolescents, future research with larger sample sizes and advanced imaging techniques is warranted. Longitudinal studies could help establish causal associations between adolescent MDD and spontaneous brain function alterations, addressing current limitations and informing more targeted interventions.

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FOOTNOTES

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Author contributions: Ding H, Zhang Q, Hou YZ, Shu YP and Wu G proposed the concept of this article and wrote the orginal draft; Tian B, Peng J, Lin LY and Li JL analyzed the data; Hou YZ and Shu YP aided critical editing and revisions to the article; Ding H and Zhang Q contributed equally to this manuscript and are therefore listed as co-first authors; Shu YP and Hou YZ contributed equally to this manuscript and are therefore listed as co-corresponding authors. Ding H and Zhang Q made equal contributions to the conception, design, and execution of the research project, conducted data analysis, and co-drafted the manuscript. Their collective efforts also encompassed the acquisition and interpretation of data, thereby ensuring the integrity and accuracy of the study's outcomes. Throughout the research process, they collaborated closely to navigate the complexities inherent in investigating major depressive disorder in adolescents and were actively involved in the meticulous review and refinement of the manuscript. Shu YP and Hou YZ contribute equally to the study and as co-corresponding authors. They have provided substantial support in guiding the research direction, refining the study design, and ensuring the analytical rigor of the data. Their contributions extend to overseeing the drafting and revision of the manuscript, providing critical intellectual content, and addressing the reviewers' comments. They have also taken responsibility for correspondence during the manuscript submission, peer review, and publication process, ensuring effective communication with the journal and among the research team. Their joint efforts as co-corresponding authors have been pivotal in bringing this research to fruition and maintaining the high standards of scientific integrity and accuracy.

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SCIENTOMETRICS

Psychological interventions for depression in children and adolescents: A bibliometric analysis

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Abstract

BACKGROUND

Depression has gradually become a common psychological disorder among children and adolescents. Depression in children and adolescents affects their physical and mental development. Psychotherapy is considered to be one of the main treatment options for depressed children and adolescents. However, our understanding of the global performance and progress of psychological interventions for depression in children and adolescents (PIDCA) research is limited.

AIM

To identify collaborative research networks in this field and explore the current research status and hotspots through bibliometrics.

METHODS

Articles and reviews related to PIDCA from January 2010 to April 2023 were identified from the Web of Science Core Collection database. The Charticulator website, CiteSpace and VOSviewer software were used to visualize the trends in publications and citations, the collaborative research networks (countries, institutions, and authors), and the current research status and hotspots.

RESULTS

Until April 16, 2023, 1482 publications were identified. The number of documents published each year and citations had increased rapidly in this field. The United States had the highest productivity in this field. The most prolific institution was the University of London. Pim Cuijpers was the most prolific author. In the context of research related to PIDCA, both reference co-citation analysis and keywords co-occurrence analysis identified 10 research hotspots, including third-wave cognitive behavior therapy, short-term psychoanalytic psychotherapy, cognitive behavioral analysis system of psychotherapy, family element in psychotherapy, modular treatment, mobile-health, emotion-regulation-based transdiagnostic intervention program, dementia risk in later life, predictors of the efficacy of psychological intervention, and risks of psychological intervention.

CONCLUSION
This bibliometric study provides a comprehensive overview of PIDCA from 2010 to present. Psychological intervention characterized as psychological-process-focused, short, family-involved, modular, internet-based, emotion-regulation-based, and personalized may benefit more young people.

Key Words: Child; Adolescent; Depression; Psychological intervention; Bibliometrics

Core Tip: This was a bibliometrics study of the research structure and hotspots of psychological interventions for depression in children and adolescents from 2010 to the present. Current research hotspots include third-wave cognitive behavior therapy, short-term psychoanalytic psychotherapy, cognitive behavioral analysis system of psychotherapy, family element in psychotherapy, modular treatment, mobile-health, emotion-regulation-based transdiagnostic intervention program, dementia risk in later life, predictors of the efficacy of psychological intervention, and risks of psychological intervention. The research hotspots may give insight into how to make psychological interventions for young people more accessible and effective.

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INTRODUCTION

In recent years, the incidence of depression has been trending toward a younger age. A recent study reported that the rate of increase in depression among children and adolescents is significantly more rapid relative to older groups[1]. Childhood and adolescence are critical periods in the growth and development of the individual, which mark the development of long-term character, the establishment and understanding of interpersonal relationships, the rapid acquisition of knowledge and skills, and the transition to further education and work[2]. As the physical and mental development of children and adolescents is not mature, depressed children and adolescents easily act on impulse, which often manifests as an externalized violent tendency and internalized self-harm and even suicide. Some studies have found depression in childhood and adolescence is strongly associated with mental health outcomes in adulthood, even across the lifespan[3].

Common treatments for depression include pharmacotherapy, psychotherapy, and combination therapy. Antidepressant medication can control symptoms and improve quality of life in a short period, but the use of medication is often accompanied by some side effects, such as insomnia, loss of mood control, and dysphoria[4]. Psychotherapy is often used as first-line or adjuvant treatment for many mental diseases. Many studies have found that cognitive behavior therapy (CBT) and interpersonal psychotherapy (IPT) are considered the best psychotherapies for depression in children and adolescents[5]. However, both of these therapies require a high level of professional qualification, and they are time-consuming and expensive compared to pharmacotherapy. To expand access to psychotherapy, scholars are still exploring brief, efficacious, time-saving, and low-cost psychotherapy for depression in children and adolescents.

At present, the number of publications concerning psychological interventions for depression in children and adolescents (PIDCA) is increasing rapidly. In the context of interdisciplinary research and practice, the theories and methods involved in this field are becoming increasingly extensive and complex. Traditional review research methods cannot quickly show the trends in publications and citations, the collaborative research networks (countries, institutions, and authors), and the research hotspots and future directions. As a scientific research method, bibliometrics provides an effective way to solve these problems, which can explore the evolution laws of the research from different perspectives to help scholars quickly understand the development features and hotspots of knowledge in a special research field[6]. So far, no papers have been published in terms of PIDCA using bibliometrics. According to the papers we reviewed initially, there has been a major shift in the mainstream of psychotherapy paradigm in the late 19th and early 20th century[7], as well as a large number of emerging studies on child and adolescent psychotherapy conducted over the past 10 years[8]. Therefore, considering the developmental process and growing trend of psychotherapy, we conducted a bibliometric analysis of PIDCA from 2010 to the present to systematically introduce the knowledge structure and theme trends through data mining and mapping.

MATERIALS AND METHODS

Data source and retrieval strategy

In our study, all the documents were retrieved and downloaded from the Science Citation Index Expanded (SCI-Expand-

ed, covered from 1998-present) of the Web of Science Core Collection database. Web of Science includes > 12000 international academic journals and is one of the most comprehensive and authoritative database platforms for obtaining global academic information. It is highly representative of evaluating the academic development of literature in a specific field.

The MeSH Database in PubMed was used to obtain synonyms. The literature search formula was set as, TS = (child* OR adolescen* OR teen* OR youth* OR student* OR juvenile*) AND TS = (depress* OR "low mood" OR "low moods" OR "low affect" OR "negative mood" OR "negative moods" OR "negative affect" OR dysthymi* OR "affective disorder" OR "affective disorders" OR "mood disorder" OR "mood disorders") AND TS = (Psychotherap*) AND PY = (2010–2023). TS (Topic) includes seeking in title, abstract, and keywords, and Published year (PY) is the document release period. The search document type was set to "Article" and "Review", the document language was set to English, and the search time range was from 2010 to 2023 (the date ends on April 16, 2023).

