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EDITORIAL

Unlocking the power of physical activity in easing psychological distress

Xin-Qiao Liu, Xin Wang

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Abstract

The severity of the current global mental health situation and the importance of maintaining psychological well-being call for more powerful, convenient, and efficient solutions for addressing psychological issues and relieving mental stress. Physical activity not only effectively improves physical fitness and reduces negative emotions such as anxiety and depression but also increases the improvement of psychological health and sense of well-being. At the same time, physical activity interventions for mental health have unique advantages, including reducing the side effects of psychological interventions and increasing necessity, convenience, and cost-effectiveness, as well as flexible adaptability across multiple methods, groups, and age ranges, providing stronger support for relieving psychological stress and addressing psychological issues. Although physical activity is an important intervention measure in relieving psychological stress, its value and role in mental health care seem to have not yet received sufficient attention, and its potential remains to be further revealed. Given the significant advantages and effectiveness of physical activity in mental health intervention practices, it is necessary to stimulate its potential in relieving psychological stress through various means in future studies to better safeguard the public's physical and mental health. Developing guidelines for physical activity for improved mental health, enhancing organic integration with other intervention measures, and providing necessary respect, encouragement, and support are important directions to consider.

Key Words: Physical activity; Psychological distress; Mental health; Artificial intelligence; Guidance

Core Tip: As a nonstigmatized, highly effective, convenient, and cost-effective nonpharmacological intervention for mental health, physical activity holds enormous potential in relieving psychological stress and improving overall well-being. To further reveal the potential of physical activity and benefit a larger population with mental health issues, it is necessary to provide scientific guidelines for physical activity and enhance its adaptability and practicality based on respect for patient preferences.

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INTRODUCTION

In recent years, there has been a proliferation of research on mental health, with an increasing number of scholars emphasizing the important value of mental health. People are increasingly recognizing the significant role of mental health in maintaining global well-being. For example, recent research by Luo *et al*[1] focused on the mental health of stroke patients, and they suggested that physical exercise may play a role in the efficacy of treatment and rehabilitation strategies for patients. Mental health is defined as a favorable or normal state of an individual in various psychological aspects and activities. Being in a healthy mental state can help individuals recognize their capabilities, cope with normal life stress, work productively, and contribute to their communities[2]. However, as a driving force for individual growth and development, mental health faces certain real constraints and challenges[3-5]. One in every eight people in the world has a mental disorder, causing 1 in 5 years lived with disability due to mental health conditions, and depression and anxiety disorders result in global economic losses of $1 trillion each year[6,7]. The continuous deterioration of global mental health and the ongoing loss of collective mental wealth not only present real challenges to achieving the goals of global mental well-being but also result in tragedy for humanity and the economy[8]. On the one hand, the emergence of mental health conditions often accompanies the violation of human rights, discrimination, and stigma, disturbing the normal order of individuals' lives and significantly affecting various aspects of daily life, including academic or work performance and intimate relationships[9]. On the other hand, mental health conditions are often associated with poor physical and mental health, problematic substance use, and risks such as suicide and death. The population with severe mental illness not only experiences both physical and mental harm while fighting the disease but also bears heavy financial burdens and may even die 20 years earlier due to preventable physical conditions[10].

The widespread transmission of coronavirus disease 2019 (COVID-19) worldwide has further threatened the global mental health situation[11], leading to a range of mental issues, including panic, anxiety, depression, posttraumatic stress disorder, and suspiciousness[12]. A cross-sectional study from Germany showed that the pandemic caused severe psychological burdens for the German population, with prevalence rates of generalized anxiety, depression, psychological distress, and COVID-19-related fears of 44.9%, 14.3%, 65.2%, and 59.0%, respectively, with women and young people showing higher mental burdens[13]. Pregnant and postpartum women were also affected by COVID-19-related stress, with 36.4%, 22.7%, and 10.3% of 1123 perinatal women from the United States of America respondents reporting clinically significant levels of depression, generalized anxiety, and posttraumatic stress disorder during the pandemic [14]. Despite the significant efforts made by various sectors to address mental health crises in recent decades, mental health remains a pressing global public health priority[15-17]. The severity of the current global mental health situation and the importance of maintaining psychological well-being call for more powerful, convenient, and efficient solutions for addressing psychological issues and relieving mental stress. Intervention measures, including education/school-based interventions[18], workplace interventions[19], community/family interventions[20], medication interventions[21], policy interventions[22], and digital interventions[23-25], are widely used in mental health practice. As an important intervention measure in the process of addressing psychological issues, exercise can effectively enhance cognitive function, reduce anxiety, depression, and negative emotions, and improve psychological health and sense of well-being, but its value and role in mental health care seem to have not been fully emphasized[26], and its potential remains to be further explored.

PHYSICAL ACTIVITY AS AN IMPORTANT MEANS OF STRESS RELIEF

As the saying goes, "life is in motion". Physical exercise is often associated with positive mental health effects, including the reduction of psychological burdens and improvement of mental health conditions[27,28]. Endorphins and mitochondria are important physiological mechanisms in the process of altering mental states. Endorphins, as endogenous opioid peptides secreted by the pituitary gland, can produce analgesic and pleasurable effects by binding to opioid receptors, helping the body endure pain during prolonged periods of pain and stress[29] and serving as a natural analgesic. Moderate exercise can promote the secretion of endorphins, thereby regulating an individual's emotional state through pain relief, increasing the sense of happiness, and enhancing the sense of achievement, which exerts a positive impact on mental health. Mitochondrial dysfunction is associated with a variety of mental illnesses, including major

depressive disorder, generalized anxiety disorder, posttraumatic stress disorder, and bipolar disorder[30]. As a potent mediator of the relationship between exercise and a reduced risk of weakness and mental illness, mitochondria's role in mental health has drawn extensive attention from researchers[31]. Moderate exercise can aid in promoting mitochondrial biogenesis, thereby enhancing physical function and improving mental health conditions, and is becoming a key factor in addressing psychological stress and mental health problems.

Physical activity (PA) has distinct advantages in mental health interventions, providing stronger support for relieving psychological stress and addressing psychological issues (Figure 1). First, physical activity reduces the side effects of psychological interventions. Drug therapy, as a traditional mental health intervention, has the potential to identify psychological problems, improve adverse psychological symptoms, and relieve psychological stress in a short period, receiving widespread attention and being applied in mental health practices[32,33]. However, while drug therapy brings benefits in relieving psychological stress, it also leads to certain adverse reactions[34], including increased risks of drug dependence and abuse, the potential for suicidal behavior, and side effects such as dry mouth, insomnia, nausea, vomiting, weight gain, increased heart rate, and gastrointestinal discomfort. If these issues occur, drug therapy not only fails to achieve the original intention of addressing psychological problems but may even have a detrimental effect, causing secondary harm to individuals affected by psychological issues. PA, as a nonpharmacological psychological intervention measure, has the advantage of not causing adverse reactions[31]. Proper, scientific, and regular physical exercise can help to reduce the side effects of psychological interventions, assisting in the relief of psychological stress and the improvement of overall well-being.

Furthermore, there is a high level of necessity, convenience, and cost-effectiveness. On the one hand, a significant portion of premature deaths due to physical health conditions in people with mental illness is preventable[35]. Targeted early intervention through physical activity plays a particularly important role in mental health practice. Scientific and reasonable early physical intervention can not only effectively relieve the psychological stress of patients and improve their mental state but also reduce their likelihood of premature death, to some extent, achieving the goal of extending the lifespan of patients. On the other hand, compared to traditional mental health intervention measures that require facilities, venues, funding, personnel, and environmental factors, physical activity can address the limitations of the external environment and material conditions. Whether by playing soccer, basketball, or walking, and whether physical activity is performed in the office, at home, or on a sports field, the public can choose the most appropriate form of physical activity based on their current physical and mental conditions, material conditions, physical activity foundation, and interests, and engage in physical exercise anytime, anywhere, and according to their preferences. At the same time, the relatively low cost of physical activity[36] also significantly reduces the economic burden on the public, providing a practical, accessible, and easily manageable method for relieving psychological stress, particularly for disadvantaged or economically challenged groups.

Finally, there is flexible adaptability across multiple methods, multiple groups, and multiple age ranges. In the relief of psychological stress, physical activity not only demonstrates a high level of necessity, convenience, and cost-effectiveness, reducing the side effects of psychological interventions but also exhibiting strong adaptability in the comprehensive integration of multiple methods in mental health interventions. Exercise prescriptions can be used not only independently but also organically by being integrated with various intervention methods, including school-based interventions, workplace interventions, community interventions, medication interventions, and digital interventions, becoming a valuable supplementary resource in the process of relieving psychological stress and enhancing the comprehensiveness of mental health interventions. For example, physical activity can embrace new electronic information technology combined with the latest digital intervention methods to provide web-based exercise intervention prescriptions for patients with depression or anxiety[37]. Additionally, the combined use of physical exercise and antidepressant medication is considered a feasible adjunctive treatment method[38]. Furthermore, physical activity also demonstrates significant advantages in adaptation to patient groups and age ranges. Whether patients are children, adolescents, elderly individuals[39,40], students, health care professionals, or freelancers, all can benefit from physical activity and achieve effective improvement in their mental state through proper and scientifically guided exercises.

CONCLUSION

PA, as an important means of relieving psychological stress and improving mental well-being, has been widely acknowledged for its efficacy in research. A meta-analysis indicated that exercise, as a destigmatized intervention, has a positive impact on mental health symptoms, alleviating depression symptoms in children, adults, and older adults and serving as a beneficial complement to medication and psychological interventions[41]. Another meta-analysis suggested that individuals with higher levels of physical activity had a lower risk of depression than those with lower physical activity levels, and higher levels of physical exercise also had a protective effect against the development of future depression [42]. Additionally, physical activity can effectively reduce the risk of anxiety disorders. Compared to individuals with low levels of self-reported PA, those who report high levels of self-reported PA have a lower likelihood of developing anxiety disorders, and higher PA levels can also prevent the onset of agoraphobia and posttraumatic stress disorder[43]. Engaging in moderate to vigorous exercise for approximately 90 min per week can significantly alleviate mental symptoms[44]. In the grand scheme of things, some exercise is better than no exercise[45]. Given the distinct advantages and effectiveness of physical activity in mental health intervention practices, we need to take more robust measures in the future to stimulate its potential in relieving psychological stress, thereby better safeguarding the physical and mental well-being of the public.

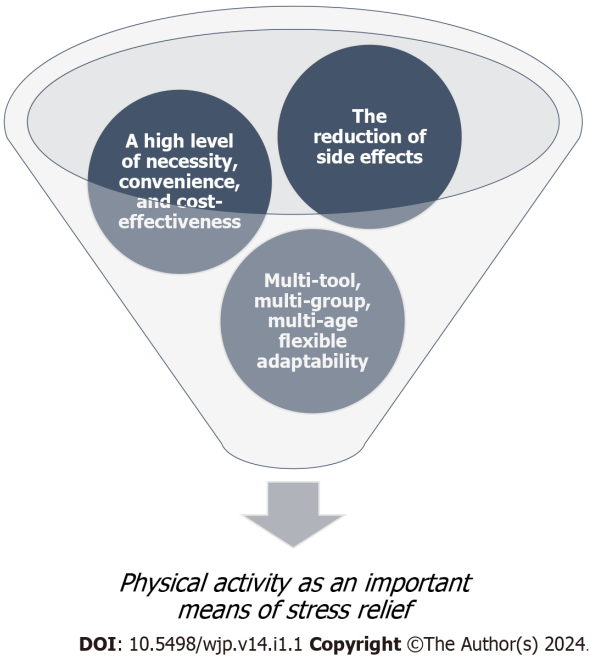

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Figure 1 Benefits of physical activity in mental health interventions.

First, physical activity guidelines should be established for mental health, providing a framework for overall health and well-being improvement[46]. To fully unleash the potential of physical activity in relieving psychological stress, it is imperative to clearly define the key elements and considerations in the implementation process of physical activity or exercise prescriptions. Stakeholders should work together to develop or update physical activity guidelines based on the latest developments in psychological research and mental health practice, providing scientific, reasonable, and comprehensive explanations and guidance on various aspects of physical activity as an exercise prescription, including types, intensity, frequency, procedures, and considerations. Additionally, the characteristics and needs of different populations should receive careful attention and be clearly described in the guidelines. Specifically, the preferences and suitable types of physical activity may differ for children, adolescents, adults, and elderly individuals. Therefore, the guidelines should present specific recommendations on the types, intensity, and focus of physical activity based on the physical capabilities, medical history, and health conditions of different age groups. The specific needs of special groups such as pregnant women and people with disabilities should be fully addressed, for instance, by providing targeted recommendations for the types and intensity of exercise suitable for pregnant women at different stages of pregnancy.

Furthermore, physical activity should be organically integrated with other mental health interventions to further enhance the comprehensiveness and effectiveness of relieving psychological stress. The development of times and advancements in technology provide the potential for further stimulation of the medical benefits of physical activity. On the one hand, the further integration of physical activity with traditional medication and clinical treatment should be promoted and physical activity should be used as a supplemental treatment for patients with serious mental health issues who require medication, achieving improvements in both the physical and mental conditions of patients. On the other hand, internet-based physical activity intervention programs should be provided. The continuous emergence of electronic information technology and the global COVID-19 pandemic have made digitally based exercise interventions *via* the internet the latest trend in relieving psychological stress. Research indicates that internet-based exercise interventions have a relieving effect on depression and anxiety in patients with neurological disorders[47]. In the future, there should be further promotion of the deep integration of physical activity and emerging information technology to provide support for the relief of psychological stress. Specifically, internet-based applications or mini-programs for mental health-related physical activity could be further developed. Additionally, artificial intelligence models such as ChatGPT can serve as important tools to provide real-time physical health monitoring and guidance for physical activity during the process of addressing psychological issues.

Finally, the necessary respect, motivation, and support should be provided. Groups experiencing psychological issues or significant psychological stress often have fragile mental states and delicate psychological conditions. Therefore, in the process of prescribing exercise, it is essential to fully respect the personal wishes of the patients. For patients who are willing, motivated, and physically healthy enough to engage in exercise, appropriate physical exercise can be recommended[48]. For patients who lack the intention to exercise, we should fully respect their thoughts and provide alternative treatment options that are more suited to their needs. Additionally, during the implementation of the exercise prescription, it is important to select exercise activities that the patients are interested in, skilled at, have confidence in, and have the ability to perform well and to provide necessary encouragement when patients reach their interim physical activity goals. This helps patients experience enjoyment and a sense of accomplishment from physical activity, thereby enhancing the effectiveness and sustainability of exercise interventions. At the same time, government and other authorities, as well as professional organizations, should effectively strengthen the construction of physical activity

support groups, exercise facilities, and sports venues such as basketball courts and soccer fields. This ensures that individuals facing psychological issues receive comprehensive support for physical activity and enjoy a harmonious environment for exercise.

FOOTNOTES

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REFERENCES

1 **Luo CY**, Jiao P, Tu SM, Shen L, Sun YM. Mediating role of physical activity in the relationship between psychological distress and intimate relationships among stroke patients. *World J Psychiatry* 2023; **13**: 1096-1105 [DOI: 10.5498/wjp.v13.i12.1096]
2 **Wahlbeck K**. Public mental health: the time is ripe for translation of evidence into practice. *World Psychiatry* 2015; **14**: 36-42 [PMID: 25655149 DOI: 10.1002/wps.20178]
3 **Bruffaerts R**, Mortier P, Kiekens G, Auerbach RP, Cuijpers P, Demyttenaere K, Green JG, Nock MK, Kessler RC. Mental health problems in college freshmen: Prevalence and academic functioning. *J Affect Disord* 2018; **225**: 97-103 [PMID: 28802728 DOI: 10.1016/j.jad.2017.07.044]
4 **Harvey SB**, Modini M, Joyce S, Milligan-Saville JS, Tan L, Mykletun A, Bryant RA, Christensen H, Mitchell PB. Can work make you mentally ill? A systematic meta-review of work-related risk factors for common mental health problems. *Occup Environ Med* 2017; **74**: 301-310 [PMID: 28108676 DOI: 10.1136/oemed-2016-104015]
5 **Liu X**, Zhang Y, Luo Y. Does Subjective Well-Being Improve Self-Rated Health from Undergraduate Studies to Three Years after Graduation in China? *Healthcare (Basel)* 2023; **11** [PMID: 37957958 DOI: 10.3390/healthcare11212813]
6 **World Health Organization**. Mental disorders. [cited 9 November 2023]. Available from: https://www.who.int/news-room/fact-sheets/detail/mental-disorders.
7 **World Health Organization**. The WHO special initiative for mental health (2019-2023): universal health coverage for mental health. 2019. [cited 9 November 2023]. Available from: https://iris.who.int/handle/10665/310981.
8 **McGorry PD**, Coghill D, Berk M. Mental health of young Australians: dealing with a public health crisis. *Med J Aust* 2023; **219**: 246-249 [PMID: 37483141 DOI: 10.5694/mja2.52047]
9 **World Health Organization**. Mental health. [cited 9 November 2023]. Available from: https://www.who.int/health-topics/mental-health#tab=tab_2.
10 **World Health Organization**. Mental health: [cited 9 November 2023]. Available from: https://www.who.int/health-topics/mental-health#tab=tab_1.
11 **Torales J**, O'Higgins M, Castaldelli-Maia JM, Ventriglio A. The outbreak of COVID-19 coronavirus and its impact on global mental health. *Int J Soc Psychiatry* 2020; **66**: 317-320 [PMID: 32233719 DOI: 10.1177/0020764020915212]
12 **Jakovljevic M**, Bjedov S, Jaksic N, Jakovljevic I. COVID-19 Pandemia and Public and Global Mental Health from the Perspective of Global Health Securit. *Psychiatr Danub* 2020; **32**: 6-14 [PMID: 32303023 DOI: 10.24869/psyd.2020.6]
13 **Bäuerle A**, Teufel M, Musche V, Weismüller B, Kohler H, Hetkamp M, Dörrie N, Schweda A, Skoda EM. Increased generalized anxiety, depression and distress during the COVID-19 pandemic: a cross-sectional study in Germany. *J Public Health (Oxf)* 2020; **42**: 672-678 [PMID: 32657323 DOI: 10.1093/pubmed/fdaa106]
14 **Liu CH**, Erdei C, Mittal L. Risk factors for depression, anxiety, and PTSD symptoms in perinatal women during the COVID-19 Pandemic. *Psychiatry Res* 2021; **295**: 113552 [PMID: 33229122 DOI: 10.1016/j.psychres.2020.113552]
15 **Thapar A**, Eyre O, Patel V, Brent D. Depression in young people. *Lancet* 2022; **400**: 617-631 [PMID: 35940184 DOI: 10.1016/S0140-6736(22)01012-1]
16 **Liang D**, Mays VM, Hwang WC. Integrated mental health services in China: challenges and planning for the future. *Health Policy Plan* 2018; **33**: 107-122 [PMID: 29040516 DOI: 10.1093/heapol/czx137]
17 **Oram S**, Fisher HL, Minnis H, Seedat S, Walby S, Hegarty K, Rouf K, Angénieux C, Callard F, Chandra PS, Fazel S, Garcia-Moreno C, Henderson M, Howarth E, MacMillan HL, Murray LK, Othman S, Robotham D, Rondon MB, Sweeney A, Taggart D, Howard LM. The Lancet Psychiatry Commission on intimate partner violence and mental health: advancing mental health services, research, and policy. *Lancet Psychiatry* 2022; **9**: 487-524 [PMID: 35569504 DOI: 10.1016/S2215-0366(22)00008-6]

18 **Barry MM**, Clarke AM, Jenkins R, Patel V. A systematic review of the effectiveness of mental health promotion interventions for young people in low and middle income countries. *BMC Public Health* 2013; **13**: 835 [PMID: 24025155 DOI: 10.1186/1471-2458-13-835]

19 **Joyce S**, Modini M, Christensen H, Mykletun A, Bryant R, Mitchell PB, Harvey SB. Workplace interventions for common mental disorders: a systematic meta-review. *Psychol Med* 2016; **46**: 683-697 [PMID: 26620157 DOI: 10.1017/S0033291715002408]

20 **Killaspy H**, Harvey C, Brasier C, Brophy L, Ennals P, Fletcher J, Hamilton B. Community-based social interventions for people with severe mental illness: a systematic review and narrative synthesis of recent evidence. *World Psychiatry* 2022; **21**: 96-123 [PMID: 35015358 DOI: 10.1002/wps.20940]

21 **Hoskins M**, Pearce J, Bethell A, Dankova L, Barbui C, Tol WA, van Ommeren M, de Jong J, Seedat S, Chen H, Bisson JI. Pharmacotherapy for post-traumatic stress disorder: systematic review and meta-analysis. *Br J Psychiatry* 2015; **206**: 93-100 [PMID: 25644881 DOI: 10.1192/bjp.bp.114.148551]

22 **Campion J**, Javed A, Lund C, Sartorius N, Saxena S, Marmot M, Allan J, Udomratn P. Public mental health: required actions to address implementation failure in the context of COVID-19. *Lancet Psychiatry* 2022; **9**: 169-182 [PMID: 35065723 DOI: 10.1016/S2215-0366(21)00199-1]

23 **Lattie EG**, Adkins EC, Winquist N, Stiles-Shields C, Wafford QE, Graham AK. Digital Mental Health Interventions for Depression, Anxiety, and Enhancement of Psychological Well-Being Among College Students: Systematic Review. *J Med Internet Res* 2019; **21**: e12869 [PMID: 31333198 DOI: 10.2196/12869]

24 **Cao XJ**, Liu XQ. Artificial intelligence-assisted psychosis risk screening in adolescents: Practices and challenges. *World J Psychiatry* 2022; **12**: 1287-1297 [PMID: 36389087 DOI: 10.5498/wjp.v12.i10.1287]

25 **Liu XQ**, Guo YX, Wang X. Delivering substance use prevention interventions for adolescents in educational settings: A scoping review. *World J Psychiatry* 2023; **13**: 409-422 [PMID: 37547731 DOI: 10.5498/wjp.v13.i7.409]

26 **Callaghan P**. Exercise: a neglected intervention in mental health care? *J Psychiatr Ment Health Nurs* 2004; **11**: 476-483 [PMID: 15255923 DOI: 10.1111/j.1365-2850.2004.00751.x]

27 **Chekroud SR**, Gueorguieva R, Zheutlin AB, Paulus M, Krumholz HM, Krystal JH, Chekroud AM. Association between physical exercise and mental health in 1·2 million individuals in the USA between 2011 and 2015: a cross-sectional study. *Lancet Psychiatry* 2018; **5**: 739-746 [PMID: 30099000 DOI: 10.1016/S2215-0366(18)30227-X]

28 **Cao XJ**, Zhang QY, Liu XQ. Cross-Lagged Relationship between Physical Activity Time, Openness and Depression Symptoms among Adolescents: Evidence from China. *Int J Ment Health Promot* 2023; **25**: 1009-1018 [DOI: 10.32604/ijmhp.2023.029365]

29 **Mikkelsen K**, Stojanovska L, Polenakovic M, Bosevski M, Apostolopoulos V. Exercise and mental health. *Maturitas* 2017; **106**: 48-56 [PMID: 29150166 DOI: 10.1016/j.maturitas.2017.09.003]

30 **Tanaka M**, Szabó Á, Spekker E, Polyák H, Tóth F, Vécsei L. Mitochondrial Impairment: A Common Motif in Neuropsychiatric Presentation? The Link to the Tryptophan-Kynurenine Metabolic System. *Cells* 2022; **11** [PMID: 36010683 DOI: 10.3390/cells11162607]

31 **Deslandes AC**. Exercise and Mental Health: What did We Learn in the Last 20 Years? *Front Psychiatry* 2014; **5**: 66 [PMID: 24982639 DOI: 10.3389/fpsyt.2014.00066]

32 **Slee A**, Nazareth I, Bondaronek P, Liu Y, Cheng Z, Freemantle N. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. *Lancet* 2019; **393**: 768-777 [PMID: 30712879 DOI: 10.1016/S0140-6736(18)31793-8]

33 **Cipriani A**, Zhou X, Del Giovane C, Hetrick SE, Qin B, Whittington C, Coghill D, Zhang Y, Hazell P, Leucht S, Cuijpers P, Pu J, Cohen D, Ravindran AV, Liu Y, Michael KD, Yang L, Liu L, Xie P. Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis. *Lancet* 2016; **388**: 881-890 [PMID: 27289172 DOI: 10.1016/S0140-6736(16)30385-3]

34 **Solmi M**, Fornaro M, Ostinelli EG, Zangani C, Croatto G, Monaco F, Krinitski D, Fusar-Poli P, Correll CU. Safety of 80 antidepressants, antipsychotics, anti-attention-deficit/hyperactivity medications and mood stabilizers in children and adolescents with psychiatric disorders: a large scale systematic meta-review of 78 adverse effects. *World Psychiatry* 2020; **19**: 214-232 [PMID: 32394557 DOI: 10.1002/wps.20765]

35 **Garvey L**, Benson AC, Benger D, Short T, Banyard H, Edward KL. The perceptions of mental health clinicians integrating exercise as an adjunct to routine treatment of depression and anxiety. *Int J Ment Health Nurs* 2023; **32**: 502-512 [PMID: 36369663 DOI: 10.1111/inm.13089]

36 **Fiuza-Luces C**, Garatachea N, Berger NA, Lucia A. Exercise is the real polypill. *Physiology (Bethesda)* 2013; **28**: 330-358 [PMID: 23997192 DOI: 10.1152/physiol.00019.2013]

37 **Carneiro L**, Rosenbaum S, Ward PB, Clemente FM, Ramirez-Campillo R, Monteiro-Júnior RS, Martins A, Afonso J. Web-based exercise interventions for patients with depressive and anxiety disorders: a systematic review of randomized controlled trials. *Braz J Psychiatry* 2022; **44**: 331-341 [PMID: 34852034 DOI: 10.1590/1516-4446-2021-2026]

38 **Kvam S**, Kleppe CL, Nordhus IH, Hovland A. Exercise as a treatment for depression: A meta-analysis. *J Affect Disord* 2016; **202**: 67-86 [PMID: 27253219 DOI: 10.1016/j.jad.2016.03.063]

39 **Dale LP**, Vanderloo L, Moore S, Faulkner G. Physical activity and depression, anxiety, and self-esteem in children and youth: An umbrella systematic review. *Ment Health Phys Act* 2019; **16**: 66-79 [DOI: 10.1016/j.mhpa.2018.12.001]

40 **Callow DD**, Arnold-Nedimala NA, Jordan LS, Pena GS, Won J, Woodard JL, Smith JC. The Mental Health Benefits of Physical Activity in Older Adults Survive the COVID-19 Pandemic. *Am J Geriatr Psychiatry* 2020; **28**: 1046-1057 [PMID: 32713754 DOI: 10.1016/j.jagp.2020.06.024]

41 **Ashdown-Franks G**, Firth J, Carney R, Carvalho AF, Hallgren M, Koyanagi A, Rosenbaum S, Schuch FB, Smith L, Solmi M, Vancampfort D, Stubbs B. Exercise as Medicine for Mental and Substance Use Disorders: A Meta-review of the Benefits for Neuropsychiatric and Cognitive Outcomes. *Sports Med* 2020; **50**: 151-170 [PMID: 31541410 DOI: 10.1007/s40279-019-01187-6]

42 **Schuch FB**, Vancampfort D, Firth J, Rosenbaum S, Ward PB, Silva ES, Hallgren M, Ponce De Leon A, Dunn AL, Deslandes AC, Fleck MP, Carvalho AF, Stubbs B. Physical Activity and Incident Depression: A Meta-Analysis of Prospective Cohort Studies. *Am J Psychiatry* 2018; **175**: 631-648 [PMID: 29690792 DOI: 10.1176/appi.ajp.2018.17111194]

43 **Schuch FB**, Stubbs B, Meyer J, Heissel A, Zech P, Vancampfort D, Rosenbaum S, Deenik J, Firth J, Ward PB, Carvalho AF, Hiles SA. Physical activity protects from incident anxiety: A meta-analysis of prospective cohort studies. *Depress Anxiety* 2019; **36**: 846-858 [PMID: 31209958 DOI: 10.1002/da.22915]

44 **Firth J**, Cotter J, Elliott R, French P, Yung AR. A systematic review and meta-analysis of exercise interventions in schizophrenia patients. *Psychol Med* 2015; **45**: 1343-1361 [PMID: 25650668 DOI: 10.1017/S0033291714003110]

45 **Martin Ginis KA**, van der Ploeg HP, Foster C, Lai B, McBride CB, Ng K, Pratt M, Shirazipour CH, Smith B, Vásquez PM, Heath GW. Participation of people living with disabilities in physical activity: a global perspective. *Lancet* 2021; **398**: 443-455 [PMID: 34302764 DOI:

10.1016/S0140-6736(21)01164-8]

46 **Teychenne M**, White RL, Richards J, Schuch FB, Rosenbaum S, Bennie JA. Do we need physical activity guidelines for mental health: What does the evidence tell us? *Ment Health Phys Act* 2020; **18**: 100315 [DOI: 10.1016/j.mhpa.2019.100315]

47 **Zhang H**, Wang R, Kong Z, Yu J, Hou X, Zhang S. Effect of web-implemented exercise interventions on depression and anxiety in patients with neurological disorders: a systematic review and meta-analysis. *Front Neurol* 2023; **14**: 1225356 [PMID: 37533470 DOI: 10.3389/fneur.2023.1225356]

48 **Josefsson T**, Lindwall M, Archer T. Physical exercise intervention in depressive disorders: meta-analysis and systematic review. *Scand J Med Sci Sports* 2014; **24**: 259-272 [PMID: 23362828 DOI: 10.1111/sms.12050]

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MINIREVIEWS

Effects of psychological intervention on negative emotions and psychological resilience in breast cancer patients after radical mastectomy

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Abstract

Breast cancer (BC)is the most common malignant tumor in women, and the treatment process not only results in physical pain but also significant psychological distress in patients. Psychological intervention (PI) has been recognized as an important approach in treating postoperative psychological disorders in BC patients. It has been proven that PI has a significant therapeutic effect on postoperative psychological disorders, improving patients' negative emotions, enhancing their psychological resilience, and effectively enhancing their quality of life and treatment compliance.

Key Words: Breast cancer; Psychological intervention; Negative emotions; Psychological resilience; Radical surgery

Core Tip: Breast cancer (BC) has become the leading cancer worldwide. Psychological intervention has been proven to have significant therapeutic effects on postoperative psychological disorders in BC patients. It can improve patients' negative emotions, enhance their psychological resilience, effectively enhance their quality of life, and improve treatment compliance.

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INTRODUCTION

Breast cancer (BC) is the most common cancer in women worldwide[1]. According to the Global Cancer Data 2020 report published by the International Agency for Research on Cancer[2], BC has surpassed lung cancer as the leading cancer. In 2020, there were approximately 2.3 million new cases of BC globally, accounting for 11.7% of all cancer cases[3-4]. The occurrence and metastasis of BC are associated with various factors[5-6]. The high incidence rate of BC is a global concern, and the alarming increase in the number of BC patients suggests that healthcare professionals need to pay attention to patients from multiple perspectives[7]. Due to the psychological challenges such as anxiety, pain, depression, low self-esteem, heightened sensitivity, and post-traumatic stress disorder among cancer patients, as well as the immense psychological and economic pressures faced by their families[8], psychological intervention (PI) becomes an important treatment method in clinical practice. PI has been proven to have significant therapeutic benefits for postoperative psychological disorders in BC patients, improving their quality of life and treatment compliance. This study aims to investigate the impact of PI on negative emotions and psychological resilience in BC patients after radical mastectomy, providing a reference for subsequent clinical psychological treatments.

NEGATIVE EMOTIONS AND BREAST CANCER

Negative emotions can lead to an increased incidence of BC, and the development and prognosis of BC are also closely related to emotions[6-8] (Figure 1). Negative emotions refer to the adverse feelings that arise psychologically from undesirable events in life. Regarding the association between emotions and malignant tumors, the ancient Greek physician Galen mentioned centuries ago that women who were long-term depressed and anxious were more likely to develop BC than women who were lively and cheerful. Multiple studies have shown that negative emotions are closely associated with the occurrence of cancer[9-10]. In a study by He *et al*[11] which included 200 BC patients, it was found that patients' negative emotions, such as depression and anxiety, were significantly reduced after emotional management, and the recovery of BC patients was good. Many studies have also found that negative emotions greatly affect the incidence of BC[12-15]. In a study by Xu *et al*[12] a total of 9343 studies were screened, aiming to explore the connection between negative emotions and the incidence of BC, as well as possible risk factors. The researchers analyzed 129621 female patients with negative emotions, of whom 2080 women were diagnosed with BC. They were followed up for 4-24 years, and the results showed that negative emotions were significantly related to BC ($P < 0.0001$, relative risk = 1.59, 95%CI: 1.15-2.19).

Radical mastectomy remains an important surgical method for treating BC in clinical practice and is widely performed in China. This surgical treatment results in various psychological and physical changes in patients. Due to removal of the breast, patients experience significant changes in their self-image and become highly sensitive to subtle changes in themselves. As a result, they often visit the hospital for multiple follow-up examinations of their physical condition[16-17]. In a study conducted by Thakur *et al*[18], it was found that successfully treated BC patients often adopt a defensive mentality and refuse further examinations and treatments. They also exhibit significant suspicion and show more resistance to terms such as "breast" and "cancer" compared to the general population. Another study by Hernández-Blanquisett *et al*[19] revealed that patients who underwent radical mastectomy believed that their romantic or marital relationships were affected, suggesting that the absence of the breast directly influences patients' lives and has a certain impact on their physical and mental well-being. Female sexual dysfunction refers to a category of diseases in which women experience disorders in one or more stages of the sexual response cycle, affecting the normal conduct of sexual activity. It includes symptoms such as vaginal dryness and decreased sexual desire[20-21]. Haris *et al*[22] discovered in their survey analysis that the frequency of sexual activity reduced after surgery in the BC patients, and some patients even reported a lack of sexual activity. This can lead to a strong sense of inferiority in patients, as they believe they have lost their feminine charm. It also results in an increased psychological burden and lower marital satisfaction. Furthermore, patients may experience varying degrees of anxiety or depression due to the side effects of chemotherapy or radiotherapy after surgery. Clinical studies have found that family conditions during the treatment process play a decisive role in influencing the patients' emotions, including the support from family members and financial support. When patients experience psychological stress and negative emotions, their anxiety and depression scores increase. In severe cases, they may develop suicidal tendencies. Relevant research data indicate that BC patients undergoing radical mastectomy are more likely to develop anxiety and depression compared to general cancer patients[22-25].

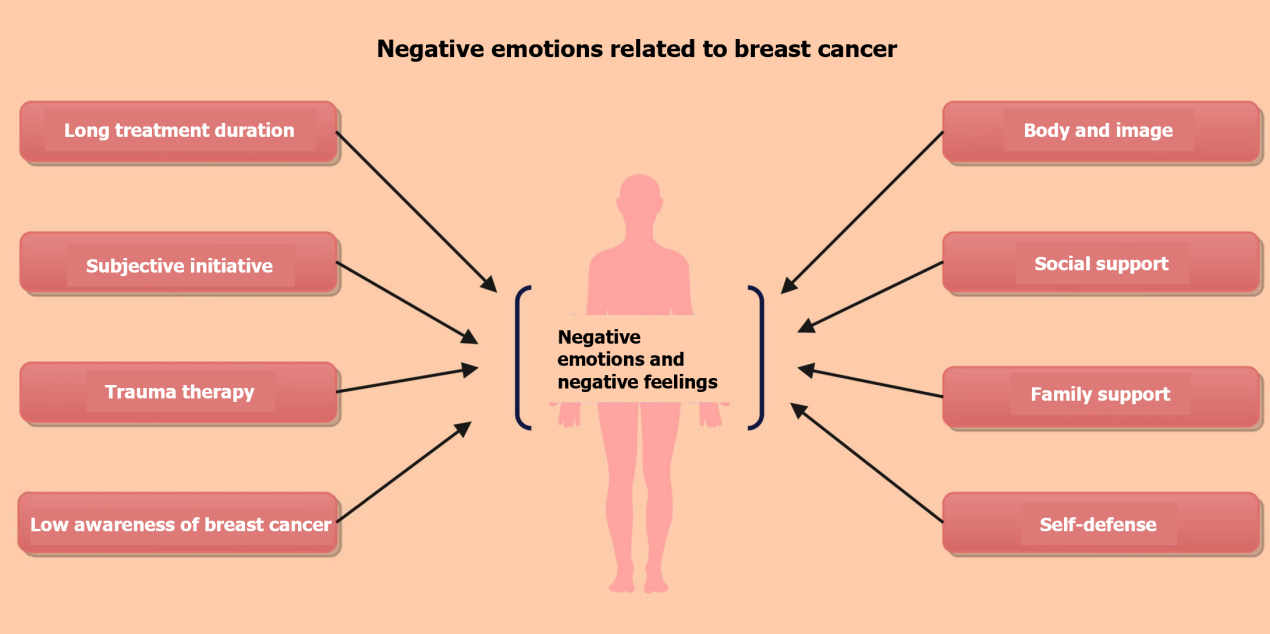

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Figure 1 Negative emotions related to breast cancer.

PSYCHOLOGICAL RESILIENCE AND BREAST CANCER

BC is a common malignancy that imposes significant stress on patients during the diagnosis and treatment process. Patients with higher psychological resilience are better able to cope with stress, actively participate in treatment, and achieve better treatment outcomes. Simultaneously, these patients experience faster postoperative recovery, and have lower rates of tumor recurrence and mortality. Psychological resilience refers to the psychological and behavioral response of the body to external environments and various stimuli. It is a dynamic state with a certain level of flexibility that changes with the environment and allows for dynamic regulation and adaptation. Individuals with higher psychological resilience recover faster after experiencing stressful events[26-27]. The level of psychological resilience in BC patients is influenced by factors such as gender, age, education level, and disease severity. Studies have shown that males tend to have higher levels of psychological resilience compared to females, and that psychological resilience is positively correlated with age. Additionally, patients with higher levels of education generally exhibit better psychological resilience. The stage and prognosis of BC also have an impact on the psychological resilience of patients. Psychological resilience is gaining increasing attention as a research area within positive psychology. Theoretical frameworks for psychological resilience intervention include cognitive-behavioral theory, mindfulness theory, and the adolescent resilience model[27]. Currently, the primary tools for measuring psychological resilience are the Connor-Davidson Resilience Scale (CD-RISC) and the Resilience Scale for Adults[28]. Several clinical studies have demonstrated that targeted intervention measures can effectively reduce negative emotions, enhance psychological resilience, and promote recovery and growth in postoperative BC patients. In Liu *et al*[29], it was found that incentive-based interventions can better implement the concept of humanistic care and achieve targeted and diversified approaches. By educating and guiding family members to actively participate in the postoperative care of patients, they can provide maximum family care and support, drawing strength from love and positively motivating patients to inspire their confidence in treatment and recovery. Through sincere communication, showing care, and other methods, patients can experience respectful, understanding, and unique clinical care, which fills them with strength, effectively guides and eliminates pessimistic emotions, and maintains an optimistic mindset, leading to improved psychological resilience. Zhang *et al*[30] utilized the CD-RISC to assess the psychological resilience of patients and found that psychological resilience is an important indicator of subjective initiative and emotion regulation. Intervention measures can alleviate the fear of disease progression in BC patients after radical surgery, improve psychological resilience, and reduce the occurrence of complications.

PSYCHOLOGICAL INTERVENTION

With the development of the bio-psycho-social medical model, PIs and social support have become highly valued aspects of cancer treatment[31]. There is a close relationship between psychological status, immune function, and the occurrence and progression of tumors[32]. Studying the relationship between PI, psychological stress, immune function, and tumor progression is of great significance for the clinical treatment of BC. PI refers to the systematic and planned influence on the psychological activities or issues of a specific target guided by psychological theories, in order to promote desired

changes in the target[33]. PI is now widely applied in various clinical departments and primarily involves three aspects: cognitive reconstruction, psychological regulation, and physical behavioral training. Specific intervention measures include cognitive-behavioral therapy (CBT), music therapy, group interventions, yoga exercises, and comprehensive intervention methods, among others[34-35]. Traditional PI focuses on alleviating or reducing patients' negative emotions, while neglecting the stimulation and cultivation of various positive qualities and strengths. Positive psychology emphasizes problem-solving with an optimistic attitude, helping individuals unleash their potential, and enabling them to better cope with illness and life challenges[36-37]. Patients who have undergone radical surgery for BC can experience positive emotional changes through emotional and psychological adaptation. Psychological therapies and supportive methods have been proven effective in managing psychological disorders in BC patients. Every BC patient should receive psychological support throughout their entire treatment period to improve their quality of life and treatment adherence (Table 1)[1,38-40].

CBT is a PI that focuses on the interaction between cognition, emotion, and behavior to change dysfunctional behaviors and thought patterns. It aims to correct patients' misconceptions, establish correct cognitive models, and improve their quality of life. Traditionally, CBT has been used for mental health disorders such as depression and anxiety, but its application in nursing is gaining increasing attention. In fact, it has been proven to be the most successful PI in improving cancer-related issues, with data suggesting that it may enhance the overall quality of life in cancer survivors[41-44]. In a study by Park *et al*[31], 74 BC patients were randomly divided into an intervention group and a control group for an 8-wk CBT intervention. The control group received standard treatment, while the intervention group received CBT in addition to standard treatment. The results showed significant improvements ($P < 0.05$) in cognitive function, quality of life, and mental state in the intervention group compared to the control group. CBT has been shown to improve patients' health conditions, including psychological, physical, and mental domains, and these positive effects can be sustained for up to 4 wk. Following a PubMed search, Vance *et al*[45] identified 21 intervention studies on cognitive deficits and found that CBT can effectively improve cognitive deficits and enhance patients' cognitive abilities. CBT holds promise as an adjunctive therapy in medical treatments to achieve clinical therapeutic goals.

Mindfulness-based therapy (MBT), on the other hand, is a PI that combines meditation, relaxation, controlled breathing, physical stretching, and social interaction. Its core aim is to alleviate stress through mindfulness and help individuals better cope with illnesses[46-47]. This therapy typically involves 6-8 wk of mindfulness training, including practices such as mindfulness breathing, mindfulness meditation, mindfulness yoga, breathing exercises, and mindful walking[48]. Studies by Duval *et al*[49] and Shao *et al*[50] have demonstrated the effectiveness of MBT in improving patients' cognitive abilities and reducing cancer-related concerns. Zheng *et al*[51] conducted a systematic search across multiple databases to study the application and effects of mindfulness-based stress reduction (MBSR) therapy in BC patients. The results indicated that MBSR therapy can improve anxiety, depression, fatigue, and stress to varying degrees, with significant short-term effects. However, studies also pointed out that the long-term effects of this therapy are uncertain, and further research with high-quality and large sample sizes is needed for validation. In a study by Luo *et al*[52], the effects of group mindfulness-based cognitive therapy on psychological resilience and self-efficacy in BC patients during chemotherapy were explored. They recruited 120 BC patients undergoing chemotherapy and randomly divided them into a study group and a control group. The control group received routine treatment and care, while the study group received group mindfulness-based cognitive therapy for a total of 4 wk. The researchers assessed psychological resilience and general self-efficacy using questionnaires. The results showed that patients in the study group exhibited better psychological resilience and self-efficacy compared to those in the control group after the intervention. This confirms that mindfulness training can enhance disease outcomes, promote positive emotions, and effectively improve quality of life in BC patients. Schellekens *et al*[53] conducted a study involving 271 BC survivors and randomly assigned them to a mindfulness-based cancer recovery (MBCR) group, a supportive expressive therapy (SET) group, or a waitlist control group. The MBCR group received mindfulness yoga and meditation practices, as well as guided group discussions on mindfulness, for 8 wk. The results showed that both MBCR and SET improved patients' emotional distress and stress symptoms, with MBCR demonstrating a more significant improvement ($P < 0.01$).

CONCLUSION

Currently, as the incidence of cancer continues to rise, PI measures are gradually being developed. This review article focuses on PI for BC patients, exploring the relationship between negative emotions and psychological resilience and BC. The results show that negative emotions are closely associated with BC. BC patients with better psychological resilience can increase their survival rate after surgery and maintain a good psychological state. However, at present, psychological research related to BC is scarce. Studies on negative emotions and psychological resilience of BC patients after radical mastectomy are mainly cross-sectional, and in-depth longitudinal research is lacking. In clinical trials, due to budget and personnel constraints, the trial period and follow-up duration are short, and the changes in patients' negative emotions and psychological resilience are thus not fully investigated. It is suggested that future research on the negative emotions and psychological resilience of BC patients should establish a corresponding PI framework, explore the changes in negative emotions and psychological resilience of BC patients at different stages, and adopt effective intervention methods. This will provide specific theoretical and practical methods for PIs at different stages of BC.