Data analysis and visualization

We used three bibliometric tools to conduct a visual analysis regarding PIDCA, including the Charticulator website and the VOSviewer, CiteSpace software. The Charticulator (https://charticulator.com/) is a powerful and free online visualization platform developed by Microsoft Research. This website was used to conduct the collaborative analysis of countries.

The VOSviewer (version 1.6.17, Leiden University, Leiden, the Netherlands) is a free Java-based bibliometric software [9]. We used VOSviewer to conduct cooperative network analysis (institutions and authors) and co-occurrence analysis of keywords. The size of the node in each map was proportional to the number of publications of the institution and author or the occurrence times of keywords. The color of the nodes represented different clusters on the network visualization maps. Different clusters represented potential research groups in the distribution of institutions and author collaboration networks. In the overlay visualization map, all these keywords were also marked with different colors according to the average PY (APY) by VOSviewer. Keywords that appeared earlier were colored in yellow, while keywords with a more recent appearance were colored blue. VOSviewer determined the extent of the collaboration between two institutions and authors, or illustrates the relationship between keywords by considering the width of the connecting line and the size of nodes.

CiteSpace is another free Java-based bibliometric software developed by Chen and Song[10]. In our study, CiteSpace (version 6.2. R2) was utilized to perform the reference co-citation cluster analysis and the burst detection algorithm (reference and keywords). Reference co-citation cluster analysis can be used to identify important regions of research by classifying references. Nodes in the network are tree ring nodes, with an outer purple ring that indicated high centrality, which is an indicator used by CiteSpace to measure the importance of nodes in the network. In the reference co-citation analysis map, nodes represent references, and node size, color rings, and links between nodes indicated the number of reference citations, different years, and the strength of the co-citation relationship, respectively. The burst detection algorithm is an effective tool to capture the sharp increases in references and keywords during a certain period. In this map, the blue lines indicated the time interval and the red the period when the reference and keywords burst occurred. From this map, we can see the time interval clearly and the intensity with which the paper was widely cited.

RESULTS

Annual publication outputs and citation trends

Annual publications and citation trends can reflect the development profile of a particular field. Ultimately, 1482 publications, which consisted of 1157 articles and 325 reviews, were obtained as the final database in our study. The specific distribution of annual publications and citation trends regarding PIDCA is shown in Figure 1. The annual number of publications appeared to be low between 2016 and 2017, but the number of publications showed an ascending tendency as a whole. In particular, the annual number of publications soared from 2017 to 2019, with a growth rate of > 30%. It is known from the citation report that the cumulative number of citations reached 45111 times (43300 times after excluding self-citations), with an average of 30.44 citations per publication. The H-index was 84, which indicated that 84 publications were cited > 84 times. Regarding the annual number of citations, we could see that it exhibited a linearly increasing trend. The dynamic changes in these two indicators also suggest a booming trend in this field.

Country ranking and collaboration analysis

The top 10 publishing countries are listed in Table 1. The leadership of the United States is evident in the ranking of publications. The top 10 countries were mostly concentrated in North America, Western Europe, and Australia. Figure 2A shows in detail the annual number of publications in these countries. Prior to 2021, the United States, Germany, and the United Kingdom dominated in this field in terms of publication outputs, while China experienced rapid growth since 2017 and even surpassed the United Kingdom and Germany for the first time in 2022. The country collaboration network analysis is illustrated in Figure 2B. The thickness of the links reflects the intensity of collaboration. We can see that the United States had close partnerships with the United Kingdom, Netherlands, Germany, Canada, Australia and Italy.

Institution ranking and collaboration analysis

Table 2 illustrates the top 10 most popular institutions for publishing papers linking PIDCA. The University of London was the most prolific institution, with an H-index of 31. Harvard University ranked first in the H-index despite being second in the total number of publications, which indicated the high quality of its published papers. Of the top 10 insti-

Table 1 Top 10 countries with most publications regarding psychological interventions for depression in children and adolescents

Rank	Country	Output	% of 1482	H-index
1	United States	581	39.20	69
2	Germany	235	15.86	41
3	United Kingdom	230	15.52	46
4	Australia	134	9.04	36
5	Canada	122	8.23	31
6	Netherlands	110	7.42	35
7	China	97	6.61	20
8	Italy	73	4.93	23
9	Switzerland	55	3.71	24
10	Spain	55	3.71	18

Table 2 Top 10 institutions with most publications regarding psychological interventions for depression in children and adolescents

Rank	Institutions	Output	% of 1482	H-index
1	University of London	116	7.83	31
2	Harvard University	89	6.01	33
3	University of California	67	4.52	27
4	Vrije Universiteit Amsterdam	59	3.91	24
5	Columbia University	55	3.71	25
6	University of Melbourne	52	3.51	21
7	University of Toronto	50	3.37	18
8	University of Pittsburgh	46	3.10	25
9	ORYGEN1	41	2.77	21
10	University of Amsterdam	37	2.50	15

ORYGEN1 refers to The National Centre of Excellence in Youth Mental Health.

tutions, four were in the United States, two in the Netherlands and Australia, and one each in the United Kingdom and Canada. In addition, we found that, despite being the second most prolific country, no institutions in Germany appeared in the top 10. This suggested that German institutions were more evenly distributed and developed. Figure 3A is a network visualization map showing the collaboration between institutions, which shows a close collaboration between the Universities of London, Cambridge, Manchester and Sheffield, and a more active collaboration between Harvard University, University of California, Columbia University and Vrije Universiteit Amsterdam.

Author ranking and collaboration analysis

The top 10 most prolific authors are listed in Table 3. Pim Cuijpers from Vrije Universiteit Amsterdam was the most productive, with 30 publications, followed by Nick Midgley from the University of London and Sarah E. Hetrick from the University of Melbourne. The number of highly cited publications written by these authors indicated that they occupied an important position in this field. According to the H-index, the most influential authors were Pim Cuijpers and Sarah E Hetrick, both with an H-index of 15, followed by John R. Weisz from Harvard University who had an H-index of 12. We studied the author collaboration network by VOSviewer (see Figure 3B). Different colors represented different clusters, and all authors were clustered into 10 small groups. Some of the groups were closely linked to each other, with the top prolific authors acting as a bridge for collaboration, such as Pim Cuijpers, Nick Midgley, and Sarah E. Hetrick. In addition, there were only a few links between other groups.

Journal ranking and discipline distribution

Journal publications are an important medium for academic knowledge dissemination and learning exchange. The top 10 journals are listed in Table 4. The Journal of Affective Disorders was the most prolific journal. Among the top 10 journals, five were in Q1, four in Q2 and only one in Q3, which represented PIDCA as a popular subject in high-level journals. We

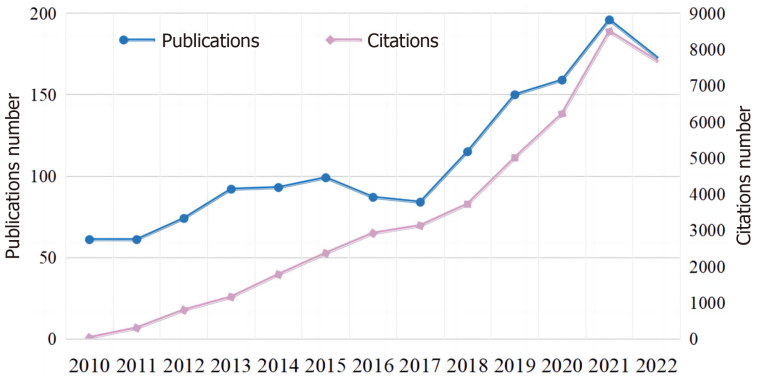


Figure 1 Annual publication outputs and citation trends regarding psychological interventions for depression in children and adolescents from 2010 to 2023.