Table 1 Specific psychological intervention measures for postoperative breast cancer patients

Item	Psychological intervention measures
Cognitive Behavioral Therapy	Provide disease handbooks to patients based on their specific conditions, including information on preventive measures, surgical procedures, dietary guidance, chemotherapy-related knowledge, psychological support, and other relevant topics. Ensure that key content is accompanied by detailed illustrations to enhance understanding. Engage in detailed conversations with patients to better understand their cultural background and level of comprehension. Based on this understanding, recommend books that align with their interests and preferences. Offer training in coping strategies tailored to each patient's condition. Select appropriate methods for venting emotions based on the patient's situation. Teach techniques for expressing and communicating feelings effectively. Encourage patients to confide in someone they trust about their innermost worries. Suggest activities such as watching movies they enjoy, writing journals, and maintaining contact with family or friends through WeChat, phone calls, text messages, *etc*. These activities can help patients cope with their emotions and maintain social connections during their journey
Mindfulness Therapy	Teach techniques for body scanning and guide patients to practice experiencing the interaction between their mind and body through body scanning exercises. This involves mindfully observing and being aware of one's physical sensations and discomfort without rejecting them, allowing oneself to slowly feel and become familiar with the discomfort. Provide mindfulness practices for dealing with thoughts. Teach patients to accept their thoughts with an open attitude, simply being aware of their thoughts without judgment or rejection. Introduce the A-B-C theory of cognition, helping patients identify the thoughts and beliefs that underlie their emotions. Make them aware that it is their cognition that influences their emotional reactions, rather than the events themselves. Teach patients to be mindful of their thoughts and beliefs, and guide them in making appropriate adjustments. Share personal experiences of applying mindfulness in daily life and cognitive-behavioral therapy. Discuss the benefits gained from participating in group therapy sessions
Music Therapy	Starting from admission and the first day after surgery, it is recommended that patients listen to their favorite music for 30 min each morning before 8:00 and again before bedtime at night
Aerobic Exercise	The aerobic exercise program should take into consideration the patient's individual conditions and preferences to develop a reasonable and scientific rehabilitation plan. The main exercise methods should include walking, jogging, cycling, stair climbing, and yoga. Additionally, dance exercises can be incorporated based on simple limb functional exercises. The exercise duration should be controlled at 30 min, with three aerobic exercise sessions per week. Limb exercises should be gradually introduced by nursing staff based on the patient's postoperative wound recovery conditions, with aerobic exercises generally conducted after limb exercises. The exercise content should be shared through WeChat group chats and health education manuals to ensure correct and professional aerobic exercise rehabilitation. To evaluate the effectiveness of the exercise program, detailed records of the aerobic exercises performed by the patient should be maintained. Face-to-face communication should be conducted to understand the patient's subjective feelings and address any nursing issues they may have. Patients and their families should be encouraged to self-evaluate during aerobic exercises and provide timely feedback on any problems encountered. Active cooperation during the intervention period is essential to improve exercise compliance. Due to individual differences among patients, different types of aerobic exercise programs should be developed based on their specific conditions. It is important to follow the principle of gradual progression when arranging exercise plans

FOOTNOTES

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REFERENCES

1 **Dinapoli L**, Colloca G, Di Capua B, Valentini V. Psychological Aspects to Consider in Breast Cancer Diagnosis and Treatment. *Curr Oncol Rep* 2021; **23**: 38 [PMID: 33709235 DOI: 10.1007/s11912-021-01049-3]
2 **Kashyap D**, Pal D, Sharma R, Garg VK, Goel N, Koundal D, Zaguia A, Koundal S, Belay A. Global Increase in Breast Cancer Incidence: Risk Factors and Preventive Measures. *Biomed Res Int* 2022; **2022**: 9605439 [PMID: 35480139 DOI: 10.1155/2022/9605439]
3 **Zhang YN**, Xia KR, Li CY, Wei BL, Zhang B. Review of Breast Cancer Pathologigcal Image Processing. *Biomed Res Int* 2021; **2021**: 1994764 [PMID: 34595234 DOI: 10.1155/2021/1994764]
4 **Barzaman K**, Karami J, Zarei Z, Hosseinzadeh A, Kazemi MH, Moradi-Kalbolandi S, Safari E, Farahmand L. Breast cancer: Biology, biomarkers, and treatments. *Int Immunopharmacol* 2020; **84**: 106535 [PMID: 32361569 DOI: 10.1016/j.intimp.2020.106535]
5 **Houghton SC**, Hankinson SE. Cancer Progress and Priorities: Breast Cancer. *Cancer Epidemiol Biomarkers Prev* 2021; **30**: 822-844 [PMID: 33947744 DOI: 10.1158/1055-9965.EPI-20-1193]

6 **Sung H**, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [PMID: 33538338 DOI: 10.3322/caac.21660]

7 **Pedersen RN**, Esen BÖ, Mellemkjær L, Christiansen P, Ejlertsen B, Lash TL, Nørgaard M, Cronin-Fenton D. The Incidence of Breast Cancer Recurrence 10-32 Years After Primary Diagnosis. *J Natl Cancer Inst* 2022; **114**: 391-399 [PMID: 34747484 DOI: 10.1093/jnci/djab202]

8 **Pan S**, Sun S, Liu B, Hou Y. Pan-cancer Landscape of the RUNX Protein Family Reveals their Potential as Carcinogenic Biomarkers and the Mechanisms Underlying their Action. *J Transl Int Med* 2022; **10**: 156-174 [PMID: 35959452 DOI: 10.2478/jtim-2022-0013]

9 **Adolfo CS**, Albougami ASB, Roque MY, Aruta JJBR, Almazan JU. An integrative review of negative emotions of older adults in later life. *Nurs Forum* 2022; **57**: 1452-1464 [PMID: 35962773 DOI: 10.1111/nuf.12785]

10 **Schunk F**, Trommsdorff G, König-Teshnizi D. Regulation of positive and negative emotions across cultures: does culture moderate associations between emotion regulation and mental health? *Cogn Emot* 2022; **36**: 352-363 [PMID: 34761731 DOI: 10.1080/02699931.2021.1997924]

11 **He R**, He X, Su Y, Wang Y, Liang T, Cui Z, Zhang L. Effect of ABC Theory Model on Negative Emotion of Young Patients with Breast Cancer During Treatment. *J Multidiscip Healthc* 2023; **16**: 1883-1888 [PMID: 37425248 DOI: 10.2147/JMDH.S405564]

12 **Xu C**, Ganesan K, Liu X, Ye Q, Cheung Y, Liu D, Zhong S, Chen J. Prognostic Value of Negative Emotions on the Incidence of Breast Cancer: A Systematic Review and Meta-Analysis of 129,621 Patients with Breast Cancer. *Cancers (Basel)* 2022; **14** [PMID: 35158744 DOI: 10.3390/cancers14030475]

13 **Li M**, Xie X, Xu H, Li H. A Psychological Nursing Intervention for Patients with Breast Cancer on Inflammatory Factors, Negative Emotions and Quality of Life. *Iran J Public Health* 2022; **51**: 2041-2047 [PMID: 36743364 DOI: 10.18502/ijph.v51i9.10559]

14 **Hajj A**, Hachem R, Khoury R, Hallit S, ElJEBBAWI B, Nasr F, El Karak F, Chahine G, Kattan J, Rabbaa Khabbaz L. Clinical and genetic factors associated with anxiety and depression in breast cancer patients: a cross-sectional study. *BMC Cancer* 2021; **21**: 872 [PMID: 34330229 DOI: 10.1186/s12885-021-08615-9]

15 **Gallagher N**. Cancer and the emotions in 18th-century literature. *Med Humanit* 2020; **46**: 257-266 [PMID: 31694870 DOI: 10.1136/medhum-2018-011639]

16 **Jossa V**, Olivier F, Lifrange E, Crevecoeur A, Courtois A, Coibion M, Jerusalem G. From modified radical mastectomy to infra-radical mastectomy: a phase I study for surgical de-escalation focusing on pathological analyses. *Gland Surg* 2021; **10**: 1931-1940 [PMID: 34268077 DOI: 10.21037/gs-21-48]

17 **Shekhar N**, Jaiswal R, Joseph L, Jain S, Kr A, Yashas N, Fernandes A, G C, S V, Reddy T, Reddy L, Kumar R. An Overview of Psychological Analysis of Breast Cancer Patients undergoing Modified Radical Mastectomy and Breast Conservation Surgery and its impact on Objectified Body Consciousness at a Tertiary Care Cancer Centre in South India. *Clin Breast Cancer* 2023; **23**: e394-e400 [PMID: 37400311 DOI: 10.1016/j.clbc.2023.05.017]

18 **Thakur M**, Sharma R, Mishra AK, Singh K, Kar SK. Psychological distress and body image disturbances after modified radical mastectomy among breast cancer survivors: A cross-sectional study from a tertiary care centre in North India. *Lancet Reg Health Southeast Asia* 2022; **7**: 100077 [PMID: 37383931 DOI: 10.1016/j.lansea.2022.100077]

19 **Hernández-Blanquisett A**, Quintero-Carreño V, Álvarez-Londoño A, Martínez-Ávila MC, Diaz-Cáceres R. Sexual dysfunction as a challenge in treated breast cancer: in-depth analysis and risk assessment to improve individual outcomes. *Front Oncol* 2022; **12**: 955057 [PMID: 35982958 DOI: 10.3389/fonc.2022.955057]

20 **Charos D**, Vivilaki V. Sexual dysfunction in women with breast cancer: The role of community midwives in early detection. *Eur J Midwifery* 2022; **6**: 70 [PMID: 36591330 DOI: 10.18332/ejm/156900]

21 **Chang CP**, Ho TF, Snyder J, Dodson M, Deshmukh V, Newman M, Date A, Henry NL, Hashibe M. Breast cancer survivorship and sexual dysfunction: a population-based cohort study. *Breast Cancer Res Treat* 2023; **200**: 103-113 [PMID: 37160510 DOI: 10.1007/s10549-023-06953-9]

22 **Haris I**, Hutajulu SH, Astari YK, Wiranata JA, Widodo I, Kurnianda J, Taroeno-Hariadi KW, Hardianti MS, Purwanto I, Prabandari YS. Sexual Dysfunction Following Breast Cancer Chemotherapy: A Cross-Sectional Study in Yogyakarta, Indonesia. *Cureus* 2023; **15**: e41744 [PMID: 37449290 DOI: 10.7759/cureus.41744]

23 **Perez-Tejada J**, Labaka A, Vegas O, Larraioz A, Pescador A, Arregi A. Anxiety and depression after breast cancer: The predictive role of monoamine levels. *Eur J Oncol Nurs* 2021; **52**: 101953 [PMID: 33813184 DOI: 10.1016/j.ejon.2021.101953]

24 **Kim K**, Park H. Factors affecting anxiety and depression in young breast cancer survivors undergoing radiotherapy. *Eur J Oncol Nurs* 2021; **50**: 101898 [PMID: 33465702 DOI: 10.1016/j.ejon.2021.101898]

25 **Liu W**, Liu J, Ma L, Chen J. Effect of mindfulness yoga on anxiety and depression in early breast cancer patients received adjuvant chemotherapy: a randomized clinical trial. *J Cancer Res Clin Oncol* 2022; **148**: 2549-2560 [PMID: 35788727 DOI: 10.1007/s00432-022-04167-y]

26 **Wang Z**, Xu XY, Liu QY, Mao XR, Min LH. [Research progress on Psychological resilience of pain at home and abroad]. *Xiandai Linchuang Yixue* 2023; **49**: 226-229 [DOI: 10.11851/j.issn.1673-1557.2023.03.020]

27 **Tuxunjiang X**, Li L, Zhang W, Sailike B, Wumaier G, Jiang T. Mediation effect of resilience on pregnancy stress and prenatal depression in pregnant women. *Zhong Nan Da Xue Xue Bao Yi Xue Ban* 2023; **48**: 557-564 [PMID: 37385618 DOI: 10.11817/j.issn.1672-7347.2023.220338]

28 **Li Y**, Zhang YL, Song YY, He WH. [Effect of WeChat continuous intervention on functional exercise compliance,self-care ability,psychological resilience,and quality of life in patients after radical mastectomy for breast cancer]. *Aizheng Jinzhan* 2022; **20**: 2245-2248 [DOI: 10.11877/j.issn.1672-1535.2022.20.21.20]

29 **Liu J**, Zhang L, Zhang FJ, Li Q. [Influence of focus on motivational care intervention on psychological resilience of patients undergoing radical mastectomy]. *Linchuang Yixue Yanjiu Yu Shijian* 2022; **7**: 179-181 [DOI: 10.19347/j.cnki.2096-1413.202231050]

30 **Zhang Y**, Li J, Wang AX. [The effect of psychological intervention based on emotional adaptation theory combined with group cognitive behavioral intervention on fear of disease progression, Psychological resilience and complications of patients after radical surgery for breast cancer]. *Linchuang Yixue Yanjiu Yu Shijian* 2023; **8**: 181-183 [DOI: 10.19347/j.cnki.2096-1413.202305053]

31 **Park S**, Sato Y, Takita Y, Tamura N, Ninomiya A, Kosugi T, Sado M, Nakagawa A, Takahashi M, Hayashida T, Fujisawa D. Mindfulness-Based Cognitive Therapy for Psychological Distress, Fear of Cancer Recurrence, Fatigue, Spiritual Well-Being, and Quality of Life in Patients With Breast Cancer-A Randomized Controlled Trial. *J Pain Symptom Manage* 2020; **60**: 381-389 [PMID: 32105790 DOI: 10.1016/j.jpainsymman.2020.02.017]

32 **Ruano A**, García-Torres F, Gálvez-Lara M, Moriana JA. Psychological and Non-Pharmacologic Treatments for Pain in Cancer Patients: A Systematic Review and Meta-Analysis. *J Pain Symptom Manage* 2022; **63**: e505-e520 [PMID: 34952171 DOI: 10.1016/j.jpainsymman.2021.12.021]

33 **Yang M**, Zhang Z, Nice EC, Wang C, Zhang W, Huang C. Psychological intervention to treat distress: An emerging frontier in cancer prevention and therapy. *Biochim Biophys Acta Rev Cancer* 2022; **1877**: 188665 [PMID: 34896258 DOI: 10.1016/j.bbcan.2021.188665]

34 **Wu L**, Zou Y. Psychological nursing intervention reduces psychological distress in patients with thyroid cancer: A randomized clinical trial protocol. *Medicine (Baltimore)* 2020; **99**: e22346 [PMID: 32957406 DOI: 10.1097/MD.0000000000022346]

35 **Tavares R**, Oliveira AR, Brandão T, Matos PM. Psychological group intervention to support parenting: Qualitative study about needs and preferences of mothers with breast cancer. *Eur J Oncol Nurs* 2022; **61**: 102197 [PMID: 36228405 DOI: 10.1016/j.ejon.2022.102197]

36 **Benoit V**, Gabola P. Effects of Positive Psychology Interventions on the Well-Being of Young Children: A Systematic Literature Review. *Int J Environ Res Public Health* 2021; **18** [PMID: 34831827 DOI: 10.3390/ijerph182212065]

37 **Allen JG**, Romate J, Rajkumar E. Mindfulness-based positive psychology interventions: a systematic review. *BMC Psychol* 2021; **9**: 116 [PMID: 34362457 DOI: 10.1186/s40359-021-00618-2]

38 **Lyu MM**, Siah RC, Lam ASL, Cheng KKF. The effect of psychological interventions on fear of cancer recurrence in breast cancer survivors: A systematic review and meta-analysis. *J Adv Nurs* 2022; **78**: 3069-3082 [PMID: 35696315 DOI: 10.1111/jan.15321]

39 **Moragón S**, Di Liello R, Bermejo B, Hernando C, Olcina E, Chirivella I, Lluch A, Cejalvo JM, Martínez MT. Fertility and breast cancer: A literature review of counseling, preservation options and outcomes. *Crit Rev Oncol Hematol* 2021; **166**: 103461 [PMID: 34461268 DOI: 10.1016/j.critrevonc.2021.103461]

40 **Samami E**, Shahhosseini Z, Hamzehgardeshi Z, Elyasi F. Psychological Interventions in Chemotherapy-Induced Nausea and Vomiting in Women with Breast Cancer: A Systematic Review. *Iran J Med Sci* 2022; **47**: 95-106 [PMID: 35291438 DOI: 10.30476/ijms.2020.86657.1660]

41 **Asarnow LD**, Manber R. Cognitive Behavioral Therapy for Insomnia in Depression. *Sleep Med Clin* 2019; **14**: 177-184 [PMID: 31029185 DOI: 10.1016/j.jsmc.2019.01.009]

42 **Apolinário-Hagen J**, Drüge M, Fritsche L. Cognitive Behavioral Therapy, Mindfulness-Based Cognitive Therapy and Acceptance Commitment Therapy for Anxiety Disorders: Integrating Traditional with Digital Treatment Approaches. *Adv Exp Med Biol* 2020; **1191**: 291-329 [PMID: 32002935 DOI: 10.1007/978-981-32-9705-0_17]

43 **Carson AJ**, McWhirter L. Cognitive Behavioral Therapy: Principles, Science, and Patient Selection in Neurology. *Semin Neurol* 2022; **42**: 114-122 [PMID: 35675820 DOI: 10.1055/s-0042-1750851]

44 **Addison S**, Shirima D, Aboagye-Mensah EB, Dunovan SG, Pascal EY, Lustberg MB, Arthur EK, Nolan TS. Effects of tandem cognitive behavioral therapy and healthy lifestyle interventions on health-related outcomes in cancer survivors: a systematic review. *J Cancer Surviv* 2022; **16**: 1023-1046 [PMID: 34357555 DOI: 10.1007/s11764-021-01094-8]

45 **Vance DE**, Frank JS, Bail J, Triebel KL, Niccolai LM, Gerstenecker A, Meneses K. Interventions for Cognitive Deficits in Breast Cancer Survivors Treated With Chemotherapy. *Cancer Nurs* 2017; **40**: E11-E27 [PMID: 26918390 DOI: 10.1097/NCC.0000000000000349]

46 **Lee SH**, Cho SJ. Cognitive Behavioral Therapy and Mindfulness-Based Cognitive Therapy for Depressive Disorders. *Adv Exp Med Biol* 2021; **1305**: 295-310 [PMID: 33834406 DOI: 10.1007/978-981-33-6044-0_16]

47 **Green AA**, Kinchen EV. The Effects of Mindfulness Meditation on Stress and Burnout in Nurses. *J Holist Nurs* 2021; **39**: 356-368 [PMID: 33998935 DOI: 10.1177/08980101211015818]

48 **Van Lith T**, Cheshure A, Pickett SM, Stanwood GD, Beerse M. Mindfulness based art therapy study protocol to determine efficacy in reducing college stress and anxiety. *BMC Psychol* 2021; **9**: 134 [PMID: 34479649 DOI: 10.1186/s40359-021-00634-2]

49 **Duval A**, Davis CG, Khoo EL, Romanow H, Shergill Y, Rice D, Smith AM, Poulin PA, Collins B. Mindfulness-based stress reduction and cognitive function among breast cancer survivors: A randomized controlled trial. *Cancer* 2022; **128**: 2520-2528 [PMID: 35385137 DOI: 10.1002/cncr.34209]

50 **Shao D**, Zhang H, Cui N, Sun J, Li J, Cao F. The efficacy and mechanisms of a guided self-help intervention based on mindfulness in patients with breast cancer: A randomized controlled trial. *Cancer* 2021; **127**: 1377-1386 [PMID: 33332582 DOI: 10.1002/cncr.33381]

51 **Zheng QY**, Zhao L, Wei W, Ren XJ, Wang C, Sun R, Cong MH, Yu L, Yang M. [Mindfulness-based Stress Reduction Can Improve Psychological Condition in Breast Cancer Patients: an Overview of Systematic Reviews]. *Zhongguo Quanke Yixue* 2023; **26**: 1503-1512 [DOI: 10.12114/j.issn.1007-9572.2022.0649]

52 **Luo XZ**, Lei XZ, Sun Q, Xie LL, Hu XY. [Effect of group mindfulness cognitive therapy on the psychological resilience and self-efficacy of breast cancer patients during chemotherapy]. *Linchuang Jingshen Yixue Zazhi* 2022; **32**: 291-293 [DOI: 10.3969/j.issn.1005-3220.2022.04.011]

53 **Schellekens MPJ**, Tamagawa R, Labelle LE, Speca M, Stephen J, Drysdale E, Sample S, Pickering B, Dirkse D, Savage LL, Carlson LE. Mindfulness-Based Cancer Recovery (MBCR) versus Supportive Expressive Group Therapy (SET) for distressed breast cancer survivors: evaluating mindfulness and social support as mediators. *J Behav Med* 2017; **40**: 414-422 [PMID: 27722908 DOI: 10.1007/s10865-016-9799-6]

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ORIGINAL ARTICLE

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Association between inflammatory bowel disease and all-cause dementia: A two-sample Mendelian randomization study

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Abstract

BACKGROUND

Numerous observational studies have documented a correlation between inflammatory bowel disease (IBD) and an increased risk of dementia. However, the causality of their associations remains elusive.

AIM

To assess the causal relationship between IBD and the occurrence of all-cause dementia using the two-sample Mendelian randomization (MR) method.

METHODS

Genetic variants extracted from the large genome-wide association study (GWAS) for IBD (the International IBD Genetics Consortium, n = 34652) were used to identify the causal link between IBD and dementia (FinnGen, n = 306102). The results of the study were validated *via* another IBD GWAS (United Kingdom Biobank, n = 463372). Moreover, MR egger intercept, MR pleiotropy residual sum and outlier, and Cochran's Q test were employed to evaluate pleiotropy and heterogeneity. Finally, multiple MR methods were performed to estimate the effects of genetically predicted IBD on dementia, with the inverse variance weighted approach adopted as the primary analysis.

RESULTS

The results of the pleiotropy and heterogeneity tests revealed an absence of significant pleiotropic effects or heterogeneity across all genetic variants in outcome GWAS. No evidence of a causal effect between IBD and the risk of dementia was identified in the inverse variance weighted [odds ratio (OR) = 0.980, 95%CI : 0.942-1.020, P value = 0.325], weighted median (OR = 0.964, 95%CI : 0.914-

1.017, *P* value = 0.180), and MR-Egger (OR = 0.963, 95%CI : 0.867-1.070, *P* value = 0.492) approaches. Consistent results were observed in validation analyses. Reverse MR analysis also showed no effect of dementia on the development of IBD. Furthermore, MR analysis suggested that IBD and its subtypes did not causally affect all-cause dementia and its four subtypes, including dementia in Alzheimer's disease, vascular dementia, dementia in other diseases classified elsewhere, and unspecified dementia.

CONCLUSION

Taken together, our MR study signaled that IBD and its subentities were not genetically associated with all-cause dementia or its subtypes. Further large prospective studies are warranted to elucidate the impact of intestinal inflammation on the development of dementia.

Key Words: Inflammatory bowel disease; All-cause dementia; Mendelian randomization; Causal effect; Risk factor

Core Tip: Dementia is a major disease burden for public health and healthcare systems worldwide. This study used two-sample Mendelian randomization (MR) to assess the causal relationship between inflammatory bowel disease (IBD) and all-cause dementia. Multiple MR methods have failed to find that IBD increases the risk of developing all-cause dementia and its four subtypes. The present study suggests that genetically predicted IBD is not associated with risk of all-cause dementia and that dementia prevention interventions for patients with IBD can be similar to those for the healthy population.

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INTRODUCTION

Dementia is a syndrome arising from brain disorders, usually of a chronic or progressive nature, characterized by acquired behavioral and cognitive deficits, including domains such as memory, communication and language abilities, concentration and attention span, reasoning and judgment, and visual perception[1]. It is a global health concern and has emerged as a pandemic in the aging population. Over 1315 million people are predicted to be affected by the mid-21st century[2]. Mounting evidence suggests that intestinal homeostasis is involved in psychiatric and neurologic disorders through the bidirectional microbiome-gut-brain axis. Besides conventional brain-gut disorders (*e.g.*, functional gastrointestinal disorders), recent studies point toward a potential role of the interaction between the gut and central nervous system in depression, anxiety, Parkinson's disease, autism spectrum disorders, and other related disorders[3].

Inflammatory bowel disease (IBD), comprising ulcerative colitis (UC) and Crohn's disease (CD), refers to a chronic intestinal disorder featured by a relapsing and remitting course. Its cause remains to be elucidated, but its pathogenesis may involve environmental factors triggering an aberrant immune response between the gut microbiota and the intestinal immune system in genetically susceptible hosts, thereby eliciting intestinal mucosal inflammation[4]. The genome-wide association study (GWAS) identified gene loci associated with IBD susceptibility, influencing not only gut microbial recognition and clearance but also the maintenance of intestinal immune homeostasis[5].

Several studies have reported that IBD patients are at increased risk of neurodegenerative diseases such as Parkinson's disease, multiple sclerosis, and dementia[6-8]. A Taiwanese population-based cohort study determined a significantly increased risk of developing dementia among IBD patients, whereas a Danish study concluded that IBD patients had a marginally increased risk of all-cause dementia[9,10]. Contrastingly, a longitudinal cohort study found no association between IBD and dementia[8]. To date, the causal relationship between IBD and dementia remains underexplored. Furthermore, the aforementioned observational studies might be susceptible to various measurement errors, underlying biases, and confounding factors, which could have compromised the results or even reverse causality.

Mendelian randomization (MR) is conceptually similar to randomized controlled trials (RCTs), using genetic variants as instrumental variables (IVs) to infer causality between an exposure and an outcome based on the principle of random assortment of alleles during gamete formation and conception[11,12]. The former utilizes genetic data, such as single nucleotide polymorphisms (SNPs) associated with an exposure (in this study, IBD), as IVs to examine the causal effect of the exposure on the target outcome (in this study, dementia)[13]. The intrinsic nature of the random assortment of genetic variants at conception dictates that their effects on outcomes remain unaffected by postnatal environmental, behavioral, and economic confounders. Besides, they are not susceptible to reverse causality bias[14]. Given that these confounding factors are inherently balanced across subgroups at conception, MR closely mimics the randomization process in RCTs.

A large number of MR studies have been undertaken to investigate the causal effect of IBD on neurodegenerative diseases, encompassing Alzheimer's disease (AD), Parkinson's disease, and amyotrophic lateral sclerosis[15-17]. While Li and Wen[15] did not identify a correlation between IBD and AD, Guo *et al*[17] found that IBD exerted a genetically

protective effect against AD. There are currently no MR studies or RCTs focusing on the effect of IBD on the risk of dementia subtypes other than AD. Based on the publicly available GWAS data from a large population, a two-sample MR analysis was adopted to identify the effect of IBD on all-cause dementia and its subtypes, which holds clinical implications for the formulation of interventions to delay cognitive decline and mitigate the burden of dementia in the IBD population. Our results may provide novel insights into the bidirectional interactions in the gut-brain axis.

MATERIALS AND METHODS

Study design

A two-sample MR method was conducted to evaluate the causal relationship between IBD and all-cause dementia. MR follows three key assumptions (Figure 1): (1) The IVs are strongly associated with the exposure (IBD); (2) the IVs are unrelated to confounder factors linked to the selected exposure and outcome, and (3) the IVs exclusively influence the outcome (dementia and its six subtypes) *via* IBD. Considering that this study used publicly available datasets from participant studies conducted in compliance with ethical standards, the requirement for ethical approval was waived.

IBD GWAS and genetic instrumental variants

The GWAS summary data for IBD were extracted from the International IBD Genetics Consortium (IIBDGC)[18] that is composed of 15 cohorts of European ancestry (enrolled cohorts are listed in Supplementary Table 1) and contained data on IBD as a whole (12882 cases; 21770 controls) and also on CD (5956 cases; 14927 controls) and UC (6968 cases; 20464 controls). All cases were confirmed using standard clinical, endoscopic, and histopathological criteria. The validation analysis incorporated summary statistics acquired from a United Kingdom Biobank GWAS involving European participants (7045 self-reported cases and 456327 controls) wherein IBD cases were identified using the International Classification of Diseases 10th Revision (ICD-10) codes F50 and F51[19]. Information about the GWAS of exposure is summarized in Table 1.

Independent genetic IVs were extracted from the respective exposure based on several criteria. To begin, SNPs strongly associated with the exposure were selected (P-value < 5 × 10^{-8}). Following this, to ensure the inclusion of IVs without linkage disequilibrium (LD), the clumping procedure (R^2 < 0.001, window size = 10000 kb) was executed utilizing European samples to calculate the LD. Thirdly, SNPs associated with other potential risk factors at genome-wide significance, which may act as confounders and interfere with the effect of IBD (including UC and CD) on dementia, were excluded using PhenoScanner (http://www.phenoscanner.medschl.cam.ac.uk/). Known risk factors for dementia include diabetes, hypertension, atrial fibrillation or flutter, obesity, chronic obstructive pulmonary disease, cerebrovascular disease, smoking, and hypothyroidism[8-10]. SNPs associated with dementia due to other diseases identified by the ICD-10 code F02 were also excluded in this analysis. The strength of the relationship between IVs and exposure was estimated using the F statistic (F statistics < 10 indicating a weak IV bias)[20]. For each IV, the F statistic was calculated using the following formula: F= [R^2 × (N-2)/(1 -R^2), where N denotes the sample size, R^2 represents the variance of exposure explained by the IVs (R^2 = 2 × beta^2 × eaf × (1-eaf)/[2 × beta^2 × eaf × (1-eaf) + 2 × se × N × eaf × (1-eaf)], eaf stands for the effect allele frequency, se represents standard error, and beta is the estimated effect of the SNP) [21-23].

Extraction of IVs from dementia GWAS

All-cause dementia was defined as ICD-10 codes F00 (dementia in AD), F01 [vascular dementia [VaD)], F02 (dementia in other diseases classified elsewhere) and F03 (unspecified dementia)[24]. The GWAS summary statistics for dementia were utilized as a whole and its subtypes from the FinnGen study[25]. The sample of all-cause dementia consisted of 11602 cases (ICD-10 F00-F03, ICD-9 290 | 3310 | 4378A, ICD-8 290) and 294500 controls; the sample of dementia in AD consisted of 3540 cases (ICD-10 F00, ICD-8 29010) and 294500 controls; the sample of VaD consisted of 1602 cases (ICD-10 F01, ICD-9 4378) and 297552 controls; the sample of dementia in other diseases classified elsewhere consisted of 882 cases (ICD-10 F02) and 294500 controls; and the sample of unspecified dementia consisted of 2729 cases (ICD-10 F03, ICD 290 | 2941, ICD-8 2900 | 29019) and 294500 controls. Details on the outcome of GWAS are listed in Table 1.

IVs were sequentially extracted from the outcome GWASs as described above, while outcome-related SNPs were eliminated. Subsequently, ambiguous SNPs with incompatible alleles (*e.g.*, A/G *vs*. A/C) and palindromic SNPs (*e.g.*, A/T or G/C) were excluded when harmonizing exposure and outcome datasets[26]. SNPs absent in the outcome data were substituted by proxy SNPs obtained from the online platform LDlink (https://Ldlink.nih.gov/) based on high LD from European data. Proxies were required to have a minimum R^2 value of 0.8, and palindromic SNP strands were aligned using a minor allele frequency of up to 0.3[27]. The summary characteristics of all genetic IVs are illustrated in Supplementary Tables 2-4. The correlations between IBD (including UC and CD) genetic IVs and the GWAS datasets for dementia and its subtypes are displayed in Supplementary Tables 5-7. Additionally, a comprehensive summary of IVs associated with the validation analysis is presented in Supplementary Tables 8 and 9.

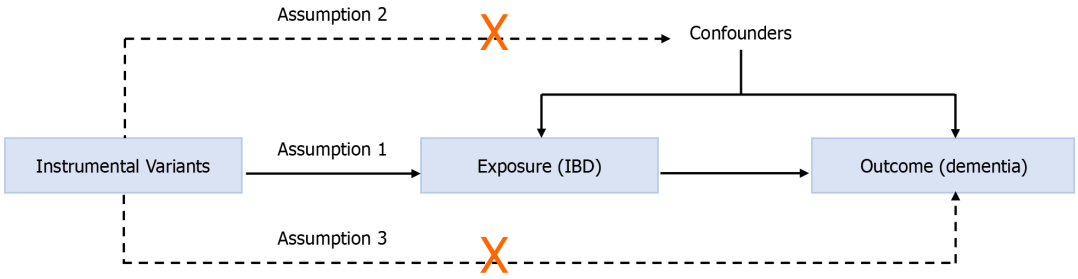
Pleiotropy and heterogeneity assessments

MR egger intercept and MR pleiotropy residual sum and outlier (MR-PRESSO) tests are typically used to assess horizontal pleiotropy[28]. If the selected IVs are not pleiotropic, the MR Egger intercept term tends to approach zero with an increase in sample size[29]. MR-PRESSO can correct horizontal pleiotropy by eliminating underlying outliers prior to each MR analysis[28]. The harmonized SNPs underwent the MR-PRESSO test (NbDistribution=10000). A P > 0.05 in the MR-PRESSO global test indicates no significant pleiotropy of all IBD-associated IVs in the dementia GWAS dataset. In the

Table 1 Details of the genome-wide association studies included in the Mendelian randomization

Phenotype	Consortium	Year	Ncase	Ncontrol	Population
IBD	IIBDGC	2015	12882	21770	European
UC	IIBDGC	2015	6968	20464	European
CD	IIBDGC	2015	5956	14927	European
IBD (val)	United Kingdom Biobank	2021	7045	449282	United Kingdom
All-cause dementia	FinnGen	2022	11602	294500	Finnish
Dementia in AD	FinnGen	2022	3540	294500	Finnish
VaD	FinnGen	2022	1602	297552	Finnish
Dementia in other diseases classified elsewhere	FinnGen	2022	882	294500	Finnish
Unspecified dementia	FinnGen	2022	2729	294500	Finnish

IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn's disease; AD: Alzheimer's disease; VaD: Vascular dementia; IIBDGC: International Inflammatory Bowel Disease Genetics Consortium.



Assumption 1: The instrumental variants are strongly associated with exposure;

Assumption 2: The instrumental variants are not associated with confounders;

Assumption 3: The instrumental variants influence the outcome only through the exposure.

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Figure 1 Diagram of the two-sample Mendelian randomization study for the associations of inflammatory bowel disease with dementia.
IBD: Inflammatory bowel disease.

MR-PRESSO outlier test, outliers with a *P*-value less than 0.05 should be removed. The Cochran's *Q* statistic was employed to evaluate heterogeneity, which is extensively employed in MR Egger and inverse variance weighted (IVW) analyses[30,31]. A $P > 0.05$ indicates the absence of significant heterogeneity. The summarized results of the pleiotropy and heterogeneity tests are shown in Supplementary Table 10.

MR analysis

Three different MR methods (IVW, weighted median, and MR Egger) were performed to estimate the effect of the exposure on outcome susceptibility. IVW was selected as the primary method, with the remaining MR methods assessing the sensitivity of our findings with robust estimates. IVW represents the weighted average of Wald ratio estimates of the causal impact for each variant and provides the most accurate estimate when all IVs are valid[32]. The weighted median yields consistent estimates even if up to 50% of selected SNPs are not valid[28,29]. MR Egger accounts for pleiotropy among all IVs but requires that the associations between genetic variants and exposure remain independent of the effects of genetic variants on the outcome[33]. Additionally, a "leave one out" analysis was carried out to systematically exclude each SNP individually to examine the influence of SNPs on the MR estimate[34].

All analyses in this MR study were performed using the Package "TwoSampleMR version 0.5.6" in R version 4.2.2. The significance threshold was set at $P < 0.05/X/Y = 0.05/3/5 = 0.003$, corrected by the Bonferroni method (X: the number of exposures, Y: the number of outcomes). An overview of our study's process is presented in Figure 2.

Reverse MR analysis

Genetic IVs were selected from the dementia GWAS summary data based on several criteria: (1) *P*-value (genome-wide significance threshold $< 5 \times 10^{-8}$); (2) an LD R^2 of < 0.001, and < 10000 kb from the index variant; and (3) no effects on potential risk factors, including inflammation, immune response, and gut microbiota. Then, IVs were extracted from the IBD GWAS. The IBD GWAS and dementia GWAS were sourced from the IIBDGC and FinnGen, respectively (Table 1).

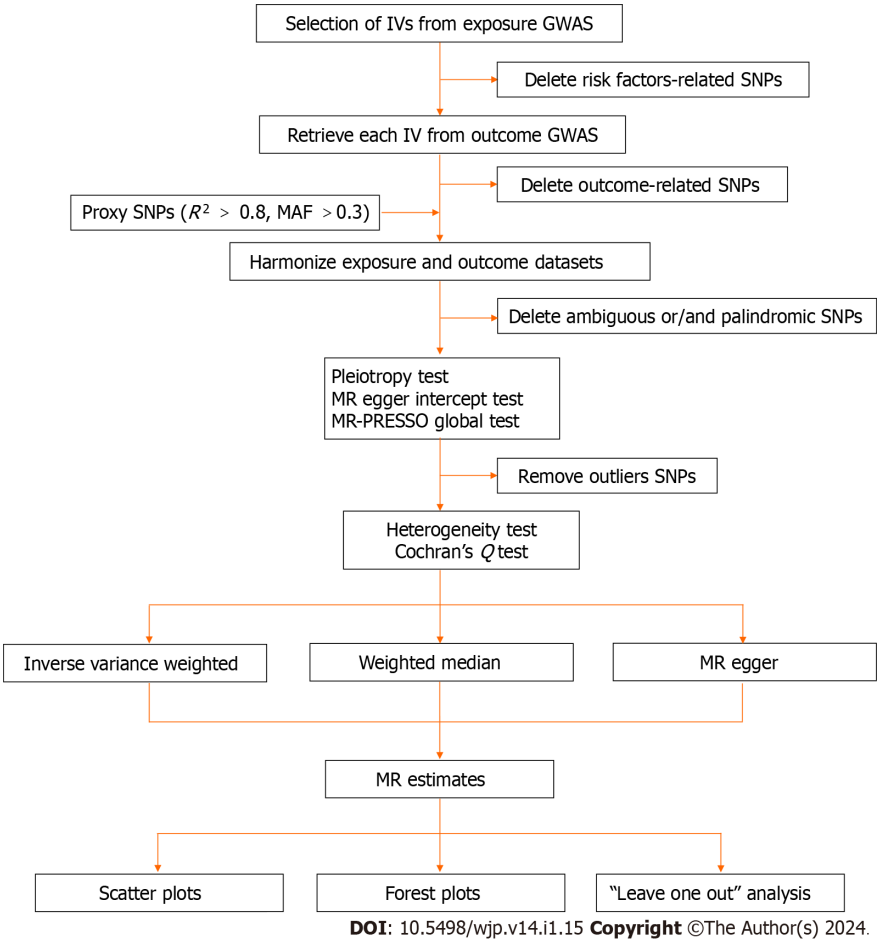

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Figure 2 Flow chart of this Mendelian randomization study. MR: Mendelian randomization; SNPs: Single nucleotide polymorphisms; GWAS: Genome-wide association study; IV: Instrumental variables.

The summary characteristics of dementia IVs and their association with IBD GWAS are depicted in Supplementary Table 11 and 12.

The MR Egger intercept and PRESSO methods were applied to determine the pleiotropy of dementia-associated IVs in IBD GWAS, whilst MR Egger and IVW in Cochran's *Q* statistic were employed to determine the heterogeneity of dementia-associated IVs in IBD GWAS (Supplementary Table 10). The methods of reverse MR analysis were consistent with those described above.

RESULTS

Genetic instrumental variants

In the primary analysis investigating the causal impact of IBD on dementia, 65 SNPs were screened as potential genetic IVs, of which 19 SNPs related to other potential risk factors were excluded, nine SNPs could not be extracted from the outcome GWASs, and five SNPs were ambiguous or/and palindromic (Supplementary Table 2). In the analysis concerning the impact of UC on dementia, 39 SNPs were screened as potential genetic IVs, of which 13 SNPs related to other potential risk factors were excluded, four SNPs could not be extracted from the outcome GWASs, and three SNPs were ambiguous or/and palindromic (Supplementary Table 3). In the analysis of the impact of CD on dementia, 53 SNPs were initially identified as potential genetic IVs, among which 19 SNPs related to other potential risk factors were excluded, two SNPs could not be extracted from the outcome GWASs, and five SNPs were ambiguous or/and palindromic (Supplementary Table 4). Besides, 19 SNPs were identified as IVs in the validation analyses (Supplementary 8). The selected IVs could explain 6.75%, 4.36%, and 9.06% variance of IBD, UC, and CD, respectively. Additionally, the accounted variance by IVs was 0.19% in the validation analyses. The *F*-statistic of all selected IVs was > 10, demonstrating a marginal possibility of a weak instrument bias (Supplementary Table 2-4 and 8).

MR egger intercept and MR-PRESSO global tests both exposed the absence of significant pleiotropy (Supplementary Table 10). Furthermore, no statistical heterogeneity was detected in the MR egger and IVW in Cochran's *Q* tests (Supplementary Table 10). Thus, all selected genetic SNPs were regarded as effective IVs in this MR study.

Causal effects of IBD on the risk of all-cause dementia

In the primary analysis, the IVW method determined that IBD was not causally related to all-cause dementia [odds ratio (OR) = 0.980, 95%CI : 0.942-1.020, *P* value = 0.325] (Figure 3). Subsequently, the causal relationship between IBD and the four subtypes of dementia was examined. Subgroup analyses did not support a significant association between IBD and dementia in AD (OR = 0.957, 95%CI : 0.899-1.018, *P* value = 0.165), VaD (OR = 0.944, 95%CI : 0.866-1.030, *P* value = 0.195), dementia in other diseases classified elsewhere (OR = 1.089, 95%CI : 0.952-1.246, *P* value = 0.214), and unspecified dementia (OR = 1.011, 95%CI : 0.936-1.092, *P* value = 0.776) (Figure 3). Similarly, the weighted median and MR Egger methods provided no evidence of a genetic causal relationship between IBD and all-cause dementia and its subtypes (Supplementary Table 13). As anticipated, these results were corroborated by the validation sample (Figure 4; Supplementary Table 13). The scatter plots and forest plots of the single SNP effect and combined effects are displayed in Supplementary Figure 1-4. The "leave one out" sensitivity analysis indicated that no individual SNP influenced the MR estimates (Supplementary Figures 5 and 6).

Furthermore, the causal effects of UC and CD on all-cause dementia and its four subtypes were assessed in a similar approach. The IVW method revealed that UC and CD were not causally related to all-cause dementia and its four subtypes, including dementia in AD, VaD, dementia in other diseases classified elsewhere, and unspecified dementia (Figure 3). The results of the weighted median and MR Egger are presented in Supplementary Table 13. All scatter plots, forest plots, and "leave one out" analysis plots for MR analyses of UC and CD on dementia are shown in Supplementary Figures 7-12.

Causal effect of dementia on IBD

To explore reverse causality, 12 SNPs were selected from dementia GWAS summary statistics as potential IVs, of which three SNPs associated with potential risk factors were excluded, whilst another SNP was excluded due to palindrome after harmonization of dementia GWAS and IBD GWAS (Supplementary Tables 11 and 12). The intercept term from the MR Egger regression and MR-PRESSO global test demonstrated no significant pleiotropy among the eight independent dementia-associated IVs in IBD GWAS. Importantly, Cochran's *Q* test did not identify significant heterogeneity among the effects of dementia-associated SNPs on IBD (Supplementary Table 10). Therefore, all eight dementia-associated SNPs could be regarded as valid genetic IVs for the ensuing MR analysis. In the reverse MR analysis, the results of IVW, weighted median, and MR Egger uncovered no genetically causal effect of dementia on IBD (Supplementary Table 14). The scatter plot, forest plot, and "leave one out" analysis plot for reverse MR analysis are shown in Supplementary Figure 13.

DISCUSSION

Herein, a two-sample MR approach was employed to comprehensively evaluate the causal relationship between genetically predicted IBD (including UC and CD) and the risk of all-cause dementia and its subtypes, namely, AD, VaD, dementia in other diseases classified elsewhere and unspecified dementia. The results of several methods of MR analyses did not indicate that IBD played a genetic role in the development of dementia (Supplementary Table 13). The findings were further confirmed by conducting a validation analysis in another summary statistics of IBD GWAS (Supplementary Table 13). Likewise, the reverse MR analysis did not support a causal role of all-cause dementia in the risk of IBD (Supplementary Table 14).

IBD is etiologically related to gut microbiota dysbiosis, which induces proinflammatory activity in the gut that is transmitted to the nervous system *via* the microbiome-gut-brain axis, eventually resulting in neuroinflammation[35,36]. Recently, compelling evidence from population-based observational studies has insinuated an association between IBD and an increased risk of dementia. For instance, a longitudinal cohort study including 1742 patients with IBD and 17420 controls from the Taiwanese population demonstrated an increased risk of all-cause dementia following the diagnosis of IBD [hazard ratio (HR) = 2.54, 95%CI : 1.91-3.37], especially at younger ages, compared to controls[9]. Two other retrospective cohort studies from Germany and Denmark reported significant but less pronounced effects of IBD on the risk of dementia[10,37]. A recent systematic review and meta-analysis based on six studies including 2334472 subjects suggested an increased risk for developing dementia in IBD patients (HR = 1.27, 95%CI : 1.10-1.47)[38]. Notably, this result was in line with the findings of other systematic reviews and meta-analyses[39,40]. Furthermore, a large case-control study established systemic inflammation as a potential risk factor for AD, while the latest meta-analysis concluded that chronic elevation in the level of the inflammatory biomarker C-reactive protein was directly correlated with the lifetime risk of developing dementia[41,42]. Interestingly, drugs for the treatment of IBD, such as tumor necrosis factor blocking agents, might be associated with a lower risk of developing AD[41,43]. In a mouse model of IBD induced by sodium dextran sulfate, Kaneko *et al*[44] observed that neutrophils infiltrated the brain parenchyma of AD mice and accelerated amyloid plaque accumulation during acute colitis. Meanwhile, He *et al*[45] found that intestinal inflammation disrupted glymphatic clearance and triggered neuroinflammation, resulting in increased amyloid-β deposition and, ultimately, cognitive impairment.

However, the results of observational studies are largely inconsistent. A longitudinal cohort study of 497775 participants recruited from 2006 to 2010 in the UK Biobank highlighted an HR of 1.14 for incident dementia among IBD patients, but the differences were not significant (95%CI : 0.94-1.39, *P* value = 0.182). Besides, there was no statistically significant difference in the anatomical and tissue-specific volumes of their brains on magnetic resonance images[8]. Furthermore, a recent meta-analysis including seven observational studies (six cohort studies and one case-control study) and 20174 cases did not identify a significant association between UC [relative risks (RR) = 1.16, 95%CI : 0.96-1.41) or CD

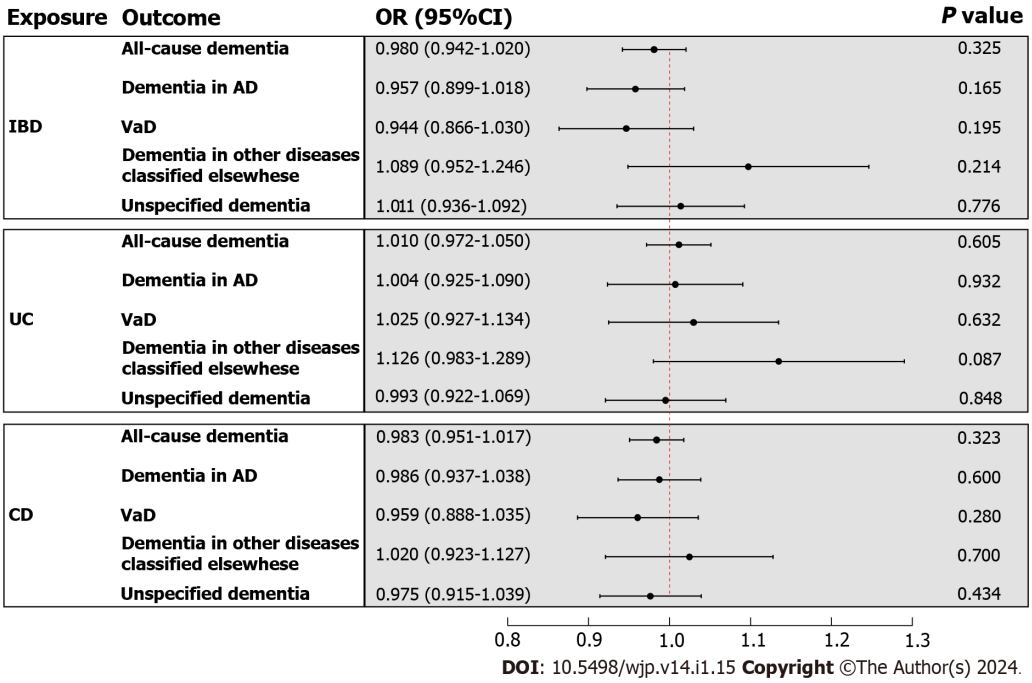

Figure 3 The inverse variance weighted estimates of inflammatory bowel disease on dementia. The exposure is inflammatory bowel disease and subentities including ulcerative colitis and Crohn's disease, and the outcome is all-cause dementia and its subtypes including dementia in Alzheimer's disease, vascular dementia, dementia in other diseases classified elsewhere, and unspecified dementia. The inverse variance weighted estimates, presented as odds ratios (OR) and 95% confidence intervals, are the summed ORs calculated from the individual instrumental variables. IBD: Inflammatory bowel disease; AD: Alzheimer's disease; VaD: Vascular dementia; UC: Comprising ulcerative colitis; CD: Crohn's disease.

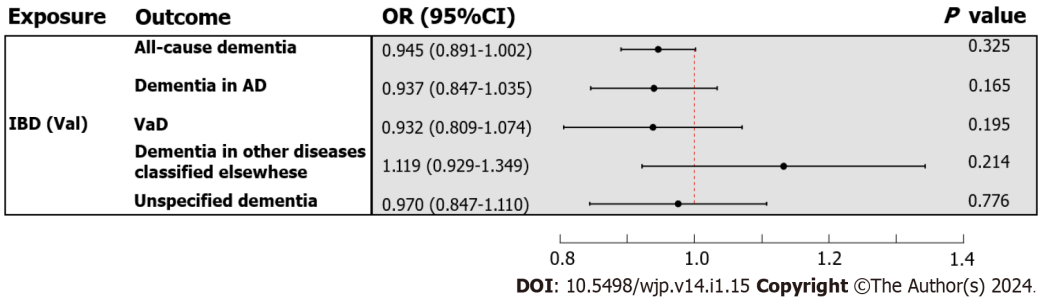

Figure 4 The inverse variance weighted estimates of inflammatory bowel disease (validation) on dementia. The exposure is inflammatory bowel disease (validation), and the outcome is all-cause dementia and its four subtypes. The inverse variance weighted estimates, presented as odds ratios (OR) and 95% confidence intervals, are the summed ORs calculated from the individual instrumental variables. IBD: Inflammatory bowel disease; AD: Alzheimer's disease; VaD: Vascular dementia.

(RR = 1.17, 95%CI : 0.84-1.62] and the risk of AD[43]. Another meta-analysis encompassing nine studies, including seven cohort studies, one cross-sectional study, and one case-control study, described that a previous diagnosis of IBD did not influence the risk of subsequent all-cause dementia (RR = 1.32, 95%CI : 0.98-1.77) and AD (RR = 1.62, 95%CI : 0.96-2.76) [46]. Of note, subgroup analysis based on the study of the above meta-analysis implied that IBD increased the risk of all-cause dementia but not AD in the cohort study, UC increased the risk of subsequent all-cause dementia and AD, and CD only increased the risk of all-cause dementia[46]. So far, the causal relationship between IBD and dementia has not been established.

In the present MR study, no causal relationship was discovered between genetically predicted IBD and subentities and all-cause dementia and its four subtypes, which contradicts the results of the above-mentioned studies implicating an association between IBD and dementia (Supplementary Table 13). What's more, our finding is not in agreement with that of Guo *et al*[17]. It is worthwhile emphasizing that their MR study had some limitations, including sample selection bias in the selected AD dataset that included older clinically diagnosed patients but excluded patients with shortened life expectancy due to IBD-related comorbidities, thus reducing or even reversing the MR estimated effect. In addition, Guo *et al*[17] used univariable MR to estimate the causal roles of UC and CD in AD, which might have led to horizontal pleiotropy due to IV overlapping. Excitingly, a recent study published in Neurology with a large sample size carried out an observational analysis combined with MR analysis corroborated our findings. The observational analysis using data from the United Kingdom Clinical Practice Research Datalink described that the overall incidence of AD was higher in

patients with IBD (HR = 1.17, 95%CI : 1.15-1.19, *P* value = 2.1 × 10^{-4}). Nonetheless, their MR analysis yielded no association between IBD and AD, suggesting that confounding factors may compromised the observed association[47]. Observational studies are susceptible to inherent methodological shortcomings, such as bias and confounding variables. For instance, the recruitment of the majority of participants from Medicare databases or inpatient registries could have increased the risk of selection bias. Surveillance bias also may increase the likelihood of a positive correlation. The gut microbiota, obesity, and other factors have been established as risk factors for both IBD and dementia in previous studies [5,48-50]. On the other side, the use of medications such as proton pump inhibitors and tumor necrosis factor blocking agents might interfere with the results when assessing the association between IBD and dementia[51,52]. At the same time, shared genetic components, such as PPARG and NOS2, could also increase genetic susceptibility to both diseases [53]. Furthermore, meta-analyses typically exhibit statistical heterogeneity arising from differences in study populations, study designs, and inclusion criteria. Finally, two large-scale GWAS comprehensively evaluated the genetic overlap between cognitive traits or AD and gastrointestinal disorders, with neither detecting significant genetic overlap and correlation with IBD[54,55].

A major strength of our study is that the causal effects between IBD and the risk of all-cause dementia and its six subtypes were assessed by utilizing a two-sample MR design, which mitigates limitations inherent noted in observational studies, including measurement error, residual confounding, and reverse causation bias. This MR study incorporated independent and robust genetic variants as IVs, not only to limit the effect of LD and weak instrument bias but also to circumvent the time-consuming and labor-intensive challenges generally encountered in observational studies (Supplementary Tables 2-9). Furthermore, our methodology utilized an iterative approach that is conservative and resilient against the influence of outliers (Supplementary Table 10). A series of pleiotropy and heterogeneity tests were also conducted to ensure the consistency of causal estimates and to confirm the robustness of the present findings (Supplementary Table 10). Finally, our findings were validated through a second, largely independent GWAS that yielded concordant results (Supplementary Table 13). Nevertheless, our study has several limitations. Despite the strength of all selected IVs, they collectively accounted for only 6.75% of the variance in the IBD sample (Supplementary Table 2). In addition, the datasets used in this study were based on subjects of European ancestry (Table 1), thereby restricting the generalizability of our observations to other ethnicities.

CONCLUSION

Herein, no association was identified between the risk of all-cause dementia and genetically predicted IBD. While there is no clear genetic evidence to support IBD as a risk factor for dementia, the possibility of a potential association between the two diseases cannot be ruled out. Further research is necessitated to identify factors that exert a causal effect on the development of dementia.

ARTICLE HIGHLIGHTS

Research background

Evidence from observational studies has not been able to establish a causal link between inflammatory bowel disease (IBD) and dementia.

Research motivation

Gut homeostasis is implicated in many psychiatric and neurological disorders through the bidirectional microbiome-gut-brain axis.

Research objectives

The aim was to find out whether IBD was causally related to all-cause dementia.

Research methods

Based on the publicly available genome-wide association study data from large population, multiple methods of Mendelian randomization (MR) were performed to estimate the effects of genetically predicted IBD on dementia, and inverse variance weighted was considered as the primary analysis. MR egger intercept, MR pleiotropy residual sum and outlier, and Cochran's *Q* test were used to test pleiotropy and heterogeneity.

Research results

No evidence for a causal effect of IBD on dementia risk was found in three MR methods of MR, which was consistent with validation analyses. Furthermore, MR analysis suggested that IBD and subentities did not causally affect all-cause dementia and its four subtypes.

Research conclusions

Our MR study found no association between the risk of all-cause dementia and genetically predicted IBD.

Research perspectives

Genetically predicted IBD is not associated with all-cause dementia risk, and dementia prevention interventions for patients with IBD can be similar to those in healthy populations.

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FOOTNOTES

Co-corresponding authors: Qin Du and Guo-Chun Lou.

Author contributions: Liao OL designed the study, acquired and analyzed data, and wrote the manuscript; Xie SY contributed to conceptualization and methodology; Ye J contributed to writing review and editing; Du Q and Lou GC designed, refined the study protocol, and supervised this study. All authors were involved in the critical review of the results and have contributed to, read, and approved the final manuscript. Du Q and Lou GC contributed equally to this work as co-corresponding authors. Firstly, both researchers were co-principal investigators of this study and have made equally significant contributions throughout the study process. Designating them as co-corresponding authors accurately reflects the allocation of responsibilities related to completing the study. Secondly, both researchers shared responsibility for ensuring the authenticity of the manuscript's content and credibility of its conclusions, as well as handling communication and consultation work. Therefore, we believe that designating Du Q and Lou GC as co-corresponding authors is appropriate, reflecting the collaborative spirit and equal contributions of our team.

Institutional review board statement: No institutional review board statement is required since this study was based on public databases.

Clinical trial registration statement: The data was from large sample size GWAS, and no Clinical Trial Registration Statement is required.

Informed consent statement: The data was from large sample size genome-wide association study, and no informed consent statement is required.

Conflict-of-interest statement: The authors have no conflict of interest to report.

Data sharing statement: The summary statistics of IBD, UC, and CD GWAS (IIBDGC) is available at https://gwas.mrcieu.ac.uk/datasets/ieu-a-31, https://gwas.mrcieu.ac.uk/datasets/ieu-a-32, and https://gwas.mrcieu.ac.uk/datasets/ieu-a-30, respectively. The summary data for the second IBD GWAS (UK Biobank) is provided at https://cnsgenomics.com/data/wu_et_al_2021_nc/5_IBD_summary. The summary statistics of all-cause dementia, dementia in AD, VaD, dementia in other diseases classified elsewhere, and unspecified dementia GWAS (FinnGen) is available at https://storage.googleapis.com/finngen-public-data-r7/summary_stats/finngen_R7_F5_DEMENTIA.gz, https://storage.googleapis.com/finngen-public-data-r7/summary_stats/finngen_R7_F5_ALZHDEMENT.gz, https://storage.googleapis.com/finngen-public-data-r7/summary_stats/finngen_R7_F5_VASCDEM.gz, https://storage.googleapis.com/finngen-public-data-r7/summary_stats/finngen_R7_F5_DEMINOTH.gz, and https://storage.googleapis.com/finngen-public-data-r7/summary_stats/finngen_R7_F5_DEMNAS.gz, respectively. All datasets were downloaded on 2023-7-11.

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REFERENCES

1 **Maloney B**, Lahiri DK. Epigenetics of dementia: understanding the disease as a transformation rather than a state. *Lancet Neurol* 2016; **15**: 760-774 [PMID: 27302240 DOI: 10.1016/S1474-4422(16)00065-X]
2 **Shah H**, Albanese E, Duggan C, Rudan I, Langa KM, Carrillo MC, Chan KY, Joanette Y, Prince M, Rossor M, Saxena S, Snyder HM, Sperling R, Varghese M, Wang H, Wortmann M, Dua T. Research priorities to reduce the global burden of dementia by 2025. *Lancet Neurol* 2016; **15**: 1285-1294 [PMID: 27751558 DOI: 10.1016/S1474-4422(16)30235-6]
3 **Martin CR**, Osadchiy V, Kalani A, Mayer EA. The Brain-Gut-Microbiome Axis. *Cell Mol Gastroenterol Hepatol* 2018; **6**: 133-148 [PMID:

30023410 DOI: 10.1016/j.jcmgh.2018.04.003]
4 **Matsuoka K**, Kanai T. The gut microbiota and inflammatory bowel disease. *Semin Immunopathol* 2015; **37**: 47-55 [PMID: 25420450 DOI: 10.1007/s00281-014-0454-4]
5 **Lee M**, Chang EB. Inflammatory Bowel Diseases (IBD) and the Microbiome-Searching the Crime Scene for Clues. *Gastroenterology* 2021; **160**: 524-537 [PMID: 33253681 DOI: 10.1053/j.gastro.2020.09.056]
6 **Brudek T**. Inflammatory Bowel Diseases and Parkinson's Disease. *J Parkinsons Dis* 2019; **9**: S331-S344 [PMID: 31609699 DOI: 10.3233/JPD-191729]
7 **Wang X**, Wan J, Wang M, Zhang Y, Wu K, Yang F. Multiple sclerosis and inflammatory bowel disease: A systematic review and meta-analysis. *Ann Clin Transl Neurol* 2022; **9**: 132-140 [PMID: 35092169 DOI: 10.1002/acn3.51495]
8 **Sun Y**, Geng J, Chen X, Chen H, Wang X, Chen J, Li X, Hesketh T. Association Between Inflammatory Bowel Disease and Dementia: A Longitudinal Cohort Study. *Inflamm Bowel Dis* 2022; **28**: 1520-1526 [PMID: 34849925 DOI: 10.1093/ibd/izab300]
9 **Zhang B**, Wang HE, Bai YM, Tsai SJ, Su TP, Chen TJ, Wang YP, Chen MH. Inflammatory bowel disease is associated with higher dementia risk: a nationwide longitudinal study. *Gut* 2021; **70**: 85-91 [PMID: 32576641 DOI: 10.1136/gutjnl-2020-320789]
10 **Rønnow Sand J**, Troelsen FS, Horváth-Puhó E, Henderson VW, Sørensen HT, Erichsen R. Risk of dementia in patients with inflammatory bowel disease: a Danish population-based study. *Aliment Pharmacol Ther* 2022; **56**: 831-843 [PMID: 35781292 DOI: 10.1111/apt.17119]
11 **Lawlor DA**, Harbord RM, Sterne JA, Timpson N, Davey Smith G. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. *Stat Med* 2008; **27**: 1133-1163 [PMID: 17886233 DOI: 10.1002/sim.3034]
12 **Smith GD**, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol* 2003; **32**: 1-22 [PMID: 12689998 DOI: 10.1093/ije/dyg070]
13 **Burgess S**, Small DS, Thompson SG. A review of instrumental variable estimators for Mendelian randomization. *Stat Methods Med Res* 2017; **26**: 2333-2355 [PMID: 26282889 DOI: 10.1177/0962280215597579]
14 **Zheng J**, Baird D, Borges MC, Bowden J, Hemani G, Haycock P, Evans DM, Smith GD. Recent Developments in Mendelian Randomization Studies. *Curr Epidemiol Rep* 2017; **4**: 330-345 [PMID: 29226067 DOI: 10.1007/s40471-017-0128-6]
15 **Li H**, Wen Z. Effects of ulcerative colitis and Crohn's disease on neurodegenerative diseases: A Mendelian randomization study. *Front Genet* 2022; **13**: 846005 [PMID: 36046231 DOI: 10.3389/fgene.2022.846005]
16 **Freuer D**, Meisinger C. Association between inflammatory bowel disease and Parkinson's disease: A Mendelian randomization study. *NPJ Parkinsons Dis* 2022; **8**: 55 [PMID: 35534507 DOI: 10.1038/s41531-022-00318-7]
17 **Guo X**, Chong L, Zhang X, Li R. Letter to the editor: Genetically determined IBD is associated with decreased risk of Alzheimer's disease: a Mendelian randomisation study. *Gut* 2022; **71**: 1688-1689 [PMID: 34750207 DOI: 10.1136/gutjnl-2021-325869]
18 **Liu JZ**, van Sommeren S, Huang H, Ng SC, Alberts R, Takahashi A, Ripke S, Lee JC, Jostins L, Shah T, Abedian S, Cheon JH, Cho J, Dayani NE, Franke L, Fuyuno Y, Hart A, Juyal RC, Juyal G, Kim WH, Morris AP, Poustchi H, Newman WG, Midha V, Orchard TR, Vahedi H, Sood A, Sung JY, Malekzadeh R, Westra HJ, Yamazaki K, Yang SK; International Multiple Sclerosis Genetics Consortium; International IBD Genetics Consortium, Barrett JC, Alizadeh BZ, Parkes M, Bk T, Daly MJ, Kubo M, Anderson CA, Weersma RK. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. *Nat Genet* 2015; **47**: 979-986 [PMID: 26192919 DOI: 10.1038/ng.3359]
19 **Wu Y**, Murray GK, Byrne EM, Sidorenko J, Visscher PM, Wray NR. GWAS of peptic ulcer disease implicates Helicobacter pylori infection, other gastrointestinal disorders and depression. *Nat Commun* 2021; **12**: 1146 [PMID: 33608531 DOI: 10.1038/s41467-021-21280-7]
20 **Pierce BL**, Ahsan H, Vanderweele TJ. Power and instrument strength requirements for Mendelian randomization studies using multiple genetic variants. *Int J Epidemiol* 2011; **40**: 740-752 [PMID: 20813862 DOI: 10.1093/ije/dyq151]
21 **Palmer TM**, Lawlor DA, Harbord RM, Sheehan NA, Tobias JH, Timpson NJ, Davey Smith G, Sterne JA. Using multiple genetic variants as instrumental variables for modifiable risk factors. *Stat Methods Med Res* 2012; **21**: 223-242 [PMID: 21216802 DOI: 10.1177/0962280210394459]
22 **Gill D**, Efstathiadou A, Cawood K, Tzoulaki I, Dehghan A. Education protects against coronary heart disease and stroke independently of cognitive function: evidence from Mendelian randomization. *Int J Epidemiol* 2019; **48**: 1468-1477 [PMID: 31562522 DOI: 10.1093/ije/dyz200]
23 **Levin MG**, Judy R, Gill D, Vujkovic M, Verma SS, Bradford Y; Regeneron Genetics Center, Ritchie MD, Hyman MC, Nazarian S, Rader DJ, Voight BF, Damrauer SM. Genetics of height and risk of atrial fibrillation: A Mendelian randomization study. *PLoS Med* 2020; **17**: e1003288 [PMID: 33031386 DOI: 10.1371/journal.pmed.1003288]
24 **Esteban-Cornejo I**, Ho FK, Petermann-Rocha F, Lyall DM, Martinez-Gomez D, Cabanas-Sánchez V, Ortega FB, Hillman CH, Gill JMR, Quinn TJ, Sattar N, Pell JP, Gray SR, Celis-Morales C. Handgrip strength and all-cause dementia incidence and mortality: findings from the UK Biobank prospective cohort study. *J Cachexia Sarcopenia Muscle* 2022; **13**: 1514-1525 [PMID: 35445560 DOI: 10.1002/jcsm.12857]
25 **Kurki MI**, Karjalainen J, Palta P, Sipilä TP, Kristiansson K, Donner KM, Reeve MP, Laivuori H, Aavikko M, Kaunisto MA, Loukola A, Lahtela E, Mattsson H, Laiho P, Della Briotta Parolo P, Lehisto AA, Kanai M, Mars N, Rämö J, Kiiskinen T, Heyne HO, Veerapen K, Rüeger S, Lemmelä S, Zhou W, Ruotsalainen S, Pärn K, Hiekkalinna T, Koskelainen S, Paajanen T, Llorens V, Gracia-Tabuenca J, Siirtola H, Reis K, Elnahas AG, Sun B, Foley CN, Aalto-Setälä K, Alasoo K, Arvas M, Auro K, Biswas S, Bizaki-Vallaskangas A, Carpen O, Chen CY, Dada OA, Ding Z, Ehm MG, Eklund K, Färkkilä M, Finucane H, Ganna A, Ghazal A, Graham RR, Green EM, Hakanen A, Hautalahti M, Hedman ÅK, Hiltunen M, Hinttala R, Hovatta I, Hu X, Huertas-Vazquez A, Huilaja L, Hunkapiller J, Jacob H, Jensen JN, Joensuu H, John S, Julkunen V, Jung M, Junttila J, Kaarniranta K, Kähönen M, Kajanne R, Kallio L, Kälviäinen R, Kaprio J; FinnGen, Kerimov N, Kettunen J, Kilpeläinen E, Kilpi T, Klinger K, Kosma VM, Kuopio T, Kurra V, Laisk T, Laukkanen J, Lawless N, Liu A, Longerich S, Mägi R, Mäkelä J, Mäkitie A, Malarstig A, Mannermaa A, Maranville J, Matakidou A, Meretoja T, Mozaffari SV, Niemi MEK, Niemi M, Niiranen T, O Donnell CJ, Obeidat ME, Okafo G, Ollila HM, Palomäki A, Palotie T, Partanen J, Paul DS, Pelkonen M, Pendergrass RK, Petrovski S, Pitkäranta A, Platt A, Pulford D, Punkka E, Pussinen P, Raghavan N, Rahimov F, Rajpal D, Renaud NA, Riley-Gillis B, Rodosthenous R, Saarentaus E, Salminen A, Salminen E, Salomaa V, Schleutker J, Serpi R, Shen HY, Siegel R, Silander K, Siltanen S, Soini S, Soininen H, Sul JH, Tachmazidou I, Tasanen K, Tienari P, Toppila-Salmi S, Tukiainen T, Tuomi T, Turunen JA, Ulirsch JC, Vaura F, Virolainen P, Waring J, Waterworth D, Yang R, Nelis M, Reigo A, Metspalu A, Milani L, Esko T, Fox C, Havulinna AS, Perola M, Ripatti S, Jalanko A, Laitinen T, Mäkelä TP, Plenge R, McCarthy M, Runz H, Daly MJ, Palotie A. FinnGen provides genetic insights from a well-phenotyped isolated population. *Nature* 2023; **613**: 508-518 [PMID: 36653562 DOI: 10.1038/s41586-022-05473-8]
26 **Hartwig FP**, Davies NM, Hemani G, Davey Smith G. Two-sample Mendelian randomization: avoiding the downsides of a powerful, widely applicable but potentially fallible technique. *Int J Epidemiol* 2016; **45**: 1717-1726 [PMID: 28338968 DOI: 10.1093/ije/dyx028]

27 **Ou YN**, Yang YX, Shen XN, Ma YH, Chen SD, Dong Q, Tan L, Yu JT. Genetically determined blood pressure, antihypertensive medications, and risk of Alzheimer's disease: a Mendelian randomization study. *Alzheimers Res Ther* 2021; **13**: 41 [PMID: 33563324 DOI: 10.1186/s13195-021-00782-y]

28 **Verbanck M**, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet* 2018; **50**: 693-698 [PMID: 29686387 DOI: 10.1038/s41588-018-0099-7]

29 **Burgess S**, Thompson SG. Interpreting findings from Mendelian randomization using the MR-Egger method. *Eur J Epidemiol* 2017; **32**: 377-389 [PMID: 28527048 DOI: 10.1007/s10654-017-0255-x]

30 **Greco M FD**, Minelli C, Sheehan NA, Thompson JR. Detecting pleiotropy in Mendelian randomisation studies with summary data and a continuous outcome. *Stat Med* 2015; **34**: 2926-2940 [PMID: 25950993 DOI: 10.1002/sim.6522]

31 **Zhou S**, Zhu G, Xu Y, Gao R, Zhang M, Zeng Q, Su W, Wang R. Mendelian randomization study on the causal effect of chickenpox on dementia. *J Med Virol* 2023; **95**: e28420 [PMID: 36546403 DOI: 10.1002/jmv.28420]

32 **Burgess S**, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. *Genet Epidemiol* 2013; **37**: 658-665 [PMID: 24114802 DOI: 10.1002/gepi.21758]

33 **Bowden J**, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol* 2015; **44**: 512-525 [PMID: 26050253 DOI: 10.1093/ije/dyv080]

34 **Hemani G**, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, Laurin C, Burgess S, Bowden J, Langdon R, Tan VY, Yarmolinsky J, Shihab HA, Timpson NJ, Evans DM, Relton C, Martin RM, Davey Smith G, Gaunt TR, Haycock PC. The MR-Base platform supports systematic causal inference across the human phenome. *Elife* 2018; **7** [PMID: 29846171 DOI: 10.7554/eLife.34408]

35 **Kim JS**, Chen MH, Wang HE, Lu CL, Wang YP, Zhang B. Inflammatory Bowel Disease and Neurodegenerative Diseases. *Gut Liver* 2023; **17**: 495-504 [PMID: 36843420 DOI: 10.5009/gnl220523]

36 **Wang D**, Zhang X, Du H. Inflammatory bowel disease: A potential pathogenic factor of Alzheimer's disease. *Prog Neuropsychopharmacol Biol Psychiatry* 2022; **119**: 110610 [PMID: 35908596 DOI: 10.1016/j.pnpbp.2022.110610]

37 **Zingel R**, Bohlken J, Kostev K. Association Between Inflammatory Bowel Disease and Dementia: A Retrospective Cohort Study. *J Alzheimers Di***80**: 1471-1478 [PMID: 33720902 DOI: 10.3233/JAD-210103]

38 **Liu M**, Li D, Hong X, Sun Z. Increased Risk for Dementia in Patients With Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis of Population-Based Studies. *Front Neurol* 2022; **13**: 813266 [PMID: 35645979 DOI: 10.3389/fneur.2022.813266]

39 **Zhang MN**, Shi YD, Jiang HY. The risk of dementia in patients with inflammatory bowel disease: a systematic review and meta-analysis. *Int J Colorectal Dis* 2022; **37**: 769-775 [PMID: 35325272 DOI: 10.1007/s00384-022-04131-9]

40 **Zuin M**, De Giorgio R, Capatti E, Boschetti E, Zuliani G. Inflammatory bowel disease as a new risk factor for dementia. *Aging Clin Exp Res* 2022; **34**: 1725-1728 [PMID: 35075587 DOI: 10.1007/s40520-022-02076-1]

41 **Zhou M**, Xu R, Kaelber DC, Gurney ME. Tumor Necrosis Factor (TNF) blocking agents are associated with lower risk for Alzheimer's disease in patients with rheumatoid arthritis and psoriasis. *PLoS One* 2020; **15**: e0229819 [PMID: 32203525 DOI: 10.1371/journal.pone.0229819]

42 **Cooper J**, Pastorello Y, Slevin M. A meta-analysis investigating the relationship between inflammation in autoimmune disease, elevated CRP, and the risk of dementia. *Front Immunol* 2023; **14**: 1087571 [PMID: 36776896 DOI: 10.3389/fimmu.2023.1087571]

43 **Xing Y**, Li P, Jia Y, Zhang K, Liu M, Jiang J. Association of inflammatory bowel disease and related medication exposure with risk of Alzheimer's disease: An updated meta-analysis. *Front Aging Neurosci* 2022; **14**: 1082575 [PMID: 36711203 DOI: 10.3389/fnagi.2022.1082575]

44 **Kaneko R**, Matsui A, Watanabe M, Harada Y, Kanamori M, Awata N, Kawazoe M, Takao T, Kobayashi Y, Kikutake C, Suyama M, Saito T, Saido TC, Ito M. Increased neutrophils in inflammatory bowel disease accelerate the accumulation of amyloid plaques in the mouse model of Alzheimer's disease. *Inflamm Regen* 2023; **43**: 20 [PMID: 36922861 DOI: 10.1186/s41232-023-00257-7]

45 **He XF**, Li LL, Xian WB, Li MY, Zhang LY, Xu JH, Pei Z, Zheng HQ, Hu XQ. Chronic colitis exacerbates NLRP3-dependent neuroinflammation and cognitive impairment in middle-aged brain. *J Neuroinflammation* 2021; **18**: 153 [PMID: 34229722 DOI: 10.1186/s12974-021-02199-8]

46 **Liu N**, Wang Y, He L, Sun J, Wang X, Li H. Inflammatory bowel disease and risk of dementia: An updated meta-analysis. *Front Aging Neurosci* 2022; **14**: 962681 [PMID: 36275009 DOI: 10.3389/fnagi.2022.962681]

47 **Huang J**, Su B, Karhunen V, Gill D, Zuber V, Ahola-Olli A, Palaniswamy S, Auvinen J, Herzig KH, Keinänen-Kiukaanniemi S, Salmi M, Jalkanen S, Lehtimäki T, Salomaa V, Raitakari OT, Matthews PM, Elliott P, Tsilidis KK, Jarvelin MR, Tzoulaki I, Dehghan A. Inflammatory Diseases, Inflammatory Biomarkers, and Alzheimer Disease: An Observational Analysis and Mendelian Randomization. *Neurology* 2023; **100**: e568-e581 [PMID: 36384659 DOI: 10.1212/WNL.0000000000201489]

48 **Saji N**, Niida S, Murotani K, Hisada T, Tsuduki T, Sugimoto T, Kimura A, Toba K, Sakurai T. Analysis of the relationship between the gut microbiome and dementia: a cross-sectional study conducted in Japan. *Sci Rep* 2019; **9**: 1008 [PMID: 30700769 DOI: 10.1038/s41598-018-38218-7]

49 **Chauhan N**, Tay ACY, Marshall BJ, Jain U. Helicobacter pylori VacA, a distinct toxin exerts diverse functionalities in numerous cells: An overview. *Helicobacter* 2019; **24**: e12544 [PMID: 30324717 DOI: 10.1111/hel.12544]

50 **Gorospe EC**, Dave JK. The risk of dementia with increased body mass index. *Age Ageing* 2007; **36**: 23-29 [PMID: 17124253 DOI: 10.1093/ageing/afl123]

51 **Papazoglou A**, Arshaad MI, Henseler C, Daubner J, Broich K, Haenisch B, Weiergräber M. The Janus-like Association between Proton Pump Inhibitors and Dementia. *Curr Alzheimer Res* 2021; **18**: 453-469 [PMID: 34587884 DOI: 10.2174/1567205018666210929144740]

52 **Watad A**, McGonagle D, Anis S, Carmeli R, Cohen AD, Tsur AM, Ben-Shabat N, Luigi Bragazzi N, Lidar M, Amital H. TNF inhibitors have a protective role in the risk of dementia in patients with ankylosing spondylitis: Results from a nationwide study. *Pharmacol Res* 2022; **182**: 106325 [PMID: 35752359 DOI: 10.1016/j.phrs.2022.106325]

53 **Dong L**, Shen Y, Li H, Zhang R, Yu S, Wu Q. Shared Genes of PPARG and NOS2 in Alzheimer's Disease and Ulcerative Colitis Drive Macrophages and Microglia Polarization: Evidence from Bioinformatics Analysis and Following Validation. *Int J Mol Sci* 2023; **24** [PMID: 36982725 DOI: 10.3390/ijms24065651]

54 **Adewuyi EO**, O'Brien EK, Nyholt DR, Porter T, Laws SM. A large-scale genome-wide cross-trait analysis reveals shared genetic architecture between Alzheimer's disease and gastrointestinal tract disorders. *Commun Biol* 2022; **5**: 691 [PMID: 35851147 DOI: 10.1038/s42003-022-03607-2]

55 **Adewuyi EO**, O'Brien EK, Porter T, Laws SM. Relationship of Cognition and Alzheimer's Disease with Gastrointestinal Tract Disorders: A Large-Scale Genetic Overlap and Mendelian Randomisation Analysis. *Int J Mol Sci* 2022; **23** [PMID: 36555837 DOI: 10.3390/ijms232416199]

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ORIGINAL ARTICLE

Retrospective Cohort Study

Effects of ulinastatin combined with dexmedetomidine on cognitive dysfunction and emergence agitation in elderly patients who underwent total hip arthroplasty

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Abstract

BACKGROUND

With the continuous growth of the modern elderly population, the risk of fracture increases. Hip fracture is a common type of fracture in older people. Total hip arthroplasty (THA) has significant advantages in relieving chronic pain and promoting the recovery of hip joint function.

AIM

To investigate the effect of ulinastatin combined with dexmedetomidine (Dex) on the incidences of postoperative cognitive dysfunction (POCD) and emergence agitation in elderly patients who underwent THA.

METHODS

A total of 397 patients who underwent THA from February 2019 to August 2022. We conducted a three-year retrospective cohort study in Shaanxi Provincial People's Hospital. Comprehensive demographic data were obtained from the electronic medical record system. We collected preoperative, intraoperative, and postoperative data. One hundred twenty-nine patients who were administered Dex during the operation were included in the Dex group. One hundred fifty patients who were intravenously injected with ulinastatin 15 min before anesthesia induction were included in the ulinastatin group. One hundred eighteen patients who were administered ulinastatin combined with Dex during the operation were included in the Dex + ulinastatin group. The patients' perioperative conditions, hemodynamic indexes, postoperative Mini-Mental State Examination (MMSE) scores, Ramsay score, incidence of POCD, and serum inflammatory cytokines were evaluated.

RESULTS

There was a significant difference in the 24 h visual analogue scale score among

the three groups, and the score in the Dex + ulinastatin group was the lowest ($P < 0.05$). Compared with the Dex and ulinastatin group, the MMSE scores of the Dex + ulinastatin group were significantly increased at 1 and 7 d after the operation (all $P < 0.05$). Compared with those in the Dex and ulinastatin groups, incidence of POCD, levels of serum inflammatory cytokines in the Dex + ulinastatin group were significantly decreased at 1 and 7 d after the operation (all $P < 0.05$). The observer's assessment of the alertness/sedation score and Ramsay score of the Dex + ulinastatin group were significantly different from those of the Dex and ulinastatin groups on the first day after the operation (all $P < 0.05$).

CONCLUSION

Ulinastatin combined with Dex can prevent the occurrence of POCD and emergence agitation in elderly patients undergoing THA.

Key Words: Ulinastatin; Dexmedetomidine; Postoperative cognitive dysfunction; Inflammatory cytokines; Total hip arthroplasty

Core Tip: In this study, we found a significant difference in the score of 24 h visual analogue scale among the three groups, and the score in the dexmedetomidine (Dex)+ ulinastatin group was the lowest. Compared with the Dex and ulinastatin group, the Mini-Mental State Examination scores of the Dex + ulinastatin group were significantly increased at 1 and 7 d after the operation. Compared with the Dex and ulinastatin group, the incidence of postoperative cognitive dysfunction (POCD), the levels of serum inflammatory cytokines of the Dex + ulinastatin group were significantly decreased at 1 and 7 d after the operation. The observer's assessment of the alertness/sedation score and Ramsay score of the Dex + ulinastatin group were significantly different from those of the Dex and ulinastatin groups on the first day after the operation. We observed that ulinastatin combined with dexmedetomidine can prevent the occurrence of POCD and the emergence of agitation in elderly patients undergoing total hip arthroplasty.

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INTRODUCTION

Older adults are prone to fall because of their slow response and unstable gait. With the continuous growth of the elderly population, the risk of fracture has increased. Hip fracture is a common type of fracture in older people[1]. Traditional conservative treatment is prone to delay healing and cause muscle atrophy, joint stiffness, and other problems, seriously affecting the quality of life of elderly patients[2]. With the improvement of modern surgical technology, an increasing number of elderly patients with fractures choose surgical treatment[3]. Total hip arthroplasty (THA) has significant advantages in relieving chronic pain and promoting the recovery of hip joint function[4]. However, most elderly patients have chronic diseases, and their tolerance to surgery is poor, so they are prone to various complications in the perioperative period, such as postoperative delirium, cognitive dysfunction, and pressure sores[5]. The occurrence of postoperative complications is closely related to the physical stress response, so corresponding intervention measures should be taken perioperatively to reduce postoperative stress reactions and the occurrence of complications in elderly patients.

Dexmedetomidine (Dex) is a specific α2 adrenoceptor agonist that is effective for surgical analgesia and sedation[6]. Dex can effectively relief postoperative pain and reduce the stress reaction in elderly patients undergoing medullary joint replacement[7]. Emerging evidence suggests that intraoperative application of Dex can reduce the risk of postoperative delirium and cognitive dysfunction[8]. Remarkably, it has been shown recently that Dex can protect the nervous system by reducing surgical stress and inflammatory responses[9]. Ulinastatin is a trypsin inhibitor that can effectively inhibit the decomposition of many enzymes and the release of inflammatory factors[10]. As reported previously, ulinastatin reduced neuronal apoptosis by inhibiting inflammatory factors such as interleukin (IL)-6 and C-reactive protein (CRP), thus relieving postoperative cognitive impairment and reducing the incidence of postoperative cognitive dysfunction (POCD)[11]. However, it is unclear whether the combination of ulinastatin and Dex can further reduce the incidence of POCD in elderly patients undergoing THA. Therefore, the aim of the current study is to evaluate the effect of ulinastatin combined with Dex on the incidences of POCD and emergence agitation. We also investigated the observer's assessment of alertness/sedation (OAA/S) scale scores of the elderly patients undergoing THA.

MATERIALS AND METHODS

Study design and patients

We conducted a three-year (February 2019 to August 2022) retrospective cohort study in Shaanxi Provincial People's Hospital. Comprehensive demographic data were obtained from the electronic medical record system. The Ethics Committee of the Shaanxi Provincial People's Hospital permitted this study, which was carried out according to the Declaration of Helsinki. We retrospectively reviewed the medical records of patients who underwent unilateral THA.

The inclusion criteria in this retrospective study were as follows: (1) Patients undergoing THA under general anesthesia in our hospital; (2) Patients aged 65 to 80 years old; (3) Patients with an American Society of Anesthesiologists (ASA) class I-III; and (4) Patients with a body mass index (BMI) 18-25kg/m^2. We excluded: (1) Patients with delirium or those diagnosed with dementia, depression, schizophrenia or epilepsy, Parkinson's disease, hypertension, coronary heart disease, diabetes, severe liver and kidney dysfunction, or hearing impairment in the past; and (2) Patients with severe hepatorenal dysfunction, severe malnutrition, blood coagulation disorders, and immune system diseases.

Data collection

Preoperative information of qualified patients, including sex, age, BMI, ASA classification, mental disease, and cognitive damage, was obtained from the medical records. Intraoperative statistics were collected from anesthesia records, including anesthesia and surgery method, operation time, intraoperative data, blood loss volume, urine volume, and Dex and ulinastatin dosage. Record the heart rate (HR) and mean arterial pressure (MAP) of three groups of patients before anesthesia, 10 min of anesthesia, and 60 min of anesthesia. Postoperative data, including visual analogue scale (VAS) scores[12] at 24 h after the operation, Ramsay scores, Mini-Mental State Examination (MMSE) scores, OAA/S scale scores, serum CRP and IL-6, were collected. The Ramsay score is 1-6 points, with 1 point indicating restlessness; 2 points: Clear and able to follow commands; 3 points: Sleepy, able to follow instructions; 4 points: Shallow sleep state, able to awaken; 5 points: Call response is slow; 6 points: Deep sleep state, no response; the higher the score, the better the sedative effect. The MMSE score[13] included 10 points for orientation, 9 points for language and spatial structure, 5 points for attention and calculation, 3 points for recognition memory, and 3 points for memory, for a total of 30 points. Those with a score 2 points lower than those before anesthesia were considered to have cognitive impairment. The VAS score was evaluated by a visual analog scale, with a total score of 10. The higher the score, the more severe the pain. The OAA/S sedation score[14] is divided into five levels: Level 1: The patient is unconscious and does not respond to gentle tapping on the body but responds to noxious stimuli. Level 2: The patient's level of consciousness is vague but consciousness is not wholly lost, and there is no response when the name is called loudly; Level 3: The level of consciousness is vague but consciousness is not wholly lost, and there is a response to tapping the body; Level 4: The patient's level of consciousness is vague, and there is a response when calling the name; Level 5: The patient is conscious and can respond to the questions asked by the nursing staff.

Outcome measures and statistical analysis

By examining the patients' electronic medical records, 576 elderly patients who underwent THA in our hospital from February 2019 to August 2022 were selected. Among them, 129 patients who were administered Dex 0.3 μg/kg/h during the operation were included in the Dex group. One hundred fifty patients who were intravenously injected with 5000 U/kg ulinastatin 15 min before anesthesia were included in the ulinastatin group. During the operation, one hundred eighteen patients who were administered 5000 U/kg ulinastatin (15 min before anesthesia) combined with Dex 0.3 μg/kg/h were included in the Dex + ulinastatin group. Data were evaluated by SPSS 22.0 (IBM Corporation). The categorical data are indicated as *n* (%), and continuous variables are indicated as the mean ± SD. Continuous variables were compared with one-way ANOVA or the Mann-Whitney *U* test. Categorical variables were compared with Fisher's exact test. $P < 0.05$ was considered statistically significant.

RESULTS

Patient inclusion process

The original investigation of our hospital's electronic medical system showed that 576 patients underwent THA from February 2019 to August 2022. Fifty-eight patients who were either under age 65 years or over 80 years were disqualified. After excluding 63 patients complicated with severe chronic physical diseases and 58 patients with incomplete data, 397 patients were eligible for this study. A flowchart describing the selection of patients included in this retrospective study is shown in Figure 1.

Patient characteristics

The Dex cohort (129 cases) consisted of patients who received Dex during the operation. The ulinastatin cohort (150 cases) consisted of patients who received ulinastatin 15 min before anesthesia. In the Dex + ulinastatin group, 118 patients received Dex (during the operation) combined with ulinastatin (15 min before anesthesia). The descriptive statistics between the three cohorts were not statistically significant (all $P > 0.05$, Table 1).

Comparison of perioperative conditions

Table 2 shows no significant difference in operation duration, intraoperative blood loss volume, operation time,

Table 1 Descriptive statistics of the demographics of patients.

	Dex group (*n* = 129)	Ulinastatin group (*n* = 150)	Dex + ulinastatin group (*n* = 118)	*F*/χ^2	*P* value
Sex, *n*				1.240	0.092
Male	62	74	53		
Female	67	76	65		
Age (yr), mean ± SD	71.72 ± 2.45	71.23 ± 4.91	72.25 ± 2.65	1.217	0.301
Weight (kg), mean ± SD	59.12 ± 6.90	61.21 ± 7.13	59.23 ± 6.18	0.680	0.509
BMI, mean ± SD	24.80 ± 4.69	24.72 ± 5.04	24.90 ± 4.82	1.207	0.304
Intraoperative hypotension, *n*	8	7	9	2.447	0.099
Marital status, *n*				0.669	0.095
Single	10	7	6		
Married	119	143	112		
ASA classification (level III)	5	6	4	0.519	0.082

BMI: Body mass index; ASA classification: American Society of Anesthesiologists classification; Dex: Dexmedetomidine.

Table 2 Comparison of perioperative conditions among the three groups

	Dex group (*n* = 129)	Ulinastatin group (*n* = 150)	Dex + ulinastatin group (*n* = 118)	*F* value	*P* value
Intraoperative blood loss (mL)	33.12 ± 3.75	34.27 ± 3.81	32.73 ± 3.85	2.297	0.107
Operation duration (min)	206.45 ± 36.32	201.65 ± 40.03	199.85 ± 40.38	0.690	0.082
Preoperative MMSE score	28.70 ± 0.82	28.84 ± 0.92	28.52 ± 0.84	0.379	0.686
VAS score 24 h after the operation	3.25 ± 0.37	3.30 ± 0.52	3.13 ± 0.25	3.878	0.024
Time of anesthesia (min)	217.18 ± 42.79	220.51 ± 38.94	223.35 ± 41.67	1.550	0.980
Infusion volume (mL)	1558.72 ± 170.56	1489.54 ± 187.46	1580.67 ± 191.88	0.673	0.058
Urine volume (mL)	174.87 ± 42.57	165.38 ± 56.16	168.48 ± 58.16	1.097	0.779

Dex: Dexmedetomidine; MMSE: Mini-Mental State Examination.

preoperative MMSE scores, infusion volume, total blood loss volume, or urine volume among the three groups (all $P > 0.05$). There were significant differences in VAS scores at 24 h after the operation among the three groups, and the score in the Dex + ulinastatin group was the lowest ($P < 0.05$).

Comparison of MMSE scores

Compared with those of the Dex and ulinastatin groups, the MMSE scores of the Dex + ulinastatin group were significantly increased at 1 and 7 d after the operation (all $P < 0.05$, Table 3 and Figure 2A).

Comparison of the incidence of POCD

Compared with that in the Dex and ulinastatin groups, the incidence of POCD in the Dex + ulinastatin group significantly decreased at 1 and 7 d after the operation (all $P < 0.05$, Table 4 and Figure 2B).

Comparison of serum inflammatory cytokines

Compared with those in the Dex and ulinastatin groups, the levels of serum inflammatory cytokines (CRP and IL-6) in the Dex + ulinastatin group were significantly decreased at 1 and 7 d after the operation (all $P < 0.05$, Figure 3).

Comparison of OAA/S sedation score and Ramsay score on the first day after the operation

As shown in Table 5, OAA/S sedation score and Ramsay score of the Dex + ulinastatin group were significantly different from those of the Dex and ulinastatin groups on the first day after the operation (all $P < 0.05$).

Comparison of hemodynamic indexes among the three groups

Compared with those of the Dex and ulinastatin groups, HR and MAP of the Dex + ulinastatin group significantly

Table 3 Comparison of Mini-Mental State Examination scores among the three groups

	Dex group (*n* = 129)	Ulinastatin group (*n* = 150)	Dex + ulinastatin group (*n* = 118)
Preoperative MMSE score	28.70 ± 0.82	28.84 ± 0.92	28.52 ± 0.84
One day after the operation	21.87 ± 6.35[a]	20.72 ± 5.45[b]	23.70 ± 2.46
Seven days after the operation	26.29 ± 2.86[a]	25.16 ± 3.90[b]	27.60 ± 1.76

[a]$P < 0.05$, dexmedetomidine + ulinastatin *vs* dexmedetomidine.
[b]$P < 0.01$, dexmedetomidine + ulinastatin *vs* ulinastatin.
MMSE: Mini-Mental State Examination; Dex: Dexmedetomidine.

Table 4 Comparison of the incidence of postoperative cognitive dysfunction among the three groups

	Dex group (*n* = 129)	Ulinastatin group (*n* = 150)	Dex + ulinastatin group (*n* = 118)
One day after the operation	19 (14.73%)[a]	28 (18.67%)[b]	6 (5.08%)
Seven days after the operation	12 (9.30%)[a]	18 (12.00%)[b]	2 (1.69%)

[a]$P < 0.05$, dexmedetomidine + ulinastatin *vs* dexmedetomidine.
[b]$P < 0.01$, dexmedetomidine + ulinastatin *vs* ulinastatin.
Dex: Dexmedetomidine.

Table 5 Comparison of observer's assessment of the alertness/sedation scores and Ramsay score on the first day after the operation among the three groups

	Dex group (*n* = 129)	Ulinastatin group (*n* = 150)	Dex + ulinastatin group (*n* = 118)	*F* value	*P* value
OAA/S sedation score	3.60 ± 0.61	3.51 ± 0.60	2.21 ± 0.40	9.501	< 0.001
Ramsay score	1.98 ± 0.23	2.02 ± 0.33	3.21 ± 1.02	15.698	< 0.001

Dex: Dexmedetomidine; OAA/S: Observer's assessment of the alertness/sedation.

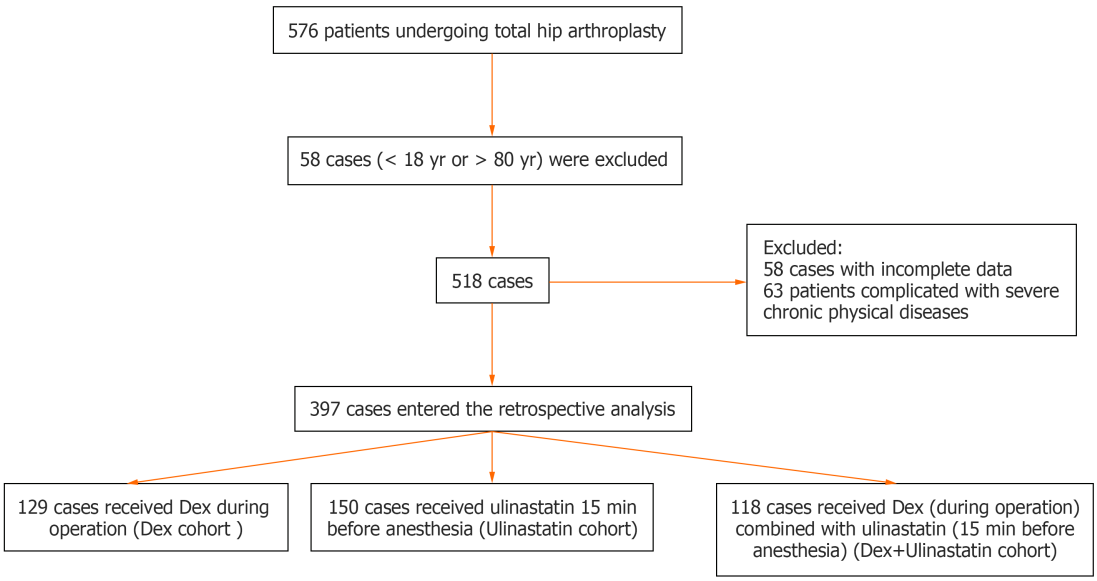

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Figure 1 Flow diagram describing the selection of patients involved in this retrospective study. Dex: Dexmedetomidine.

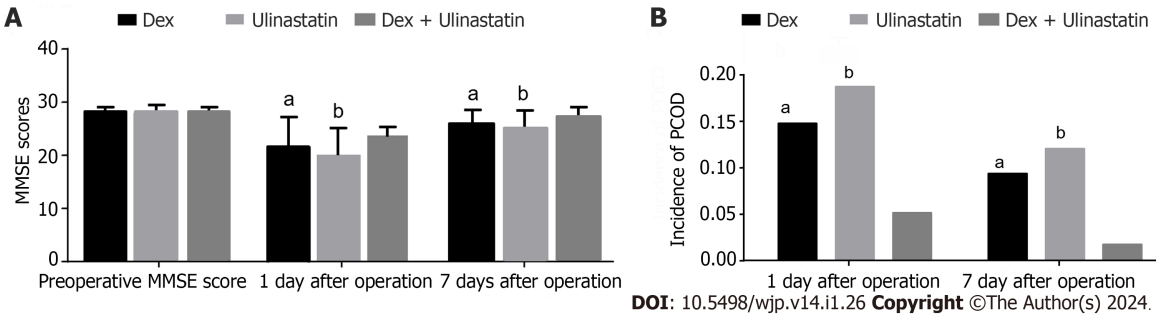

Figure 2 Comparison of Mini-Mental State Examination scores and the incidence of postoperative cognitive dysfunction among the three groups. A: Mini-Mental State Examination scores; B: The incidence of postoperative cognitive dysfunction. [a]*P* < 0.05, dexmedetomidine + ulinastatin *vs* dexmedetomidine. [b]*P* < 0.01, dexmedetomidine + ulinastatin *vs* ulinastatin. MMSE: Mini-Mental State Examination; POCD: Postoperative cognitive dysfunction; Dex: Dexmedetomidine.