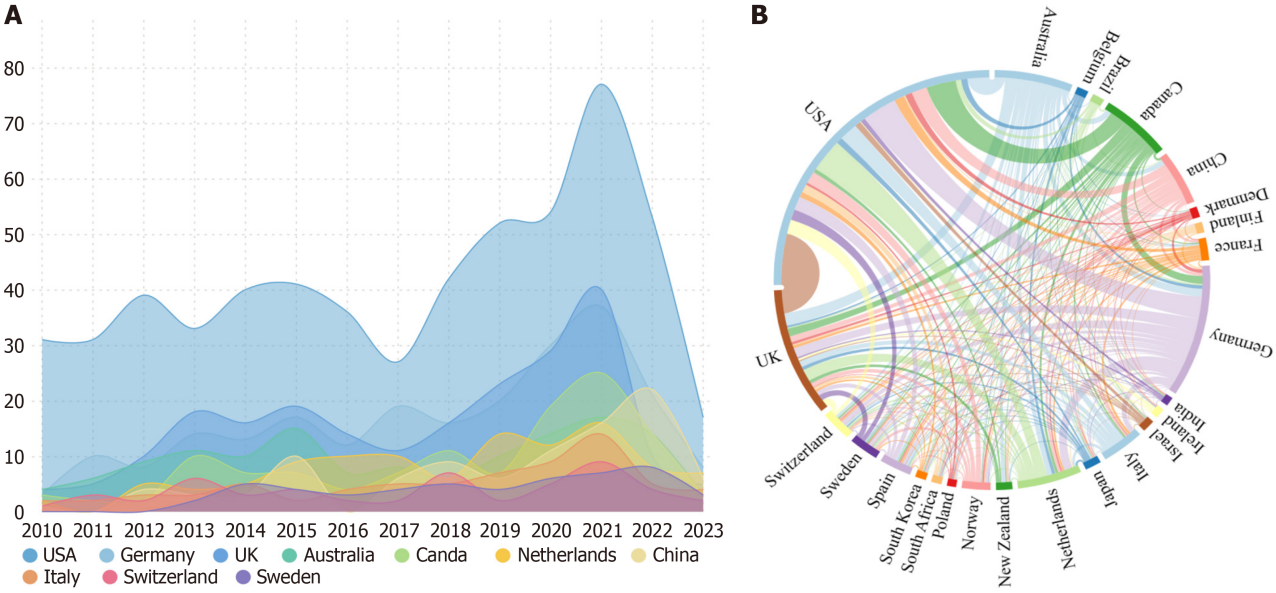


Figure 2 Visualization of country analysis. A: Annual number of publications in the top 10 most productive countries; B: International collaboration analysis among different countries.

also analyzed the published and co-cited journals using a journal dual-map overlay (Figure 4). In the dual-map overlays, the referential links originated from a citing journal on the left side of the dual-map and pointed at a cited journal on the right side. The color of the links distinguished the discipline of the source. With this approach, we could determine how knowledge flowed in different disciplines. There were three core citation paths shown in Figure 4. The green path implied that most papers published in the journals of psychology/education/social were likely to be biased to cite papers published in the journals of medicine/medical/clinical. The two blue paths implied that most papers published in both health/nursing/medicine and psychology/education/social journals were likely to be biased to cite papers published in journals within psychology/education/health.

Reference co-cited cluster analysis and burst detection

Reference analysis is a valuable technique to explore the knowledge structure and evolution in a specific research field. With the help of CiteSpace software, a cluster visualization network map of cited references was plotted (Figure 5A). The parameters were set as follows: time range: 2010–2023, time slice was 1 year. Notably, the modularity value (Q) and mean silhouette value (S) were two valuable parameters to evaluate cluster results. In the map of Figure 3A, Q = 0.7949 > 0.3, S = 0.9191 > 0.7, and the clustering result was considered reasonable. Some of the clusters had a silhouette of 1 and a small size value, which was less informative and therefore not shown on the map.

All the co-cited references were divided into 18 clusters, and antidepressant (#0) was the largest cluster (Figure 5A). Table 5 summarizes the specific information of the 18 clusters in the reference co-citation analysis. The colors of the clusters in Figure 5A and the cluster mean year in Table 5 suggested that the research hotspots had gradually shifted to CBT (#4), mobile-health (M-health, #5), cognitive behavioral analysis system of psychotherapy (CBASP, #7), and psychoanalytic psychotherapy (PP, #18). Figure 5B lists the top 25 references with the strongest citation bursts. The most-cited study was by Zhou *et al*[11], with a strength of 11.19, which suggested that IPT and CBT should be considered the best

Table 3 Top 10 authors with most publications regarding psychological interventions for depression in children and adolescents

Rank	Authors	Output	% of 1482	H-index
1	Pim Cuijpers	30	2.02	15
2	Nick Midgley	22	1.48	10
3	Sarah E Hetrick	20	1.35	15
4	John R Weisz	20	1.35	12
5	Peng Xie	16	1.08	9
6	Xin-Yu Zhou	16	1.08	9
7	Randi Ulberg	15	1.01	5
8	Yu-Qing Zhang	13	0.88	8
9	Gerhard Andersson	13	0.88	7
10	David A Brent	12	0.81	10

psychotherapy for children and adolescents. Exploring highly cited references could also help us identify hotspots over time. The papers that have experienced a sudden increase in citations over the last 3 years are important for understanding recent research hotspots within the field.

Keywords co-occurrence analysis and burst detection

Keywords analysis is another important method to explore knowledge structure and evolution. After excluding several topic-related or meaningless keywords and merging keywords with the same meaning, Figure 6A shows the co-occurrence of keywords by the APY. Figure 6B shows the frequency distribution of the top 15 high-frequency keywords. It can be seen that CBT ranks first, which represents that CBT is treated as an important choice for children and adolescents with depression. Also, in addition to the keyword "efficacy", "validation" and "quality of life", the other common keywords include "predictors" and "risk". These keywords, such as "program" and "emotion regulation (ER)" showed the latest APY, which indicated that these topics may have gained increasing attention recently and have the potential to become a research hotspot soon. Apart from this, we used CiteSpace for keyword-citation burst detection. There were 22 keywords that had strong bursts (Figure 6C). Figure 6C shows that "internet-based treatment" (strength = 4.33), "persistent depressive disorder (PDD, strength = 2.71)", "family" (strength = 2.82), and "family therapy" (strength = 2.92) have been a focus topic in recent years.