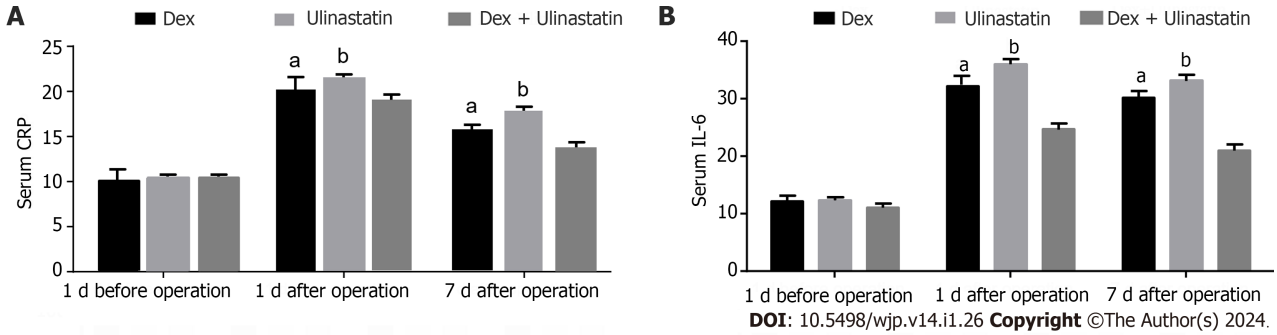

Figure 3 Comparison of serum inflammatory cytokines among the three groups. A: Serum C-reactive protein; B: Serum interleukin-6. [a]*P* < 0.05, dexmedetomidine + ulinastatin *vs* dexmedetomidine. [b]*P* < 0.01, dexmedetomidine + ulinastatin *vs* ulinastatin. Dex: Dexmedetomidine; CRP: C-reactive protein; IL-6: Interleukin-6.

reduced on the 10 minutes of anesthesia and 60 min of anesthesia (all $P < 0.05$, Table 6).

DISCUSSION

THA is a standard approach for the surgical treatment of hip paralysis that mainly involves replacement of the damaged hip joint with an artificial hip[15]. The efficacy and safety of THA have improved in recent years. However, patients still have a particular risk of postoperative complications, mainly due to various stress reactions caused by bleeding intraoperatively, performing the operation, and making the surgical incision[16]. Postoperative pain is a common complication after hip arthroplasty, and pain can cause symptoms such as increased HR and high blood pressure[17]. Effective analgesic measures should be taken to prevent various complications caused by postoperative stress reactions[18].

Dex is an α2 receptor agonist with a high affinity for α2 receptors and is often used in sedation therapy in the intensive care unit and surgery. The drug's half-life is 6 min after intravenous injection, excreted in urine after extensive metabolism, and the clearance half-life is two hours[19]. Because the drug is injected through the kidney, patients with impaired renal function may have more adverse reactions[20]. Therefore, patients with hepatic and renal dysfunction were excluded from this study. Ulinastatin is isolated in and excreted through human urine, and widely used because of its broad spectrum of enzyme inhibition[21]. Previous studies have shown that ulinastatin can inhibit the organic inflammatory response and improve learning and memory dysfunction by reducing the apoptosis of nerve cells, which is beneficial in reducing the incidence of postoperative cognitive impairment in elderly patients[22]. Combining two drugs with the same effect has a synergistic effect. However, the effect of the combination of Dex and ulinastatin on elderly patients undergoing THA remains unknown. Therefore, this retrospective cohort study investigated the effect of Dex combined with ulinastatin on the incidences of POCD and emergence agitation in elderly patients who underwent THA.

As reported previously, ulinastatin has an excellent anti-inflammatory response, reduces the level of inflammatory mediators, relieves postoperative pain, and reduces the postoperative stress response. The clearance rate of the drug in elderly patients is slower than that in young patients, and because the kidney does not metabolize the drug, it can be used even if it the patient has impaired renal function[23]. In this study, we observed that the combination of ulinastatin and Dex could effectively reduce the stress response and improve the quality of life of patients after the operation. The VAS scores of the Dex + ulinastatin group were lower than those of the ulinastatin or Dex group at 24 h after the operation, indicating that the analgesic scheme of ulinastatin combined with Dex could effectively relieve postoperative pain

Table 6 Comparison of hemodynamic indexes among the three groups

Item		Dex group (*n* = 129)	Ulinastatin group (*n* = 150)	Dex + ulinastatin group (*n* = 118)	*F* value	*P* value
HR (times/min)	T0	78.02 ± 3.28	78.66 ± 3.49	78.51 ± 3.64	1.140	0.323
	T1	84.32 ± 5.47	85.74 ± 5.48	81.07 ± 5.55	7.084	0.001
	T2	85.16 ± 5.39	86.63 ± 5.73	80.39 ± 5.85	18.882	< 0.001
MAP (mmHg)	T0	91.72 ± 8.74	92.04 ± 8.38	91.69 ± 8.77	0.033	0.965
	T1	96.31 ± 7.05	97.72 ± 7.37	92.11 ± 6.38	7.417	0.001
	T2	95.87 ± 7.85	96.48 ± 7.69	91.05 ± 7.94	8.289	< 0.001

Dex: Dexmedetomidine; HR: Heart rate; MAP: Mean arterial pressure; T0: Before anesthesia; T1: 10 min of anesthesia; T2: 60 min of anesthesia.

symptoms in elderly patients who underwent total joint replacement. The Ramsay score and OAA/S sedation score mainly reflects the sedation of patients after the operation[24]. In this study, OAA/S sedation score and Ramsay score of the Dex + ulinastatin group were significantly different from those of the Dex and ulinastatin groups on the first day after the operation, meanwhile, compared with those of the Dex and ulinastatin groups, HR and MAP of the Dex + ulinastatin group significantly reduced on the 10 min of anesthesia and 60 min of anesthesia, indicating that preemptive analgesia with ulinastatin combined with Dex could effectively reduce the postoperative stress response and improve the sedation effect.

Previous studies have shown that systemic inflammatory response syndrome caused by surgical trauma, postoperative pain, body stress, and the release of different types of cytokines play an essential role in the development of perioperative neurocognitive impairment[25]. The body's immune system can be activated by surgical trauma, leading to a robust inflammatory response[26]. Therefore, the levels of inflammatory factors in surgical patients' central nervous system and peripheral tissues increase. At the same time, surgery can lead to enhanced production of proinflammatory cytokines, such as plasma IL-6 and IL-1β, and the degree of increase is related to the decline in cognitive function[27]. Changes in cerebral oxygenation during THA may cause different degrees of nerve injury and induce POCD[28]. Therefore, how to reduce the incidence of POCD in elderly patients undergoing THA and improve their quality of life in their later years is particularly important. Our results found that compared with those of the Dex and ulinastatin groups, the MMSE scores of the Dex + ulinastatin group were significantly increased at 1 and 7 d after the operation, suggesting that preinjection of Dex and ulinastatin might play a significant role in preventing POCD and that the combined infusion is more helpful in preventing the occurrence of early POCD. A prophylactic combination of Dex and ulinastatin during knee arthroplasty in older adults is beneficial in reducing the incidence of POCD. The possible mechanism is that Dex inhibits excessive stress responses, such as inhibiting the concentration of plasma cortisol and reducing the damage of catecholamines to brain nerves. At the same time, ulinastatin protects the brain by inhibiting the release of proinflammatory cytokines (IL-6 and CRP).

This study also has some limitations. At present, multiscale combined evaluation is recommended for the diagnosis of POCD. This study used the MMSE scale to evaluate cognitive function, and some postoperative patients with cognitive impairment may not have been identified. Therefore, whether there are other mechanisms by which Dex combined with ulinastatin reduces the incidence of POCD in elderly patients undergoing THA should be further studied.

CONCLUSION

In summary, ulinastatin combined with Dex can reduce the incidence of POCD in elderly patients undergoing THA, and the mechanism may be related to the reduction in plasma levels of CRP and IL-6. In addition, we also observed that applying ulinastatin combined with Dex can reduce postoperative pain and improve the postoperative stress response in elderly patients undergoing THA.

ARTICLE HIGHLIGHTS

Research background

Most elderly patients are prone to various complications in the perioperative period, such as postoperative delirium and cognitive dysfunction. Cognitive dysfunction seriously affects the postoperative rehabilitation of patients, prolongs hospital stay, increases the incidence of postoperative complications and mortality, in addition to a serious decline in personal quality of life, but also increases the burden of the family and society. Many researchers believe that advanced age and "major surgery" are important risk factors for cognitive dysfunction in patients undergoing non-cardiac surgery. Therefore, cognitive dysfunction is an important issue in the medical field at present, and the study of the occurrence factors, pathogenesis, effective prevention, and treatment of cognitive dysfunction is an important topic in the field of

anesthesiology.

Research motivation

It is unclear whether the combination of ulinastatin and dexmedetomidine (Dex) can further reduce the incidence of postoperative cognitive dysfunction (POCD) in elderly patients undergoing total hip arthroplasty (THA). Therefore, the current study aims to evaluate the effect of ulinastatin combined with Dex on POCD and emergence agitation. Therefore, solving these problems could effectively improve the postoperative stress response and improve the sedation effect for elderly patients undergoing THA. This is the first study to explore the effect of ulinastatin combined with Dex on POCD and emergence agitation in elderly patients undergoing THA.

Research objectives

In view of the high incidence of POCD in elderly orthopedic patients, this study will compare the effects of different anesthetic methods on the early cognitive function of elderly patients after THA, and explore the related factors, to provide some guidance for the anesthetic mode and anesthetic management of clinical orthopedic surgery in the future. The purpose of this study is to provide clinical basis for the selection of anesthesia in elderly patients undergoing hip arthroplasty.

Research methods

In this study, we collected the postoperative data, including visual analogue scale (VAS) scores at 24 h after operation, postoperative stress response indicators [Mini-Mental State Examination (MMSE) scores, hemodynamic indexes, observer's assessment of alertness/sedation (OAA/S) scale and Ramsay score], inflammatory cytokines [C-reactive protein (CRP) and interleukin (IL)-6]. A total of 129 patients administrated with Dex 0.3 μg/kg/h during the operation were included in the Dex group. One hundred fifty patients who were intravenously injected 5000 U/kg of ulinastatin 15 min before anesthesia were included in the ulinastatin group. One hundred eighteen patients who were administrated with 5000 U/kg of ulinastatin (15 min before anesthesia) combined with Dex 0.3 μg/kg/h during the operation were included in the Dex + ulinastatin group.

Research results

The findings of this study demonstrated that ulinastatin combined with Dex could reduce the incidence of POCD in elderly patients undergoing THA, and the mechanism might be associated with the lessening of plasma levels of CRP and IL-6. Moreover, the combination of ulinastatin and Dex can reduce postoperative pain and postoperative stress response in elderly patients undergoing THA. Our results validated that the combination therapy can effectively improve the cognitive function of nervous system after operation and improved the quality of life for patients.

Research conclusions

This is the first study explored the efficacy of ulinastatin combined with Dex on POCD and emergence agitation in elderly patients undergoing THA. We collected the postoperative data, including VAS scores at 24 h after operation, postoperative stress response indicators (MMSE scores, hemodynamic indexes, OAA/S scale, CRP, and IL-6). The results of this study not only demonstrate that combination therapy can reduce postoperative cognitive impairment, but also find that the mechanism may be related to the reduction of plasma levels of CRP and IL-6.

Research perspectives

In future research, we will focus on the specific mechanisms related to the combined therapy through *in vitro* and *in vivo* experiments.

FOOTNOTES

Author contributions: Huo QF and Guo JW initiated the project and designed the experiment; Zhu LJ and Jiang YN conducted clinical data collection; Huo QF and Zhu LJ performed postoperative follow-up and recorded data; Guo JW, Jiang YN, and Zhao J conducted a number of collation and statistical analysis; Zhao J wrote the original manuscript and revised the paper; and all authors reviewed and approved the paper, and approved the final manuscript.

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REFERENCES

1 **Meinberg E**, Ward D, Herring M, Miclau T. Hospital-based Hip fracture programs: Clinical need and effectiveness. *Injury* 2020; **51** Suppl 2: S2-S4 [PMID: 32386840 DOI: 10.1016/j.injury.2020.03.046]
2 **Pech-Ciau BA**, Lima-Martínez EA, Espinosa-Cruz GA, Pacho-Aguilar CR, Huchim-Lara O, Alejos-Gómez RA. [Hip fracture in the elderly: epidemiology and costs of care]. *Acta Ortop Mex* 2021; **35**: 341-347 [PMID: 35139593]
3 **Alexiou KI**, Roushias A, Varitimidis SE, Malizos KN. Quality of life and psychological consequences in elderly patients after a hip fracture: a review. *Clin Interv Aging* 2018; **13**: 143-150 [PMID: 29416322 DOI: 10.2147/CIA.S150067]
4 **Scott CEH**, Clement ND, Davis ET, Haddad FS. Modern total hip arthroplasty: peak of perfection or room for improvement? *Bone Joint J* 2022; **104-B**: 189-192 [PMID: 35094584 DOI: 10.1302/0301-620X.104B2.BJJ-2022-0007]
5 **Stibolt RD Jr**, Patel HA, Huntley SR, Lehtonen EJ, Shah AB, Naranje SM. Total hip arthroplasty for posttraumatic osteoarthritis following acetabular fracture: A systematic review of characteristics, outcomes, and complications. *Chin J Traumatol* 2018; **21**: 176-181 [PMID: 29773451 DOI: 10.1016/j.cjtee.2018.02.004]
6 **Wen G**, Xin N. Dexmetomidine promotes the activity of breast cancer cells through miR-199a/HIF-1α axis. *Transl Cancer Res* 2021; **10**: 4817-4828 [PMID: 35116334 DOI: 10.21037/tcr-21-1937]
7 **Li X**, Li X, Wang R, Hua T, Li G. Application of dexmetomidine in gynecological laparoscopic surgery and its effect on S-100 β protein and cognitive function in patients. *Minerva Med* 2022; **113**: 599-601 [PMID: 34586767 DOI: 10.23736/S0026-4806.21.07723-5]
8 **Deiner S**, Luo X, Lin HM, Sessler DI, Saager L, Sieber FE, Lee HB, Sano M; and the Dexlirium Writing Group, Jankowski C, Bergese SD, Candiotti K, Flaherty JH, Arora H, Shander A, Rock P. Intraoperative Infusion of Dexmedetomidine for Prevention of Postoperative Delirium and Cognitive Dysfunction in Elderly Patients Undergoing Major Elective Noncardiac Surgery: A Randomized Clinical Trial. *JAMA Surg* 2017; **152**: e171505 [PMID: 28593326 DOI: 10.1001/jamasurg.2017.1505]
9 **Muñoz-Leyva F**, Jack JM, Bhatia A, Chin KJ, Gandhi R, Perlas A, Jin R, Chan V. No Benefits of Adding Dexmedetomidine, Ketamine, Dexamethasone, and Nerve Blocks to an Established Multimodal Analgesic Regimen after Total Knee Arthroplasty. *Anesthesiology* 2022; **137**: 459-470 [PMID: 35867857 DOI: 10.1097/ALN.0000000000004326]
10 **Lv B**, Jiang XM, Wang DW, Chen J, Han DF, Liu XL. Protective Effects and Mechanisms of Action of Ulinastatin against Cerebral Ischemia-Reperfusion Injury. *Curr Pharm Des* 2020; **26**: 3332-3340 [PMID: 32124689 DOI: 10.2174/1381612826666200303114955]
11 **Zhang YH**, Guo XH, Zhang QM, Yan GT, Wang TL. Serum CRP and urinary trypsin inhibitor implicate postoperative cognitive dysfunction especially in elderly patients. *Int J Neurosci* 2015; **125**: 501-506 [PMID: 25105909 DOI: 10.3109/00207454.2014.949341]
12 **Han Y**, Wang M, Shen J, Zhang Z, Zhao M, Huang J, Chen Y, Chen Z, Hu Y, Wang Y. Differential efficacy of methylcobalamin and alpha-lipoic acid treatment on symptoms of diabetic peripheral neuropathy. *Minerva Endocrinol* 2018; **43**: 11-18 [PMID: 27901334 DOI: 10.23736/S0391-1977.16.02505-0]
13 **Lauretani F**, Ticinesi A, Gionti L, Prati B, Nouvenne A, Tana C, Meschi T, Maggio M. Short-Physical Performance Battery (SPPB) score is associated with falls in older outpatients. *Aging Clin Exp Res* 2019; **31**: 1435-1442 [PMID: 30515724 DOI: 10.1007/s40520-018-1082-y]
14 **Lim TW**, Choi YH, Kim JY, Choi JB, Lee SK, Youn EJ, Lee JS. Efficacy of the bispectral index and Observer's Assessment of Alertness/Sedation Scale in monitoring sedation during spinal anesthesia: A randomized clinical trial. *J Int Med Res* 2020; **48**: 300060519893165 [PMID: 31875756 DOI: 10.1177/0300060519893165]
15 **Flevas DA**, Tsantes AG, Mavrogenis AF. Direct Anterior Approach Total Hip Arthroplasty Revisited. *JBJS Rev* 2020; **8**: e0144 [PMID: 32304500 DOI: 10.2106/JBJS.RVW.19.00144]
16 **Moerenhout K**, Derome P, Laflamme GY, Leduc S, Gaspard HS, Benoit B. Direct anterior versus posterior approach for total hip arthroplasty: a multicentre, prospective, randomized clinical trial. *Can J Surg* 2020; **63**: E412-E417 [PMID: 33009898 DOI: 10.1503/cjs.012019]
17 **Goh GS**, Parvizi J. Nerve Injuries Following Total Hip Arthroplasty: The Influence of Surgical Approach. *Orthop Clin North Am* 2022; **53**: 129-137 [PMID: 35365257 DOI: 10.1016/j.ocl.2021.12.002]
18 **Urish KL**, Giori NJ, Lemons JE, Mihalko WM, Hallab N. Trunnion Corrosion in Total Hip Arthroplasty-Basic Concepts. *Orthop Clin North Am* 2019; **50**: 281-288 [PMID: 31084829 DOI: 10.1016/j.ocl.2019.02.001]
19 **Persson NDÅ**, Uusalo P, Nedergaard M, Lohela TJ, Lilius TO. Could dexmedetomidine be repurposed as a glymphatic enhancer? *Trends Pharmacol Sci* 2022; **43**: 1030-1040 [PMID: 36280451 DOI: 10.1016/j.tips.2022.09.007]
20 **Eizaga Rebollar R**, García Palacios MV, Fernández Riobó MC, Torres Morera LM. Dexmedetomidine and perioperative analgesia in children. *Rev Esp Anestesiol Reanim (Engl Ed)* 2022; **69**: 487-492 [PMID: 36100555 DOI: 10.1016/j.redare.2022.08.003]
21 **Wei X**, Zhu X, Jiang L, Long M, Du Y. Recent research progress on the role of ulinastatin in chronic kidney disease. *Nephrology (Carlton)* 2021; **26**: 708-714 [PMID: 34050574 DOI: 10.1111/nep.13906]
22 **Chen L**, Jin S, Yang M, Gui C, Yuan Y, Dong G, Zeng W, Zeng J, Hu G, Qiao L, Wang J, Xi Y, Sun J, Wang N, Wang M, Xing L, Yang Y, Teng Y, Hou J, Bi Q, Cai H, Zhang G, Hong Y, Zhang Z. Integrated Single Cell and Bulk RNA-Seq Analysis Revealed Immunomodulatory Effects of Ulinastatin in Sepsis: A Multicenter Cohort Study. *Front Immunol* 2022; **13**: 882774 [PMID: 35634310 DOI:

10.3389/fimmu.2022.882774]

23 **Hong Y**, Meng S, Wang S, Liu T, Liu J. Ulinastatin Alleviates Repetitive Ketamine Exposure-Evoked Cognitive Impairment in Adolescent Mice. *Neural Plast* 2022; **2022**: 6168284 [PMID: 36545238 DOI: 10.1155/2022/6168284]

24 **Sieber F**, Neufeld K, Oh ES, Gottschalk A, Wang NY. Effect of baseline cognitive impairment on association between predicted propofol effect site concentration and Bispectral index or sedation score. *BMC Anesthesiol* 2020; **20**: 129 [PMID: 32466776 DOI: 10.1186/s12871-020-01043-5]

25 **Liao YL**, Zhou XY, Ji MH, Qiu LC, Chen XH, Gong CS, Lin Y, Guo YH, Yang JJ. S100A9 Upregulation Contributes to Learning and Memory Impairments by Promoting Microglia M1 Polarization in Sepsis Survivor Mice. *Inflammation* 2021; **44**: 307-320 [PMID: 32918665 DOI: 10.1007/s10753-020-01334-6]

26 **Bortolotti P**, Faure E, Kipnis E. Inflammasomes in Tissue Damages and Immune Disorders After Trauma. *Front Immunol* 2018; **9**: 1900 [PMID: 30166988 DOI: 10.3389/fimmu.2018.01900]

27 **Wang J**, Zhou Y, Li K, Li X, Guo M, Peng M. A Noradrenergic Lesion Attenuates Surgery-Induced Cognitive Impairment in Rats by Suppressing Neuroinflammation. *Front Mol Neurosci* 2021; **14**: 752838 [PMID: 34916906 DOI: 10.3389/fnmol.2021.752838]

28 **Lin R**, Zhang F, Xue Q, Yu B. Accuracy of regional cerebral oxygen saturation in predicting postoperative cognitive dysfunction after total hip arthroplasty: regional cerebral oxygen saturation predicts POCD. *J Arthroplasty* 2013; **28**: 494-497 [PMID: 23151365 DOI: 10.1016/j.arth.2012.06.041]

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ORIGINAL ARTICLE

Retrospective Study

Survey and clinical considerations of gender identity in lower primary school children

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Abstract

BACKGROUND

Gender consciousness directly affects the development of gender identity, which is a continuous and lifelong process. Meanwhile, hospitalization is a part of many children's lives and has an impact on their gender development.

AIM

To investigate the current situation of gender identity in lower primary school children by conducting a survey of 202 hospitalized children in the lower grades and to provide a theoretical basis and foundation for the cultivation of gender identity and medical treatment of children based on the results. This study aims to inspire clinical medical staff to scientifically and reasonably arrange hospital wards for lower primary school children and pay attention to gender protection during the medical treatment process and to help children shape a unified and clear gender identity, which will enable them to better integrate into society and promote their personality development.

METHODS

The gender consciousness scale for elementary and middle school students was

used for the survey.

RESULTS
Gender identity was already present in lower primary school children. The children's gender roles and gender equality consciousness were strong, exceeding the critical value, but their gender characteristics, gender identity, and gender ideal consciousness were weak. Children aged 6 had the weakest gender identity, and girls had significantly stronger gender identity than boys.

CONCLUSION
Gender identity is already present in lower primary school children, providing a basis and inspiration for the cultivation of gender identity and medical treatment of lower primary school children. Clinical medical staff should be aware of and understand these results and should scientifically and reasonably arrange hospital wards for lower primary school children.

Key Words: School-age children; Gender consciousness; Gender identity; Hospitalization; Gender weakening

Core Tip: Investigate the gender consciousness of hospitalized elementary school children and their current development status from a social gender perspective. Enable children to better integrate into society and promote the development of their personality and sound gender consciousness.

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INTRODUCTION

Gender consciousness is one of the important aspects of self-awareness, which refers to the perception and understanding as a member of a certain gender of the group's situation in the social system and structural domain and the identification, evaluation, and inclination to act based on this information[1,2]. Gender consciousness directly affects the development of gender identity, which is a continuous and lifelong process. Researchers believe that biological factors guide and restrict the development of males and females, and social factors also play an important role in the process of individuals' formation of gender roles[3]. Physiological and social factors interact to determine individuals' gender consciousness and role identity[4]. Currently, research on gender consciousness in China mainly focuses on adult women, with less attention given to children and even less to hospitalized children[5]. Hospitalization is a part of many children's lives and has an impact on their gender development. In clinical practice, the random allocation of hospital rooms for children and the lack of privacy curtains during examinations overlook the important influence of individual gender factors on children, although these factors have an undeniable impact on children's identity formation. This study aims to investigate the gender consciousness of hospitalized elementary school children and their current development status from a social gender perspective. Based on this, this study proposes scientific and reasonable recommendations and strategies for hospitalization and provides timely interventions and guidance to help children shape a unified and clear gender orientation. This will enable children to better integrate into society and promote the development of their personality and sound gender consciousness.

Problem statement

Despite enormous changes in social development, the stereotypical understanding of gender that has been ingrained in people's minds still affects and dominates individuals' related cognition and behavior. For example, in home decoration, boys' rooms are often blue or green, while girls' rooms are pink or orange[6]. However, when children are hospitalized, health care workers weaken their gender identity by placing boys and girls in the same ward. This gender-neutral arrangement can weaken a child's consciousness of his or her own gender, create confusion in the child's psychological and gender identity, and lead to a nondifferentiated understanding of the same sex and the opposite sex. Especially in the early years of schooling, children have not yet mastered complex classification skills, and gender-neutral arrangements that weaken gender identity increase their gender-biased thinking, hindering their exploration of all potential and comprehensive development and affecting their physical and mental health. Erikson's theory of personality development considers the influence of biology on individual development and incorporates the impact of culture and society. Erikson suggests that individuals' growth process is influenced by physiological, psychological, and social events, and interaction with the surrounding environment plays a dominant role in personality development[2]. Currently, hospitals do not give sufficient attention to gender consciousness, such as bed arrangements and privacy protection. Although these

phenomena are often overlooked, they create direct or potential obstacles to individuals' personal development, such as patients' personality development and gender identity. Especially for younger children who have not yet mastered complex classification skills, such arrangements weaken their gender identity and increase gender-biased thinking, which has a significant impact on their psychological and behavioral development and hinders their development of a healthy gender identity.

MATERIALS AND METHODS

Objects

This study was approved by the Hospital Ethics Committee. The inclusion criteria were as follows: (1) Age: $6 \leq Y < 10$; and (2) hospitalization for at least 2 d. The exclusion criteria were as follows: (1) Single room admission; (2) patients with mental disorders who could not communicate; (3) patients with unstable vital signs; and (4) patients with significant organ dysfunction. From August to September 2022, a convenience sampling method was used to select eligible children from a pediatric hospital in Zhejiang Province as the study subjects.

Methods

Survey tools: General information survey tool: Based on a literature review, the researcher designed a general information survey form for the children, including gender, age, grade, whether they were only children, family structure, personality, and current home address.

Gender consciousness scale: Referring to the gender consciousness scale for elementary and middle school students in the research conducted by Huang Fengjuan in Taiwan, this scale includes five dimensions: Gender identity, gender ideals, gender traits, gender roles, and gender equality. A total of 36 items are rated on a 5-point Likert scale, with 1 to 5 representing strongly agree, agree, neutral, disagree, and strongly disagree, respectively. The gender identity dimension includes Items 1, 6, 11, 16, 21, 23, and 28; the gender ideals dimension includes items 2, 7, 12, 17, 24, 29, and 33; the gender traits dimension includes items 3, 8, 13, 18, 25, 30, and 34; the gender roles dimension includes items 4, 9, 14, 19, 22, 26, 31, and 35; and the gender equality dimension includes items 5, 10, 15, 20, 27, 32, and 36. The scores of the 36 items are summed and divided by 36 to obtain the overall average score of the participant's gender consciousness, which represents the overall level of gender consciousness. The score of each dimension is calculated by adding the scores of each item in that dimension and dividing.

Data collection methods

Based on the principle of voluntariness, we obtained the consent and cooperation of medical parents and strictly selected research subjects according to the inclusion and exclusion criteria. The researchers explained the purpose, significance, and questionnaire content of the survey to the research subjects in a unified manner. After obtaining consent, the research subjects completed an online electronic questionnaire. After completing the information, the questionnaires were checked one by one on the spot and collected. A total of 202 questionnaires were distributed in this survey and 202 valid questionnaires were collected, with an effective recovery rate of 100%.

Statistical methods

The original data were input into Excel and imported into SPSS 20.0 software for data analysis. The analysis methods included descriptive statistics, independent sample *t* tests, analysis of variance, and multiple comparisons. A significance level of $P < 0.05$ was accepted to denote significance.

RESULTS

General analysis of the children

This study investigated the gender consciousness status of 202 hospitalized children in the early grades of primary school and conducted statistical analysis on the scores of various dimensions of gender consciousness. The specific information of the basic sociodemographic characteristics of the 202 hospitalized children is detailed in Table 1. There were 95 girls and 107 boys. In terms of age, there were 15 children aged 6 years (6.0 years to 6 years and 11 mo), accounting for 7.4% of the total sample; 65 children aged 7 years (7.0 years to 7 years and 11 mo), accounting for 32.2% of the total sample; 100 children aged 8 years (8.0 years to 8 years and 11 mo), accounting for 49.5% of the total sample; and 22 children aged 9 years (9.0 years to 9 years and 11 mo), accounting for 10.9% of the total sample. From the perspective of grade distribution, the number of students in the first to third grades was roughly the same, with the second grade having the most students, accounting for 86.1% of the total number. With regard to whether the participants were only children, non-only children accounted for 56.9%. With regard to the children's family structure, children who were mainly cared for by parents accounted for the majority (57.9%), which is related to the current family structure still being dominated by nuclear families. With regard to the children's personality type, extraverted personality types accounted for the majority (57.4%). With regard to the children's current residential address, 194 children (96%) lived in urban areas, which is related to the location of the study, a first-tier coastal city in the eastern region.

Table 1 Basic demographic and social characteristics of school-aged children in lower grades (mean ± SD), *n* (%)

Social demographic characteristics	Total	Male	Female	F/χ^2	*P* value
Age				0.993	0.803
6 ≤ Y < 7	15 (7.4)	9 (4.5)	6 (3.0)		
7 ≤ Y < 8	65 (32.2)	32 (15.8)	33 (16.3)		
8 ≤ Y < 9	100 (49.5)	53 (26.2)	47 (23.3)		
9 ≤ Y < 10	22 (10.9)	13 (6.4)	9 (4.5)		
Grade				0.830	0.660
First grade	25 (12.4)	15 (7.4)	10 (5.0)		
Second grade	174 (86.1)	90 (44.5)	84 (41.6)		
Third grade	3 (1.5)	2 (1.0)	1 (0.5)		
Only child				0.352	0.553
Yes	87 (43.1)	44 (21.8)	43 (21.3)		
No	115 (56.9)	63 (31.2)	52 (25.7)		
Family structure				0.079	0.962
Nuclear family	182 (90.1)	97 (48.0)	85 (42.0)		
Large family	4 (2.0)	2 (1.0)	2 (1.0)		
Single parent family	16 (7.9)	8 (2.5)	8 (2.5)		
Character				2.917	0.233
Introversion	55 (27.2)	25 (12.4)	30 (14.9)		
Extroversion	116 (57.4)	62 (30.7)	54 (26.7)		
Other	31 (15.3)	20 (9.9)	11 (5.4)		
Current home address				3.820	0.148
City	194 (96.0)	105 (52.0)	89 (44.1)		
Countryside	5 (2.5)	2 (1.0)	3 (1.5)		
Town	3 (1.5)	0 (0.0)	3 (1.5)		

Gender consciousness scores of primary school children in the early grades

As shown in Table 2, the overall average score of gender consciousness of primary school children in the early grades was 2.80, slightly lower than the critical value of 3, indicating that the gender consciousness of primary school children in the early grades was at a medium to low level. The scores for gender roles and gender equality were 3.03 and 3.32, respectively, which were higher than the medium critical value, indicating that the gender role and gender equality consciousness of primary school children in the early grades were relatively strong. The average scores for gender identity, gender ideals, and gender traits were slightly lower than the critical value, indicating that the level of gender consciousness of primary school children in the early grades in these three dimensions was at a medium to low level.

Gender consciousness of primary school children in the early grades of different genders and ages

Table 3 of this study shows the independent-sample t tests on the gender consciousness scores of primary school children in the early grades from a gender perspective. The results show that there were significant differences between male and female children in the five dimensions of gender identity, gender ideals, gender traits, gender roles, and gender equality (t = -4.250, t = -3.207, t = -3.487, t = -2.695, t = -3.120, P < 0.05), indicating that female children had significantly stronger gender consciousness in the five dimensions. This result is consistent with the widely held belief that girls mature earlier than boys[7].

Based on Erikson's theory of personality development, most researchers have focused on adolescents, and there is a lack of systematic research on the expression and education of gender consciousness in children of different ages[8]. The primary school stage is a crucial period for shaping and developing children's gender consciousness and laying the foundation of their personality development[9]. During this period, the shaping and development of children's gender consciousness greatly affect their personality traits as adolescents as well as their self-consciousness of gender-related issues[10]. According to Table 4, there was no significant difference in the overall score of gender consciousness among children in the four age groups (P = 0.066, P > 0.05). However, there were slight differences in the scores on various dimensions. After multiple post hoc comparisons, it was found that the scores of children with leukemia aged 6 (6 ≤ Y <

Table 2 Gender consciousness scores of school-aged children in lower grades

Table of latitudes and total quantities	Number	Minimum value	Maximum value	Mean	SD
Gender identity	202	1.00	4.86	2.71	0.77
Gender ideals	202	1.00	4.00	2.45	0.59
Gender traits	202	1.00	4.43	2.50	0.66
Gender roles	202	1.38	4.63	3.03	0.67
Gender equality	202	1.86	4.71	3.32	0.56
Gender consciousness	202	1.64	4.15	2.80	0.55

Table 3 Gender consciousness scores of school-aged and lower grade children of different genders

Gender	Number of cases	Gender consciousness	Gender identity	Gender ideals	Gender traits	Gender roles	Gender equality
Male	107	2.66 ± 0.61	2.51 ± 0.70	2.32 ± 0.53	2.34 ± 0.62	2.91 ± 0.66	3.20 ± 0.53
Female	95	2.96 ± 0.66	2.95 ± 0.78	2.59 ± 0.62	2.66 ± 0.67	3.16 ± 0.66	3.44 ± 0.56
t		3.357	4.225	3.336	3.525	2.687	3.128
P value		0.000	0.000	0.002	0.001	0.008	0.002
95%CI		0.124-0.476	0.234-0.645	0.110-0.429	0.141-0.499	0.067-0.433	0.089-0.391

Table 4 Gender consciousness scores of school-aged children of different ages

Age	Number of cases	Gender consciousness	Gender identity	Gender ideals	Gender traits	Gender roles	Gender equality
6 ≤ Y < 7	15	2.52 ± 0.54	2.26 ± 0.75	2.23 ± 0.67	2.27 ± 0.57	2.59 ± 0.67	3.27 ± 0.52
7 ≤ Y < 8	65	2.86 ± 0.56	2.81 ± 0.79[a]	2.45 ± 0.62	2.51 ± 0.70	3.10 ± 0.70[a]	3.41 ± 0.58
8 ≤ Y < 9	100	2.84 ± 0.54	2.76 ± 0.75[a]	2.49 ± 0.58	2.56 ± 0.65	3.07 ± 0.66[a]	3.32 ± 0.54
9 ≤ Y < 10	22	2.63 ± 0.48	2.52 ± 0.72	2.38 ± 0.47	2.30 ± 0.65	2.90 ± 0.51	3.06 ± 0.55
F value		2.434	2.753	0.990	1.576	2.839	2.155
P value		0.066	0.044	0.399	0.196	0.039	0.095

[a]*P* < 0.05 *vs* 6 ≤ Y < 7.

7) for gender identity and gender roles were significantly lower than those of children aged 7 and 8 (7 ≤ Y < 8 and 8 ≤ Y < 9). Specifically, in terms of gender identity, the score difference between 6-year-old (6 ≤ Y < 7) and 7-year-old (7 ≤ Y < 8) children was *P* = 0.016, 95%CI: 0.104 to 0.996, while the score difference between 6-year-old (6 ≤ Y < 7) and 8-year-old (8 ≤ Y < 9) children was *P* = 0.012, 95%CI: 0.114 to 0.906. In terms of gender roles, the score difference between 6-year-old (6 ≤ Y < 7) and 7-year-old (7 ≤ Y < 8) children was *P* = 0.012, 95%CI: 0.114 to 0.906, while the score difference between 6-year-old (6 ≤ Y < 7) and 8-year-old (8 ≤ Y < 9) children was *P* = 0.010, 95%CI: *P* = 0.012, 95%CI: 0.114 to 0.906. There was no significant difference in the scores on the five dimensions among children aged 7 to 9, indicating that younger children's understanding of their gender is limited to the physiological level and that overall, their gender consciousness is relatively vague. The overall performance of gender consciousness development shows that the scores of children aged 6 (6 ≤ Y< 7) were significantly lower than the scores of children aged 7 (7 ≤ Y < 8) and 8 (8 ≤ Y < 9).

DISCUSSION

The formation of gender identity undergoes a long process of development and has a long-lasting and profound impact on the individual[11]. Conflict between an individual's biological and social identities can lead to gender dysphoria, causing severe psychological distress and various feelings of confusion that can affect the individual's social functioning and mental health. Therefore, during this period, individuals need to determine the roles they want to assume and unify their self-perception and how they are perceived by others. The formation of gender identity and personal identification in young children in the early grades of primary school has an important impact on their personality development.

Respect the development of the patient's gender identity and provide reasonable hospitalization and medical care

The formation of gender consciousness undergoes a long developmental process and has a lasting impact on individuals. If an individual's physiological identity conflicts with his or her social identity, it can lead to gender confusion and "gender anxiety", causing severe psychological discomfort and various forms of confusion that can affect social function and psychological health. Therefore, during this period, individuals need to determine the roles they want to take on and unify their own and others' perceptions of themselves. The formation of gender identity in the personal identification of young patients in the early school years plays an important role in personality development.

Physiological and social factors interact to determine an individual's gender consciousness and gender identity. Although the overall score of gender consciousness did not differ significantly among the four groups of patients of different ages, the results showed that the gender consciousness of young patients in the early school years was at a lower-medium level. This is determined by the psychological and physiological development characteristics of the patients and is also the result of the combined influence of family and education. Young patients in their early school years have only a basic understanding of their gender identity, which mainly remains at the physiological level. Overall, their gender consciousness is relatively vague, especially for 6-year-old patients. Therefore, medical staff should respect the physiological and psychological development characteristics of young patients in their early school years and formulate specific, reasonable procedures and content that are conducive to gender education and sexual psychological health during hospitalization and medical care to implement gender-specific differences in hospitalization and medical care in a targeted manner[12]. On the one hand, we should respect the development of patients' gender identity and provide appropriate guidance to help young patients in their early school years form a healthy and reasonable gender identity. On the other hand, we should combine the requirements of national diagnosis related groups to promote the rational and efficient use of medical social insurance.

Cultivating health care workers' gender concepts and emphasizing gender guidance for pediatric patients

Hospitals are important places for gender consciousness education and subtle influence. Appropriate and reasonable gender role behavior and gender consciousness demonstrated by health care workers provide pediatric patients with role models to imitate and an environment that influences them. Medical treatment and hospitalization have an incomparable advantage in gender education activities, and conducting scientific gender education activities during hospitalization is beneficial to the cultivation of children's gender roles and lays a good foundation for adolescent sex education. In this study, we found that the consciousness of gender traits in pediatric patients is relatively weak, which provides a challenge and an opportunity for health care workers. On the one hand, based on traditional gender concepts, we should recognize the differences between males and females and cultivate consciousness of gender differences in pediatric patients. On the other hand, we should overcome traditional and stereotypical gender education methods in families, such as favoring boys over girls, which have negative effects on pediatric patients. Health care workers have an obligation to treat pediatric patients differently based on gender when assigning hospital rooms, emphasizing gender role guidance, helping them establish correct gender consciousness, and distinguishing between same-sex and opposite-sex patients. This can help them understand that certain activities are only for the same sex, while others are only for the opposite sex. This can promote the combination and complementarity of gender consciousness education in medical treatment and family education and help pediatric patients establish correct gender concepts for healthy and harmonious development.

Encourage reasonable opposite-sex interactions through gender-based hospitalization and guidance for pediatric patients

This study found that pediatric patients of different ages had a strong sense of gender equality. This is related to the current social and family environment, where there is an increasing trend toward gender equality in both career development and family roles[13]. Gender equality consciousness is conducive to mutual respect among opposite-sex patients. Arranging different hospital rooms for patients based on their gender is not an acceptance of traditional harmful gender stereotypes that hold a cognitive bias of "male superiority and female inferiority". Rather, it is a concrete manifestation of respect for each other's physiological differences and the promotion of gender equality consciousness. Therefore, in clinical practice, we should guide pediatric patients to have a correct understanding of the meaning of gender equality, teach them how to interact with the opposite sex, and increase their ability to cooperate and communicate with their peers.

CONCLUSION

In summary, our study found that lower grade school-age children have a low level of gender consciousness. Gender consciousness issues require more attention during children's hospitalization. In clinical practice, we should take measures to help children understand and establish correct gender concepts. At the same time, through the cultivation of gender consciousness among medical personnel and positive and indiscriminate treatment measures, we should ensure the right of children to seek medical treatment and ensure that male and female children receive equal medical resources to achieve gender equality in medical treatment. Overall, promoting gender equality in the health care sector is crucial for the healthy and harmonious development of all children.

ARTICLE HIGHLIGHTS

Research background

Hospitalization is a part of many children's lives and has an impact on their gender development. In clinical practice, the random allocation of hospital rooms for children and the lack of privacy curtains during examinations overlook the important influence of individual gender factors on children, although these factors have an undeniable impact on children's identity formation.

Research motivation

Currently, research on gender consciousness in China mainly focuses on adult women, with less attention given to children and even less to hospitalized children.

Research objectives

To investigate the current situation of gender identity in lower primary school children by conducting a survey.

Research methods

Based on a literature review, the researcher designed a general information survey form for the children, including gender, age, grade, whether they were only children, family structure, personality, and current home address. The gender consciousness scale for elementary and middle school students was used for the survey.

Research results

Lower grade school-age children have a low level of gender consciousness. Children aged 6 had the weakest gender identity, and girls had significantly stronger gender identity than boys.

Research conclusions

Gender consciousness issues require more attention during children's hospitalization.

Research perspectives

This study proposes scientific and reasonable recommendations and strategies for hospitalization and provides timely interventions and guidance to help children shape a unified and clear gender orientation.

FOOTNOTES

Author contributions: Zhang YL and Pan XC conceived and designed the study; Zhang HM guided the study; Xu JX and Zhou QY collected the clinical date; Zhang YL and Wang H analyzed the data; all authors drafted and revised the manuscript.

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REFERENCES

1 **Zhao F**, Li X, Tang G. [Investigation and Educational Reflection on Gender Consciousness of Students in Different Stages of Elementary School]. *Xibei Chengren Jiaoyu Xueyuan Xuebao* 2020; **1**: 105-109

2 **Carver PR**, Yunger JL. Gender Identity and Adjustment in Middle Childhood. *Sex Roles* 2003; **49**: 95-109

3 **Zhu XY**. [Empirical Study on Gender Identity of Female College Students]. *Xi'an Dianzi Keji Daxue Xuebao(Shehui Kexueban)* 2002; **12**: 5

4 **Liu H**. Research on the Influencing Factors of Female College Students' Physical Exercise from the Perspective of Social Gender Theory. *Sports Fash* 2021; **10**: 259-260

5 **He Y**. [Analysis of the Influence of Female Identity on Employment and Entrepreneurship of Female College Students]. *Henan Caizheng Shuiwu Gaodeng Zhuanke Xuexiao Xuebao Zazhi* 2021; **35**: 34-36+87

6 **Liu L**, Yang LZ. [Formation of Children's Gender Self-concept]. *DiShiyijie Quanguo Xinlixue Dahui Lunwenji* 2007; 579

7 **Chen QH**. [Art, Gender and Education: Life Images of Six Female Planters]. Sanmin Shuju 2012. Available from: http://xueshu.baidu.com/usercenter/paper/show?paperid=163g0tc0r92r0a80hb1d04s0aj326705&site=xueshu_se

8 **Qin J**, Li XP. [Current Situation and Strategies of Preschool Children's Gender Role Education]. *Qingdao Zhiye Jishu Xueyuan Xuebao* 2017; **30**: 58-60

9 **Yu JH**. [Development of Preschool Children's Gender Stereotypes and Their Influence on Peer Selection]. M.Sc. Thesis, Guangxi Normal University. 2022. Available from: https://kns.cnki.net/kcms2/article/abstract?v=hqt_j-uEELGJtK98MoUoXOkBG8mwmJMNl3hrA32EdtR4RNtcNoXoik9bfA3_YCngMEHTQ5ZmkY8JcLMBvfBM17oyxJBGBEYwHzuBWg1axAYBFLuUq8pvGQ4FXSUoSrlvmjf0CehE3UaUzB3eWncMXQ==&uniplatform=NZKPT&language=CHS

10 **Li LY**, Lin L. [Qualitative Study on Social Gender Differentiation in Children's Peer Games]. *Neimenggu Shifan Daxue Xuebao (Jiaoyu Kexueban)* 2021; **34**: 43-55

11 **Chen L**, Tian YL, Yue HL, Chen CF. [The Influence of Grandparental Rearing on Children's Gender Role Development]. *Jiankang Yanjiu* 2021; **41**: 612-616

12 **Zhang XJ**, Chen YM, Li J, Wang HB, Liu XX, Yao M. [Discussion on the Performance Allocation Strategy of Public Hospitals under the Reform of Medical Insurance Payment Method]. *Zhongguo Weisheng Jingji* 2022; **41**: 57-60

13 [Qin JF, Li XP. A Study on the Present Situation and Strategies of Children's Gender Role Education]. *Qingdao Zhiye Jishu Xueyuan Xuebao* 2017; **30**: 58-60

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ORIGINAL ARTICLE

Retrospective Study

Improvement of the nutritional support management system for patients in intensive care units

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Abstract

BACKGROUND

Nutritional support for patients hospitalized in the intensive care unit (ICU) is an important part of clinical treatment and care, but there are significant implementation difficulties.

AIM

To introduce a modified nutritional support management system for ICU patients based on closed-loop information management and psychological counseling.

METHODS

The division of functions, personnel training, system construction, development of an intelligent decision-making software system, quality control, and improvement of the whole process were carried out to systematically manage nutritional support for ICU patients.

RESULTS

Following the implementation of the whole process management system, the scores of ICU medical staff's knowledge, attitudes/beliefs, and practices regarding nutritional support were comprehensively enhanced. The proportion of hospital bed-days of total enteral nutrition (EN) in ICU patients increased from 5.58% to 11.46%, and the proportion of EN plus parenteral nutrition increased from 42.71% to 47.07%. The rate of EN initiation within 48 h of ICU admission increased from 37.50% to 48.28%, and the EN compliance rate within 72 h elevated from 20.59% to 31.72%. After the implementation of the project, the Self-rating Anxiety Scale score decreased from 61.07 ± 9.91 points to 52.03 ± 9.02 points, the Self-rating Depression Scale score reduced from 62.47 ± 10.50 points to 56.34 ± 9.83 points, and the ICU stay decreased from 5.76 ± 2.77 d to 5.10 ± 2.12 d.

CONCLUSION

The nutritional support management system based on closed-loop information management and psychological counseling achieved remarkable results in clinical applications in ICU patients.

Key Words: Closed-loop information; Psychological counseling; Intensive care unit patients; Nutritional support; Management system

Core Tip: Nutritional support for patients hospitalized in the intensive care unit is an indispensable part of clinical treatment and care, but there are problems in achieving nutritional support goals. This study has launched a nutrition support management system based on closed-loop information management and psychological counseling to try to address this issue and has made some progress.

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INTRODUCTION

Nutritional support for critically ill patients has become an indispensable part of clinical treatment, especially for intensive care patients[1]. However, in clinical practice, it is difficult to achieve the goal of nutritional support for patients hospitalized in intensive care units (ICUs), mainly due to the poor standardization and compliance of nutritional support for medical staff[2,3]. Domestic and foreign studies have shown that the establishment and implementation of a standardized nutrition management system can improve the rate of achieving nutrition goals for inpatients and reduce the incidence of nutrition-related complications[4-7]. In addition, providing psychological support to ICU patients is conducive to reducing their mental anxiety and negative emotions induced by continuous treatment and pain, and helps to improve their treatment compliance and quality of life. Based on further modifications to the nutritional support management system, standardized training of medical staff, and great attention given to psychological counseling intervention measures, our hospital used information technology to form a closed loop of the information required and data obtained during the nutritional support of ICU patients. In this way, the diagnosis and treatment procedures, nutrient solution configuration and transmission, nutrition-related physiological indicator acquisition, whole-process quality index monitoring of medical staff related to clinical nutritional support can be integrated and supplemented by psychological intervention to build a nutritional support management system for ICU patients based on closed-loop information and psychological counseling. The improvement process and effects are reported below. In addition, this study aims to improve the medical experience of ICU patients by constructing a nutritional support management system based on closed-loop information and psychological counseling combined with psychological interventions.