DISCUSSION

This bibliometric analysis offers a comprehensive overview of PIDCA research. For over a decade, there has been significant growth in worldwide research interest in this topic, with an accelerating trend for the past 5 years. The United States, Germany and United Kingdom were the main contributing countries to the publications, and the quality of publications was also among the highest in the world. In general, the top 10 countries were concentrated in the developed regions of the world, and had close partnerships, while developing countries had less collaboration regarding PIDCA, showing an uneven developmental trend. In recent years, the publication outputs of China in this field have increased annually, which means it has a promising development potential. The top 10 institutions were mostly concentrated in a few countries with well-established mental health services, and collaboration was close between those prolific institutions. The author collaboration network was characterized by extensive dispersion with localized concentrations, indicating that the collaboration is not yet well developed. Most of the top 10 journals were in Q2 or above, indicating that PIDCA is a valuable and worthwhile topic for scholars to continue exploring.

We may gain insight into the structure and evolution of knowledge in this field and clarify the current research hotspots by analyzing the four aspects of the reference co-citation clusters, references with the strongest citation bursts, keywords with the largest occurrence times, and keywords with the strongest citation bursts. After combining the results of the mapping analysis and the research foundation of our research team in this field, we summarize the obtained research hotspots and introduce them as follows.

The third-wave CBT: The cluster "CBT" is often considered the most recognized psychological intervention for children and adolescents with depression, which can help people learn to identify relationships between cognition, behavior, and mood, and break the cycle of depression by changing distorted cognition or avoidance behaviors[11]. In recent years, the third-wave CBT approach has been becoming popular, and promising results for the use of third-wave CBT with youth were found in a large meta-analysis[8]. By contrast to traditional syndrome-specific CBT, the third-wave CBT has become more flexible and process-focused[7], which targets core psychological processes of change that are functionally important to long-term outcomes in psychological disease[12]. Instead of focusing specifically on changing the form, frequency, or situational sensitivity of bad emotions or thoughts, it advocates individuals improving the capacity of metacognitive awareness of psychological processes, which means taking an accepting attitude to objectively evaluating their emotions

Table 4 Top 10 journals with most publications regarding psychological interventions for depression in children and adolescents

Rank	Journals	Output	% of 1482	JIF1 (2022)	Quartile in category2 (2022)
1	*Journal of Affective Disorders*	85	5.74	6.6	Q1
2	*Frontiers in Psychiatry*	66	4.45	4.7	Q2
3	*Journal of the American Academy of Child and Adolescent Psychiatry*	42	2.83	13.3	Q1
4	*Cochrane Database of Systematic Reviews*	39	2.63	8.4	Q1
5	*BMC Psychiatry*	33	2.23	4.4	Q2
6	*Trials*	29	1.96	2.5	Q3
7	*European Child & Adolescent Psychiatry*	26	1.75	6.4	Q1
8	*Plos One*	26	1.75	3.7	Q2
9	*BMJ Open*	25	1.69	2.9	Q2
10	*Depression and Anxiety*	24	1.62	7.4	Q1

JIF1 (2022) refers to the impact factor of the Journal; Quartile in category2 (2022) is the division to which the journal belongs. Journal Citation Reports split journals into four equal parts based on JIF value, among which the top 25% attributed to Q1 and the top 25%–50% being Q2, *etc*.

or thoughts[13]. The third-wave CBT methods, such as mindfulness-based cognitive therapy[14], dialectical behavior therapy[15], and acceptance and commitment therapy (ACT)[16], can help depressed adolescents improve their metacognitive awareness, which in turn improve their depressive symptoms. Those approaches represent a paradigm shift in intervention science, called process-based therapy (PBT)[17]. PBT offers us an alternative approach to understanding and treating psychological problems, which would be more committed to fitting treatment methods to the needs of people [18].

The short-term PP: To our knowledge, cluster "PP" has a strong evidence base in the treatment of adult depression, and for its application in children and adolescents, the evidence base has been accumulating since the success of Trowell *et al*'s first trial in 2007[19], indicating that a brief version of a psychological treatment using key therapeutic components might be as effective as the original. The working principle of short-term PP (STPP) assumes that people's behavioral and emotional responses are based on their early experience of relationships, and the therapist can help the children and adolescents give up the emotional connection patterns that stubborn depression relies on by exploring these relationships and develop emotional insight and awareness[20]. In a recent highly cited reference, Goodyer *et al*[21] found that CBT or STPP was equally effective with the brief psychosocial intervention in the treatment of depressed adolescents in a randomized controlled trial, the Improving Mood with Psychoanalytic and Cognitive Therapies (IMPACT) in 2017[21]. However, most adolescents responded to STPP well in this trial, but subgroups of depressed adolescents with higher depression severity and comorbidity at baseline did not respond well to STPP[22]. If we can identify adolescents who are likely to respond poorly before treatment and design personalized intervention methods for them, we might be more effective in improving the cost-effectiveness of psychological interventions[23].

The application of CBASP: The cluster "CBASP" is the only psychotherapy method developed specifically for PDD, which refers to chronic forms of depression in which the depression lasts for 2 years or longer. PDD is a serious mental disorder that may occur in childhood and adolescence accompanied by greater interpersonal difficulties, lower quality of life, and higher frequency of suicide attempts and hospitalization, often using psychotherapy as the core treatment[24]. In the CBASP model, preoperational functioning characterized by global and prelogical thinking, egocentricity, communication in largely monologue form, poor affective control under stress, and an inability to express interpersonal empathy is resulted from childhood maltreatment[25], which would drive patients to disconnect from others to avoid hurtful social encounters, and leads to reduced social connectedness. The focus of CBASP is on breaking this vicious cycle[26]. In the treatment of PDD, the combination therapy of CBASP and drugs often showed significant superiority is superior to when they are applied alone[27]. The baseline depression, anxiety, previous medications, and traumatic childhood experiences might moderate the efficacy of CBASP, which also suggests the most appropriate treatment decisions should take into account individual characteristics[27-29]. In addition, the most frequently reported negative effect was dependence on the therapist, which might be associated with a worse treatment outcome[26]. However, our knowledge of the specific mechanisms of care dependency is little, it should be investigated broadly in future research[30].

The family element in psychotherapy: "family" and "family therapy" were found as keywords with the strongest citation bursts. Involving caregivers/family members of children and adolescents in psychotherapy could increase its efficacy, as their engagement can help address the difficulties that patients may encounter[31], and the understanding and support of caregiver/family member is of benefit to recovery from depression[32]. What matters is the circumstances and the form in which they are effectively involved in psychotherapy, when caregivers/family members are involved. The caregivers/family members have many different ways of participating in treatment, which include conducting sessions with the children/adolescents and meeting afterward or separately with the caregiver/family; joint participation in sessions; or the different proportion, frequency, and quality of caregiver/family involvement[33]. The intervention

Table 5 The clusters information of references co-citation analysis

Cluster ID	Size	Silhouette	Mean (year)	Top terms (log-likelihood ratio, p-level)
0	72	0.881	2008	Antidepressants
1	53	0.931	2017	Depression
2	32	0.887	2015	Self-harm
3	27	0.906	2015	College students
4	26	0.96	2019	Cognitive behavior therapy
5	25	0.887	2018	M-health
6	25	0.851	2012	FMRI
7	24	0.871	2017	CBASP
8	23	0.906	2011	Review
9	23	0.998	2009	Mothers
11	20	0.958	2012	Prevention and Control
12	14	0.964	2016	Dementia
13	13	0.985	2010	Interpersonal psychotherapy
14	12	0.992	2007	Very young children
15	11	0.978	2015	Therapy
18	5	0.988	2018	Psychoanalytic psychotherapy
19	4	0.997	2011	Intervention study
26	3	0.997	2013	Late adolescent

outcomes tend to be heterogeneous for different ways of involvement. However, there are fewer relevant studies discussing the choice of participation methods[33]. It is indisputable that patient age should be considered when making the choice of intervention. Family therapy is also an important form of psychosocial intervention that can alleviate the negative family influences on depressed children and adolescents by strengthening harmonious interactions between family members[34]. Positive relationships between family caregivers and adolescents have a long-term supportive effect on the physical and mental development of children and adolescents.