MATERIALS AND METHODS

General information

A retrospective cohort study design was adopted. The inclusion criteria of the subjects are as follows: (1) Length of ICU stay ≥ 3 d; (2) No enteral or parenteral nutrition (PN) contraindications, and (3) Age > 16. The following are exclusion criteria: Patients with a ventilator-dependent ICU stay > 14 d due to a specific etiology, as well as unconscious or uncooperative patients. Patients admitted to ICUs between July and August 2021 were classified as the control group, and those admitted between March 2022 and April 2022 were classified as the improvement group. All enrolled patients met the inclusion criteria described above.

The SoJump online survey platform was used to investigate the knowledge, attitudes/beliefs, and practices regarding nutritional support among all medical staff in the Department of Critical Care Medicine before and after project implementation. In the survey, there were 10 questions on nutrition knowledge, with 10 points for each correct answer and 0 for a wrong answer and a score range of 0-100; the score was proportional to nutrition knowledge. In terms of nutritional attitudes/beliefs, 10 questions were answered on a 5-point Likert scale as follows: 1 = completely disagree, 2 = somewhat disagree, 3 = not sure, 4 = somewhat agree, and 5 = completely agree; the total score ranged from 10 to 50, with higher scores suggesting more active and positive nutritional beliefs and attitudes. The nutritional practice subscale consisted of 10 questions answered on a 5-point Likert scale, with 1, 2, 3, 4, and 5 points indicating never, rarely, sometimes, often, and always, respectively; on a 10-50-point scale, a higher score represented more active nutritional support practices. There were 4 questions in the psychological knowledge questionnaire answered on a 4-point Likert scale (0 = I do not know, 1 = I have heard of it, 2 = I know it generally, 3 = I know it fairly well, 4 = I know it very well), with the total score ranging from 0 to 16; better psychological knowledge was indicated by a higher score. The psychological nursing attitudes/beliefs subscale consisted of 11 questions that were scored using a 4-point Likert-scale, with 0, 1, 2, 3, and 4 indicating strongly disagree, disagree, somewhat agree, agree, and completely agree, respectively; on a 44-point scale, higher scores were associated with more active and positive psychological nursing attitudes and beliefs. A total of three questions were asked about psychological nursing practices, using a 4-point Likert scale with scores of 0, 1, 2, 3, and 4 indicating none, seldom, sometimes, frequently, and persistently, respectively; the total score ranged from 0 to 12 points, and higher scores suggested more active psychological nursing practices. This questionnaire was conducted anonymously using Sojump. All medical staff in the Department of Critical Care Medicine were instructed to complete the questionnaire following the instructions and submit it on their personal mobile phones.

Methods

Team establishment: Standardized and effective management of the whole nutritional support for critically ill patients requires overall resource allocation and relies on the hospital's various functional departments as the operational link. Therefore, this project team was an interdisciplinary team represented by clinical medicine, nursing, pharmacy, nutrition and information technology (including 1 chief physician, 1 attending physician, 1 chief nurse, 1 deputy chief nurse, 3 nurses, 1 intermediate nutritionist, 1 pharmacist in charge, and 1 senior medical information software engineer). Among them, the clinical medical staff were mainly responsible for project process sorting, process re-engineering, project implementation and effect inspection; the clinical functional departments were primarily responsible for evidence retrieval and quality control during the system process transformation; and the information department was responsible for the implementation of the software system.

Personnel training: Given that the participants of the whole nutritional support process for ICU patients were mainly medical staff in the Department of Critical Care Medicine, the knowledge, attitudes/beliefs, and practices of medical care personnel regarding nutritional support directly affected the nutritional support for ICU patients[8]. In addition, psychological support diagnosis and treatment activities can also affect the treatment compliance of ICU patients to a certain extent. Therefore, the project team organized experienced professionals in the hospital and invited well-known experts in the industry to train all ICU medical staff in the Department of Critical Care Medicine on nutritional support and diagnosis activities in the form of special lectures, academic meetings and workshops, spanning two months with a total of 17 class hours, covering the key points, difficulties and new progress of nutritional support for critically ill patients. The medical staff were assessed after the training. Long-term regular standardized nutrition training courses were developed.

System improvement: All nutritional support procedures, such as nutrition screening, evaluation, planning, prescription, prescription review, implementation, and monitoring, were defined; the management key points and responsibilities of various departments, such as the ICU, medicine, nutrition, and information technology, were detailed; and the key points of inspection during the implementation and the indicators in the quality management process were monitored. The team members summarized the nutrition-related work systems and processes at the hospital and department levels, conducted detailed discussions, consulted a large number of references, and learned from the existing systems of benchmarking hospitals to form norms and standards through intragroup discussions. Experts were then invited to review and further modify the system before it was submitted to the Quality Management Section for review and the Dean's Office for approval. Finally, an in-hospital management system applicable to the actual situation of nutritional support diagnosis and treatment in our hospital was formed, which was used and promoted in clinical practice. In addition, the medical, nursing and nutrition departments conducted regular clinical inspections to track the effects and provide feedback.

System research and development and application: The core component of the nutritional support management system construction was the establishment of a standardized, intelligent and efficient information system to provide decision support functions for nutritional support, thus facilitating high-quality and more comprehensive development of nutritional support diagnosis and treatment. Through participating in the nutrition management courses, referring to and learning the major advanced nutrition measurement systems, and taking into account the current situation of nutrition management of ICU patients in our hospital, the group members designed a framework of nutrition monitoring system for critically ill patients that met the national conditions and clinical applications of the hospital after several rounds of expert discussions and checked the system design through a professional novelty-checking institution to determine its innovativeness. With the support of the hospital, the system was developed after obtaining a docking permission with the hospital's clinical application system related to nutrition management.

To ensure the consistency, timeliness, and accuracy of the data applied in the process of nutrition diagnosis and treatment to enable in-depth and effective use of the data and reduce the workload of medical staff and dietitians in clinical departments, the design adopted database access, FTP file acquisition and Web service for data exchange and application integration. The nutrition management system was expected to work in tandem with the databases of the clinical information system, with the nutritional support as the main line of the whole-process business management, focusing on the work required for nutritional diagnosis and treatment of patients after admission.

The major procedures were as follows: (1) Nutritional screening after patient admission and transfer to another department: For nutritional risk-positive patients, the system automatically carried out risk warnings with special characters and colors on the evaluation page, nursing bedside card, patient homepage, doctor's preview page, pharmacy preview page, and nutrition department system; (2) The system automatically prompted the doctor when a nutrition consultation was needed; (3) The system calculated the nutritional requirements of patients and notified clinicians and nurses automatically; (4) When the clinician performed a prescription operation, the system calculated the liquid and energy of the prescription synchronously; (5) The system supported the pharmacy department in conducting intelligent prescription reviews, with the results automatically fed back to the doctor; (6) During nursing, the patient's homepage in the nursing system allowed for visual monitoring of the proportion of energy infusion components and the display of the corresponding relationship between energy and liquid on the day of implementation; (7) The daily target energy compliance rate was displayed by way of a line chart on the homepage of nursing medical records; (8) On the patient 360-degree holographic display of the doctor's medical record, the system visually displayed all relevant holographic data of the patient's nutritional support over time; (9) On the homepage of nursing cases and patients, the note and follow functions of nutrition indices could be customized, and the changing trend of the index could be obtained by clicking; (10) All nutrition-related indicators could be retrieved with one click in the test system, which was convenient for clinicians and nurses to extract nutrition evaluation data in clusters; (11) Nutritionists could collect information across the hospital on nutritionally at risk patients, and proactively review the status of nutritional support for patients to inform doctors whether nutrition-related medical orders were the most appropriate scheme; (12) The system could intelligently prompt a 7-d nutrition review; and (13) The system automatically summarized the quality control data of nutritional support and ultimately formed a closed loop of nutritional support management.

After the completion of system development, the information department technicians trained the members of the project team and the key personnel of the Department of Critical Care Medicine, focusing on explaining the system's operating methods and precautions. The system was trialed on a small scale in ICUs. During the application, patients' energy and nutrient proportions were counted by using both the system intelligent calculation method and the manual calculation method for comparative analysis, so as to find problems and correct them. After the system was stabilized, all members of the ICU, pharmacy, and nutrition departments were given one week of on-site training to explain the standardized operation of the system in detail. The system was gradually applied in clinical practice. During implementation, IT technicians were on standby 24 h a day to provide technical support and solve difficult problems.

Psychological counseling: The medical staff provided timely and effective negative emotion counseling for patients. Although ICU inpatients have passed the high-risk period of illness, the pain and fear of death caused by the disease during the high-risk period can negatively affect their emotions. Therefore, the medical staff specifically told the patients that the disease had passed the critical stage and would not cause their death and gave timely medication and physical relief when there was heart pain. In addition, the nursing staff kept a close eye on the patients' negative emotions caused by other potential reasons and provided appropriate psychological counseling. Furthermore, the causes of the disease, treatment, surgery, nursing methods, and postoperative prevention and treatment methods were detailed to the patients, and targeted prognostic analysis was carried out according to their specific conditions so that they could rebuild confidence in the future and feel the care and love of medical staff, thus establishing a sense of trust and improving compliance. Moreover, the hospital provided patients with a good ward environment that was clean, tidy, and well ventilated with suitable temperature and humidity so that they could maintain psychological and physical comfort during residential nursing. Appropriate music and relaxing TV and movie programs were also played for patients to distract them. If necessary, painkillers or antianxiety drugs and antidepressants were given.

Effect analysis

Evaluation indicators: (1) The proportions of hospital bed-days of patients receiving different nutritional support methods, such as total PN, PN + enteral nutrition (EN), and total EN, were calculated; (2) The scores of ICU nurses' knowledge, attitudes/beliefs, and practices regarding nutritional support were assessed; (3) The survey scores of ICU nurses' knowledge, attitudes/beliefs, and practices regarding psychological support were analyzed; (4) The rate of EN initiation within 48 h of admission to the ICU (number of patients initiating EN within 48 h during the same period/number of ICU patients included in the survey during the statistical period) was counted; (5) The EN compliance rate within 72 h of ICU admission (the number of patients who achieved the EN standards within 72 h during the same period/the number of ICU patients included in the survey during the statistical period) was counted; (6) Patients' anxiety and depression before and after project implementation were assessed by the Self-rating Anxiety Scale (SAS) and Self-rating Depression Scale (SDS), respectively, and (7) The length of ICU stay was recorded. Notes: (1) The day of admission to the ICU was recorded as day 0; (2) The standard for achieving EN standards for patients within 72 h of ICU admission was the total energy intake of EN consumed by patients on the third day of ICU admission ≥ 20 kcal/kg.

Statistical methods

Relevant data were imported into SPSS 19.0 for statistical analysis. The scores of medical staff's knowledge, attitudes/beliefs, and practices regarding nutritional support were analyzed by one-way analysis of variance (ANOVA). After

Table 1 Comparison of general data between the two groups

Groups	Proportion of males (%)	Proportion of females (%)	Age (yr)	APACHE II score (points)	NRS 2002 score (points)
Improvement group (n = 145)	64.14	35.86	63.68 ± 13.71	26.02 ± 10.23	4.57 ± 1.21
Control group (n = 136)	64.71	35.29	64.99 ± 13.45	25.85 ± 10.71	4.57 ± 1.30
P value	> 0.1	> 0.1	> 0.1	> 0.1	> 0.1

APACHE: Acute Physiology and Chronic Health Evaluation; NRS: Numeric Rating Scale.

Table 2 Comparative analysis of knowledge, attitudes/beliefs, and practices regarding nutritional support among medical staff in the Department of Critical Care Medicine before and after project implementation

Groups	Number of cases (n)	Knowledge	Attitudes/beliefs	Practices
Before project implementation	88.00	54.09 ± 19.45	45.37 ± 5.25	39.27 ± 7.60
After project implementation	83.00	94.57 ± 7.86	47.23 ± 4.07	44.45 ± 5.77
P value		< 0.01	< 0.05	< 0.01

testing for normality, the measurement data (represented by mean ± SD) were analyzed by the independent sample t test. The count data, described as frequencies (rates), were analyzed by the χ^2 test. In all tests, a significance level of 5% (P < 0.05) was adopted.

RESULTS

One hundred and forty-five cases were enrolled in the improvement group with a valid hospital stay of 733 d. The control group included 136 cases with 789 d of effective hospitalization. No significant difference was identified between the two groups in age, sex, Acute Physiology and Chronic Health Evaluation II score, or Numeric Rating Scale 2002 score on the day of ICU admission (P > 0.1), as shown in Table 1.

Knowledge, attitudes/beliefs, and practices regarding nutritional and psychological support were investigated among medical staff in the Department of Critical Care Medicine. Ninety questionnaires were distributed before and after project implementation, with 88 and 83 valid questionnaires recovered, respectively. Through comparison before and after project implementation, the knowledge, attitudes/beliefs, and practices scores regarding nutritional support treatment in the critical medicine department improved significantly. The survey also revealed significantly enhanced psychological support of the medical staff in the Department of Critical Care Medicine in terms of knowledge, attitudes/beliefs, and practices (see Tables 2 and 3 for details).

The proportions of hospital bed-days of total PN support, total EN support and EN + PN support in ICU patients were statistically analyzed. After project implementation, the proportions of hospital bed-days of total EN support and EN + PN support in ICU patients increased significantly (P < 0.05), while total PN support did not alter markedly (P > 0.05) (Table 4).

The EN initiation rate among ICU patients within 48 h of admission increased from 37.50% to 48.28%; the EN compliance rate within 72 h of ICU admission elevated from 20.59% to 31.72%; the differences were statistically significant, as shown in Table 5. After improvement, a lower SAS score (52.03 ± 9.02 *vs* 61.07 ± 9.91) and a lower SDS score (56.34 ± 9.83 *vs* 62.47 ± 10.50) were observed in the improvement group compared with the control group (P < 0.01; Table 6). After project implementation, the total length of ICU stay of patients in the improvement group was 5.10 ± 2.12 d, lower than the 5.76 ± 2.77 d in the control group (P < 0.01), as shown in Table 7.

DISCUSSION

Patients hospitalized in ICUs are critically ill with symptoms such as high energy metabolism, increased calorie demands, and negative nitrogen balance. Their emotions are also easily affected by illness and bodily function, resulting in negative emotions such as anxiety and depression that adversely affect treatment effectiveness. Previous studies have confirmed that early, reasonable, and standardized nutritional support can reduce patient mortality, shorten the length of ICU stay, and reduce medical expenses[9,10]. However, for various reasons, many studies still show a high incidence of malnutrition among critically ill patients during hospitalization, and there are nonstandard diagnostic and treatment practices for EN and PN support[11]. The purpose of this project is to improve the compliance of medical staff in carrying

Table 3 Comparative analysis of knowledge, attitudes/beliefs, and practices regarding psychological support among medical staff in the Department of Critical Care Medicine before and after project implementation

Groups	Number of cases (*n*)	Knowledge	Attitudes/beliefs	Practices
Before project implementation	88.00	9.50 ± 3.22	29.49 ± 4.74	8.17 ± 1.51
After project implementation	83.00	13.05 ± 2.27	37.17 ± 4.71	9.76 ± 1.58
P value		< 0.01	< 0.01	< 0.01

Table 4 Comparison of each nutritional support mode as a percentage of total effective hospital stay between the two groups

Groups	Total parenteral nutrition	Parenteral nutrition + enteral nutrition	Total enteral nutrition
Improvement group (*n* = 733)	261 (35.61%)	345 (47.07%)	84 (11.46%)
Control group (*n* = 789)	293 (37.14%)	337 (42.71%)	44 (5.58%)
P value	> 0.05	< 0.05	< 0.01

Table 5 Comparison of the enteral nutrition initiation rate within 48 h and compliance rate within 72 h after admission to the intensive care unit between the two groups

Groups	Enteral nutrition initiation rate within 48 h after ICU admission	Enteral nutrition compliance rate within 72 h after ICU admission
Improvement group (*n* = 145)	48.28% (66)	31.72% (*n* = 46)
Control group (*n* = 136)	37.50% (47)	20.59% (*n* = 28)
P value	< 0.05	< 0.05

ICU: Intensive care unit.

Table 6 Comparison of Self-rating Anxiety Scale and Self-rating Depression Scale scores between the two groups

Indicators	Improvement group (*n* = 145)	Control group (*n* = 136)	*t* value	*P* value
SAS (points, mean ± SD)	52.03 ± 9.02	61.07 ± 9.91	8.004	< 0.01
SDS (points, mean ± SD)	56.34 ± 9.83	62.47 ± 10.50	5.055	< 0.01

SAS: Self-rating Anxiety Scale; SDS: Self-rating Depression Scale.

Table 7 Comparison of intensive care unit length of stay between the two groups of patients

Indicators	Improvement group (*n* = 145)	Control group (*n* = 136)	*t* value	*P* value
Length of ICU stay	5.10 ± 2.12	5.76 ± 2.77	2.28	< 0.05

ICU: Intensive care unit.

out nutritional support diagnosis and treatment according to the norms and to standardize nutritional support diagnosis and treatment practices. Moreover, nutritional support and psychological counseling were combined to validate the clinical application advantages of this system in ICU patients. After the implementation of the project, the knowledge, attitudes/beliefs, and practices of ICU medical staff regarding nutritional and psychological support were greatly improved. In addition, the improvement group focused more on the early development of EN in terms of nutritional and psychological support, using a more diverse and rationalized nutritional support structure. Therefore, the patients' nutritional compliance rate was also significantly improved, their SAS and SDS scores were significantly reduced, and their stay in the ICU was significantly shortened. The construction and implementation of a nutritional support management system based on closed-loop information and psychological counseling has further optimized the diagnosis

and treatment process of nutritional support, improved the nutritional compliance rate of patients, and relieved their psychological negative emotions, which is of great importance in improving patient outcomes.

The construction of a nutritional support management system follows the medical development context of the strengthening of clinical nutritional support diagnosis and treatment, with the key cornerstone being the closed-loop information nutritional support intelligent management system, which is in line with the hospital's information development strategy. The software system covers the whole management of nutritional diagnosis and treatment practices, including nutritional risk screening, assessment, prescription, implementation, effect monitoring, and quality control. A large number of applications, such as dynamic data trends and 360-degree holographic display, are used, which highlights the awareness of dynamic monitoring in the implementation process of nutritional support, avoids the shortcomings of "fan out from a point to an area" in most target management models, and improves the clarity of medical staff's understanding of patients' nutritional support dynamic information, thus improving work efficiency and increasing work initiative. At the same time, most of the data in the system are displayed in visual charts, transforming complex dynamic monitoring data into visual images to provide medical staff with the most intuitive visual reflection, which is conducive to the assessment of the nutritional status of critically ill patients and facilitates timely adjustment of nutritional management programs to ensure that patients receive timely and effective nutritional support[12]. Dynamic displays and visual early warnings reflect more scientific, refined and humanized management, which is crucial to improve the safety and standardization of patient nutrition implementation.

CONCLUSION

The ICU patient nutritional support management system based on closed-loop information and psychological counseling uses informatization, modernization and process management methods to focus on solving the difficulties of clinical nutritional support management, providing medical staff with more accurate decision-making support based on personalized dynamic assessment of patients, and ensuring multidimensional protection of patient physical and mental health. However, after implementation, it was found that there is still room for further improvement in EN initiation for patients within 48 h of ICU admission, EN compliance within 72 h of admission, and alleviation of negative emotions, which warrants continuous modifications during future promotion of the homogenization and management of nutritional support for patients in the whole hospital.

ARTICLE HIGHLIGHTS

Research background

Due to the poor standardization and compliance of nutritional support for patients by medical staff, it is difficult to achieve the goal of nutritional support for intensive care unit (ICU) inpatients.

Research motivation

This study intends to optimize the clinical nutritional support of ICU patients by constructing a nutrition support management system based on closed-loop information and psychological counseling combined with psychological interventions.

Research objectives

To explore the value of the nutritional support management system based on closed-loop information management and psychological counseling in the clinical application of ICU patients.

Research methods

Through the division of functions, personnel training, system construction, development of an intelligent decision-making software system, quality control, and improvement of the whole process, the nutritional and psychological support of ICU patients are systematically managed. In addition, the valid number of hospital stays of patients with different nutritional support methods after the implementation of systematic management, the scores of ICU nurses' knowledge, attitudes/beliefs and practices of nutritional or psychological support, and the rate of total enteral nutrition (EN) initiated within 48 h or 72 h after admission to the ICU were counted. Moreover, the anxiety and depression of patients before and after the implementation of the project and the length of stay in the ICU were recorded.

Research results

After the implementation of the whole-process management system, the scores of nutritional or psychological support knowledge, attitudes/beliefs and practices of ICU medical staff were significantly enhanced, and the proportions of hospital bed-days of total EN and EN plus parenteral nutrition (PN) of ICU patients were significantly increased. The EN initiation rate also increased significantly within 48 h or 72 h after admission to the ICU. Moreover, markedly reduced Self-rating Anxiety Scale, Self-rating Depression Scale scores and ICU stays were observed in ICU patients after the implementation of the project.

Research conclusions

The nutritional support management system based on closed-loop information management and psychological counseling plus psychological interventions has significant advantages in the clinical application of ICU patients. It can not only improve the awareness and executive abilities of ICU medical staff, but also significantly increase the application of EN support and EN plus PN support for CU patients. Moreover, it is effective in relieving patients' negative emotions and shortening the length of ICU stay.

Research perspectives

The nutrition support management system for ICU patients based on closed-loop information and psychological counseling combined with psychological interventions can not only improve the clinical practice of medical staff, but also optimize the medical management of ICU patients. However, there is still room for improvement in aspects such as EN initiation within 48 h of admission to the ICU, EN compliance within 72 h of admission, and negative emotional relief, warranting continuous improvement.

FOOTNOTES

Author contributions: Zhang YY and Feng ZX designed the research and wrote the first manuscript, and conducted the analysis and provided guidance for the research; Zhang YY, Wang CY, Guo DX, Gao HN, Jin XS, Wu YL, Chen LH, and Feng ZX contributed to conceiving the research and analyzing data; and all authors reviewed and approved the final manuscript.

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REFERENCES

1 **Gostyńska A**, Stawny M, Dettlaff K, Jelińska A. Clinical Nutrition of Critically Ill Patients in the Context of the Latest ESPEN Guidelines. *Medicina (Kaunas)* 2019; **55** [PMID: 31810303 DOI: 10.3390/medicina55120770]
2 **Lin Z**, Xu Y, Ge WX, Li X, Gu Q. Survey and Analysis of Clinical Practice of Nutritional Support Guidelines for Critically Ill Patients by Some Doctors of Intensive Care Units in Jiangsu and. *Parenteral Enteral Nutrition* 2018; **25**: 342-345
3 **Yang L**. A preliminary study of the implementation of the main guidelines in the ICU and their influencing factors. Journal of Zhejiang University, 2015
4 **Bermejo de Las Heras S**, De la Calle de la Rosa L, Arias Díaz J, Giner M, Blesa Malpica AL. Tube feeding monitoring as a clinical quality indicator at intensive care units. *Nutr Hosp* 2018; **35**: 6-10 [PMID: 29565142 DOI: 10.20960/nh.1187]
5 **De la Calle de la Rosa L**, Bermejo de Las Heras S, Blesa A, Giner M, Arias Díaz J. Assessment of the clinical quality indicator "early enteral nutrition" in intensive care units. *Nutr Hosp* 2017; **34**: 1288-1291 [PMID: 29280641 DOI: 10.20960/nh.1171]
6 **Bahar M**. A Different Approach to the Nutritional Therapy in Intensive Care Units: Nutrition Software (ICNUS). *Turk J Anaesthesiol Reanim* 2017; **45**: 251-259 [PMID: 29114408 DOI: 10.5152/TJAR.2017.190901]
7 **Zhang Y**, Hou SK, Hou Y, Liu JP. Design and implementation of clinical nutrition treatment system. *Chinese Medical Equipment J* 2015; **36**: 71-73 [DOI: 10.7687/J.ISSN1003-8868.2015.07.071]
8 **Zeng W**, Guo YH, Wu GF, Fang Q. Investigation on the knowledge, attitude, practice and obstacles of enteral nutrition among nurses in Guizhou Province. *Guizhou Medical J* 2018; 383-384
9 **Sun RH**, Jiang RL, Huang M, Cai GL. Expert consensus on clinical practice of early enteral nutrition in critically ill patients. *Chinese Critical*

Care Medicine 2018; **30**: 715-721 [DOI: 10.3760/cma.j.issn.2095-4352.2018.08.001]

10 **Yao M**, Feng X, Guo Z, Huang X, Jin J. Early enteral nutrition dose selection in critically ill patients: a meta analysis. *Chinese J Emergency Medicine* 2018; **27**: 866-871 [DOI: 10.3760/cma.j.issn.1671-0282.2018.08.010]

11 **Leite HP**, de Lima LF, de Oliveira Iglesias SB, Pacheco JC, de Carvalho WB. Malnutrition may worsen the prognosis of critically ill children with hyperglycemia and hypoglycemia. *JPEN J Parenter Enteral Nutr* 2013; **37**: 335-341 [PMID: 22930337 DOI: 10.1177/0148607112458124]

12 **Luo H**, Wang P, Zhao HY. Visualization analysis and application based on medical big data. *China Medical Devices* 2020; **35**: 122-128

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ORIGINAL ARTICLE

Retrospective Study

Assessing myocardial indices and inflammatory factors to determine anxiety and depression severity in patients with chronic heart failure

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Abstract

BACKGROUND

Patients with chronic heart failure (CHF) have a progressive disease that is associated with poor quality of life and high mortality. Many patients experience anxiety and depression (A&D) symptoms, which can further accelerate disease progression. We hypothesized that indicators of myocardial function and inflammatory stress may reflect the severity of A&D symptoms in patients with CHF. Changes in these biomarkers could potentially predict whether A&D symptoms will deteriorate further in these individuals.

AIM

To measure changes in cardiac and inflammatory markers in patients with CHF to determine A&D severity and predict outcomes.

METHODS

We retrospectively analyzed 233 patients with CHF treated at the Jingzhou Hospital, Yangtze University between 2018-2022 and grouped them according to Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS) scores. We compared clinical data in the no-A&D, mild-A&D, moderate-A&D, and severe-A&D groups, the SAS and SDS scores with the New York Heart Association (NYHA) functional classification, and cardiac markers and inflammatory factors between the no/mild-A&D and moderate/severe-A&D groups. Regression analysis was performed on the markers with $P < 0.05$ to determine their ability to predict A&D severity in patients and the area under the receiver operating characteristic curve (AUROC) was used to evaluate their accuracy.

RESULTS

In the inter-group comparison, the following variables had an effect on A&D severity in patients with CHF: NYHA class, left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter, N-terminal pro-brain natriuretic peptide (NT-proBNP), interleukin-6 (IL-6), and tumor necrosis factor-alpha ($P < 0.05$). Other variables did not differ significantly between the A&D groups ($P > 0.05$). In addition, we found that higher NYHA classes were associated with higher the SAS and SDS scores ($P < 0.05$). Regression analysis showed that LVEF, NT-proBNP, and IL-6 were independent risk factors for A&D severity ($P < 0.05$). Among them, NT-proBNP had the best predictive ability as a single indicator (AUROC = 0.781). Furthermore, the combination of these three indicators exhibited a good predictive effect toward discriminating the extent of A&D severity among patients (AUROC = 0.875).

CONCLUSION

Cardiac and inflammatory biomarkers, such as LVEF, NT-proBNP, and IL-6, are correlated with A&D severity in patients with CHF and have predictive value.

Key Words: Chronic heart failure; Anxiety; Depression; Cardiac markers; Inflammatory factors; Prediction

Core Tip: We investigated patients with chronic heart failure (CHF) with varying degrees of anxiety and depression (A&D) symptoms and assessed changes in myocardial markers and inflammatory factors to determine their associations with A&D severity. We used independent risk factors as predictive indicators and assessed their discriminative accuracy in predicting A&D severity using the area under the receiver operating characteristic curve. We demonstrated that A&D symptoms can affect the progression of CHF and lead to worse outcomes for patients.

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INTRODUCTION

Chronic heart failure (CHF), or congestive heart failure, is a progressive disease that commonly manifests as fatigue, reduced physical fitness, shortness of breath, persistent coughing, and arrhythmia. Typically, the New York Heart Association (NYHA) classification is used to evaluate patients according to the severity of their symptoms, alongside cardiovascular functional capacity and blood test results[1]. Currently, treatment aims to ease the impact of these symptoms on daily life activities of patients and improve the quality of life. However, studies have shown that > 50% of patients with CHF develop anxiety and depression (A&D) symptoms[2,3], which has been associated with unfavorable outcomes, such as increased CHF-related hospitalization and mortality rates. However, distinguishing whether certain symptoms are related to A&D or are symptoms of CHF remains a challenge. Therefore, if the A&D status of patients with CHF can be accurately diagnosed and treated, the overall condition and life expectancy of patients is expected to improve [4,5].

In China, the incidence of CHF is on the rise, especially left ventricular dysfunction[6]. Although there has been extensive research on the general demographic characteristics and A&D data of CHF patients, studies on myocardial markers and inflammation factor levels are still limited. Research by Wang *et al*[7] showed that in the CHF population, white blood cell interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) are higher than those in the healthy population; Yasuhara *et al*[8] reported that these inflammation factor levels are positively correlated with B-type natriuretic peptide levels; Liu *et al*[9] showed in subsequent studies that systemic inflammation indicators, such as hypersensitive C-reactive protein (hs-CRP), are supplementary indicators for CHF diagnosis. Therefore, these inflammation factors can well reflect the physiological state of CHF patients. Furthermore, immune abnormalities of inflammatory mediators such as IL-6, TNF-α, *etc.*, may be related to the pathophysiology of depression, and are also potential markers for the classification of A&D states[10,11]. Therefore, these inflammation factors can reflect the physiological state of CHF patients, and also have the potential to classify A&D states in CHF.

Currently, the assessment of A&D relies on subjective patient-reported measures; hence, differential levels of myocardial markers and inflammatory factors could serve as objective measure to assist clinicians in assessing and classifying A&D severity. This measure could facilitate a more precise distinction between CHF patients with different degrees of A&D, enable physicians to better manage and rationally allocate medical resources, and provide the potential for personalized treatment.

Therefore, this retrospective study aimed to explore the differences in myocardial markers, inflammatory factors, and A&D severity in patients of CHF and potentially reveal an association that can used as a reference for clinical assessment of A&D status in patients with CHF in the future.

MATERIALS AND METHODS

Patient characteristics

This retrospective study obtained data from patients with CHF treated at Jingzhou Hospital, Yangtze University, from January 2018 to December 2022. The inclusion criteria were as follows: (1) A confirmed diagnosis of CHF and relevant medical records; (2) Records of A&D symptoms; (3) Patients aged > 18 years; and (4) Information on inflammatory factors and myocardial markers. The exclusion criteria were as follows: (1) Severe cardiovascular disease, such as myocardial infarction or heart valve disease; (2) Severe comorbid systemic diseases, such as cancer or renal failure; (3) History of severe psychological disorders that affect cognition and mood, such as schizophrenia and bipolar disorder; (4) Recent treatments that impact inflammatory and myocardial markers, such as corticosteroid therapy; and (5) History of alcohol or substance abuse. All diagnoses were based on the left ventricular ejection fraction (LVEF) < 50% and N-terminal pro-Brain natriuretic peptide (NT-proBNP) ≥ 125 ng/L one week after hospitalization. The Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS) scales were used to assess A&D, respectively[4,5]. Overall, 233 eligible patients were included in this study. The study was approved by the Institutional Review Board of Jingzhou Hospital, Yangtze University (2023-053-01).

Group comparisons

The patients were first grouped according to the degree of A&D indicated by the SAS and SDS scores as follows: No-A&D (SAS < 50 and SDS < 53; n = 65); mild-A&D (SAS 50-59 and SDS 53-62, n = 42); moderate-A&D (SAS 60-69 and SDS 63-72, n = 93); and severe-A&D (SAS > 69 and SDS > 72, n = 33). If the two scores did not meet any of the group requirements simultaneously, the highest SAS or SDS score was used as the grouping criterion.

The demographic and clinical data of the patients in each group were compared to identify indicators of statistically significant differences in A&D. Then, the patients were divided into groups based on the NYHA classification (I, II, III, and IV) and the SAS and SDS scores were compared among the groups[1]. Finally, we determined the effect of A&D on the daily lives of patients based on SAS and SDS scores, with the no/mild-A&D (N/M) group considered not affected and the moderate/severe-A&D (M/S) group considered affected and required targeted intervention[12,13]. Hence, the patients from groups A and B and the patients from groups C and D were combined into the N/M and M/S groups, respectively. We compared the significant indicators between the two groups using regression analysis and evaluated their predictive value using the area under the receiver operating characteristic (AUROC) curve.

Observed indicators

The data included in the analysis were as follows: Sex, age, disease course, NYHA classification, myocardial indicators such as LVEF, left ventricular end-diastolic dimension (LVEDd), NT-proBNP, and soluble growth stimulation expressed gene 2 protein, and inflammatory factors such as IL-6, TNF-α, hs-CRP, and high sensitivity cardiac troponin.

Statistical analysis

All statistical analyses were conducted using SPSS software for Windows (version 26.0; IBM Corp., Armonk, NY, United States). Quantitative data are expressed as the mean ± SD, while qualitative data are expressed as the number of cases (n) and proportions (%). For inter-group comparisons, t-tests, analysis of variance (ANOVA), or non-parametric tests were used depending on whether the quantitative data followed normal distribution and homogeneity of variances. χ^2 tests were used for inter-group comparisons of qualitative data. Logistic regression was used for multivariate analysis to calculate the odds ratios (OR) and 95% confidence intervals (CI). P values < 0.05 were considered statistically significant.

RESULTS

Clinical characteristics

In the inter-group analysis, differences in LVEDd (P < 0.05) and in NYHA class, LVEF, NT-proBNP, IL-6, and TNF-α (P < 0.001) were observed between the no-A&D and severe-A&D groups. No other variables exhibited differences between the two groups (P > 0.05) (Table 1). Since LVEF, NT-proBNP, IL-6, and TNF-α were quantitative variables with large inter-group differences, post hoc multiple comparisons were performed (Figure 1).

The LVEF and IL-6 levels in the no-A&D group were clearly different than those of the mild-A&D, moderate-A&D, and severe-A&D groups (P < 0.01), which all had similar levels (P > 0.05) (Figure 1A and D). LVEDd exhibited differences in the no-A&D and moderate-A&D/severe-A&D group comparisons (P < 0.05). However, when the moderate-A&D group was compared with the other groups, the differences were not significant (P > 0.05) (Figure 1B). The NT-proBNP levels showed no significant differences between no-A&D and mild-A&D groups or between the moderate and severe-A&D groups (P > 0.05). However, differences in NT-proBNP levels were observed and highlighted when the no-A&D and mild-A&D groups were compared with the moderate-A&D and severe-A&D groups (P < 0.001) (Figure 1C). Furthermore, significant differences in TNF-α levels were found between the no-A&D/mild-A&D and moderate-A&D/severe A&D groups (P < 0.05), the no-A&D and mild-A&D groups (P < 0.05) but not between the moderate-A&D and severe-A&D groups (P > 0.05) (Figure 1E).

The effect of NYHA on SAS and SDS scores

We found that the SAS and SDS scores of patients with CHF increased as the NYHA class improved (P < 0.05) (Table 2).

Table 1 Comparison of general patient data between the different anxiety and depression groups

Observation indices	No-A&D (*n* = 65)	Mild-A&D (*n* = 42)	Moderate-A&D (*n* = 93)	Severe-A&D (*n* = 33)	*P* value
Sex					0.686
Male	27 (41.54)	20 (47.61)	47 (50.54)	17 (51.52)	
Female	38 (58.46)	22 (52.39)	46 (49.46)	16 (48.48)	
Age (yr, mean ± SD)	63.20 ± 14.75	64.93 ± 12.81	66.08 ± 10.99	66.67 ± 12.78	0.476
Course of disease (month, mean ± SD)	68.00 ± 17.74	66.36 ± 20.49	68.53 ± 15.97	68.97 ± 20.40	0.948
NYHA, *n* (%)					< 0.001
I	16 (24.62)	6 (14.29)	3 (3.23)	4 (12.12)	
II	27 (41.54)	8 (19.05)	26 (27.96)	8 (24.24)	
III	21 (32.31)	24 (57.14)	54 (58.06)	17 (51.52)	
IV	1 (1.53)	4 (9.52)	10 (10.75)	4 (12.12)	
LVEF (%, mean ± SD)	38.72 ± 3.32	37.08 ± 3.03	36.24 ± 2.59	36.32 ± 3.16	< 0.001
LVEDd (mm, mean ± SD)	59.86 ± 5.22	61.38 ± 4.99	61.85 ± 4.95	62.36 ± 4.52	0.047
NT-proBNP (ng/L, mean ± SD)	1830.32 ± 421.64	1913.90 ± 447.93	2364.98 ± 490.56	2482.70 ± 541.86	< 0.001
ST2 (μg/L, mean ± SD)	51.26 ± 10.25	53.76 ± 9.92	52.97 ± 8.74	53.61 ± 8.07	0.382
IL-6 (ng/L, mean ± SD)	15.13 ± 2.98	17.66 ± 4.33	18.85 ± 3.84	19.38 ± 5.17	< 0.001
TNF-α (ng/L, mean ± SD)	28.89 ± 5.85	31.72 ± 7.08	34.68 ± 5.84	35.32 ± 5.1	< 0.001
hs-CRP (ng/L, mean ± SD)	12.27 ± 2.67	12.49 ± 2.71	13.03 ± 2.45	13.22 ± 2.54	0.185
hs-cTn (ng/L, mean ± SD)	22.94 ± 7.83	24.53 ± 7.99	24.45 ± 6.22	24.40 ± 6.67	0.293

NYHA: New York Heart Association; A&D: Anxiety and depression; LVEF: Left ventricular ejection fraction; LVEDd: Left ventricular end-diastolic dimension; NT-proBNP: N-terminal pro-brain natriuretic peptide; ST2: Growth stimulation expressed gene 2; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-alpha; hs-CRP: Hypersensitive C-reactive protein; hs-cTn: High sensitivity cardiac troponin.

Table 2 Comparison of Self-Rating Anxiety Scale and Self-Rating Depression Scale scores among different New York Heart Association classes

Observation indices	I (*n* = 29)	II (*n* = 69)	III (*n* = 116)	IV (*n* = 19)	*P* value
SAS (mean ± SD)	51.17 ± 16.54	53.84 ± 17.87	59.82 ± 15.51	65.58 ± 16.76	0.003
SDS (mean ± SD)	53.52 ± 16.85	56.72 ± 17.60	62.46 ± 14.75	68.89 ± 12.40	0.001

SAS: Self-Rating Anxiety Scale; SDS: Self-Rating Depression Scale.

Patients with NYHA class III and IV CHF had higher SAS and SDS scores than those with NYHA class I and II ($P < 0.05$) (Figure 2).

Prediction of early intervention

When comparing the myocardial and inflammatory level indicators, we found that the effects of LVEF, LVEDd, NT-proBNP, IL-6, TNF-α, and hs-CRP were larger than other observed indicators between the N/M and M/S groups ($P < 0.05$). Further details are presented in Table 3. The regression analysis identified LVEF, NT-proBNP, and IL-6 as independent predictors of CHF ($P < 0.05$), with IL-6 having the strongest predictive value (OR = 1.271, 95%CI: 1.095-1.476), followed by NT-proBNP (OR = 1.004, 95%CI: 1.003-1.006). We also found that LVEF was a protective factor against A&D as it increased (OR = 0.350, 95%CI: 0.226-0.541). The other variables were not deemed statistically significant in the regression analysis. Further details are presented in Table 4. The AUROC curve of the three independent factors showed that NT-proBNP had the best predictive effect, with an AUROC of 0.781 (0.724-0.839), whereas the predictive effects of LVEF and IL-6 were moderate and similar, with AUROCs of 0.661 (0.591-0.732) and 0.691 (0.624-0.758), respectively. The overall combined predictive value of the three indicators was relatively good, with an AUROC of 0.875 (0.820-0.929). Further details are shown in Figure 3.

Table 3 Inter-group comparison of the observed indicators of anxiety and depressive severity in patients, divided based on the requirement for early intervention

Observation indices	No/mild-A&D (N/M) (*n* = 107)	Moderate/severe-A&D (N/S) (*n* = 126)	*t*/*Z*/χ^2	*P* value
LVEF (%, mean ± SD)	38.08 ± 3.30	36.26 ± 2.72	4.536	< 0.001
LVEDd (mm, mean ± SD)	60.46 ± 5.16	61.98 ± 4.83	2.778	0.005
NT-proBNP (ng/L, mean ± SD)	1863.13 ± 432.00	2395.81 ± 505.30	8.656	< 0.001
ST2 (μg/L, mean ± SD)	52.24 ± 10.15	53.14 ± 8.54	0.908	0.364
IL-6 (ng/L, mean ± SD)	16.12 ± 3.76	18.99 ± 4.21	5.024	< 0.001
TNF-α (ng/L, mean ± SD)	30.00 ± 6.48	34.84 ± 5.64	6.105	< 0.001
hs-CRP (ng/L, mean ± SD)	12.36 ± 2.67	13.08 ± 2.46	2.144	0.033
hs-cTn (ng/L, mean ± SD)	23.56 ± 7.89	24.44 ± 6.31	1.301	0.193

A&D: Anxiety and depression; LVEF: Left ventricular ejection fraction; LVEDd: Left ventricular end-diastolic dimension; NT-proBNP: N-terminal pro-brain natriuretic peptide; ST2: Growth stimulation expressed gene 2; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-alpha; hs-CRP: Hypersensitive C-reactive protein; hs-cTn; High sensitivity cardiac troponin; N/M: No/mild.

Table 4 Regression analysis of the myocardial and inflammatory level indicators between the no/mild and moderate/severe groups

Observation indices	*β*	OR	*P* value	95%CI
LVEF	-1.050	0.350	< 0.001	0.226-0.541
LVEDd	-0.182	0.834	0.095	0.673-1.032
NT-proBNP	0.004	1.004	< 0.001	1.003-1.006
IL-6	0.240	1.271	0.002	1.095-1.476
TNF-α	-0.002	0.957	0.998	0.928-1.073
hs-CRP	-0.430	0.651	0.060	0.416-1.019

LVEF: Left ventricular ejection fraction; LVEDd: Left ventricular end-diastolic dimension; NT-proBNP: N-terminal pro-brain natriuretic peptide; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-alpha; hs-CRP: Hypersensitive C-reactive protein; OR: Odds ratio; CI: Confidence interval.

DISCUSSION

Heart failure remains a global public health burden. Since mental health affects the incidence and outcomes of various health conditions[14], the psychological status of patients with CHF warrants attention, in addition to investigating diagnostic and treatment methods.

In this study, when comparing the no-A&D to severe-A&D groups, we observed an increase in LVEDd, NT-proBNP, IL-6 and TNF-α levels as the degree of A&D increased, whereas LVEF levels decreased. This finding indicates that patients with CHF may experience increased A&D symptoms as a result of abnormal myocardial parameters and inflammatory stress, resulting in worse outcomes. Physiologically, A&D symptoms manifest as part of the body's response to chronic stress exposure, which causes a maladaptive stress response in which the sympathetic nervous system and hypothalamic-pituitary-adrenal axis are activated. This increases the heart rate, output, and load[15,16] and, over time, the blood flow through the coronary arteries decreases, ultimately leading to myocardial ischemia[17]. While CHF is accompanied by some extent of myocardial dysfunction, the stress response aggravates this by causing further myocardial cell injury, impairing myocardial contractile function, and leading to a reduction in LEVF and an increase in LVEDd. When under significant load, myocardial cells secrete NT-proBNP, which functions as a natriuretic, diuretic, and vasodilator, to reduce pressure and restore homeostasis[18]. NT-proBNP levels increase with the degree of A&D symptoms and changes in LVEF and NT-proBNP levels indicate that A&D further aggravates myocardial dysfunction in patients with CHF. Research has shown that higher serum levels of inflammatory factors can lead to weakening of the strength and mass of the myocardium, a specialized type of tissue in the human body[19]. Therefore, patients with CHF are vulnerable to high levels of inflammation. Additionally, A&D can lead to endocrine and immune system imbalances that promote inflammatory responses in the body[20]. In the current study, IL-6 and TNF-α expression levels gradually increased as the extent of A&D increased, which is consistent with Lamers *et al*[10].

Our results suggest an association between myocardial indicators, inflammatory factor levels, and the degree of A&D. Therefore, when treating patients with both CHF and A&D symptoms, physicians should be aware of the increased risk

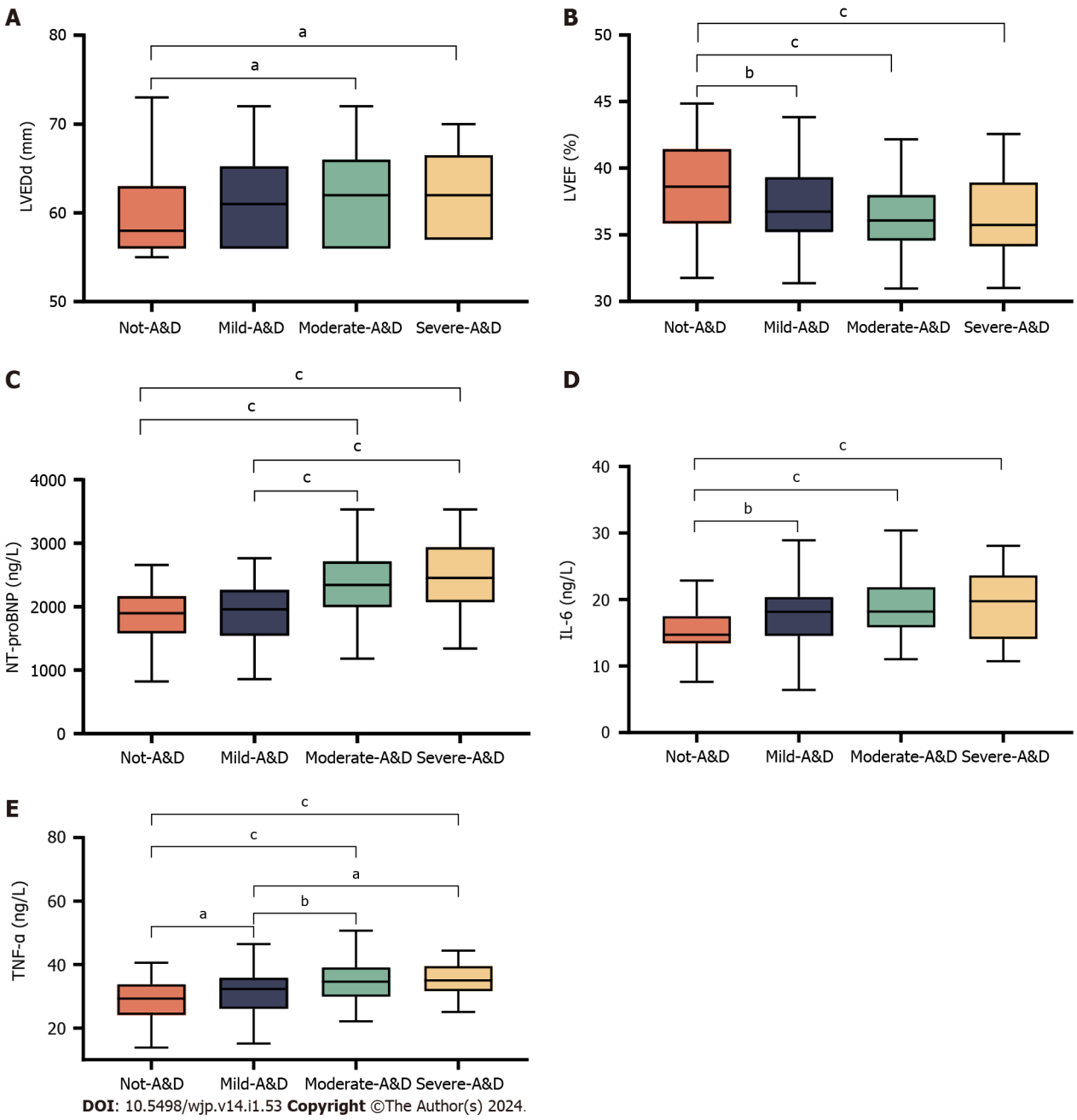

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Figure 1 Post hoc multiple comparisons of significant influencing factors in patients with different levels of anxiety and depression. A: Post hoc multiple comparisons of the left ventricular ejection fraction; B: Post hoc multiple comparisons of the left ventricular end-diastolic dimensions; C: Post hoc multiple comparisons of N-terminal pro-brain natriuretic peptide; D: Post hoc multiple comparisons of interleukin-6; E: Post hoc multiple comparisons of tumor necrosis factor-alpha (TNF-α). $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$. A&D: Anxiety and depression; No-A&D: No anxiety and depression symptoms; Mild-A&D: Mild anxiety and depression symptoms; Moderate-A&D: Moderate anxiety and depression symptoms; Severe-A&D: Severe anxiety and depression symptoms; LVEF: Left ventricular ejection fraction; LVEDd: Left ventricular end-diastolic dimensions; NT-proBNP: N-terminal pro-brain natriuretic peptide; TNF-α: Tumor necrosis factor-alpha; IL-6: Interleukin-6.

of myocardial ischemia and inflammation and prepare the appropriate prophylactic interventions, such as administering calcium overload inhibitors and anti-inflammatory drugs. Zhao *et al*[21] found that the administration of active oxygen nanomaterials effectively improved drug treatment and reduced side effects. The side effects of any pharmacological intervention for CHF and A&D should be considered to avoid worsening the prognosis of patients. Recent studies have indicated that cognitive behavioral therapy and collaborative care have positive effects on alleviating A&D[22,23], and present a safer way to avoid psychotropic drug-induced secondary myocardial damage.