The modular treatments: As the latest high-frequency keyword "program", modular treatments also can be interpreted as multicomponent psychological intervention programs. According to the paper cited up to 557 times by Weisz *et al*[35], the modular approach to therapy for children outperformed usual care and standard evidence-based treatments (EBTs) on multiple clinical outcome measures in 2012[35]. Modular treatments are more effective than EBTs, as they can focus on more for children and adolescents with depression[36]. The selection of the components of modular treatments requires decision-making by therapists after taking into account a complex array of variables, including: the therapist's expertise and experience; the therapeutic setting; conceptual approach to therapy; the characteristics and preferences of the adolescents and their parents; and the priority problems to be addressed[37]. However, there was less evidence base for how to balance those variables when therapists make decisions and how decision-making structures and procedures influence treatment outcomes. On this issue, decision aids often used the decision flow diagrams to suggest module selection and sequences depending on primary and interfering problems[38], while still relying heavily on clinician judgment. Future research should focus on developing decision recommendations based on the efficacy data from prior decision-making, and figuring out how these recommendations can be combined with factors such as clinician judgment and client preferences.

The M-health: Although the efficacy of numerous psychological interventions has been validated, a substantial proportion of depressed children and adolescents do not receive adequate professional psychological interventions[39]. It was reported that up to 80% of depressed children and adolescents did not receive formal psychological treatment due to the accessibility of psychotherapy and patients' reluctance to seek help face-to-face as a result of perceived mental illness stigma or a preference for self-help[40]. In cluster "M-health", digital health interventions (DHIs), such as internet- and mobile-based psychological interventions (DHI_{PSY}), could overcome many limitations of the traditional medical model and thereby make treatments accessible to children and adolescents, thanks to these advantages including promising cost-effectiveness, guaranteed privacy and security, and a high degree of flexibility and autonomy[41]. In 2015, Ebert *et al* [42], in a meta-analysis that was cited 271 times, found that when evidence-based face-to-face treatment is not feasible, computer- or internet-based CBT might be promising alternatives [42]. Artificial intelligence (AI) has begun to be applied in multiple domains of mental health care in recent years, and many scholars wonder whether psychological interventions could be delivered someday by mental health chatbots in the ChatGPT era. However, there are still some challenges on the path to psychotherapy delivered by AI consisting of limited knowledge of the active ingredients of psychotherapy, therapeutic relationships delivered by non-human agents, and human-like AI being capable of delivering fully-fledged

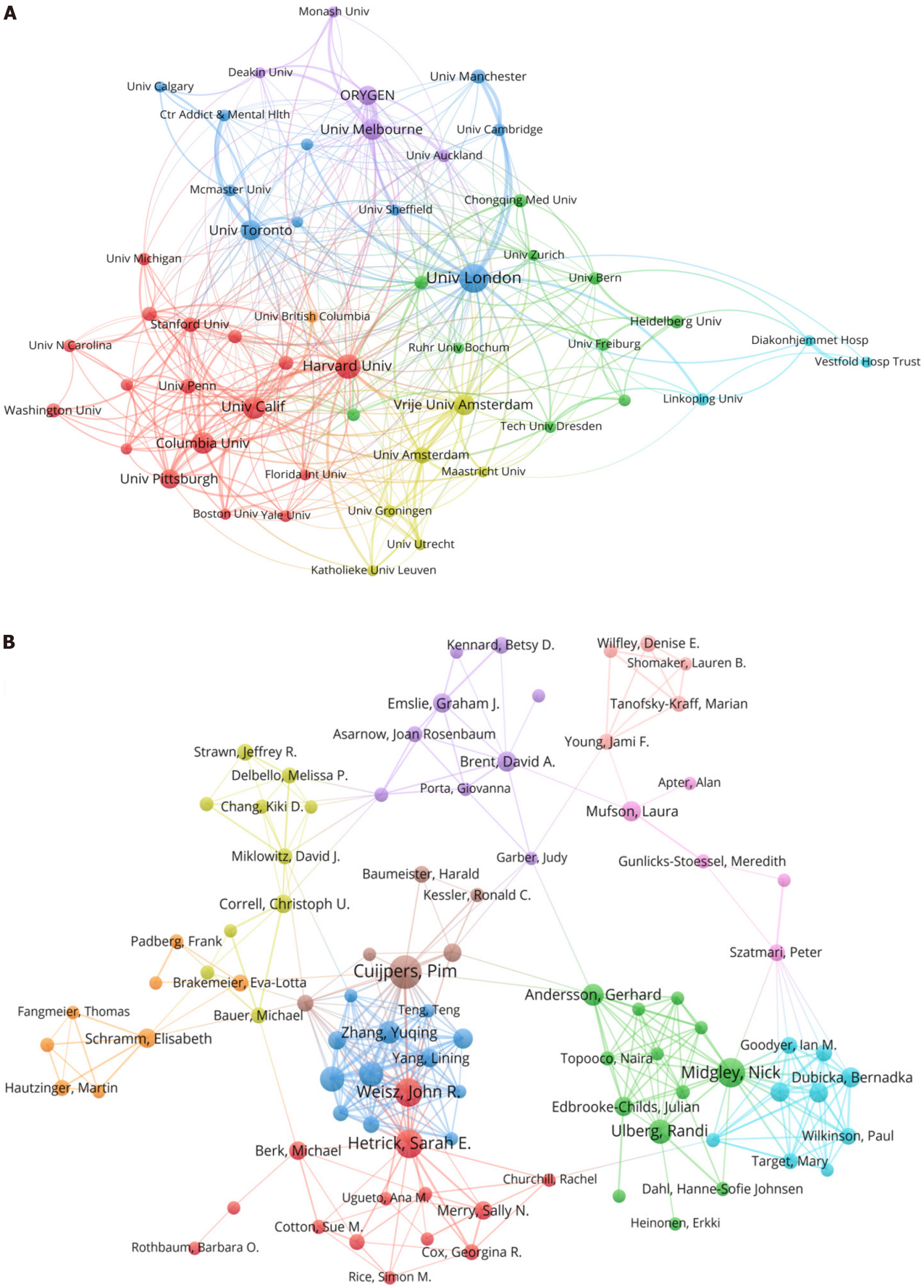


Figure 3 Visualization of institution and author analysis. A: Network visualization map of institution collaboration analysis; B: Network visualization map of author collaboration analysis.

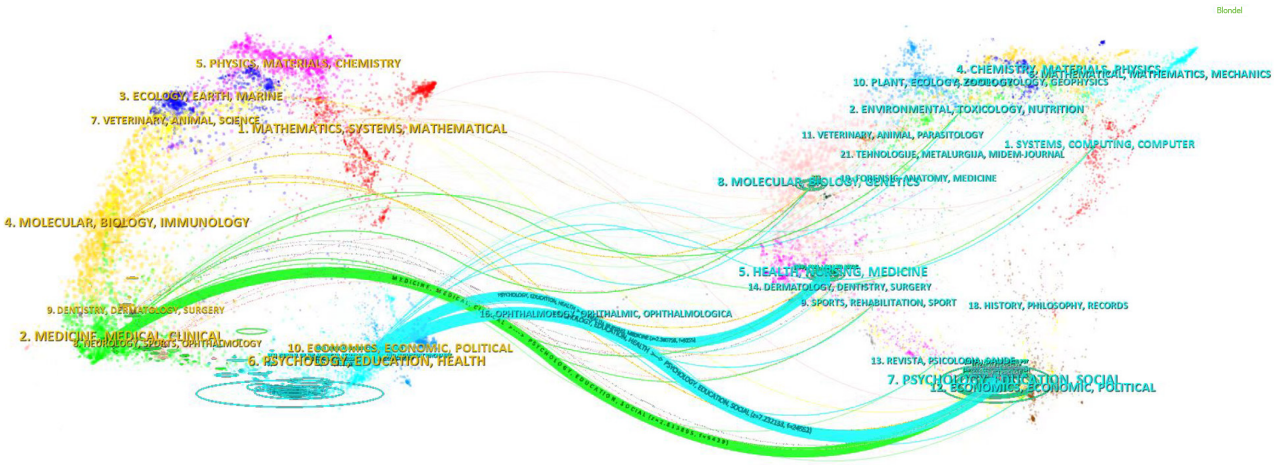


Figure 4 Dual-map overlay of academic journals.

psychotherapy is undeveloped[43].

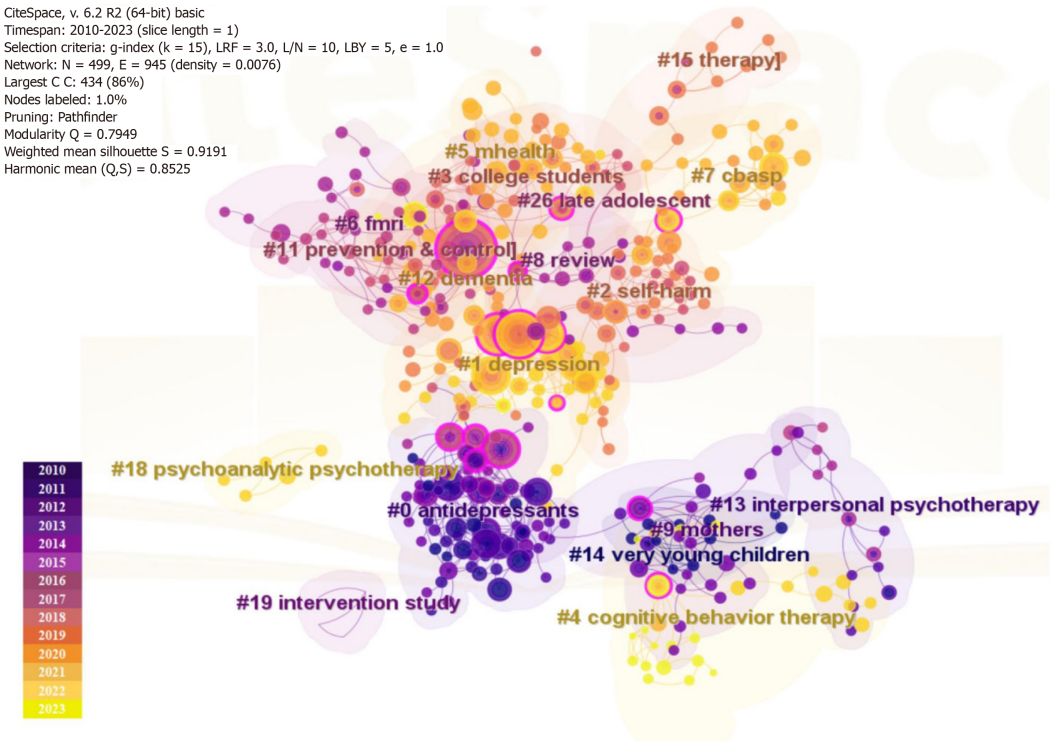
The ER-based transdiagnostic intervention program: The latest high-frequency keyword "ER" has recently become a popular theme in psychotherapy research, which refers to regulatory processes for modifying emotional responses[44]. Emotion dysregulation (ED), is the inability to flexibly respond to and manage emotions, which is a central component of psychopathology in adolescence[45]. Psychological interventions such as CBT, which may help improve ER strategies indirectly, were proven to be effective, with improvements in psychopathology[46]. In view of the general importance of ER in psychological therapies, ER is considered to be a transdiagnostic mediator that leads to positive therapeutic change [47]. The Unified Protocol for Emotional Disorders, the ER-based transdiagnostic intervention program, explicitly targets improving ER strategies for reducing psychological distress and improving overall well-being regardless of diagnostic status[48]. Longitudinal data suggest that ED happens before depressive disorders, so the primary intervention goal of most early intervention programs was ER[49], and the ER strategies are likely to protect them from bad moods and possibly even prevent the onset of mental disorders[16]. Over the last few decades, different theoretical models have developed different ER strategies (distraction, acceptance, problem-solving, reappraisal, *etc.*), which refer to some methods to keep emotional stability. Further advanced understanding of the ER process can provide a basis for refining ER models and intervention methods[50]. Of the ER studies, ecological momentary assessment and/or intervention could be useful to show how specific ER strategies in daily life link to dysregulated emotions and behaviors, and how these associations may change throughout the intervention[51].

Dementia risk in later life: In terms of the cluster "dementia", we found that the incidence of dementia increases significantly with average life expectancy. Dementia can cause considerable deterioration in cognitive functioning, which not only seriously reduces the quality of life of patients in their later years, but also brings a heavy burden to their families and even to society. Intervention strategies targeting the risk factors in early life could reduce the incidence of dementia or substantially delay its onset[52]. Recent studies have found that low adolescent cognitive ability[53,54] and adverse childhood experiences[55,56] have a significant association with dementia risk in later life. Depression that occurs in childhood and adolescence is often accompanied by varying degrees of cognitive impairment in attention, memory, and executive functioning, or even interrupted educational trajectories[4]. Researchers have tried to figure out the relationships and action paths between early cognitive ability, childhood experiences, depression, and dementia, and whether the prevalence of dementia in the population would be lower if depression could be prevented or adequately treated [57]. A lot of research still needs to be done into the relationships of the variables involved. However, it is difficult to conduct prospective cohort studies due to the wide age range.

The predictors of the efficacy of psychological intervention: For the high-frequency keyword "predictors", we found that a better understanding of predictors of treatment outcome may guide the selection of individualized treatment approaches or adjustment of treatment intensity. In 2017, the prolific author Weersing *et al*[5] suggested that there was a strong demand to increase the evidence related to predictors of efficacy of treatment of depression in children and adolescents in a recent highly cited evidence update paper. In the next two highly cited papers in 2020, Eckshtain *et al*[58] stated that the choice of psychological interventions should consider depressed children and adolescents' individual characteristics, and Cuijpers *et al*[59] found that psychological interventions were less effective in younger patients, especially in children aged ≤ 13 years. It follows that age might be an important factor in the efficacy of psychological interventions. This might be related to the fact that the therapies for children and adolescents are primarily age-adapted versions of therapies originally designed for adults. Another possibility is that different from adults, young people's potential for recovery from depression is constrained by parental and family characteristics, which they have little opportunity to escape from or alter.