The NYHA classification assesses the self-reported functional status of patients with CHF and indirectly reflects cardiac function. In the present study, the mean SAS and SDS scores consistently increased with each NYHA class, which is consistent with a previous study[24] exploring depression in patients with coronary heart disease. This finding was unsurprising because the NYHA classification closely reflects the patient's quality of life and the higher the NYHA class, the more restrictions the patient experiences in daily life and mobility, such as inability to work, participate in their hobbies, and socialize, all of which induce A&D[25]. Moreover, A&D can lead to reduced compliance with treatment

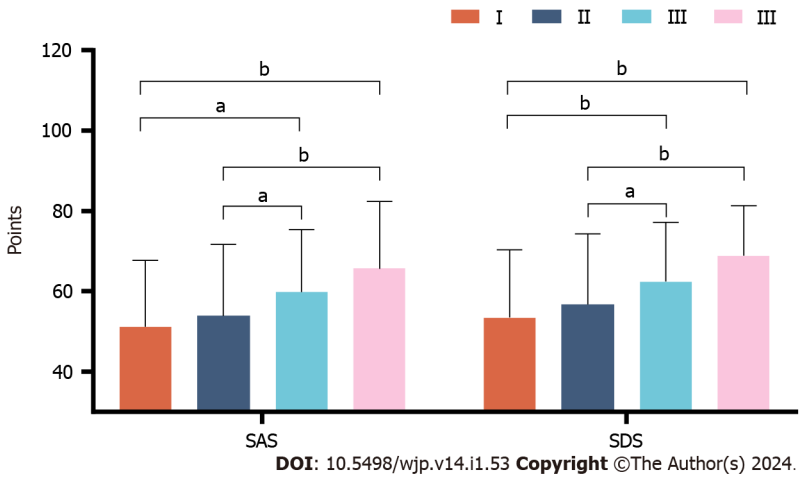

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Figure 2 Post hoc multiple comparisons of Self-Rating Anxiety Scale and Self-Rating Depression Scale scores among different New York Heart Association classes. [a]*P* < 0.05, [b]*P* < 0.01. SAS: Self-Rating Anxiety Scale; SDS: Self-Rating Depression Scale.

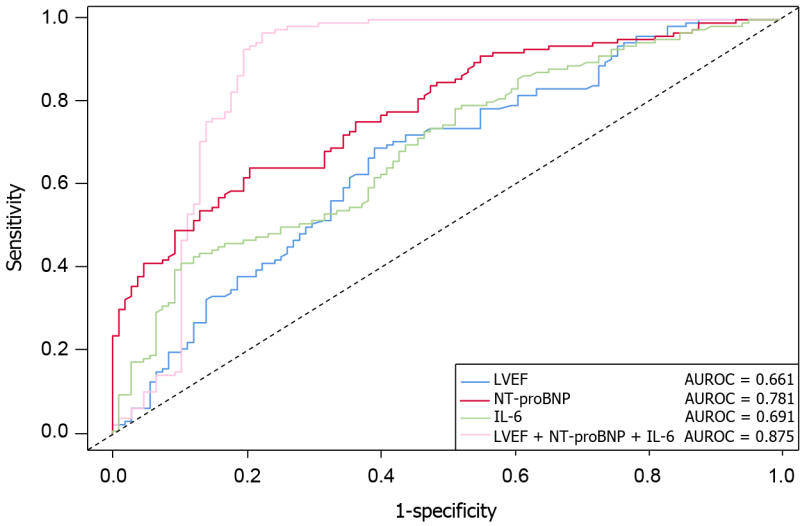

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Figure 3 Dichotomous evaluation of left ventricular ejection fraction, N-terminal pro-brain natriuretic peptide, and interleukin-6 by region under receiver operating characteristics. LVEF: Left ventricular ejection fraction; NT-proBNP: N-terminal pro-brain natriuretic peptide; IL-6: Interleukin-6; AUROC: Area under the receiver operating characteristic curve.

regimens, which further impacts quality of life, resulting in more individuals progressing to higher NYHA classes, increased hospitalization, and mortality. Hence, medical health providers must consider psychological status in the treatment and management of patients with CHF, in addition to physical symptoms and cardiac function. Providing psychological support, educating patients on disease management, and encouraging them to engage in suitable physical activities and socialization are important measures to improve health outcomes of patients with A&D.

In patients where daily activities have not yet been affected by A&E, we do not recommend targeted interventions such as personalized psychological counselling and cognitive behavioral therapy[13,26]. In this study, we observed different SAS and SDS scores in the N/M and M/S groups. Regression analysis revealed that the combination of LEVF, NT-proBNP, and IL-6 had good predictive and discriminative value between the N/M and M/S groups. These factors comprehensively reflect cardiac function, heart load, and inflammatory state; therefore, compared with single-index predictions, they can more accurately determine A&D severity in patients with CHF. Severe A&D is a complex multifactorial disorder that is influenced by genetic, biological, psychological, and environmental factors. Existing studies have shown the predictive value of conventional biochemical indices, such as leukocytes in the hematopoietic system and uric acid in inflammatory mediators, in discriminating bipolar disorder and depression in the general population, with females exhibiting better predictive effects than males (AUROC = 0.793)[27]. Similarly, in the present study, we constructed a model using myocardial indices and inflammatory factors to predict A&D severity in patients with CHF and demonstrated a relatively good prediction effect (AUROC = 0.875). Perhaps, this was attributable to the targeted groupings used in the analysis.

Overall, the combination of biochemical indicators of A&D severity provides an objective reference for the classification of patients, which is essential for accurate diagnosis. Specialized prediction models for comorbidities, such as patients with both A&D and CHF, are also warranted.

In this study, we found a preliminary association between A&D levels, myocardial indicators, and inflammation in patients with CHF and identified potential indicators and models for classifying A&D on a physiological basis. However, this single-center retrospective study had some limitations in terms of the sample size and reliance on standardized self-reported questionnaires. Future longitudinal studies with larger sample sizes are warranted to validate the association between myocardial indicators, inflammation levels, and A&D.

CONCLUSION

Cardiac parameters (NT-proBNP and LVEF) and levels of inflammatory factors (IL-6 and TNF-α) significantly vary with the degree of A&D. IL-6, NT-proBNP, and LVEF are independent factors that can distinguish between moderate and severe A&D from no A&D or mild A&D. When combined, they have a high discriminative ability towards A&D.

ARTICLE HIGHLIGHTS

Research background

Anxiety and depression (A&D) are common in patients with chronic heart failure (CHF). While extensive research on the general demographic characteristics and A&D data in patients with CHF has been conducted, research on myocardial markers and inflammatory factor levels remains limited. Uncovering the relationship between myocardial markers, inflammatory factor levels, and the degree of A&D in patients with CHF can further supplement and assist in evaluating and classifying A&D severity in patients.

Research motivation

The differential levels of myocardial markers and inflammatory factors depending on A&D severity in patients with CHF could serve as objective evidence to assist clinicians in assessing and classifying the extent of A&D. This could correct for the subjectivity of the general assessment scales, facilitating a more precise distinction between CHF patients with different degrees of A&D, enabling physicians to better manage and rationally allocate medical resources, and providing the potential for personalized treatment.

Research objectives

We classified patients with CHF with varying degrees of A&D based on myocardial markers and inflammatory factor levels and showed that some factors had good discriminative ability, providing the possibility of establishing and assisting in the evaluation of A&D severity in patients with CHF based on biochemical markers.

Research methods

We further explored the inter-group differences in myocardial and inflammatory indicators and showed their ability to predict A&D severity in patients with CHF using regression and the area under the receiver operating characteristic curve (AUROC) analyses.

Research results

Left ventricular ejection fraction, N-terminal pro-brain natriuretic peptide, and interleukin-6 were used in combination to predict and classify 233 patients with CHF in this study into no/mild- and moderate/severe-A&D and achieved good results (AUROC = 0.875, 95% confidence interval: 0.820-0.929).

Research conclusions

Based on our retrospective analysis, we propose that the combination of myocardial and inflammatory factor levels could assist in assessing and classifying the severity of A&D in patients with CHF.

Research perspectives

We plan to further combine other biochemical markers, such as hormone levels, with these classification-effective factors and apply targeted interventions to observe patient outcomes and evaluate changes in A&D severity among patients. This will help to validate our preliminary findings and investigate the potential roles of these biochemical markers in guiding CHF management.

FOOTNOTES

Co-first authors: Li Zhang and Qiang Wang.

Author contributions: Zhang L and Wang Q contributed equally to this work as first co-authors. Zhang L and Wang Q conceived, designed, and refined the study protocol; Cui HS was involved in data collection and analysis; Luo YY guided and supervised the research; and all authors were involved in the critical review of the results and have contributed to, read, and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Jingzhou Hospital, Yangtze University Institutional Review Board (2023-053-01).

Informed consent statement: The requirement for informed consent was waived given the retrospective nature of the study.

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Data sharing statement: The clinical data used in this study can be obtained from the corresponding author upon request.

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REFERENCES

1 **McDonagh TA**, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2022; **24**: 4-131 [PMID: 35083827 DOI: 10.1002/ejhf.2333]

2 **Al Shamiri MQ**, Almushawah AA, Alsomali AH, Alsuwayegh MB, Aljaffer MA, Hayajneh AM, Prajjwal P. The Prevalence of Depression and Anxiety in Heart Failure Patients in Saudi Arabia: An Original Study. *Cureus* 2023; **15**: e36997 [PMID: 37139016 DOI: 10.7759/cureus.36997]

3 **Manolis TA**, Manolis AA, Melita H, Manolis AS. Neuropsychiatric disorders in patients with heart failure: not to be ignored. *Heart Fail Rev* 2023; **28**: 821-858 [PMID: 36547867 DOI: 10.1007/s10741-022-10290-2]

4 **Alhurani AS**, Dekker RL, Abed MA, Khalil A, Al Zaghal MH, Lee KS, Mudd-Martin G, Biddle MJ, Lennie TA, Moser DK. The association of co-morbid symptoms of depression and anxiety with all-cause mortality and cardiac rehospitalization in patients with heart failure. *Psychosomatics* 2015; **56**: 371-380 [PMID: 25556571 DOI: 10.1016/j.psym.2014.05.022]

5 **Celano CM**, Villegas AC, Albanese AM, Gaggin HK, Huffman JC. Depression and Anxiety in Heart Failure: A Review. *Harv Rev Psychiatry* 2018; **26**: 175-184 [PMID: 29975336 DOI: 10.1097/HRP.0000000000000162]

6 **Hao G**, Wang X, Chen Z, Zhang L, Zhang Y, Wei B, Zheng C, Kang Y, Jiang L, Zhu Z, Zhang J, Wang Z, Gao R; China Hypertension Survey Investigators. Prevalence of heart failure and left ventricular dysfunction in China: the China Hypertension Survey, 2012-2015. *Eur J Heart Fail* 2019; **21**: 1329-1337 [PMID: 31746111 DOI: 10.1002/ejhf.1629]

7 **Wang Z**, Cai Z, Ferrari MW, Liu Y, Li C, Zhang T, Lyu G. The Correlation between Gut Microbiota and Serum Metabolomic in Elderly Patients with Chronic Heart Failure. *Mediators Inflamm* 2021; **2021**: 5587428 [PMID: 34744513 DOI: 10.1155/2021/5587428]

8 **Yasuhara S**, Maekawa M, Bamba S, Kurihara M, Nakanishi N, Yamamoto T, Sakai H, Yagi N, Nakagawa Y, Sasaki M. Energy Metabolism and Nutritional Status in Hospitalized Patients with Chronic Heart Failure. *Ann Nutr Metab* 2020; **76**: 129-139 [PMID: 32259814 DOI: 10.1159/000507355]

9 **Liu Z**, Xv Y, Liu X, Zhou X. Associations of systemic inflammatory markers with the risks of chronic heart failure: A case-control study. *Clinics (Sao Paulo)* 2022; **77**: 100056 [PMID: 35714381 DOI: 10.1016/j.clinsp.2022.100056]

10 **Lamers F**, Milaneschi Y, Smit JH, Schoevers RA, Wittenberg G, Penninx BWJH. Longitudinal Association Between Depression and Inflammatory Markers: Results From the Netherlands Study of Depression and Anxiety. *Biol Psychiatry* 2019; **85**: 829-837 [PMID: 30819515 DOI: 10.1016/j.biopsych.2018.12.020]

11 **Zou W**, Feng R, Yang Y. Changes in the serum levels of inflammatory cytokines in antidepressant drug-naïve patients with major depression. *PLoS One* 2018; **13**: e0197267 [PMID: 29856741 DOI: 10.1371/journal.pone.0197267]

12 **Zung WW**. A rating instrument for anxiety disorders. *Psychosomatics* 1971; **12**: 371-379 [PMID: 5172928 DOI: 10.1016/S0033-3182(71)71479-0]

13 **Zung WW**. A SELF-RATING DEPRESSION SCALE. *Arch Gen Psychiatry* 1965; **12**: 63-70 [PMID: 14221692 DOI: 10.1001/archpsyc.1965.01720310065008]

14 **Cai W**, Mueller C, Li YJ, Shen WD, Stewart R. Post stroke depression and risk of stroke recurrence and mortality: A systematic review and meta-analysis. *Ageing Res Rev* 2019; **50**: 102-109 [PMID: 30711712 DOI: 10.1016/j.arr.2019.01.013]

15 **Mifsud KR**, Reul JMHM. Mineralocorticoid and glucocorticoid receptor-mediated control of genomic responses to stress in the brain. *Stress* 2018; **21**: 389-402 [PMID: 29614900 DOI: 10.1080/10253890.2018.1456526]

16 **Ketchesin KD**, Stinnett GS, Seasholtz AF. Corticotropin-releasing hormone-binding protein and stress: from invertebrates to humans. *Stress* 2017; **20**: 449-464 [PMID: 28436309 DOI: 10.1080/10253890.2017.1322575]

17 **Sara JDS**, Toya T, Ahmad A, Clark MM, Gilliam WP, Lerman LO, Lerman A. Mental Stress and Its Effects on Vascular Health. *Mayo Clin Proc* 2022; **97**: 951-990 [PMID: 35512885 DOI: 10.1016/j.mayocp.2022.02.004]

18 **Alawieh H**, Chemaly TE, Alam S, Khraiche M. Towards Point-of-Care Heart Failure Diagnostic Platforms: BNP and NT-proBNP Biosensors. *Sensors (Basel)* 2019; **19** [PMID: 31744130 DOI: 10.3390/s19225003]

19 **Tuttle CSL**, Thang LAN, Maier AB. Markers of inflammation and their association with muscle strength and mass: A systematic review and meta-analysis. *Ageing Res Rev* 2020; **64**: 101185 [PMID: 32992047 DOI: 10.1016/j.arr.2020.101185]

20 **Qiu W**, Cai X, Zheng C, Qiu S, Ke H, Huang Y. Update on the Relationship Between Depression and Neuroendocrine Metabolism. *Front Neurosci* 2021; **15**: 728810 [PMID: 34531719 DOI: 10.3389/fnins.2021.728810]

21 **Zhao T**, Wu W, Sui L, Huang Q, Nan Y, Liu J, Ai K. Reactive oxygen species-based nanomaterials for the treatment of myocardial ischemia reperfusion injuries. *Bioact Mater* 2022; **7**: 47-72 [PMID: 34466716 DOI: 10.1016/j.bioactmat.2021.06.006]

22 **Freedland KE**, Skala JA, Carney RM, Steinmeyer BC, Rubin EH, Rich MW. Sequential Interventions for Major Depression and Heart Failure Self-Care: A Randomized Clinical Trial. *Circ Heart Fail* 2022; **15**: e009422 [PMID: 35973032 DOI: 10.1161/CIRCHEARTFAILURE.121.009422]

23 **Bekelman DB**, Allen LA, McBryde CF, Hattler B, Fairclough DL, Havranek EP, Turvey C, Meek PM. Effect of a Collaborative Care Intervention vs Usual Care on Health Status of Patients With Chronic Heart Failure: The CASA Randomized Clinical Trial. *JAMA Intern Med* 2018; **178**: 511-519 [PMID: 29482218 DOI: 10.1001/jamainternmed.2017.8667]

24 **Yin H**, Liu Y, Ma H, Liu G, Guo L, Geng Q. Associations of mood symptoms with NYHA functional classes in angina pectoris patients: a cross-sectional study. *BMC Psychiatry* 2019; **19**: 85 [PMID: 30836983 DOI: 10.1186/s12888-019-2061-3]

25 **Nabdi S**, Boujraf S, Benzagmout M. The influence of physical activity, social relationships, and diet intake on depression: a case-series study. *Ann Med Surg (Lond)* 2023; **85**: 1395-1402 [PMID: 37229093 DOI: 10.1097/MS9.0000000000000406]

26 **Plati DK**, Tripoliti EE, Bechlioulis A, Rammos A, Dimou I, Lakkas L, Watson C, McDonald K, Ledwidge M, Pharithi R, Gallagher J, Michalis LK, Goletsis Y, Naka KK, Fotiadis DI. A Machine Learning Approach for Chronic Heart Failure Diagnosis. *Diagnostics (Basel)* 2021; **11** [PMID: 34679561 DOI: 10.3390/diagnostics11101863]

27 **Trivedi MH**. Major Depressive Disorder in Primary Care: Strategies for Identification. *J Clin Psychiatry* 2020; **81** [PMID: 32220155 DOI: 10.3389/fpsyt.2022.875141]

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ORIGINAL ARTICLE

Retrospective Study

Postpartum quality of life and mental health in women with heart disease: Integrated clinical communication and treatment

Jia-Lin Liu, Qi Wang, Dong-Ying Qu

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Abstract

BACKGROUND

Postpartum quality of life (QoL) in women with heart disease has been neglected.

AIM

To improve clinical communication and treatment, we integrated medical data and subjective characteristics to study postpartum QoL concerns.

METHODS

The study assessed QoL 6 wk after birth using the 12-Item Short-Form Health Survey. The Edinburgh Postnatal Depression Scale, Cardiac Anxiety Questionnaire, European Heart Failure Self-Care Behavior Scale, and a self-designed questionnaire based on earlier research were also used to assess patient characteristics. Patient data were collected. Prediction models were created using multiple linear regression.

RESULTS

This retrospective study examined postpartum QoL in 105 cardiac patients. Postpartum QoL scores were lower (90.69 ± 13.82) than those of women without heart disease, with physical component scores (41.09 ± 9.91) lower than mental component scores (49.60 ± 14.87). Postpartum depression (33.3%), moderate anxiety (37.14%), pregnancy concerns (57.14%), offspring heart problems (57.14%), and life expectancy worries (48.6%) were all prevalent. No previous cardiac surgery, multiparity, higher sadness and cardiac anxiety, and fear of unfavorable

pregnancy outcomes were strongly related to lower QoL ($R^2 = 0.525$).

CONCLUSION

Postpartum QoL is linked to physical and mental health in women with heart disease. Our study emphasizes the need for healthcare workers to recognize the unique characteristics of these women while developing and implementing comprehensive management approaches during their maternity care.

Key Words: Heart disease; Pregnancy; Postpartum; Quality of life; Mental health

Core Tip: This study illuminates the intimate connection between quality of life (QoL) and physical and psychological well-being in postpartum women with cardiac conditions. Results showed lower postpartum QoL scores, including higher depression and cardiac anxiety, and worry about adverse pregnancy outcomes. Thus, healthcare providers must recognize their unique features when developing and implementing comprehensive obstetric care plans for these women.

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INTRODUCTION

Heart disease during pregnancy includes pre-existing or newly diagnosed congenital heart disease, pulmonary hypertension, aortic disease, valvular heart disease, coronary artery disease, cardiomyopathy, heart failure, and arrhythmias[1]. It complicates 1%-4% of pregnancies and accounts for 15% of maternal deaths[2]. Due to the rise in the proportion of high-risk individuals in the modified World Health Organization (WHO) pregnancy risk classification, cardiovascular disease has become the leading cause of maternal mortality worldwide[2].

Women with heart disease experience pregnancies with a 1% mortality rate, which is 100 times higher than those without heart disease[3]. Dramatic hemodynamic changes during pregnancy-increased blood volume and cardiac output, contractions and pain during delivery, and postpartum inferior vena cava reflux[4] increase the heart burden and worsen heart failure symptoms. Strict multidisciplinary team management (MDT) is needed, resulting in increased obstetric examinations and hospitalizations throughout pregnancy for 25% of affected women[3]. Compared to women without heart disease, women with heart disease are more likely to experience pregnancy comorbidities, cesarean section rates, unfavorable pregnancy outcome, neonatal preterm delivery and complications, and shorter gestational periods[2,3,5].

In addition, these women suffer notable psychological stress. Following a diagnosis, they desire to parent[6-11] but lack autonomy and control over pregnancy decisions[7,12]. When experiencing cardiac symptoms during and after pregnancy, they feel helpless, isolated, frightened, and vulnerable[7,10,11,13-15], wondering about their safety and their children's health and care[6-8,10-12,16]. With complex diagnoses, people struggle to comprehend their illness fully and precisely[6,8,9,16], rely heavily on medical institutions and personnel[6,11,16], and demand more social support[7,11,16,17]. They suffer physical and psychological deterioration due to prognostic uncertainty and the complexity of pregnancy, delivery, and postpartum rehabilitation. Long-term effects include poorer quality of life (QoL), impaired postpartum recovery, heart disease self-management challenges, compromised mother-infant relationships, increased illness burden, and family and social issues[15,16]. Guidelines emphasize the importance of MDT management and continuous close care during and after pregnancy for women with heart disease[1,18]. This approach ensures safe pregnancies and seamless transitions, requiring strong cooperation with patients and their families[19]. These women need good medical care throughout pregnancy, delivery, and postpartum recovery[7,16,17].

Compared to their healthy peers, women with heart disease during and after pregnancy had a reduced QoL[20-22], as well as physical discomfort and mental health problems[14,15,20-23]. These issues result in decreased adherence and bad healthcare practices[10,21,23]. Existing research focuses on the clinical and physiological outcomes of these pregnancies [21,24]. However, it lacks comprehensive subjective and objective data on patients' health lists, heart disease, and emotional-psychological effects on postpartum QoL[21,24]. Moreover, there are inadequate assessments of the factors influencing postpartum QoL. Due to the unique characteristics of these women, web-based patient data are often collected long after delivery, which may not accurately reflect the crucial short-term postpartum transition period. In addition, the healthcare system continues to fall short of meeting the needs of women experiencing high-risk pregnancies [13].

This study examined the postpartum QoL of women with heart disease about their demographic, clinical and pregnancy features and self-reported mental health status. Furthermore, the study aimed to explore the factors influencing healthcare professionals' (HCPs) knowledge of physical and mental health in women with high-risk pregnancies. This information seeks to improve two-way communication and provide a reference for patient-centered

continuous MDT management during and after pregnancy.

MATERIALS AND METHODS

Study protocol

Patients from the Maternal Cardiology Consultation Center of The General Hospital of Northern Theater were chosen for this cross-sectional retrospective study. Between March 2021 and March 2023, these patients received MDT consultations and successfully gave birth. Six weeks postpartum, participants completed an electronic version of the questionnaire, and study staff was quickly accessible for consultation in case of data loss.

Participants

Inclusion criteria: (1) Pregnant women diagnosed with heart disease according to the 2018 European Society of Cardiology Guidelines[1]; (2) delivered one or more infants after 20 wk of gestation with a minimum birth weight of 400 g; (3) ≥ 18 years of age; and (4) adequate physical, cognitive and linguistic abilities to complete the self-report questionnaire. Exclusion criteria: (1) Prior history of mental illness or current use of psychotropic drugs; (2) multiple pregnancies; and (3) primary diagnosis involving immunological, renal, or respiratory disorders other than heart disease.

Measurement

We obtained demographic, clinical and pregnancy variables from the hospital information system. In addition, participants completed the Chinese versions of the Edinburgh Postnatal Depression Scale (EPDS), Cardiac Anxiety Questionnaire (CAQ), European Heart Failure Self-Care Behavior Scale (EHFScBS), and 12-Item Short-Form Health Survey (SF-12) at 6 wk postpartum. We also developed a questionnaire consisting of seven items on patient compliance, understanding of their condition, and worries linked to heart disease based on data from prior studies[20-22].

Postpartum depression

Postpartum depression is a major depressive episode within 6 wk of delivery[25]. EPDS is a well-known and authoritative screening instrument for postpartum depression, renowned for its simplicity and validity in worldwide settings [26]. Higher scores imply more severe depressive symptoms[27]. The Chinese version of the EPDS recommends a score of 10 as indicative of depressive symptoms[28]. In our study, a more alert threshold of 13 implied potential postpartum depression (sensitivity range from 0.67 to 1.0 and specificity ≥ 0.87)[27,29]. The measure showed high internal consistency with a Cronbach's α of 0.845.

Heart-focused anxiety

Heart-focused anxiety (HFA) is distinguished from general anxiety by the fear of heart-related sensations, avoidance of symptom-caused activities, and obsession with heart-related symptoms[30]. The CAQ, the most widely used scale for assessing HFA in clinical settings, has shown solid psychometric features across multiple nations and groups, including those with and without heart disease[31]. The CAQ consists of 18 items corresponding to the definition of HFA and three subscales (fear, avoidance, and heart-focused attention), each assessed on a 5-point Likert scale (ranging from 0 to 4). The total and subscale scores are averaged, with higher scores indicating a more severe HFA. Currently, there are no established clinical cutoff scores for this metric[30]. This study displayed strong internal consistency (Cronbach's α = 0.909).

Medical behavior adherence

Self-management comprises the decisions and strategies individuals use to maintain life, promote healthy functioning, and enhance well-being, and it has a significant role in enhancing the prognosis of heart failure patients[32]. The EHFScBS measures heart failure-related self-care behaviors recommended by American Heart Association guidelines for secondary prevention, including medication adherence, dietary management, exercise, symptom monitoring, and aid-seeking[32]. There are 12 items, and each scored on a 5-point Likert scale ranging from 1 to 5[32]. Higher scores denote poorer self-care[32]. The instrument exhibits solid internal consistency, as evidenced by a Cronbach's α of 0.880.

QoL

QoL assesses physical, mental and social well-being and can help diagnose diseases and improve patient-clinician communication[33]. QoL is commonly measured using the SF-36 Health Survey[34]. The abridged SF-12, which has strong reliability and validity, was used in this investigation[35]. The SF-12 has two subscales, Physical Component Summary (PCS) and Mental Component Summary (MCS), with each total score ranging from 0 to 100, and 12 items with minimal information loss compared to the SF-36[36]. These subscales include eight dimensions of general health, physical functioning, role-physical, bodily pain, vitality, social functioning, role-emotional and mental health. Higher total scores imply better functioning in this rating[36]. Chinese people had mean SF-12 PCS and MCS scores of 50.2 and 48.4, respectively[37]. Cronbach's α was 0.808, indicating excellent internal consistency.

Statistical methods

Our study needed at least 63 women[38]. Appendix A provides sample size calculations. Categorical data were expressed as percentages and continuous numerical variables were expressed as ranges, means ± SDs, and median ± interquartile

ranges. Correlations between continuous numerical variables (*e.g.*, gestational age, gestational weeks, newborn weight, EPDS, CAQ and EHFScBS) and SF-12 were determined using Pearson or Spearman coefficients.

Other potential physical and psychological factors were identified using univariate analysis utilizing the independent *t* test and ANOVA, followed by least significant difference *post hoc* testing. To include as many potential risk factors as possible in the linear regression model, we performed a multivariate analysis of variance with a *P* threshold of 0.10. Variables were manually screened based on their *P* values, and residual analyses were used to assess independence, normality, and homoscedasticity.

The Durbin-Watson (D-W) test was applied to further examine independence, while the variance inflation factor (VIF) and tolerance statistics were used to assess collinearity. All occurring *P* values and tests were conducted on a two-sided basis. $P < 0.05$ indicated statistical significance. SPSS Statistics 27.0 (SPSS Inc., Chicago, IL, United States) was utilized.

RESULTS

Participants

We sent out electronic questionnaires to 162 women who met the criteria and received 130 responses (participation rate of 80.25%); of which, 15 were excluded due to a lack of clarification regarding the diagnosis of heart disease during the postpartum review. Finally, 105 postnatal individuals with various heart diseases were included (Appendix B).

Objective medical characteristics and postpartum QoL

Most women with heart disease were aged 25-34 years. These women typically had a high level of education and income (> 80000 RMB), and they either did not work or worked less during pregnancy (Table 1). We examined the association between the demographic characteristics of women with heart disease and their QoL following childbirth. None of these factors were found to impact postpartum QoL in our patient population.

The findings of clinical features are reported in Table 2. Most patients were of average weight and were newly diagnosed with structural heart disease. The postpartum QoL of patients who underwent heart surgery was superior ($P = 0.007$). We classified patients using the New York Heart Association (NYHA) and modified WHO pregnancy risk classifications. Patients with worse heart function had lower postpartum QoL scores ($P < 0.001$). Those with modified WHO pregnancy risk severity grades II or III had significantly poorer postpartum QoL than those with severity grades I or III ($P = 0.003$, $P = 0.016$, respectively). Other clinical considerations had no bearing on postpartum QoL.

Table 3 displays the features of these pregnancies. Most women were primipara without complications. We observed high rates of cesarean delivery (89.52%), short gestational weeks, and low newborn weight. Postpartum QoL was lower for multiparous than primiparous women ($P = 0.026$) and correlated positively with gestational weeks ($P = 0.040$). After birth, 35.24% of neonates required hospitalization, and their mothers' postpartum QoL was poorer ($P = 0.037$). Other pregnancy factors were unrelated to postpartum QoL.

Emotional and psychological characteristics, compliance, and postpartum QoL

Table 4 presents the key results for the EPDS, CAQ, EHFScBS and SF-12, revealing that 33.33% (score ≥ 13) of the women screened positive for postpartum depression, which is considerably higher than the rate of positive perinatal screening (50.47% *vs* 40%, score ≥ 10)[39]. The sample EPDS mean score was 10.08 ± 5.08, above the usual degree of postpartum depression in Chinese women (7.09 ± 4.41)[40].

A total of 37.14% of patients demonstrated at least moderate cardiac anxiety, with the highest heart-focused attention score (2.40 ± 1.34), followed by avoidance (1.59 ± 0.82) and fear (1.52 ± 0.73). The postnatal PCS score (41.09 ± 9.91) was significantly lower than the standard population level (50.2)[37], and the MCS score (49.60 ± 14.87) on the SF-12. The Pearson correlation coefficients among the EPDS, CAQ, EHFScBS and SF-12 were significant (-0.568, $P < 0.001$; -0.461, $P < 0.001$; and -0.215, $P < 0.028$, respectively).

The majority (61.90%) of patients had their recovery and cardiac status assessed in the hospital following delivery (Table 5). Over half (55.56%) of the patients who skipped medical appointments claimed family and childcare commitments. Some patients (39.05%) were advised against having children, and most (79.05%) acknowledged the complexity of heart disease diagnosis during pregnancy. A substantial proportion of patients with heart disease were concerned about unfavorable pregnancy outcomes (57.14%) and the risk of their children developing heart issues (57.14%), followed by concerns about how heart disease might affect their future life expectancy (48.57%). Those with poorer postpartum QoL ($P < 0.05$) voiced these concerns.

Determinants of postpartum QoL

We used $P > 0.1$ as the criterion for exclusion. Gestational age, prior cardiac surgery, heart disease type, modified WHO pregnancy risk classification, NYHA classification, primiparity status, gestational comorbidities, planned pregnancy, gestational weeks, neonatal weight and hospitalization, EPDS score, CAQ score, and EHFScBS score were selected for the model. Worries about fetus heart health, future life expectancy, and adverse pregnancy outcomes were also considered. After manual exclusion, the result of the linear regression model is given in Table 6. It highlights that prepregnancy cardiac surgery, CAQ, EPDS, fear of an unfavorable pregnancy, and primiparity can successfully explain the SF-12 scores ($P < 0.001$). The model fit the data well (adjusted $R^2 = 0.525$), and there was no evidence of linearity and normality violations in the residuals. The VIF ranged from 1.020 to 1.173, while tolerance statistics varied between 0.852 and 0.980. The D-W test showed adequate variance independence. Upon analyzing the SF-12 outcomes alongside both subjective

Table 1 Demographic characteristics and postpartum quality of life (mean ± SD)

Variables	*n* (%)		*P* value
Gestational age, yr	31.00 ± 5.0 (19.0-49.0)[1]		0.064
Gestational age, yr			0.266
< 25	8 (7.62)	97.78 ± 9.00	
25-34	80 (76.19)	90.51 ± 13.81	
≥ 35	17 (16.19)	88.21 ± 15.29	
Education			0.915
No more than junior middle school	8 (7.62)	93.14 ± 10.87	
Senior high school	13 (12.38)	87.84 ± 15.43	
Junior college	24 (22.86)	91.86 ± 12.98	
Bachelor degree	49 (46.67)	90.57 ± 15.17	
Master's degree or above	11 (10.48)	90.27 ± 10.35	
Annual household income, RMB			0.559
< 30k	14 (13.33)	94.56 ± 13.24	
30k-80k	23 (21.90)	91.70 ± 12.21	
80k-120k	25 (23.81)	88.66 ± 16.69	
120k-200k	22 (20.95)	89.66 ± 14.55	
200k-300k	15 (14.29)	93.00 ± 9.55	
≥ 300k	6 (5.71)	92.58 ± 15.15	
Work conditions during pregnancy			0.337
Did not work	43 (40.95)	90.78 ± 13.53	
Reduced workload	34 (32.38)	88.27 ± 15.47	
No change and increase in workload	28 (26.67)	93.49 ± 11.96	

[1]Median ± interquartile range (range).

and objective predictors involved in the model, it was observed that prepregnancy heart surgery and reduced levels of pregnancy anxiety contributed to enhanced postpartum QoL. As EPDS scores increased, so did the value of SF-12. Similar results were observed when analyzing the CAQ variable. Additionally, postpartum QoL for primiparous women with heart disease was substantially enhanced.

DISCUSSION

Our research revealed that postpartum women with cardiac conditions typically exhibited compromised QoL and had significant physical and psychological stresses throughout their maternity journey. In addition, the deterioration of physical and mental health during and after pregnancy was substantially connected with the degree of QoL impairment these women with heart disease had. QoL is essential to postpartum recovery and secondary prevention for heart disease patients. Unlike HCPs, who prioritize clinical and physical outcomes such as mortality and mode of birth, these women and their families prioritize overall wellness[24]. Health includes physical, emotional, and role functioning, QoL, and care provision[24]. Nonetheless, many of them are dissatisfied with these qualities[15]. Following earlier research[15,20,21,41], our data suggested that postpartum QoL was generally diminished in women with heart disease. Some evidence indicates that the emotional burden of pregnancy and the postpartum period decreased over time, resulting in an increase in QoL[42] and beneficial physical and psychological results over the long run[22]. It has also been shown that persons with congenital heart disease who have children have higher health satisfaction, mental health, and social support scores [43]. However, some studies have reported that poor QoL and mental health outcomes after pregnancy may not necessarily improve beyond 6 wk postpartum[21,23]. As a result, these issues can be long-lasting and may not return to baseline mental and physical fitness levels[15]. Low QoL negatively affects the prognosis of heart failure patients, increases the incidence of adverse cardiac events[44], impedes postpartum recovery, and can damage mothers, newborns, families and society[15]. Consequently, QoL assessment should be critical in the ongoing clinical therapy of women with heart disease following pregnancy[23]. Additional prospective longitudinal studies and a greater focus on long-term

Table 2 Clinical characteristics and postpartum quality of life (mean ± SD)

Variables	*n* (%)		*P* value
Prepregnant BMI (kg/m^2)			0.408
< 18.5 (leaner)	12 (11.43)	90.64 ± 13.90	
18.5-24.9 (normal)	69 (65.71)	91.84 ± 14.57	
≥ 25 (overweight and obesity)	24 (22.86)	87.43 ± 11.36	
BMI increment (kg/m^2)	4.92 ± 1.89 (-0.37 to 9.86)[1]		0.319
Pregnancy diagnosis			0.206
Yes	55 (52.38)	89.06 ± 12.55	
No	50 (47.62)	92.49 ± 15.02	
Prepregnant cardiac surgery			0.007[b]
Yes	32 (30.48)	96.14 ± 12.62	
No	73 (69.52)	88.30 ± 13.73	
Type of heart disease			0.075
Structural	74 (70.48)	92.25 ± 13.93	
Functional	31 (29.52)	86.98 ± 13.03	
mWHO classification			0.026[a]
I	25 (23.81)	96.05 ± 13.48	
II	44 (41.90)	89.71 ± 13.42	
II-III	9 (8.57)	80.42 ± 14.64	
III	10 (9.52)	95.47 ± 12.85	
IV	17 (16.19)	87.97 ± 12.50	
NYHA classification			< 0.001[b]
I	64 (60.95)	94.58 ± 13.22	
II	33 (31.43)	87.01 ± 12.13	
III, IV	8 (7.62)	74.78 ± 10.11	

[1]Mean ± SD (range).
[a]$P < 0.05$.
[b]$P < 0.01$.
BMI: Body mass index; mWHO classification: modified World Health Organization pregnancy risk classification.

monitoring and management are also necessary for these women after birth.

Multiple linear regression was used to find significant characteristics of postpartum QoL in women with heart disease. Our findings demonstrated that prepregnancy heart surgery, parity, EPDS score, CAQ score, and fear of an unfavorable pregnancy throughout pregnancy were predictors of perceived postpartum QoL.

In the general cardiac population, cardiac surgery reflects the severity of the disease and is associated with a decline in QoL[43]. However, as predictors of postpartum QoL in cardiac patients, prepregnancy surgery was a positive factor for delivery, as recommended by guidelines[1,18]. In this study, prepregnancy cardiac operations included atrial septal defect repair (25.0%), ventricular septal defect repair (21.87%), mechanical valve replacement (21.87%), correction of tetralogy of Fallot (9.38%), and radiofrequency ablation (9.38%). These surgical patients, representing 64.0% (32/50 cases) of pre-conception diagnoses, underwent procedures before conception, improving cardiac function, physical state[45], pregnancy tolerance, and reducing the modified WHO pregnancy risk classification[46-48]. As a result, most of them had planned pregnancies and paid greater attention to cardiac treatment through close follow-up and stringent pregnancy management, which eventually improved pregnancy outcomes[49]. Our findings indicated the benefits of timely diagnosis and early surgical intervention on postpartum QoL.

Consistent with their counterparts without heart disease[50], primiparas had enhanced QoL at 6 wk postpartum in our study. Pregnancy generates numerous hemodynamic and physiological changes that increase cardiovascular stress, which is entirely reversed after delivery[51]. Extant research indicates that increasing parity harms women's health and elevates the risk of cardiovascular disease[52,53]. In addition, repeated cardiovascular adaptation to volume overload can lead to adverse cardiac remodeling, which is an independent risk factor for left ventricular diastolic dysfunction in

Table 3 Pregnancy characteristics and postpartum quality of life (mean ± SD)

Variables	*n* (%)		*P* value
Gravidity			0.524
1	64 (60.95)	90.26 ± 13.25	
2	27 (25.71)	89.69 ± 15.53	
≥ 3	14 (13.33)	94.58 ± 13.28	
Parity			0.026[a]
Primiparas	91 (86.67)	91.86 ± 13.60	
Multiparas	14 (13.33)	83.09 ± 13.29	
Pregnancy complications			0.052
Yes	34 (32.38)	94.47 ± 12.90	
No	71 (67.62)	88.88 ± 13.97	
Planned pregnancy			0.085
Yes	69 (65.71)	92.37 ± 13.18	
No	36 (34.29)	84.48 ± 14.62	
Delivery method			0.529
Vaginal delivery	11 (10.48)	90.51 ± 14.77	
Cesarean section	80 (76.19)	92.18 ± 13.73	
Emergency cesarean section	14 (13.33)	87.40 ± 12.69	
Gestational weeks, d	264.00 ± 19.0 (225.0-285.0)[1]		0.040[a]
Neonatal gender			0.079
Male	54 (51.43)	93.82 ± 13.66	
Female	51 (48.57)	88.78 ± 13.31	
Neonatal weight	2977.91 ± 591.63 (1640.0-4650.0)[2]		0.097
Neonatal hospitalization			0.037[a]
Yes	37 (35.24)	87.34 ± 14.57	
No	68 (64.76)	93.58 ± 12.72	
Milk-feeding way			0.965
Exclusive breastfeeding	40 (38.0)	91.02 ± 13.45	
Mixed feeding	43 (41.0)	91.38 ± 13.11	
Artificial feeding	22 (21.0)	92.07 ± 15.69	

[1]Median ± interquartile range (range).
[2]Mean ± SD (range).
[a]$P < 0.05$.

women with heart disease[54-56]. Although some studies have shown that women with heart disease have similar pregnancy outcomes in consecutive pregnancies[57], our results showed that repeated pregnancies reduced postpartum QoL. The condition underscores the importance of closely monitoring women's physical and mental health with multiple births after delivery.

Prior research has shown that the recovery of the cardiovascular system during the postpartum period does not correspond with emotional healing[15,23]. The physical limits and cognitive impairments caused by the disease substantially influence these women's lives, resulting in enduring emotional responses[42]. In our study, the prevalence of postpartum depression was 33.33%, similar to previous research on women with heart disease[22,23], twice that of the general Chinese population[58], and comparable to high-risk pregnancies[59]. Depressive disorders were identified as a potent predictor of postpartum QoL in our investigation, corroborating previous findings[41], and have also been demonstrated in the general postpartum population[60-62]. Depression is also associated with reduced health behaviors and exacerbating heart failure symptoms in mothers with heart disease[23]. We must focus on depression symptoms and intervene early to improve postpartum QoL and cardiovascular disease management.

Table 4 Descriptive statistics for the scales at 6 wk postpartum (mean ± SD)

Variables	Value	
EPDS	≤ 9	52 (49.52)[1]
	10-12	18 (17.14)[1]
	≥ 13	35 (33.33)[1]
	Total	10.08 ± 5.08
CAQ	≥ 2	39 (37.14)[1]
	Avoidance	1.59 ± 0.82
	Fear	1.52 ± 0.73
	Heart-focused attention	2.40 ± 1.34
	Total	1.79 ± 0.79
EHFScBS	Total	35.38 ± 10.51
SF-12	PCS	41.09 ± 9.91
	MCS	49.60 ± 14.87[2]
	Total	90.69 ± 13.82

[1]*n* (%).
[2]Median ± interquartile range.
EPDS: Edinburgh Postnatal Depression Scale; CAQ: Cardiac Anxiety Questionnaire; EHFScBS: European Heart Failure Self-Care Behavior Scale; SF-12: 12-Item Short-Form Health Survey; PCS: Physical components summary; MCS: Mental components summary.

In addition, HFA problems were common among our patients, resulting in a lower total CAQ score. The score was lower than that in Australian research of 43 women with cardiac disease during pregnancy and the postpartum period [21] and those with peripartum cardiomyopathy[20]. Lower scores may be because 65.71% of our patients were classified as modified WHO pregnancy risk class I and II. However, the score was considerably higher than that of the general population of women in the same age group[63], the postmyocardial infarction population[31], general cardiac patients [30], and individuals with noncardiac chest pain[64]. Prior research has also established a correlation between HFA and reduced QoL in heart disease patients, emphasizing the importance of routine diagnosis and intervention[64,65]. Such a phenomenon is akin to how general anxiety influences the QoL for the average woman during the postpartum period[61].

We also designed a standardized questionnaire, and the proportion of patients concerned about their child's heart problems is consistent with earlier research (57.7%-73.8%)[20-22]. Studies from developed countries showed that women with heart disease were more concerned about their physical health[20-22]. In contrast, our study found that more women with heart disease were concerned about their children acquiring cardiac conditions. They were considerably more likely than mothers in other countries to miss medical visits owing to child care (55.56% *vs* 10.7%-40.5%), highlighting cultural disparities. Prior research only offered descriptive statistics on these issues. However, our study incorporated these concerns into a multiple regression analysis, suggesting that women anxious about adverse pregnancy outcomes had lower postpartum QoL than their counterparts. Despite the importance of psychological factors on postpartum QoL, our results revealed that only 2.86% of the population sought psychological counseling, which was lower than that reported in developed countries[21] and comparable to general maternity trends in China[39]. The unpopularity of mental health care highlights the urgent need for HCPs to offer consultation and psychological support throughout pregnancy while ensuring continuity of care.

The following were potential limitations of our study. As an observational cross-sectional study, it cannot show causality but can serve as a basis for future research. Second, there was selection bias because the sample consisted of MDT consultation patients with more significant health literacy, and emotionally troubled patients might have refused to participate. Third, the small sample size, single-center design, and uneven participant distribution limit generalizability, despite diverse heart disease cases being included. Fourth, EPDS is a screening instrument rather than a gold standard for postpartum depression diagnosis. Finally, data on QoL and psychological status data were collected only 6 wk postpartum, without continued monitoring. Despite these limitations, this study provides valuable insights into the postpartum recovery of high-risk women and its implications for HCP care.

CONCLUSION

Our research revealed that women with heart disease typically experienced challenges during maternity. To improve their well-being, HCPs should recognize their specific requirements, offer education, improve communication, and provide psychological support. Creating individualized treatment strategies from pregnancy to postpartum can optimize

Table 5 Design-specific cardiac-related problems and quality of life at 6 wk postpartum (mean ± SD)

Variables	*N* (%)		*P* value
Compliance			
Hospital review after ending the pregnancy			0.360
Yes	65 (61.90)	91.67 ± 12.85	
No	40 (38.10)	89.11 ± 15.31	
Understanding of the disease			
Advised to avoid having children			0.125
Yes	41 (39.05)	88.10 ± 16.11	
No	64 (60.95)	92.35 ± 11.98	
Full consultation and understanding of the diagnosis			0.947
Yes	83 (79.05)	90.64 ± 14.36	
No	22 (20.95)	90.87 ± 11.84	
Medical concerns			
Seek psychological counselling			0.907
Yes	3 (2.86)	89.77 ± 15.92	
No	102 (97.14)	90.72 ± 13.85	
Fear of a bad pregnancy			< 0.001[c]
Yes	60 (57.14)	86.38 ± 13.35	
No	45 (42.86)	96.44 ± 12.39	
Worried about child's heart			0.016[a]
Yes	60 (57.14)	87.89 ± 13.76	
No	45 (42.86)	94.42 ± 13.14	
Worried about reduced longevity			0.007[b]
Yes	51 (48.57)	86.96 ± 14.16	
No	54 (51.43)	94.22 ± 12.63	

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.