The risks of psychological intervention: Although psychological interventions have always been shown to be effective in reducing levels of depression, up to 60% of adolescents still do not respond to these treatments, and clinically significant deterioration was 6%[60]. Another high-frequency keyword "risk" in most articles is often described as the risk of depression, suicide, and non-suicidal self-injury, or the risk of not receiving treatment, but it also represents the risk of receiving treatment in some publications. It is widely believed that psychological interventions are always bene-

A

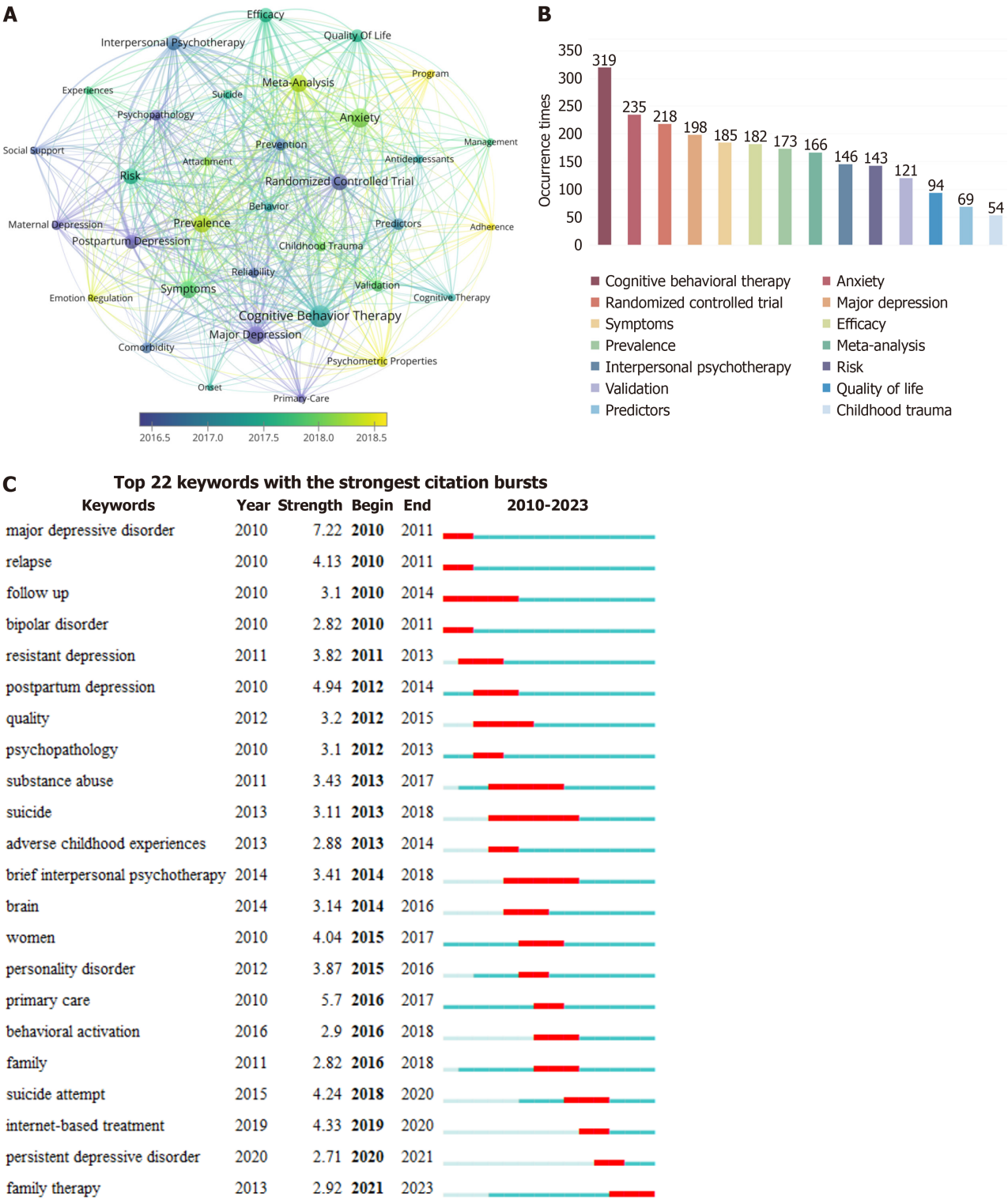


B

Top 25 references with the strongest citation bursts

References	Year	Strength	Begin	End	2010-2023
Birmaher B, 2007, J AM ACAD CHILD PSY, V46, P1503, DOI 10.1097/chi.0b013e318145ae1c, DOI	2007	9.58	2010	2012	
Brent D, 2008, JAMA-J AM MED ASSOC, V299, P901, DOI 10.1001/jama.299.8.901, DOI	2008	8.94	2010	2013	
Goodyer I, 2007, BMJ-BRIT MED J, V335, P142, DOI 10.1136/bmj.39224.494340.55, DOI	2007	8.05	2010	2012	
Mittal VA, 2011, PSYCHIAT RES, V189, P158, DOI 10.1016/j.psychres.2011.06.006, DOI	2011	7.96	2011	2016	
Asarnow JR, 2009, J AM ACAD CHILD PSY, V48, P330, DOI 10.1097/CHI.0b013e3181977476, DOI	2009	7.59	2010	2013	
March JS, 2007, ARCH GEN PSYCHIAT, V64, P1132	2007	7.54	2010	2012	
Brent DA, 2009, AM J PSYCHIAT, V166, P418, DOI 10.1176/appi.ajp.2008.08070976, DOI	2009	6.3	2010	2014	
Weisz JR, 2006, PSYCHOL BULL, V132, P132, DOI 10.1037/0033-2909.132.1.132, DOI	2006	6.18	2010	2011	
Curry J, 2006, J AM ACAD CHILD PSY, V45, P1427, DOI 10.1097/01.chi.0000240838.78984.e2, DOI	2006	5.62	2010	2011	
Bridge JA, 2007, JAMA-J AM MED ASSOC, V297, P1683, DOI 10.1001/jama.297.15.1683, DOI	2007	5.52	2010	2012	
Fristad MA, 2009, ARCH GEN PSYCHIAT, V66, P1013, DOI 10.1001/archgenpsychiatry.2009.112, DOI	2009	5.51	2010	2014	
Grote NK, 2009, PSYCHIAT SERV, V60, P313, DOI 10.1176/appi.ps.60.3.313, DOI	2009	5.29	2012	2014	
Cox GR, 2012, COCHRANE DB SYST REV, V0, P0, DOI 10.1002/14651858.CD008324.pub2, DOI	2012	5.83	2013	2017	
American Psychiatric Association, 2013, DIAGN STAT MAN MENT, V0, P0	2013	24.86	2014	2018	
Zhou XY, 2015, WORLD PSYCHIATRY, V14, P207, DOI 10.1002/wps.20217, DOI	2015	11.19	2017	2020	
Cipriani A, 2016, LANCET, V388, P881, DOI 10.1016/S0140-6736(16)30385-3, DOI	2016	7.62	2017	2021	
Weisz JR, 2017, AM PSYCHOL, V72, P79, DOI 10.1037/a0040360, DOI	2017	8.44	2018	2021	
Avenevoli S, 2015, J AM ACAD CHILD PSY, V54, P37, DOI 10.1016/j.jaac.2014.10.010, DOI	2015	5.63	2018	2019	
Goodyer IM, 2017, LANCET PSYCHIAT, V4, P109, DOI 10.1016/S2215-0366(16)30378-9, DOI	2017	8.09	2019	2023	
Moher D, 2015, SYST REV-LONDON, V4, P0, DOI 10.1186/s13643-015-0087-2, DOI	2015	5.46	2019	2020	
Weersing VR, 2017, J CLIN CHILD ADOLESC, V46, P11, DOI 10.1080/15374416.2016.1220310, DOI	2017	7.51	2020	2023	
Eckshtain D, 2020, J AM ACAD CHILD PSY, V59, P45, DOI 10.1016/j.jaac.2019.04.002, DOI	2020	6.38	2020	2023	
Nelson J, 2017, BRIT J PSYCHIAT, V210, P96, DOI 10.1192/bjp.bp.115.180752, DOI	2017	6.38	2020	2023	
R Core Team, 2019, R LANGUAGE ENV STAT, V0, P0	2019	6.55	2021	2023	
Cuijpers P, 2020, JAMA PSYCHIAT, V77, P694, DOI 10.1001/jamapsychiatry.2020.0164, DOI	2020	5.05	2021	2023	