Table 6 Linear regression model results for the 12-Item Short-Form Health Survey

Predictors	β	Standard error	*t*	*P* value	95% confidence interval for β
Constant	127.304	6.431	19.795	< 0.001	114.543 to 140.065
Without prepregnant cardiac surgery	-7.532	2.040	-3.692	< 0.001	-11.580 to -3.484
CAQ	-5.264	1.242	-4.237	< 0.001	-0.429 to -0.155
EPDS	-0.189	0.197	-6.041	< 0.001	-1.580 to -0.799
No fear of a bad pregnancy	4.193	2.035	2.060	0.042	0.155 to 8.230
Multiparas	-7.457	2.781	-2.682	0.009	-12.974 to -1.939

EPDS: Edinburgh Postnatal Depression Scale; CAQ: Cardiac Anxiety Questionnaire. $F(5,99) = 23.989$; $P < 0.001$; $R^2 = 0.548$; adjusted $R^2 = 0.525$; D-W = 1.934.

healthcare utilization, improve healing, and eventually assist these women in self-managing their heart issues.

ARTICLE HIGHLIGHTS

Research background

Postpartum quality of life (QoL) in women with heart disease has been neglected widely.

Research motivation

Diminished postpartum QoL in heart disease patients escalates disease burden and social challenges, necessitating an active healthcare approach for pregnancy and recovery.

Research objectives

This study aimed to investigate the medical data and subjective factors on postpartum QoL and develop targeted healthcare strategies to improve outcomes for these high-risk women.

Research methods

This research was a retrospective analysis of QoL at 6 wk after birth in patients with heart disease at our center, combining medical data and subjective assessments to evaluate and address QoL concerns.

Research results

According to the data from 105 postpartum cardiac patients, no previous cardiac surgery, multiparity, greater sadness and cardiac anxiety, and fear of unfavorable pregnancy outcomes were strongly related to lower QoL.

Research conclusions

Our research suggests that healthcare professionals should acknowledge and address the distinct needs of postpartum women with heart disease, integrating comprehensive management strategies into their maternity care.

Research perspectives

Future studies should focus on longitudinal research to evaluate perinatal women's QoL, social-environmental factors, and self-efficacy, guiding the development of family care and telemedicine.

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FOOTNOTES

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REFERENCES

1 **Regitz-Zagrosek V**, Roos-Hesselink JW, Bauersachs J, Blomström-Lundqvist C, Cífková R, De Bonis M, Iung B, Johnson MR, Kintscher U, Kranke P, Lang IM, Morais J, Pieper PG, Presbitero P, Price S, Rosano GMC, Seeland U, Simoncini T, Swan L, Warnes CA, Deaton C, Simpson IA, Aboyans V, Agewall S, Barbato E, Calda P, Coca A, Coman IM, De Backer J, Delgado V, Di Salvo G, Fitzsimmons S, Fitzsimons D, Garbi M, Gevaert S, Hindricks G, Jondeau G, Kluin J, Lionis C, McDonagh TA, Meier P, Moons P, Pantazis A, Piepoli MF, Rocca B, Roffi M, Rosenkranz S, Sarkozy A, Shlyakhto E, Silversides CK, Sliwa K, Sousa-Uva M, Tamargo J, Thorne S, Van de Velde M, Williams B, Zamorano JL, Windecker S, Bueno H, Collet J-P, Dean V, Gaemperli O, Jüni P, Katus HA, Knuuti J, Lancellotti P, Leclercq C, Ponikowski P, Richter DJ, Hammoudi N, Piruzyan A, Mascherbauer J, Samadov F, Prystrom A, Pasquet A, Caluk J, Gotcheva N, Skoric B, Heracleous H, Vejlstrup N, Maser M, Kaaja RJ, Srbinovska-Kostovska E, Mounier-Vehier C, Vakhtangadze T, Rybak K, Giannakoulas G, Kiss RG, Thrainsdottir IS, Erwin RJ, Porter A, Geraci G, Ibrahimi P, Lunegova O, Mintale I, Kadri Z, Benlamin H, Barysiene J, Banu CA, Caruana M, Gratii C, Haddour L, Bouma BJ, Estensen M-E, Hoffman P, Petris AO, Moiseeva O, Bertelli L, Tesic BV, Dubrava J, Koželj M, Prieto-Arévalo R, Furenäs E, Schwerzmann M, Mourali MS, Ozer N, Mitchenko O, Nelson-Piercy C. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J* 2018; **39**: 3165-3241 [PMID: 30165544 DOI: 10.1093/eurheartj/ehy340]

2 **Roos-Hesselink J**, Baris L, Johnson M, De Backer J, Otto C, Marelli A, Jondeau G, Budts W, Grewal J, Sliwa K, Parsonage W, Maggioni AP, van Hagen I, Vahanian A, Tavazzi L, Elkayam U, Boersma E, Hall R. Pregnancy outcomes in women with cardiovascular disease: evolving trends over 10 years in the ESC Registry Of Pregnancy And Cardiac disease (ROPAC). *Eur Heart J* 2019; **40**: 3848-3855 [PMID: 30907409 DOI: 10.1093/eurheartj/ehz136]

3 **Roos-Hesselink JW**, Ruys TP, Stein JI, Thilén U, Webb GD, Niwa K, Kaemmerer H, Baumgartner H, Budts W, Maggioni AP, Tavazzi L, Taha N, Johnson MR, Hall R; ROPAC Investigators. Outcome of pregnancy in patients with structural or ischaemic heart disease: results of a registry of the European Society of Cardiology. *Eur Heart J* 2013; **34**: 657-665 [PMID: 22968232 DOI: 10.1093/eurheartj/ehs270]

4 **Siu SC**, Colman JM. Heart disease and pregnancy. *Heart* 2001; **85**: 710-715 [PMID: 11359761 DOI: 10.1136/heart.85.6.710]

5 **Owens A**, Yang J, Nie L, Lima F, Avila C, Stergiopoulos K. Neonatal and Maternal Outcomes in Pregnant Women With Cardiac Disease. *J Am Heart Assoc* 2018; **7**: e009395 [PMID: 30571384 DOI: 10.1161/JAHA.118.009395]

6 **Ngu K**, Hay M, Menahem S. Perceptions and motivations of an Australian cohort of women with or without congenital heart disease proceeding to pregnancy. *Int J Gynaecol Obstet* 2014; **126**: 252-255 [PMID: 24972721 DOI: 10.1016/j.ijgo.2014.03.032]

7 **Dawson AJ**, Krastev Y, Parsonage WA, Peek M, Lust K, Sullivan EA. Experiences of women with cardiac disease in pregnancy: a systematic review and metasynthesis. *BMJ Open* 2018; **8**: e022755 [PMID: 30269070 DOI: 10.1136/bmjopen-2018-022755]

8 **Cauldwell M**, Steer PJ, Swan L, Patel RR, Gatzoulis MA, Uebing A, Johnson MR. Pre-pregnancy counseling for women with heart disease: A prospective study. *Int J Cardiol* 2017; **240**: 374-378 [PMID: 28377190 DOI: 10.1016/j.ijcard.2017.03.092]

9 **Ngu K**, Hay M, Menahem S. Case studies of the perceptions of women with high risk congenital heart disease successfully completing a pregnancy. *Heart Lung Circ* 2014; **23**: 811-817 [PMID: 24796679 DOI: 10.1016/j.hlc.2014.03.019]

10 **Al Obieat HD**, Khalaf IA, Al-Ammouri I, Obeidat HM, Bawadi HA, Al Momany MS, Harb E. Exploring the lived experiences of women with congenital heart disease during pregnancy: A phenomenological study. *Midwifery* 2023; **119**: 103630 [PMID: 36804830 DOI: 10.1016/j.midw.2023.103630]

11 **Flocco SF**, Caruso R, Barello S, Nania T, Simeone S, Dellafiore F. Exploring the lived experiences of pregnancy and early motherhood in Italian women with congenital heart disease: an interpretative phenomenological analysis. *BMJ Open* 2020; **10**: e034588 [PMID: 31980511 DOI: 10.1136/bmjopen-2019-034588]

12 **Dekker RL**, Morton CH, Singleton P, Lyndon A. Women's Experiences Being Diagnosed With Peripartum Cardiomyopathy: A Qualitative Study. *J Midwifery Womens Health* 2016; **61**: 467-473 [PMID: 27285199 DOI: 10.1111/jmwh.12448]

13 **Hutchens J**, Frawley J, Sullivan EA. The healthcare experiences of women with cardiac disease in pregnancy and postpartum: A qualitative study. *Health Expect* 2022; **25**: 1872-1881 [PMID: 35616361 DOI: 10.1111/hex.13532]

14 **Patel H**, Berg M, Barasa A, Begley C, Schaufelberger M. Symptoms in women with Peripartum Cardiomyopathy: A mixed method study. *Midwifery* 2016; **32**: 14-20 [PMID: 26515744 DOI: 10.1016/j.midw.2015.10.001]

15 **Koutrolou-Sotiropoulou P**, Lima FV, Stergiopoulos K. Quality of Life in Survivors of Peripartum Cardiomyopathy. *Am J Cardiol* 2016; **118**: 258-263 [PMID: 27239023 DOI: 10.1016/j.amjcard.2016.04.040]

16 **Liu YT**, Lu CW, Mu PF, Shu YM, Chen CW. The Lived Experience of First-time Mothers with Congenital Heart Disease. *Asian Nurs Res (Korean Soc Nurs Sci)* 2022; **16**: 140-148 [PMID: 35623555 DOI: 10.1016/j.anr.2022.05.003]

17 **Ghizzardi G**, Caruso R, Barello S, Flocco SF, Arrigoni C, Baroni I, Nania T, Dellafiore F. Barriers and facilitators of experiencing pregnancy and motherhood with congenital heart disease: A secondary qualitative analysis. *Nurs Open* 2023; **10**: 156-164 [PMID: 35871467 DOI: 10.1002/nop2.1290]

18 **American College of Obstetricians and Gynecologists' Presidential Task Force on Pregnancy and Heart Disease and Committee on Practice Bulletins—Obstetrics**. ACOG Practice Bulletin No. 212: Pregnancy and Heart Disease. *Obstet Gynecol* 2019; **133**: e320-e356 [PMID: 31022123 DOI: 10.1097/AOG.0000000000003243]

19 **Hameed AB**, Haddock A, Wolfe DS, Florio K, Drummond N, Allen C, Taylor I, Kendig S, Presumey-Leblanc G, Greenwood E. Alliance for Innovation on Maternal Health: Consensus Bundle on Cardiac Conditions in Obstetric Care. *Obstet Gynecol* 2023; **141**: 253-263 [PMID: 36649333 DOI: 10.1097/AOG.0000000000005048]

20 **Rosman L**, Salmoirago-Blotcher E, Cahill J, Sears SF. Psychosocial Adjustment and Quality of Life in Patients With Peripartum Cardiomyopathy. *J Cardiovasc Nurs* 2019; **34**: 20-28 [PMID: 30273257 DOI: 10.1097/JCN.0000000000000518]

21 **Hutchens J**, Frawley J, Sullivan EA. Quality of life and mental health of women who had cardiac disease in pregnancy and postpartum. *BMC*

Pregnancy Childbirth 2022; **22**: 797 [PMID: 36307772 DOI: 10.1186/s12884-022-05123-x]
22 **Freiberger A**, Beckmann J, Freilinger S, Kaemmerer H, Huber M, Nagdyman N, Ewert P, Pieper L, Deppe C, Kuschel B, Andonian C. Psychosocial well-being in postpartum women with congenital heart disease. *Cardiovasc Diagn Ther* 2022; **12**: 389-399 [PMID: 36033219 DOI: 10.21037/cdt-22-213]
23 **Rosman L**, Salmoirago-Blotcher E, Cahill J, Wuensch KL, Sears SF. Depression and health behaviors in women with Peripartum Cardiomyopathy. *Heart Lung* 2017; **46**: 363-368 [PMID: 28583376 DOI: 10.1016/j.hrtlng.2017.05.004]
24 **Hall C**, D'Souza RD. Patients and Health Care Providers Identify Important Outcomes for Research on Pregnancy and Heart Disease. *CJC Open* 2020; **2**: 454-461 [PMID: 33305204 DOI: 10.1016/j.cjco.2020.05.010]
25 **Molyneaux E**, Telesia LA, Henshaw C, Boath E, Bradley E, Howard LM. Antidepressants for preventing postnatal depression. *Cochrane Database Syst Rev* 2018; **4**: CD004363 [PMID: 29669175 DOI: 10.1002/14651858.CD004363.pub3]
26 ACOG Committee Opinion No. 757: Screening for Perinatal Depression. *Obstet Gynecol* 2018; **132**: e208-e212 [PMID: 30629567 DOI: 10.1097/AOG.0000000000002927]
27 **Cox JL**, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. *Br J Psychiatry* 1987; **150**: 782-786 [PMID: 3651732 DOI: 10.1192/bjp.150.6.782]
28 **Lee DT**, Yip SK, Chiu HF, Leung TY, Chan KP, Chau IO, Leung HC, Chung TK. Detecting postnatal depression in Chinese women. Validation of the Chinese version of the Edinburgh Postnatal Depression Scale. *Br J Psychiatry* 1998; **172**: 433-437 [PMID: 9747407 DOI: 10.1192/bjp.172.5.433]
29 **O'Connor E**, Rossom RC, Henninger M, Groom HC, Burda BU. Primary Care Screening for and Treatment of Depression in Pregnant and Postpartum Women: Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA* 2016; **315**: 388-406 [PMID: 26813212 DOI: 10.1001/jama.2015.18948]
30 **Eifert GH**, Thompson RN, Zvolensky MJ, Edwards K, Frazer NL, Haddad JW, Davig J. The cardiac anxiety questionnaire: development and preliminary validity. *Behav Res Ther* 2000; **38**: 1039-1053 [PMID: 11004742 DOI: 10.1016/s0005-7967(99)00132-1]
31 **Leissner P**, Held C, Rondung E, Olsson EMG. The factor structure of the cardiac anxiety questionnaire, and validation in a post-MI population. *BMC Med Res Methodol* 2022; **22**: 338 [PMID: 36581833 DOI: 10.1186/s12874-022-01820-5]
32 **Jaarsma T**, Strömberg A, Mårtensson J, Dracup K. Development and testing of the European Heart Failure Self-Care Behaviour Scale. *Eur J Heart Fail* 2003; **5**: 363-370 [PMID: 12798836 DOI: 10.1016/s1388-9842(02)00253-2]
33 **McHorney CA**. Health status assessment methods for adults: past accomplishments and future challenges. *Annu Rev Public Health* 1999; **20**: 309-335 [PMID: 10352861 DOI: 10.1146/annurev.publhealth.20.1.309]
34 **Coons SJ**, Rao S, Keininger DL, Hays RD. A comparative review of generic quality-of-life instruments. *Pharmacoeconomics* 2000; **17**: 13-35 [PMID: 10747763 DOI: 10.2165/00019053-200017010-00002]
35 **Brekke M**, Berg RC, Amro A, Glavin K, Haugland T. Quality of Life instruments and their psychometric properties for use in parents during pregnancy and the postpartum period: a systematic scoping review. *Health Qual Life Outcomes* 2022; **20**: 107 [PMID: 35810315 DOI: 10.1186/s12955-022-02011-y]
36 **Ware J Jr**, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996; **34**: 220-233 [PMID: 8628042 DOI: 10.1097/00005650-199603000-00003]
37 **Lam CL**, Tse EY, Gandek B. Is the standard SF-12 health survey valid and equivalent for a Chinese population? *Qual Life Res* 2005; **14**: 539-547 [PMID: 15892443 DOI: 10.1007/s11136-004-0704-3]
38 **Faul F**, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods* 2007; **39**: 175-191 [PMID: 17695343 DOI: 10.3758/bf03193146]
39 **Gong W**, Jin X, Cheng KK, Caine ED, Lehman R, Xu DR. Chinese Women's Acceptance and Uptake of Referral after Screening for Perinatal Depression. *Int J Environ Res Public Health* 2020; **17** [PMID: 33238480 DOI: 10.3390/ijerph17228686]
40 **Ye Y**, Chen L, Xu J, Dai Q, Luo X, Shan N, Qi H. Preeclampsia and Its Complications Exacerbate Development of Postpartum Depression: A Retrospective Cohort Study. *Biomed Res Int* 2021; **2021**: 6641510 [PMID: 33977108 DOI: 10.1155/2021/6641510]
41 **Pfeffer TJ**, Herrmann J, Berliner D, König T, Winter L, Ricke-Hoch M, Ponimaskin E, Schuchardt S, Thum T, Hilfiker-Kleiner D, Bauersachs J, Kahl KG. Assessment of major mental disorders in a German peripartum cardiomyopathy cohort. *ESC Heart Fail* 2020; **7**: 4394-4398 [PMID: 32909398 DOI: 10.1002/ehf2.12967]
42 **Donnenwirth JA**, Hess R, Ross R. Post-Traumatic Stress, Depression, and Quality of Life in Women with Peripartum Cardiomyopathy. *MCN Am J Matern Child Nurs* 2020; **45**: 176-182 [PMID: 32341249 DOI: 10.1097/NMC.0000000000000614]
43 **Eslami B**, Macassa G, Sundin Ö, Khankeh HR, Soares JJ. Quality of life and life satisfaction among adults with and without congenital heart disease in a developing country. *Eur J Prev Cardiol* 2015; **22**: 169-179 [PMID: 24249839 DOI: 10.1177/2047487313514017]
44 **Ravera A**, Santema BT, Sama IE, Meyer S, Lombardi CM, Carubelli V, Ferreira JP, Lang CC, Dickstein K, Anker SD, Samani NJ, Zannad F, van Veldhuisen DJ, Teerlink JR, Metra M, Voors AA. Quality of life in men and women with heart failure: association with outcome, and comparison between the Kansas City Cardiomyopathy Questionnaire and the EuroQol 5 dimensions questionnaire. *Eur J Heart Fail* 2021; **23**: 567-577 [PMID: 33728762 DOI: 10.1002/ejhf.2154]
45 **Roos-Hesselink JW**, Meijboom FJ, Spitaels SE, van Domburg R, van Rijen EH, Utens EM, Bogers AJ, Simoons ML. Excellent survival and low incidence of arrhythmias, stroke and heart failure long-term after surgical ASD closure at young age. A prospective follow-up study of 21-33 years. *Eur Heart J* 2003; **24**: 190-197 [PMID: 12573276 DOI: 10.1016/s0195-668x(02)00383-4]
46 **Wang K**, Xin J, Wang X, Yu H, Liu X. Pregnancy outcomes among 31 patients with tetralogy of Fallot, a retrospective study. *BMC Pregnancy Childbirth* 2019; **19**: 486 [PMID: 31823779 DOI: 10.1186/s12884-019-2630-y]
47 **Geva T**, Martins JD, Wald RM. Atrial septal defects. *Lancet* 2014; **383**: 1921-1932 [PMID: 24725467 DOI: 10.1016/S0140-6736(13)62145-5]
48 **Yap SC**, Drenthen W, Meijboom FJ, Moons P, Mulder BJ, Vliegen HW, van Dijk AP, Jaddoe VW, Steegers EA, Roos-Hesselink JW, Pieper PG; ZAHARA investigators. Comparison of pregnancy outcomes in women with repaired versus unrepaired atrial septal defect. *BJOG* 2009; **116**: 1593-1601 [PMID: 19681849 DOI: 10.1111/j.1471-0528.2009.02301.x]
49 **De Santo LS**, Romano G, Della Corte A, D'Oria V, Nappi G, Giordano S, Cotrufo M, De Feo M. Mechanical aortic valve replacement in young women planning on pregnancy: maternal and fetal outcomes under low oral anticoagulation, a pilot observational study on a comprehensive pre-operative counseling protocol. *J Am Coll Cardiol* 2012; **59**: 1110-1115 [PMID: 22421305 DOI: 10.1016/j.jacc.2011.10.899]
50 **Mokhtaryan-Gilani T**, Kariman N, Nia HS, Doulabi MA, Nasiri M, Gilani TM. Evaluation of the Predictors of the Quality of Life in the

Postpartum Period: A Cross-Sectional Study. *Iran J Public Health* 2022; **51**: 1389-1399 [PMID: 36447971 DOI: 10.18502/ijph.v51i6.9695]

51 **Cong J**, Fan T, Yang X, Squires JW, Cheng G, Zhang L, Zhang Z. Structural and functional changes in maternal left ventricle during pregnancy: a three-dimensional speckle-tracking echocardiography study. *Cardiovasc Ultrasound* 2015; **13**: 6 [PMID: 25626356 DOI: 10.1186/1476-7120-13-6]

52 **Xing Z**, Alman AC, Kirby RS. Parity and Risk of Cardiovascular Disease in Women over 45 Years in the United States: National Health and Nutrition Examination Survey 2007-2018. *J Womens Health (Larchmt)* 2022; **31**: 1459-1466 [PMID: 35727098 DOI: 10.1089/jwh.2021.0650]

53 **Wu Y**, Pang J, Wang J, Wu J, Zhang S, Yao Y, Cheng S, Tao Y, Shen Z, Li ZY, Xie L, Yang H. Fertility Histories and Heart Disease in Later Life in China. *Front Public Health* 2022; **10**: 819196 [PMID: 35719619 DOI: 10.3389/fpubh.2022.819196]

54 **Kim HJ**, Kim MA, Kim HL, Shim WJ, Park SM, Kim M, Yoon HJ, Shin MS, Hong KS, Shin GJ, Kim YH, Na JO, Jeong JO. Effects of multiparity on left ventricular diastolic dysfunction in women: cross-sectional study of the KoRean wOmen'S chest pain rEgistry (KoROSE). *BMJ Open* 2018; **8**: e026968 [PMID: 30593559 DOI: 10.1136/bmjopen-2018-026968]

55 **Beale AL**, Cosentino C, Segan L, Mariani JA, Vizi D, Evans S, Nanayakkara S, Kaye DM. The effect of parity on exercise physiology in women with heart failure with preserved ejection fraction. *ESC Heart Fail* 2020; **7**: 213-222 [PMID: 31960599 DOI: 10.1002/ehf2.12557]

56 **Mandal D**, Mandal S, Mukherjee D, Biswas SC, Maiti TK, Chattopadhaya N, Majumdar B, Panja M. Pregnancy and subsequent pregnancy outcomes in peripartum cardiomyopathy. *J Obstet Gynaecol Res* 2011; **37**: 222-227 [PMID: 21114580 DOI: 10.1111/j.1447-0756.2010.01378.x]

57 **Gelson E**, Curry R, Gatzoulis MA, Swan L, Lupton M, Steer PJ, Johnson MR. Maternal cardiac and obstetric performance in consecutive pregnancies in women with heart disease. *BJOG* 2015; **122**: 1552-1559 [PMID: 26118937 DOI: 10.1111/1471-0528.13489]

58 **Nisar A**, Yin J, Waqas A, Bai X, Wang D, Rahman A, Li X. Prevalence of perinatal depression and its determinants in Mainland China: A systematic review and meta-analysis. *J Affect Disord* 2020; **277**: 1022-1037 [PMID: 33065811 DOI: 10.1016/j.jad.2020.07.046]

59 **Ni Q**, Cheng G, Chen A, Heinonen S. Early detection of mental illness for women suffering high-risk pregnancies: an explorative study on self-perceived burden during pregnancy and early postpartum depressive symptoms among Chinese women hospitalized with threatened preterm labour. *BMC Psychiatry* 2020; **20**: 250 [PMID: 32434583 DOI: 10.1186/s12888-020-02667-0]

60 **Jeong YJ**, Nho JH, Kim HY, Kim JY. Factors Influencing Quality of Life in Early Postpartum Women. *Int J Environ Res Public Health* 2021; **18** [PMID: 33799474 DOI: 10.3390/ijerph18062988]

61 **Martínez-Galiano JM**, Hernández-Martínez A, Rodríguez-Almagro J, Delgado-Rodríguez M, Rubio-Alvarez A, Gómez-Salgado J. Women's Quality of Life at 6 Weeks Postpartum: Influence of the Discomfort Present in the Puerperium. *Int J Environ Res Public Health* 2019; **16** [PMID: 30658406 DOI: 10.3390/ijerph16020253]

62 **Papamarkou M**, Sarafis P, Kaite CP, Malliarou M, Tsounis A, Niakas D. Investigation of the association between quality of life and depressive symptoms during postpartum period: a correlational study. *BMC Womens Health* 2017; **17**: 115 [PMID: 29162087 DOI: 10.1186/s12905-017-0473-0]

63 **Fischer D**, Kindermann I, Karbach J, Herzberg PY, Ukena C, Barth C, Lenski M, Mahfoud F, Einsle F, Dannemann S, Böhm M, Köllner V. Heart-focused anxiety in the general population. *Clin Res Cardiol* 2012; **101**: 109-116 [PMID: 22015615 DOI: 10.1007/s00392-011-0371-7]

64 **Mourad G**, Alwin J, Jaarsma T, Strömberg A, Johansson P. The associations between psychological distress and health-related quality of life in patients with non-cardiac chest pain. *Health Qual Life Outcomes* 2020; **18**: 68 [PMID: 32160887 DOI: 10.1186/s12955-020-01297-0]

65 **Schmitz C**, Wedegärtner SM, Langheim E, Kleinschmidt J, Köllner V. Heart-Focused Anxiety Affects Behavioral Cardiac Risk Factors and Quality of Life: A Follow-Up Study Using a Psycho-Cardiological Rehabilitation Concept. *Front Psychiatry* 2022; **13**: 836750 [PMID: 35615455 DOI: 10.3389/fpsyt.2022.836750]

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ORIGINAL ARTICLE

Retrospective Study

Clinicopathological features, psychological status, and prognosis of 33 patients with occult breast cancer

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Abstract

BACKGROUND

Occult breast cancer (OBC) has traditionally been considered to be a carcinoma of unknown primary origin with a favorable prognosis and can be treated as stage II-III breast cancer. Due to the small number of cases and limited clinical experience, treatments vary greatly around the world and no standardized treatment has yet been established.

AIM

To investigate the clinicopathological features, psychological status and prognostic features of patients with OBC.

METHODS

The clinicopathological data of 33 OBC patients diagnosed and treated in the Affiliated Hospital of Xuzhou Medical University and Xuzhou Central Hospital from November 2015 to November 2022 were retrospectively analyzed. The psychological status of OBC patients was evaluated by the Self-rating Anxiety Scale and Self-rating Depression Scale. Patients' emotions, stress perception and psychological resilience were evaluated by the Positive and Negative Affect Schedule, the Chinese Perceived Stress Scale, and the Connor-Davidson Resilience Scale (CD-RISC), respectively. Patient survival was calculated using the Kaplan-Meier method, and survival curves were plotted for analysis with the log-rank test. Univariate and multivariate survival analyses were performed using the Cox

regression model.

RESULTS

The 33 OBC patients included 32 females and 1 male. Of the 33 patients, 30 (91%) had axillary tumors, 3 (9%) had a neck mass as the primary symptom; 18 (54.5%) had estrogen receptor-positive tumors, 17 (51.5%) had progesterone receptor-positive tumors, and 18 (54.5%) had Her-2-positive tumors; 24 (72.7%) received surgical treatment, including 18 patients who underwent modified radical mastectomy, 1 patient who underwent breast-conserving surgery plus axillary lymph node dissection (ALND), and 5 patients who underwent ALND alone; 12 patients received preoperative neoadjuvant therapy. All 30 patients developed anxiety and depression, with low positive affect scores and high negative affect scores, accompanied by a high stress level and poor psychological resilience. There were no differences in the psychological status of patients according to age, body mass index, or menopausal status. The overall survival and disease-free survival (DFS) of all the patients were 83.3% and 55.7%, respectively. Univariate analysis demonstrated that the initial tumor site ($P = 0.021$) and node stage ($P = 0.020$) were factors that may affect patient prognosis. The 5-year DFS rate of OBC patients who received radiotherapy was greater ($P < 0.001$), while the use of different surgical methods ($P = 0.687$) had no statistically significant effect on patient outcomes. Multivariate analysis revealed that radiotherapy ($P = 0.031$) was an independent prognostic factor. Receiving radiotherapy had a significant effect on the CD-RISC score ($P = 0.02$).

CONCLUSION

OBC is a rare breast disease whose diagnosis and treatment are currently controversial. There was no significant difference in the efficacy of other less invasive surgical procedures compared to those of modified radical mastectomy. In addition, radiotherapy can significantly improve patient outcomes. We should pay attention to the psychological state of patients while they receive antitumor therapy.

Key Words: Occult breast cancer; Breast cancer; Perceived Stress Scale; Axillary lymph node dissection

Core Tip: Occult breast cancer (OBC) has traditionally been considered to be a carcinoma of unknown primary origin with a favorable prognosis and can be treated as stage II-III breast cancer. This study aimed to investigate the clinicopathological features, psychological status and prognostic factors of patients with OBC. The authors found that radiotherapy can significantly improve patient outcomes. The psychological state of patients while they receive antitumor therapy should be paid more attention.

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INTRODUCTION

Occult breast cancer (OBC) is a rare form of BC that usually presents as axillary lymph node metastasis without a clear primary breast lesion[1]. OBC is a rare breast disease. According to the foreign literature, the incidence of BC accounts for approximately 0.3%-1% of all BCs[2], with a peak incidence occurring at approximately 55 years of age.

With atypical clinical manifestations, OBC usually presents with painless axillary masses initially, but a few patients seek medical help for neck masses[3]. For patients with the above symptoms, core needle biopsy or incisional biopsy should be performed first to clarify the pathology, along with immunohistochemistry to determine its possible source[4]. Mammography and breast ultrasound are commonly used tools for diagnosing breast lesions in patients with lymph node metastases of unknown origin, but the detection rate of the primary focus of OBC is low[5]. With the development of advanced diagnostic modalities, the incidence of OBC has been decreasing [6]. The 2022 Breast Cancer Diagnosis and Treatment Guidelines suggest that breast magnetic resonance imaging (MRI) has the advantage of high sensitivity compared with other breast imaging methods; additionally, breast MRI can display multifocal, multicenter or bilateral BC lesions as well as axillary lymph node metastasis at the same time and is therefore recommended for identifying the primary focus of patients with axillary lymph node metastasis[7]. Positron emission tomography-computed tomography (PET-CT) is also used to diagnose OBC. However, there is only one relevant report in the literature thus far[8], which, coupled with its high price, limits its application in OBC detection.

Although OBC is generally accepted to have similar biological behavior to lymph node-positive non-OBC, the clinicopathological features of this disease are unclear[9,10]. Several previous studies have suggested that estrogen receptor (ER) status, triple-negative status, and at least four positive lymph nodes are individual prognostic factors for

occult breast cancer[11,12]. Survival outcomes in patients with OBC are also controversial. Patients with OBC have similar or less unfavorable outcomes than non-OBC patients[13], while others have reached the opposite conclusion[14]. Therefore, this study aimed to better reveal the clinicopathological features and prognostic factors of OBC patients through a retrospective analysis of clinicopathological data.

MATERIALS AND METHODS

General information

A retrospective analysis of the clinical data of 33 OBC patients admitted to the Affiliated Hospital of Xuzhou Medical University and Xuzhou Central Hospital was conducted from November 2015 to November 2022. Approximately 0.48% (33/6835) of the 33 OBC patients were included in this study, of whom 20 (60%) were from the Affiliated Hospital of Xuzhou Medical University and 13 (40%) were from Xuzhou Central Hospital. The patient cohort consisted of 32 females and 1 male. Pathology revealed invasive breast cancer (intermediate/poorly differentiated).

Data collection

No obvious primary breast lesions were found by physical examination, breast color ultrasound, mammography or breast CT, MRI, PET-CT or other examinations. Any tumors occurring in any part of the body were confirmed to be metastatic carcinoma by pathological examination and indicated to be of breast origin by histological and immunohistochemical methods.

A total of 30 patients were scored on the Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS) for anxiety and depression assessments, and their scores were analyzed.

Patients' emotions, stress perception and psychological resilience were evaluated by the Positive and Negative Affect Schedule (PANAS), the Chinese Perceived Stress Scale (CPSS), and the Connor-Davidson Resilience Scale (CD-RISC), respectively.

Prognostic follow-up

Patients were followed up for recurrence, metastasis and death through inpatient or outpatient information or telephone follow-up. Patients were followed up until November 2022 (5 to 226 months), for a median follow-up of 38 months. Disease-free survival (DFS) and overall survival (OS) were used as follow-up indicators, where the former was defined as the time from the start of follow-up to disease recurrence or metastasis.

Statistical analysis

R 4.3.2 and SPSS27.0 statistical software were used for data analysis, with $P < 0.05$ as the threshold of statistical significance. Nonparametric comparisons between parameters were conducted using the Mann-Whitney U test. The survival rate was calculated by using the Kaplan-Meier method, and survival curves were drawn. The difference in survival rate between subgroups was tested by the log-rank test, and the factors with statistical significance in the univariate analysis were further tested by multivariate Cox regression analysis.

RESULTS

Clinicopathological features

The age of onset ranged from 28 to 66 years (median age: 53). There were 9 patients (27.0%) aged ≤ 50 years and 24 patients (73.0%) aged > 50 years. There were 1 (3.0%) male and 32 (97.0%) female patients, including 22 (66.7%) menopausal and 10 (30.3%) non-menopausal women. While 24 patients (72.7%) had a body mass index (BMI) < 24.0 and 9 patients (27.2%) had a BMI ≥ 24.0, patients' BMI, which was associated with occult breast cancer, was not related to survival (Table 1).

Thirty patients (91%) had an axillary mass at the first symptom, and only three (9.1%) patients had a neck mass at the first symptom. There were 22 patients (66.7%) in whom the lesions were located on the left side and 11 (33.3%) on the right side. There were 15 patients (45.5%) whose axillary lymph node stage was the N1, 18 patients (54.5%) whose axillary lymph node stage was N2 or N3, and 6 patients (18.2%) whose axillary lymph node stage was IV (distant metastases) (Table 1).

Immunohistochemical tests were performed on all patients. There were 18 (54.5%) OBC patients who were ER-positive and 17 (51.5%) patients who were progesterone receptor (PR) positive. There were 18 HER-2-positive patients (including 13 HER-2 IHC 3+ patients and 5 IHC 2+ patients with positive amplification according to the FISH test) and 15 HER-2-negative patients. Ki67 was detected in all patients; 8 had Ki67 ≤ 14%, and 25 had Ki67 > 14% (Table 1).

Patients' emotions, stress perception, and psychological resilience

All 30 patients developed anxiety and depression, with low positive affect scores and high negative affect scores, accompanied by a high stress level and poor psychological resilience (Tables 2 and 3).

There were no differences in the psychological status of patients according to age, BMI, or menopausal status (Figure 1).

Table 1 Clinicopathological features and 5-year disease-free survival rate of occult breast cancer patients

Clinical features	*n*	5-year DFS rate (%)	χ^2	*P* value
Whole patient cohorts	33	55.7		
Age (yr)			0.20	0.887
< 50	9	58.9		
≥ 50	24	55.8		
BMI			0.294	0.588
< 23.9	24	51.7		
≥ 23.9	9	87.5		
Menopause			2.923	0.087
Yes	23	46.9		
No	10	80.0		
N staging			5.448	0.020[a]
1	15	92.3		
≥ 2	18	34.3		
Initial tumor site			5.333	0.021[a]
Armpit	30	60.8		
Neck	3	-		
M staging			1.486	0.223
0	24	46.2		
1	9	53.3		
Ki67			0.317	0.573
≤ 14%	8	60.0		
> 14%	25	54.1		
ER			0.003	0.953
Positive	18	55.1		
Negative	15	56.0		
PR			2.355	0.125
Positive	17	67.1		
Negative	16	34.8		
Her-2			0.111	0.739
Positive	18	66.4		
Negative	15	42.2		
Molecular subtyping			1.690	0.639
Luminal A	15	73.4		
Luminal B	12	27.8		
Her-2 enriched	3	50.0		
TNBC	3	-		

[a]$P < 0.05$ between the groups.
OBC: Occult breast cancer; BMI: Body mass index; DFS: Disease free survival; ER: Estrogen receptor; PR: Progesterone receptor.

Table 2 Patients' depression and anxiety scores

Categories	Minimum	Maximum	Score
SDS	44	64	56.40 ± 4.29
SAS	48	69	60.77 ± 4.58

SDS: Self-rating depression scale; SAS: Self-rating anxiety scale.

Table 3 Patients' emotions, stress perception and psychological resilience

Categories	Minimum	Maximum	Score
Positive and negative affect schedule			
Positive	10	32	18.23 ± 4.38
Negative	22	39	27.97 ± 4.37
Chinese Perceived Stress Scale	32	48	42.13 ± 3.12
Connor-Davidson Resilience Scale	38	56	47.53 ± 4.03

Treatment

Twenty-four of the 33 patients underwent surgical treatment, with 18 patients receiving modified radical mastectomy (MRM), 1 patient receiving breast-conserving surgery (BCS) plus axillary lymph node dissection (ALND), and 5 receiving ALND only. Twelve patients received neoadjuvant therapy before surgery, including 4 patients receiving 6 cycles of PC regimen (docetaxel + carboplatin), 4 receiving 4 cycles of TE regimen (docetaxel + epirubicin), 3 receiving PC regimen for 4 cycles and sequential EC regimen for 4 cycles (docetaxel + carboplatin sequential epirubicin + cyclophosphamide), and 1 receiving TE regimen for 4 cycles (docetaxel + epirubicin). All patients received adjuvant therapy after surgery, and the treatment schemes were selected based on different factors, such as age, tumor stage and molecular subtyping. There were 20 hormone receptor-positive patients in this cohort, all of whom received endocrine therapy.

As of the follow-up date, a total of 30 OBC patients underwent SDS, SAS, PANAS, CPSS, and CD-RISC testing. The results revealed that patients who received radiotherapy had lower CD-RISC scores (P = 0.02) (Figure 2B). Surgery, neoadjuvant chemotherapy, and endocrine therapy had no significant impact on the psychological status of the OBC patients (Figure 2A, C, and D).

Prognostic characteristics

Overall survival (OS) curve of 33 patients with occult breast cancer. 5-year OS rate: 83.3%. Disease-free survival (DFS) curve of 33 patients with occult breast cancer. 5-year DFS rate: 55.7% (Figure 3).

The patients were followed up for 5-226 months (median: 38 months). A total of 12 patients relapsed and metastasized, three of whom died. Among the patients with metastasis, 4 had simple lung metastasis, 3 had lung and brain metastases, 2 had simple brain metastasis, 2 had simple skeletal metastasis, and 1 had lung and skeletal metastases.

However, there were no significant differences in 5-year DFS according to age, BMI, menopausal status, presence of distant metastasis, Ki67 index, or hormone receptor status. OBC patients with an initial tumor site in the axilla had a greater 5-year DFS rate than did those with an initial lesion in the neck (P = 0.021) (Table 1). Five-year DFS was greater in patients with few involved lymph nodes (P = 0.020) (Table 1). Age, BMI, menopausal status, node staging, initial tumor site, M staging, Ki67, ER, PR, HER-2, molecular subtyping, surgery and radiotherapy (with/without) were selected for univariate analysis using the log-rank test. The results showed that the 5-year DFS rate of OBC patients who received radiotherapy was greater than that of patients who did not receive radiotherapy (P < 0.001), while there was no difference in the 5-year DFS of patients who received different surgeries, endocrine therapies, or neoadjuvant chemotherapy (Table 4).

Furthermore, the 5-year DFS rate of the 24 patients who underwent surgical treatment was analyzed by the log-rank test, revealing no significant difference among patients who underwent different surgical treatments or neoadjuvant therapy (with/without) (Table 5).

In our case series, there were 20 receptor-positive patients, all of whom received endocrine therapy. Univariate analysis using the log-rank test also revealed no significant difference in DFS among patients receiving different endocrine therapies (Table 6).

Moreover, statistically significant factors were included in the multivariate survival analysis, and it was found that radiotherapy (with/without; P = 0.031) was an independent prognostic factor.

Table 4 Univariate and multivariate analysis of prognosis

Treatment method	*n*	5-year DFS rate (%)	χ^2	*P* value
Total	33			
Surgery			1.486	0.223
With	24	46.2		
Without	9	53.1		
Radiotherapy			10.450	< 0.001
With	16	88.9		
Without	17	21.4		

DFS: Disease-free survival.

Table 5 Five-year disease-free survival rate of patients

Surgical modalities used for patients	*n*	5-year DFS rate (%)	χ^2	*P* value
Total	24			
Surgical method			0.751	0.687
Modified radical mastectomy	18	35.7		
Axillary lymph node dissection	5	50.0		
Breast-conserving surgery + axillary lymph node dissection	1	-		
Neoadjuvant therapy			0.168	0.682
With	12	0.571		
Without	12	0.458		

DFS: Disease free survival.

Table 6 Effects of treatment modalities on disease free survival

Endocrine therapy for hormone receptor-positive patients	*n*	5-year DFS rate (%)	χ^2	*P* value
Total	20			
Drugs used for endocrine therapy			1.669	0.434
Tamoxifen	10	0.370		
Goserelin	6	1.000		
Anastrozole/letrozole	4	0.667		

DFS: Disease free survival.

DISCUSSION

In this study, 33 patients were reported in this cohort, accounting for 0.48% (33/6835) of all patients included in this study; these findings are basically consistent with the literature. All 33 OBC patients underwent relevant examinations after admission, and no primary lesions were found by mammography or ultrasound; 6 patients underwent PET-CT, and no suspicious primary lesions were detected; however, breast MRI detected 6 suspicious cancer lesions, which was significantly greater than the number of other imaging tests. A total of 18 patients underwent MRM, and 11 (11/18) patients were found to have primary lesions in ipsilateral breast tissue after surgery, for a percentage of 61.1%, which was similar to the pathological findings of 51 patients with OBC reported by Wang *et al* in 2010[15]. According to the results of the SEER database-based analysis reported by Zhu *et al*[16], ER-positive and PR-positive patients accounted for 54.1% and 50.8%, respectively, of the total OBC cases[16], which supports our findings. In addition, approximately 54.5% of the patients were Her-2 positive, which was higher than approximately 20% of the general types of BC[17].

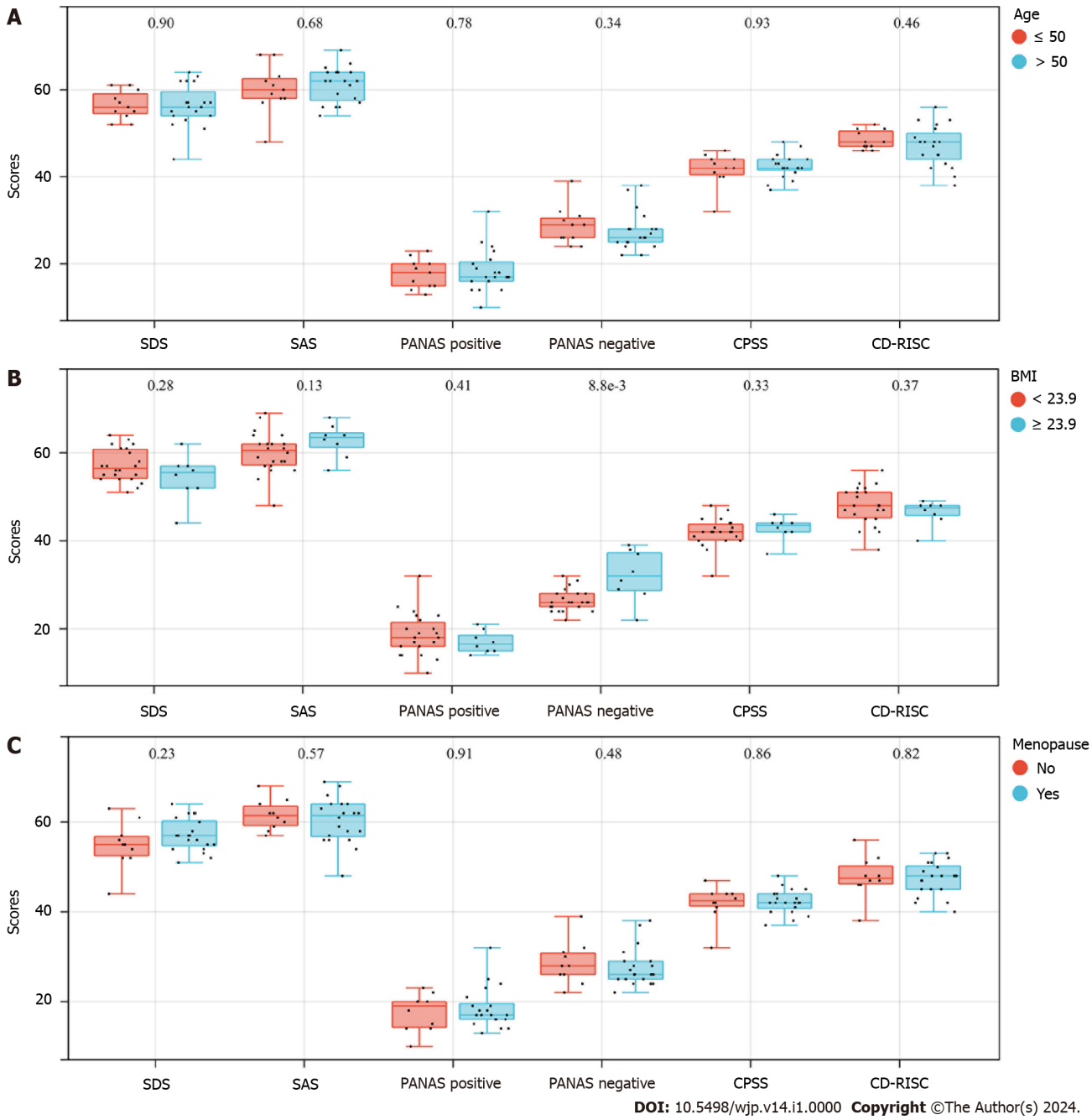

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Figure 1 Psychological status of occult breast cancer patients with different age, body mass index, and menopausal status. A: Different age; B: Different body mass index; C: Different menopausal status. SDS: Self-Rating Depression Scale; SAS: Self-Rating Anxiety Scale; PANAS: Positive and Negative Affect Schedule; CPSS: Chinese Perceived Stress Scale; CD-RISC: Connor-Davidson Resilience Scale.

Due to the low incidence of OBC and the lack of sufficient evidence, the choice of treatment methods is still controversial. A number of retrospective studies have shown that using MRM and choosing combined chemoradiotherapy or endocrine therapy according to individual differences are the traditional treatments for OBC[18,19]. However, recent research by Sohn *et al*[20] confirmed that there was no significant difference in the prognosis of patients who received ALND only, BCS plus ALND, or MRM. Tsai *et al*[21] argued that the curative effect of MRM is similar to that of radiotherapy alone. Other relevant studies have also demonstrated that less intensive surgery does not negatively affect the prognosis of OBC patients, adjuvant radiotherapy is beneficial for prolonging OS, and ALND combined with radiotherapy may be the most suitable surgical modality for OBC[22,23]. Eighteen of the 33 patients received MRM, and their prognosis was not significantly different from that of patients who underwent other surgical methods. As an independent prognostic factor, radiotherapy ($P = 0.031$) could become a mainstay treatment for OBC.