Figure 5 Visualization of reference co-citation analysis. A: Network visualization map of reference co-citation cluster analysis; B: Top 25 references with the strongest citation bursts.



C **Top 22 keywords with the strongest citation bursts**

Keywords	Year	Strength	Begin	End	2010-2023
major depressive disorder	2010	7.22	**2010**	2011	
relapse	2010	4.13	**2010**	2011	
follow up	2010	3.1	**2010**	2014	
bipolar disorder	2010	2.82	**2010**	2011	
resistant depression	2011	3.82	**2011**	2013	
postpartum depression	2010	4.94	**2012**	2014	
quality	2012	3.2	**2012**	2015	
psychopathology	2010	3.1	**2012**	2013	
substance abuse	2011	3.43	**2013**	2017	
suicide	2013	3.11	**2013**	2018	
adverse childhood experiences	2013	2.88	**2013**	2014	
brief interpersonal psychotherapy	2014	3.41	**2014**	2018	
brain	2014	3.14	**2014**	2016	
women	2010	4.04	**2015**	2017	
personality disorder	2012	3.87	**2015**	2016	
primary care	2010	5.7	**2016**	2017	
behavioral activation	2016	2.9	**2016**	2018	
family	2011	2.82	**2016**	2018	
suicide attempt	2015	4.24	**2018**	2020	
internet-based treatment	2019	4.33	**2019**	2020	
persistent depressive disorder	2020	2.71	**2020**	2021	
family therapy	2013	2.92	**2021**	2023	

Figure 6 Visualization of keyword co-occurrence analysis. A: Network visualization map of keyword co-occurrence analysis; B: Top 15 keywords with the largest occurrence times; C: Top 22 keywords with the strongest citation bursts.

ficial, but some studies have found that some patients' symptoms do not improve much after receiving psychological interventions[61] and are even accompanied by adverse events (AEs) (*e.g.* suicide, suicide attempts, mental health related hospital admissions)[62]. A systematic review by Lodewyk *et al*[63] summarized the AEs caused by psychological interventions, and they identified that AEs were of the following types, physical, cognitive and/or mental health, social and/or academic, and health care usage, and the most common event monitored was hospitalization[63]. AEs of psychological interventions were mainly, caused by ineffective engagement, ineffective practice, and accidental events[64]. However, the monitoring of AEs is largely absent in studies of psychotherapy with children and adolescents[65]. Assessing and reporting AEs comprehensively in studies of psychotherapy is crucial to improve research and service quality. Furthermore, patients sometimes experienced improvements in other domains despite a lack of depressive

symptoms reduction, which suggested that we may gain a more nuanced understanding of current treatment effects in many ways by combining qualitative perceptions and quantitative measurements of patients after the treatment[66].

Our results highlight the critical research themes and lines in the study of PIDCA, as well as recognition of insufficiently and issues that could be a basis for future studies. From the documents reviewed, it was found that the short, internet-based, multi-component, family-involved, and personalized psychological interventions were more in line with the needs of society considering cost-effectiveness and treatment adherence. Therefore, these factors could be considered in future psychological interventions for children and adolescents, depending on the study design and feasibility factors. As with any study, this was not without limitations. Firstly, the selected articles reflects the characteristics of the documents published in journals referred to in the Web of Science Core Collection database, which may have resulted in some selection bias. Secondly, to explore the latest research developments in the field of PIDCA, only studies from 2010 to the present were included; therefore, a description of the development of the field over the entire historical period cannot be made. Thirdly, the restriction of the reviewed articles to a short period reduced the opportunity to receive full citations.

CONCLUSION

Overall, the results of this study provide insight into new trends in the field of the PIDCA for over a decade. In this research, an attempt was made to review the documents in this field using a comprehensive method and multiple bibliometric tools. It turns out that the PIDCA research has received increasing attention, as reflected in both annual publications and citation quantity. The most influential journals, countries, institutions, and authors were identified, as were hotspots and the latest trends of research. Although our findings are preliminary, they imply that future mental health service trends prefer brief, convenient, and effective psychological intervention methods. We hope that the above results will give some valuable help to later scholars interested in this field.

ARTICLE HIGHLIGHTS

Research background

Child and adolescent depression is a public health problem that needs urgent attention today. Psychological intervention as a promising treatment for depression in children and adolescents. However, a significant number of child and adolescent patients do not receive professional psychological intervention due to the fact that it requires a high level of qualification for its implementation and is usually costly and time-consuming.

Research motivation

Currently, there is a rapid growth of relevant articles within the field. To understand the global performance and progress of papers related to psychological interventions for depression in children and adolescents (PIDCA), and to provide a guide for new researchers in this field.

Research objectives

To understand the distribution of global collaborative networks (countries, institutions, authors) and current research hotspots related to PIDCA in the forms of visual diagrams.

Research methods

We used bibliometric research method, the Charticulator website, CiteSpace, and VOSviewer software. Articles and reviews related to PIDCA from January 2010 to April 2023 were identified from the Web of Science Core Collection database.

Research results

We present a visual representation of the overall performance of relevant papers in the field in terms of countries, institutions, authors and journals, and the current research hotspots we identified were summarized and presented in 10 research perspectives.

Research conclusions

In our study, no new theories were used, but an attempt was made to review the papers in this field using a comprehensive method (the analysis of reference co-citation clusters, references with the strongest citation bursts, keywords with the largest occurrence times, and keywords with the strongest citation bursts) and multiple bibliometric tools (the Charticulator website, CiteSpace, and VOSviewer software).

Research perspectives

Through this study, we find that the psychological intervention characterized as psychological processes-focused, short, family-involved, modular, internet-based, emotion-regulation-based, and personalized may benefit more young people. The brief, efficacious, time-saving, and low-cost psychotherapy would be the promising psychotherapy.

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FOOTNOTES

Author contributions: Wang N formulated research questions and designed the research; Kong JQ collected the data; Zhang HY and Bai N conducted the analyses; Wang N interpreted the data and wrote the first draft; Yin M revised the article critically and provided guidance in the research process; All the authors read and approved the final manuscript.

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