OBC is a rare disease, and male OBC is even rarer than female OBC and generally has a poor prognosis regardless of sex. At present, most of the related cases reported internationally progress within a few years, which may be related to the difficulty in diagnosis and the lack of standardized treatment[24-26]. This study included one male OBC patient whose DFS and OS were significantly lower than those of the other patients in the group. Recent relevant studies have demonstrated the efficacy of immunotherapy for male OBC, and anti-androgen therapy can achieve effective control of

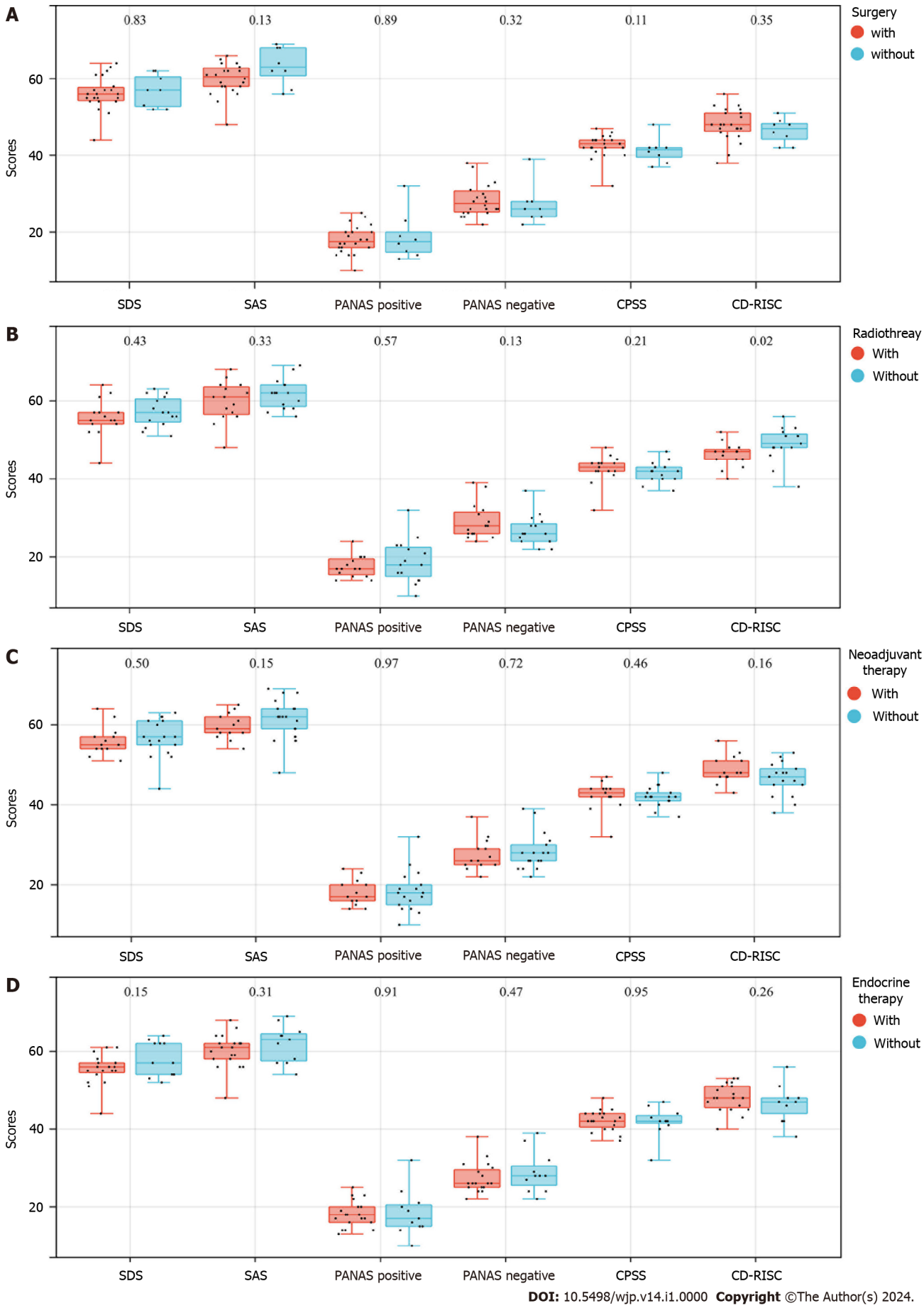

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Figure 2 Psychological status of occult breast cancer patients undergoing different treatment pattern. A: Patients undergoing surgery; B: Patients

undergoing radiotherapy; C: Patients undergoing neoadjuvant chemotherapy; D: Patients undergoing endocrine therapy. SDS: Self-Rating Depression Scale; SAS: Self-Rating Anxiety Scale; PANAS: Positive and Negative Affect Schedule; CPSS: Chinese Perceived Stress Scale; CD-RISC: Connor-Davidson Resilience Scale.

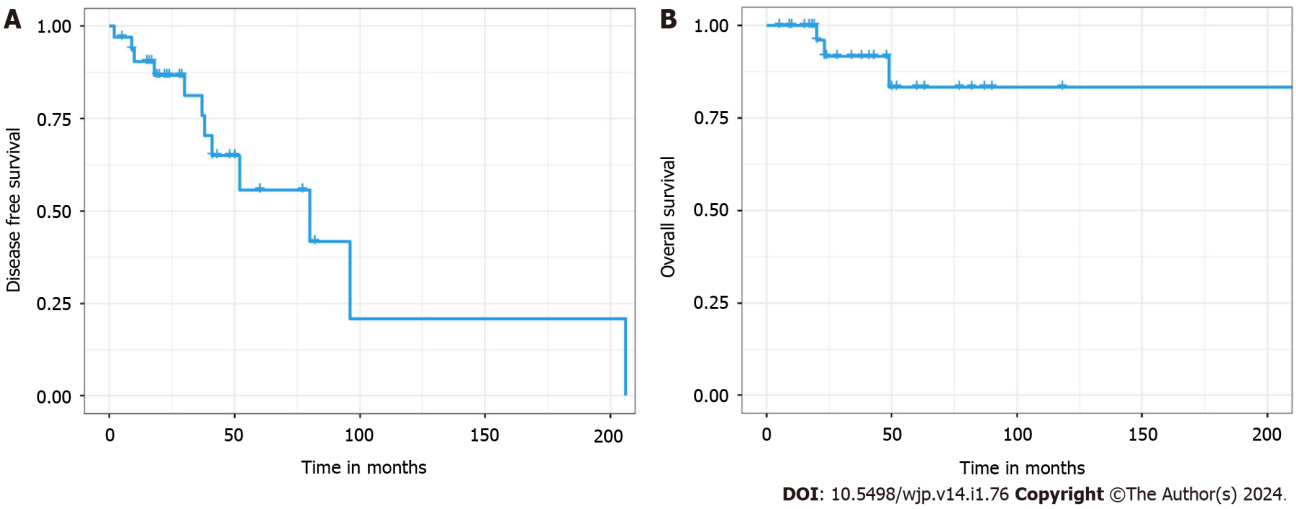

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Figure 3 The survival curves of 5-years overall survival and disease-free survival for the occult breast cancer patients. A: The disease-free survival curve; B: The 5-years overall survival curve.

disease progression with minimal toxicity[25], which provides a new idea for future male OBC management.

The psychological condition of OBC patients, a rare disease group, deserves further study. We analyzed the results of psychological questionnaires administered to OBC patients. The results showed that all 30 patients developed anxiety and depression, with low PA scores and high NA scores, accompanied by a high stress level and poor psychological resilience. It is well known that the diagnosis and treatment of cancer have both negative physical and psychological long-term side effects that affect the quality of life of patients and survivors[27,28]. Breast cancer patients and survivors experience significant changes in their evaluations of their appearance and their attitudes toward their bodies, particularly with regard to femininity[29]. For example, mastectomy or breast retention may threaten overall self-satisfaction and trigger multiple changes in body perception mediated by sensations within the breast and chest[30]. We also found significant differences in Conner-Davidson resilience scores between patients who did and did not receive radiotherapy. In this nuclear age, people have been repeatedly explained and made aware of the dangers of exposure to radiation and the need to avoid it. Therefore, when patients are receiving radiation cancer treatment, stress and anxiety can ensue. In addition, during radiation therapy, patients must lie alone on a table with a large machine above them, which can create fear, isolation, and anxiety[31]. In addition, 60% of patients have significant anxiety before treatment, and 80% have anxiety after treatment[32]. These findings remind us that, although patients receiving radiation therapy often have a better prognosis, the psychological issues associated with radiation therapy should not be overlooked. Therefore, psychological counseling is needed while patients receive antitumor therapy. We hope that patients can be physically and mentally healthy and return to society normally.

CONCLUSION

The incidence of OBC is low, and diagnosis is difficult, limiting its use in clinical practice. Our research showed that the diagnostic sensitivity of breast MRI is high, which is helpful for clinical diagnosis. In addition, a less invasive surgical modality can be selected according to the individual differences of patients, which has no obvious influence on patient disease progression. Moreover, postoperative adjuvant radiotherapy can obviously improve patient outcomes. To improve the quality of life of patients, appropriate treatment methods should be selected. Moreover, psychological problems need to be considered. The advantage of this study lies in the use of bicenter case data, but the present study still has limitations. Most of the studies were retrospective in design and included cohort selection, the impact of previous exposure to risk variables, treatment approaches, follow-up, reporting, complications, and genetic mutations. Additionally, the overall sample size was still small, and the follow-up time was short, warranting a prospective study with a large sample size to further guide the diagnosis and treatment of OBC.

ARTICLE HIGHLIGHTS

Research background

Occult breast cancer (OBC) is a rare breast disease. With atypical clinical manifestations, OBC usually presents with painless axillary masses initially, but a few patients seek medical help for neck masses.

Research motivation

Although it is generally accepted that OBC has a similar biological behavior to lymph node-positive non-OBC, the clinicopathological features of the disease are unclear.

Research objectives

This study aims at better reveal the clinicopathological features and prognostic factors of OBC patients through a retrospective analysis of their clinicopathological data.

Research methods

The clinicopathological data of 33 diagnosed OBC patients were retrospectively analyzed. The psychological status of OBC patients was evaluated by self-rating Anxiety Scale and self-rating Depression Scale. Patients' emotions, stress perception and psychological resilience were evaluated by the Positive and Negative Affect Schedule, the Chinese Perceived Stress Scale, and the Connor-Davidson Resilience Scale, respectively. Patient survival was calculated. Univariate and multivariate survival analyses were performed using the COX regression model.

Research results

There were 30 (91%) with axillary tumor and 3 (9%) with Neck mass as the first symptom; 18 (54.5%) were ER-positive, 17 (51.5%) were PR-positive, and 18 (54.5%) were Her-2-positive; 24 (72.7%) received surgical treatment, including 18 cases of modified radical mastectomy, 1 case of breast-conserving surgery plus axillary lymph node dissection (ALND), and 5 cases of ALND alone; 12 cases received preoperative neoadjuvant therapy. All the 30 patients developed certain anxiety and depression, with low positive affect scores and high negative affect scores, accompanied by a high stress level and poor psychological resilience. The overall survival and disease-free survival of all the patients was 83.3% and 55.7%, respectively. Multivariate analysis revealed that radiotherapy was an independent prognostic factor.

Research conclusions

OBC is a rare breast disease whose diagnosis and treatment are currently controversial. There was no significant difference in the efficacy of other less invasive surgical procedures compared to the modified radical mastectomy, and radiotherapy can significantly improve patient outcomes.

Research perspectives

The incidence of OBC is low and the diagnosis is difficult, which is easy to be ignored in clinical practice. In order to improve the quality of life of patients, appropriate treatment methods should be selected. At the same time, psychological problems also need to be concerned about.

FOOTNOTES

Author contributions: Wang HM, Yu AY and Li LL contributed equally to this work and are co-first authors; Wang HM and Yu AY contributed to the research design and paper writing; Li LL, Ma LY, Cao MH, Yang YL, Qin XB and Tang JJ collected and analyzed the data; Wang HM and Han ZX overall supervise the study; and all authors contributed to the article and approved the submitted version.

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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.

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REFERENCES

1 **Huang KY**, Zhang J, Fu WF, Lin YX, Song CG. Different Clinicopathological Characteristics and Prognostic Factors for Occult and Non-occult Breast Cancer: Analysis of the SEER Database. *Front Oncol* 2020; **10**: 1420 [PMID: 32974151 DOI: 10.3389/fonc.2020.01420]
2 **Ofri A**, Moore K. Occult breast cancer: Where are we at? *Breast* 2020; **54**: 211-215 [PMID: 33130487 DOI: 10.1016/j.breast.2020.10.012]
3 **Ge XC**, Yin DY, Zhang Q, Liu WJ, Xin Q. Diagnosis and treatment of occult breast cancer. *Zhonghua Ruxian Bing Zazhi* 2021; **15**: 381-383 [DOI: 10.3877/cma.j.issn.1674-0807.2021.06.009]
4 **Guo MQ**, Song W. Controversy and prospect of the diagnosis and treatment of occult breast cancer. *Zhonghua Ruxian Bing Zazhi* 2016; **10**: 305-309 [DOI: 10.3877/cma.j.issn.1674-0807.2016.05.011]
5 **Kim H**, Park W, Kim SS, Ahn SJ, Kim YB, Kim TH, Kim JH, Choi JH, Park HJ, Chang JS, Choi DH. Outcome of breast-conserving treatment for axillary lymph node metastasis from occult breast cancer with negative breast MRI. *Breast* 2020; **49**: 63-69 [PMID: 31734590 DOI: 10.1016/j.breast.2019.10.017]
6 **Urban D**, Rao A, Bressel M, Lawrence YR, Mileshkin L. Cancer of unknown primary: a population-based analysis of temporal change and socioeconomic disparities. *Br J Cancer* 2013; **109**: 1318-1324 [PMID: 23860528 DOI: 10.1038/bjc.2013.386]
7 **National Health Commission of the People's Republic of China**. Guidelines for the Diagnosis and Treatment of Breast Cancer (2022 edition). *Zhongguo Heli Yongyao Tansuo* 2022; **19**: 1-26 [DOI: 10.3969/j.issn.2096-3327.2022.10.001]
8 **Liu M**, Liu B, Song Y, Ding L, Dong L. FDG PET/CT reveals the primary tumor in a patient with occult breast carcinoma undetected by other modalities. *Clin Nucl Med* 2014; **39**: 755-757 [PMID: 24978343 DOI: 10.1097/RLU.0000000000000503]
9 **Hessler LK**, Molitoris JK, Rosenblatt PY, Bellavance EC, Nichols EM, Tkaczuk KHR, Feigenberg SJ, Bentzen SM, Kesmodel SB. Factors Influencing Management and Outcome in Patients with Occult Breast Cancer with Axillary Lymph Node Involvement: Analysis of the National Cancer Database. *Ann Surg Oncol* 2017; **24**: 2907-2914 [PMID: 28766198 DOI: 10.1245/s10434-017-5928-x]
10 **Ye X**, Yang L, He Q, Lin X, Wang J, Cui R, Xu C. Reconceptualizing the clinicopathological features, locoregional therapy and prognostic factors of occult breast cancer in the era of molecular subtyping. *Women Health* 2023; **63**: 105-114 [PMID: 36576239 DOI: 10.1080/03630242.2022.2158415]
11 **He M**, Tang LC, Yu KD, Cao AY, Shen ZZ, Shao ZM, Di GH. Treatment outcomes and unfavorable prognostic factors in patients with occult breast cancer. *Eur J Surg Oncol* 2012; **38**: 1022-1028 [PMID: 22959166 DOI: 10.1016/j.ejso.2012.08.022]
12 **Montagna E**, Bagnardi V, Rotmensz N, Viale G, Cancello G, Mazza M, Cardillo A, Ghisini R, Galimberti V, Veronesi P, Monti S, Luini A, Raviele PR, Mastropasqua MG, Goldhirsch A, Colleoni M. Immunohistochemically defined subtypes and outcome in occult breast carcinoma with axillary presentation. *Breast Cancer Res Treat* 2011; **129**: 867-875 [PMID: 21822638 DOI: 10.1007/s10549-011-1697-6]
13 **Ge LP**, Liu XY, Xiao Y, Gou ZC, Zhao S, Jiang YZ, Di GH. Clinicopathological characteristics and treatment outcomes of occult breast cancer: a SEER population-based study. *Cancer Manag Res* 2018; **10**: 4381-4391 [PMID: 30349371 DOI: 10.2147/CMAR.S169019]
14 **Svastics E**, Rónay P, Bodó M. Occult breast cancer presenting with axillary metastasis. *Eur J Surg Oncol* 1993; **19**: 575-580 [PMID: 8270047]
15 **Wang X**, Zhao Y, Cao X. Clinical benefits of mastectomy on treatment of occult breast carcinoma presenting axillary metastases. *Breast J* 2010; **16**: 32-37 [PMID: 20465598 DOI: 10.1111/j.1524-4741.2009.00848.x]
16 **Zhu HY**, Dai M, Liu CG. Treatment options and prognosis evaluation of stage II/III occult breast cancer: A study based on SEER database. *Shiyong Zhongliu Zazhi* 2020; **35**: 166-172 [DOI: 10.13267/j.cnki.syzlzz.2020.02.014]
17 **Lebert J**, Lilly EJ. Developments in the Management of Metastatic HER2-Positive Breast Cancer: A Review. *Curr Oncol* 2022; **29**: 2539-2549 [PMID: 35448182 DOI: 10.3390/curroncol29040208]
18 **Yan TT**, Jiang JR. Experience in diagnosis and treatment of 21 cases of occult breast cancer. *Xiandai Linchuang Yixue* 2019; **45**: 174-176 [DOI: 10.11851/j.issn.1673-1557.2019.03.006]
19 **Shen HY**, Hu CH, Han YT, Peng DJ, Yu YL, Xu YB, Peng P, Liu CH, Hou YF. The exploration of clinical pathological characteristics and the diagnosis and treatment strategy of 56 patients with occult breast cancer. *Zhongguo Aizheng Zazhi* 2018; **28**: 429-434 [DOI: 10.19401/j.cnki.1007-3639.2018.06.006]
20 **Sohn G**, Son BH, Lee SJ, Kang EY, Jung SH, Cho SH, Baek S, Lee YR, Kim HJ, Ko BS, Lee JW, Ahn SH. Treatment and survival of patients with occult breast cancer with axillary lymph node metastasis: a nationwide retrospective study. *J Surg Oncol* 2014; **110**: 270-274 [PMID: 24863883 DOI: 10.1002/jso.23644]
21 **Tsai C**, Zhao B, Chan T, Blair SL. Treatment for occult breast cancer: A propensity score analysis of the National Cancer Database. *Am J Surg* 2020; **220**: 153-160 [PMID: 31753317 DOI: 10.1016/j.amjsurg.2019.11.023]
22 **Zhao Z**, Zhang T, Yao Y, Lu X. Clinicopathological characteristics and treatment outcomes of occult breast cancer: a population-based study. *BMC Surg* 2022; **22**: 143 [PMID: 35430796 DOI: 10.1186/s12893-022-01472-8]
23 **Macedo FI**, Eid JJ, Flynn J, Jacobs MJ, Mittal VK. Optimal Surgical Management for Occult Breast Carcinoma: A Meta-analysis. *Ann Surg Oncol* 2016; **23**: 1838-1844 [PMID: 26832884 DOI: 10.1245/s10434-016-5104-8]
24 **Hur SM**, Cho DH, Lee SK, Choi MY, Bae SY, Koo MY, Kim S, Nam SJ, Lee JE, Yang JH. Occult breast cancers manifesting as axillary lymph node metastasis in men: a two-case report. *J Breast Cancer* 2012; **15**: 359-363 [PMID: 23091551 DOI: 10.4048/jbc.2012.15.3.359]
25 **Wang XH**, Zhang J, Wu J, He XH, Shen YR, Peng YG, An YZ. Case Report: Response to Immunotherapy and Anti-Androgen Therapy in Male Occult Triple-Negative Breast Cancer. *Front Oncol* 2022; **12**: 840453 [PMID: 35433492 DOI: 10.3389/fonc.2022.840453]
26 **Li SJ**, Zhang J, Liu X, Luo QW, Li QJ. A case of male occult breast cancer. *Yixue Lunli Yu Shijian* 2021; **34**: 1014-1015 [DOI:

10.19381/j.issn.1001-7585.2021.06.054]

27 **Sterba KR**, Burris JL, Heiney SP, Ruppel MB, Ford ME, Zapka J. "We both just trusted and leaned on the Lord": a qualitative study of religiousness and spirituality among African American breast cancer survivors and their caregivers. *Qual Life Res* 2014; **23**: 1909-1920 [PMID: 24578149 DOI: 10.1007/s11136-014-0654-3]

28 **Ahmad S**, Fergus K, McCarthy M. Psychosocial issues experienced by young women with breast cancer: the minority group with the majority of need. *Curr Opin Support Palliat Care* 2015; **9**: 271-278 [PMID: 26147915 DOI: 10.1097/SPC.0000000000000162]

29 **Sherman KA**, Przezdziecki A, Alcorso J, Kilby CJ, Elder E, Boyages J, Koelmeyer L, Mackie H. Reducing Body Image-Related Distress in Women With Breast Cancer Using a Structured Online Writing Exercise: Results From the My Changed Body Randomized Controlled Trial. *J Clin Oncol* 2018; **36**: 1930-1940 [PMID: 29688834 DOI: 10.1200/JCO.2017.76.3318]

30 **Paterson CL**, Lengacher CA, Donovan KA, Kip KE, Tofthagen CS. Body Image in Younger Breast Cancer Survivors: A Systematic Review. *Cancer Nurs* 2016; **39**: E39-E58 [PMID: 25881807 DOI: 10.1097/NCC.0000000000000251]

31 **Mungase M**, Chaudhury S, Patil AA, Jagtap B, Jain V. Stress, anxiety, depression, and resilience in cancer patients on radiotherapy. *Ind Psychiatry J* 2021; **30**: 346-352 [PMID: 35017823 DOI: 10.4103/ipj.ipj_78_20]

32 **Chen AM**, Daly ME, Vazquez E, Courquin J, Luu Q, Donald PJ, Farwell DG. Depression among long-term survivors of head and neck cancer treated with radiation therapy. *JAMA Otolaryngol Head Neck Surg* 2013; **139**: 885-889 [PMID: 23949013 DOI: 10.1001/jamaoto.2013.4072]

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ORIGINAL ARTICLE

Observational Study

Des-Arg(9) bradykinin as a causal metabolite for autism spectrum disorder

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Abstract

BACKGROUND

Early diagnosis and therapeutic interventions can greatly enhance the developmental trajectory of children with autism spectrum disorder (ASD). However, the etiology of ASD is not completely understood. The presence of confounding factors from environment and genetics has increased the difficulty of the identification of diagnostic biomarkers for ASD.

AIM

To estimate and interpret the causal relationship between ASD and metabolite profile, taking into consideration both genetic and environmental influences.

METHODS

A two-sample Mendelian randomization (MR) analysis was conducted using

summarized data from large-scale genome-wide association studies (GWAS) including a metabolite GWAS dataset covering 453 metabolites from 7824 European and an ASD GWAS dataset comprising 18381 ASD cases and 27969 healthy controls. Metabolites in plasma were set as exposures with ASD as the main outcome. The causal relationships were estimated using the inverse variant weight (IVW) algorithm. We also performed leave-one-out sensitivity tests to validate the robustness of the results. Based on the drafted metabolites, enrichment analysis was conducted to interpret the association *via* constructing a protein-protein interaction network with multi-scale evidence from databases including Infinome, SwissTargetPrediction, STRING, and Metascape.

RESULTS

Des-Arg(9)-bradykinin was identified as a causal metabolite that increases the risk of ASD (β = 0.262, SE = 0.064, $P_{IVW} = 4.64 \times 10^{-5}$). The association was robust, with no significant heterogeneity among instrument variables ($P_{MR\ Egger} = 0.663$, $P_{IVW} = 0.906$) and no evidence of pleiotropy ($P = 0.949$). Neuroinflammation and the response to stimulus were suggested as potential biological processes mediating the association between Des-Arg(9) bradykinin and ASD.

CONCLUSION

Through the application of MR, this study provides practical insights into the potential causal association between plasma metabolites and ASD. These findings offer perspectives for the discovery of diagnostic or predictive biomarkers to support clinical practice in treating ASD.

Key Words: Des-Arg(9) bradykinin; Autism spectrum disorder; Mendelian randomization; Metabolite; Enrichment analysis

Core Tip: This study employs Mendelian randomization to uncover a potential causal relationship between plasma metabolites and autism spectrum disorder (ASD), emphasizing the role of Des-Arg(9)-bradykinin in increasing the risk of ASD. The findings underscore the significance of neuroinflammation and the response to stimulus as possible mediating factors, offering new directions for the development of diagnostic and predictive biomarkers in the clinical management of ASD.

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INTRODUCTION

Autism spectrum disorder (ASD) is an early-onset neurodevelopmental disorder characterized by persistent deficits in social communication and social interaction, coupled with restricted and repetitive patterns of behavior and interests[1]. The negative impacts of ASD extend across biological, social, and cognitive functions, significantly influencing the developmental trajectory of affected children[2]. Achieving an accurate early diagnosis of ASD is crucial for enhancing the quality of life in adulthood. However, current ASD diagnosis criteria rely on behavioral pattern analysis and assessments. The early-stage clinical presentations are heterogeneous and inconspicuous, making a definitive ASD diagnosis challenging. There is a need to optimize diagnostic approaches for ASD to better align with clinical practice[3].

There is growing interest in identifying diagnostic biomarkers to support early diagnosis and effective treatments for ASD[4]. To unravel the etiology and pathogenesis of ASD, interdisciplinary approaches have been employed, gathering multi-scale evidence from genomics, metabolomics, transcriptomics, and beyond. Accumulating evidence suggests that ASD development is influenced by both genetic and environmental factors[5,6]. Risk genes such as *CHD8*, *DYRK1A* and *SHANK3* have been identified. These genes formed a functional network that indicates potential biological processes involved in the development of ASD. Moreover, genetic models have integrated risk genes such as *NRXN2* and *DYRK1A*, which are involved in neurodevelopment, to explain the inherited patterns and heterogeneity observed in ASD[7,8]. Maternal environmental factors, including inflammation and the immune response, have also been recognized as crucial contributors to ASD development[9,10]. These findings provide essential information for developing diagnostic instruments for ASD. However, due to the complexity of interactions among biological processes and the existence of undetectable confounding factors, it is still challenging to identify biomarkers on an appropriate scale, ensuring effective implementation with sufficient biological validity[11].

The utilization of metabolomics technology for estimating metabolic profiles has advanced the development of workflows in biomarker research[12]. As detectable variables reflecting both genomic and environmental effects, metabolites that participate in mitochondrial dysfunction were identified as potential biomarkers of ASD[13-15]. However, the limitations stemming from the availability of large biological samples and technical barriers in sample

preparation have impeded the attainment of standardized and reproducible results in metabolomics studies focused on ASD[16]. Additionally, confounding factors should be well handled to identify a reliable biomarker from the association between metabolites and ASD. Therefore, it is imperative to explore practical methods for identifying metabolic biomarkers that can address the shortcomings of current paradigms.

Mendelian randomization (MR) analysis utilizes genetic variants as instrumental variables to investigate the causal relationships between exposures and outcomes in observational studies[17]. Two-sample MR offers increased statistical power and enhanced flexibility by gathering instrumental variable-exposure association and instrumental variable outcome association from two different sets of participants to examine the causal relationship between an exposure and an outcome[18]. This approach eliminates the need to measure both exposure and outcome variables in the same sample, making it particularly useful in cases where the exposure or outcome is rare, challenging to measure, or when there is limited sample overlap between exposure and outcome studies[19]. Therefore, aiming at identifying candidate biomarkers to assist early diagnosis of ASD, this study attempted to uncover potential associations between metabolites and ASD taking advantage of the two sample MR. To strengthen the interpretation of the potential association, enrichment analysis was carried out with the integration of multi-scale evidence.

MATERIALS AND METHODS

Study design and data sources

We implemented a two-sample MR design using datasets of European ancestry, chosen due to their public availability, ample sample size, and population consistency. Specifically, we selected two datasets for this analysis. Firstly, we utilized the metabolite genome-wide association study (mGWAS) published by Shin *et al*[20] in 2014. This dataset provided genetic association evidence for 486 metabolites and included data from 7824 individuals across two European studies. Additionally, we employed the meta-analysis of ASD conducted by the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH) and the Psychiatric Genomics Consortium (PGC) in 2017[21]. This ASD dataset consisted of a total of 18381 ASD cases and 27969 healthy controls as shown in Table 1. These datasets were publicly available, and any missing frequency data in the ASD GWAS dataset were acquired by contacting the authors *via* email in July 2022.

The two-sample MR analysis aimed to estimate the associations between metabolite traits (from the mGWAS) and ASD (from the iPSYCH-PGC) using genetic variants as instrumental variables. The effect size was calculated as the association between a 1-standard deviation change in metabolite trait levels and ASD, with the odds ratio (OR) as the main result. This approach provided quantified potential directional associations between ASD and metabolite traits.

Quality control: To ensure the reliability of the association between metabolite and ASD, the genetic variances that exhibited a significant association ($P < 5 \times 10^{-8}$) with the metabolite from the mGWAS dataset were selected. Moreover, acknowledging the potential no-random association of alleles at two or more loci, especially those in close genomic proximity, a linkage disequilibrium (LD) analysis was performed using the European 1000G reference panel to exclude single nucleotide polymorphisms (SNPs) with a correlation coefficient (r2) less than 0.01 within a 500-kb window. The clumping procedure was conducted using the TwoSampleMR R package[22].

Assumptions: Firstly, the relevance assumption postulated that the genetic variables used as instrumental variables were associated with the metabolite of interest. Secondly, the independence assumption stated that the genetic variables were independent of potential confounding factors. Thirdly, the exclusion restriction assumption proposed that the disease outcome was solely influenced by the genetic instrument through the metabolites and not through alternative pathways. Additionally, as MR-Egger regression was employed to obtain pleiotropy-corrected causal estimates, a fourth assumption was made that the association between an SNP and the exposure variable was independent of its direct effects on the outcome.

Statistical analysis

In the two-sample MR analyses, the causal effects of metabolites on the disease were assessed using the inverse variance weighted (IVW) method. The analyses were conducted using the TwoSampleMR and MR-PRESSO packages in R 3.6.2[22, 23] with statistical significance defined as $P < 0.05$. The weighted median, Wald ratio, weighted mode, and MR-Egger algorithm were also employed to evaluate the consistency of the causal inferences, thereby safeguarding false positive results. Sensitivity analysis was performed to investigate the robustness of the estimated significant MR causal associations. To test the robustness of the results and investigate the influence of individual SNPs, a global test and the leave-one-out method were employed. Forest plots were used to show the consistency of the effect of each SNP. Horizontal pleiotropy, which refers to the presence of genetic variants affecting both the exposure and the outcome through different pathways, was assessed using the MR pleiotropy residual sum and outlier global test.

Enrichment analysis

Genes near the SNPs were searched and collected on the Infinome website. DrugBank provided information on the structure, SMILE representation, and validated target genes of the quantified causal metabolite. SwissTargetPrediction was used to predict target genes based on structural similarity and molecular affinity. In this study, we collected the top 10 predicted target genes of the metabolites for further interpretation of the causal relationship between metabolite and ASD. Meanwhile, previously reported ASD-related genes were retrieved from the Malacard dataset. To further discover potential biological clues for interpreting the causal association between metabolites and ASD, a protein-protein interaction network was constructed using the STRING database. Then enrichment analysis was performed using GO and KEGG. Cluster modules of the interaction network were identified using Metascape. Maximal cliques are identified

Table 1 Details of the genome-wide association studies consortiums

Variable	Ancestry	Ref.	Sample size	Sex	Data download
Metabolite	European	Shin *et al*[20], 2014	7824	Mixed	http://metabolomics.helmholtz-muenchen.de/gwas/
Autism spectrum disorder	European	Grove *et al*[21], 2017	Cases = 18381; Controls = 27969	Mixed	https://doi.org/10.6084/m9.figshare.14671989

and genes with high clique centrality in the network were considered as hub genes through the maximal clique centrality (MCC) algorithm in Cytoscape 3.9.1, utilizing the interaction network.

RESULTS

MR analysis result

The ASD GWAS dataset covered 9112386 SNPs from the iPSYCH-PGC consortium, and there were 207856 SNPs of 453 metabolites in the mGWAS dataset. After filtering based on the significance of the correlation between SNPs and metabolites ($P < 5 \times 10^{-8}$), a subset of 18824 SNPs was used for LD clumping, resulting in 609 SNPs as representative genetic variants for the MR analysis.

The association between each metabolite and ASD was estimated using five different methods. Among the evaluated associations, 11 were deemed significant ($P < 0.05$) with the IVW method, as shown in Table 2. Three metabolites, including M32847, M33137, and M34306, were excluded from further analysis as neither their structures nor their identification were available in the original study.

Among the remaining metabolites, two were found to be positively associated with ASD: M34420: Des-Arg(9) bradykinin (β = 0.262, SE = 0.064, $P = 4.64 \times 10^{-5}$) and M32497: 10-undecenoate (11:1n1) (β = 0.546, SE = 0.258, $P = 0.034$). Additionally, six metabolites were identified as protective factors for ASD: M02137: Biliverdin (β = -0.255, SE = 0.122, $P = 0.038$), M20675: 1,5-Anhydroglucitol (β = -0.881, SE = 0.407, $P = 0.031$), M32412: Butyrylcarnitine (β = -0.219, SE = 0.111, $P = 0.0497$), M33138: Oxidized bilirubin (β = -0.318, SE = 0.148, $P = 0.032$), M34407: Isovalerylcarnitine (β = -0.976, SE = 0.393, $P = 0.013$), and M36131: Alpha-glutamyltyrosine (β = -0.619, SE = 0.213, $P = 0.004$).

Sensitivity analysis

Scatterplots illustrating the relationship between these eight metabolites and ASD are presented in Figure 1. The consistency across the SNPs of each metabolite, except M20675: 1,5-Anhydroglucitol, M32412: Butyrylcarnitine, and M34407: Isovalerylcarnitine, was evaluated as adequate with heterogeneity $P > 0.05$ and pleiotropy assumption was satisfied with $P > 0.05$ as shown in Table 3.

However, since the heterogeneity and pleiotropy tests were not satisfied, it suggests that the assumption of instrumental variance was violated. This may be due to inconsistent estimates from the genetic variants of the metabolites or the presence of potential confounding affecting both the exposure and outcome. Consequently, these three metabolites were excluded at this stage.

We conducted a leave-one-out sensitivity analysis for the remaining five metabolites, and the corresponding forest plots are presented in Figure 2. The consistency of the estimated effect size for Des-Arg(9) bradykinin about ASD was assessed as adequate through this leave-one-out sensitivity analysis, which involved systematically excluding each SNP from the analysis. As a result, Des-Arg(9) bradykinin was ultimately identified as a causal metabolite for ASD.

The assumption regarding the consistency among SNPs influencing ASD through M02137: Biliverdin, M32497: 10-undecenoate (11:1n1), M33138: Oxidized bilirubin, and M36131: Alpha-glutamyltyrosine was found to be unsatisfactory, as indicated by the p-value of the SNP. To put it more intuitively, certain SNPs were observed to cross the vertical null value line in the horizontal line plot.

Enrichment analysis

To interpret the potential biological processes and pathways mediating the association between Des-Arg(9) bradykinin and ASD, evidence on gene-metabolite-disease interactions is collected and estimated. Firstly, nearby genes of the location of the SNPs were gathered from the Infinome database, revealing that *F12*, *GRK6* and *PFN3* were in proximity to rs2731672, while *KNG1* was near rs5030062 and *KLKB1* near rs4253311. Secondly, supported by the SwissTargetPrediction database, 10 predicted targets ranking on top of the predicted list of Des-Arg(9) bradykinin were retrieved and listed in Table 4. Among the predicted targets, the B1 receptor of bradykinin ranked the 1st which is consistent with the fact that the B1 receptor performed as a specific receptor for Des-Arg(9) bradykinin. Other markers were predicted as potential targets of Des-Arg(9)-bradykinin including *NTSR1*, *NTSR2*, *OPRM1*, *OPRD1*, *OPRK1*, *F2*, *CCNA1*, *CCNA2*, *CDK2*, *HLA-A* and *HLA-DRB3*. These targets are used as clues to discover potential biological interaction between Des-Arg(9)-bradykinin and ASD.

In the STRING database, a protein-protein interaction network was constructed based on a union set of the ASD-related gene set and the Des-Arg(9) bradykinin-related gene set as presented in Figure 3A. Pathways in the network represented potential interaction processes between Des-Arg(9) bradykinin and ASD. Furthermore, as shown in Figure 3B, five hub genes including *KNG1*, *F12*, *BDKRB1*, *CCNA2* and *CDK2* were identified with the MCC algorithm in

Table 2 Nominally significant results of the inverse variance weighted method

ID	Metabolite	Outcome	SNP, *n*	β	SE	*P* value
M02137	Biliverdin	ASD	3	-0.255	0.122	0.038
M20675	1,5-Anhydroglucitol	ASD	5	-0.881	0.407	0.031
M32412	Butyrylcarnitine	ASD	12	-0.219	0.111	0.049
M32497	10-undecenoate (11:1n1)	ASD	3	0.546	0.258	0.034
M32847	X-11530	ASD	3	-0.302	0.125	0.016
M33137	X-11792	ASD	3	0.388	0.093	3.03×10^{-5}
M33138	Oxidized bilirubin	ASD	3	-0.318	0.148	0.032
M34306	X-12696	ASD	4	-0.831	0.325	0.011
M34407	Isovalerylcarnitine	ASD	4	-0.976	0.393	0.013
M34420	Des-Arg(9) bradykinin	ASD	3	0.262	0.064	4.64×10^{-5}
M36131	Alpha-glutamyltyrosine	ASD	3	-0.619	0.213	0.004

ASD: Autism spectrum disorder; SNP: Single nucleotide polymorphism.

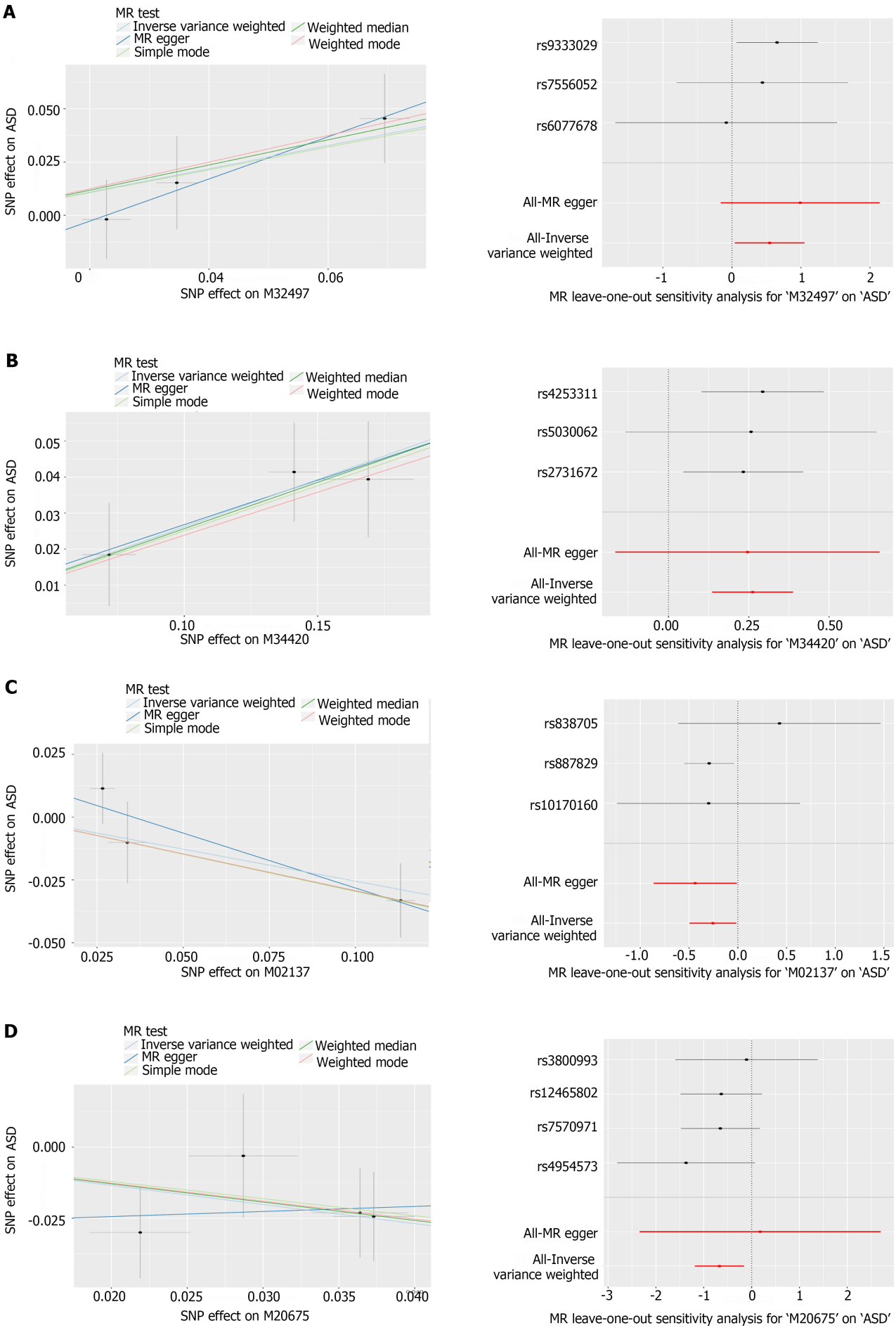
Table 3 Heterogeneity and pleiotropy tests of the 8 metabolites

Metabolite	Heterogeneity, MR Egger *P* value	Heterogeneity, IVW *P* value	Pleiotropy, *P* value
Biliverdin	0.392	0.415	0.496
1,5-anhydroglucitol	0.482	0.034	0.067
Butyrylcarnitine	0.174	0.007	0.016
10-Undecenoate (11:1n1)	0.844	0.689	0.556
Oxidized bilirubin	0.271	0.385	0.586
Isovalerylcarnitine	0.030	0.058	0.744
Des-Arg(9) bradykinin	0.663	0.906	0.949
Alpha-glutamyltyrosine	0.785	0.923	0.817

MR: Mendelian randomization; IVW: Inverse variant weight.

Table 4 Top 10 predicted targets of Des-Arg(9)-bradykinin in SwissTargetPrediction

Target	Common name	Target class	Probability
Bradykinin B1 receptor	BDKRB1	Family A G protein-coupled receptor	0.420
Neurotensin receptor 1	NTSR1	Family A G protein-coupled receptor	0.189
Thrombin	F2	Protease	0.169
HLA class I histocompatibility antigen A-3	HLA-A	Surface antigen	0.140
Mu opioid receptor	OPRM1	Family A G protein-coupled receptor	0.131
Delta opioid receptor	OPRD1	Family A G protein-coupled receptor	0.131
Kappa opioid receptor	OPRK1	Family A G protein-coupled receptor	0.122
Neurotensin receptor 2	NTSR2	Family A G protein-coupled receptor	0.122
HLA class II histocompatibility antigen DRB3-1	HLA-DRB3	Surface antigen	0.122
Cyclin-dependent kinase 2/cyclin A	CDK2, CCNA1, CCNA2	Other cytosolic protein	0.122


A
MR test
Inverse variance weighted
MR egger
Simple mode
Weighted median
Weighted mode
SNP effect on ASD
SNP effect on M32497
rs9333029
rs7556052
rs6077678
All-MR egger
All-Inverse variance weighted
MR leave-one-out sensitivity analysis for 'M32497' on 'ASD'
B
SNP effect on M34420
rs4253311
rs5030062
rs2731672
MR leave-one-out sensitivity analysis for 'M34420' on 'ASD'
C
SNP effect on M02137
rs838705
rs887829
rs10170160
MR leave-one-out sensitivity analysis for 'M02137' on 'ASD'
D
SNP effect on M20675
rs3800993
rs12465802
rs7570971
rs4954573
MR leave-one-out sensitivity analysis for 'M20675' on 'ASD'

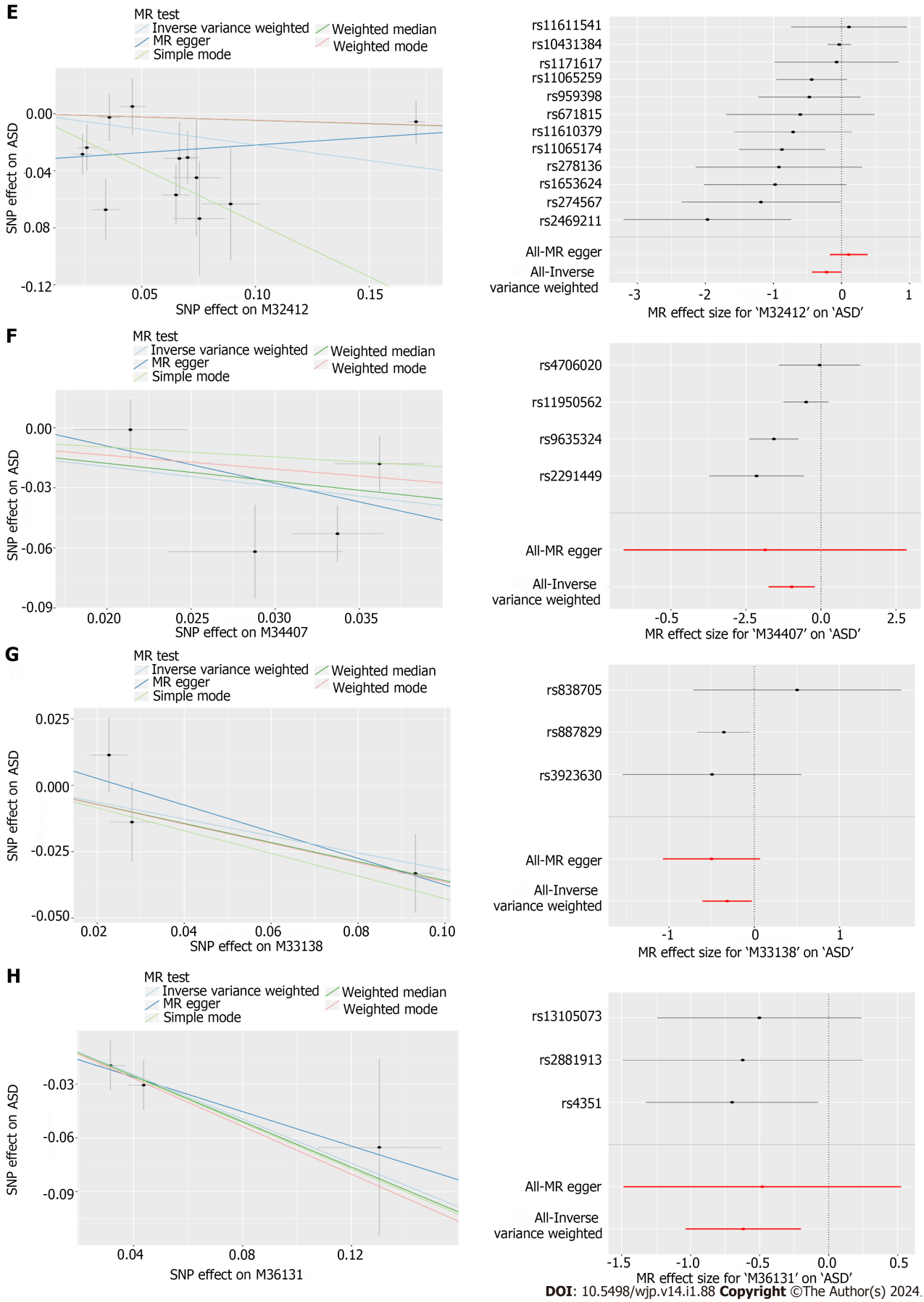


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Figure 1 Scatter plots and forest plots of Mendelian randomization effect about 8 metabolites on autism spectrum disorder. A: Scatter plot and forest plot of Mendelian randomization (MR) effect about M32497:10-undecenoate (11:1n1) on autism spectrum disorder (ASD); B: Scatter plot and forest plot of

MR effect about M34420: Des-Arg(9) bradykinin on ASD; C: Scatter plot and forest plot of MR effect about M02137: biliverdin on ASD; D: Scatter plot and forest plot of MR effect about M20675: 1,5-anhydroglucitol on ASD; E: Scatter plot and forest plot of MR effect about M32412: butyrylcarnitine on ASD; F: Scatter plot and forest plot of MR effect about M34407: isovalerylcarnitine on ASD; G: Scatter plot and forest plot of MR effect about M33138: oxidized bilirubin on ASD; H: Scatter plot and forest plot of MR effect about M36131: alpha-glutamyltyrosine on ASD. MR: Mendelian randomization; SNP: Single nucleotide polymorphism.

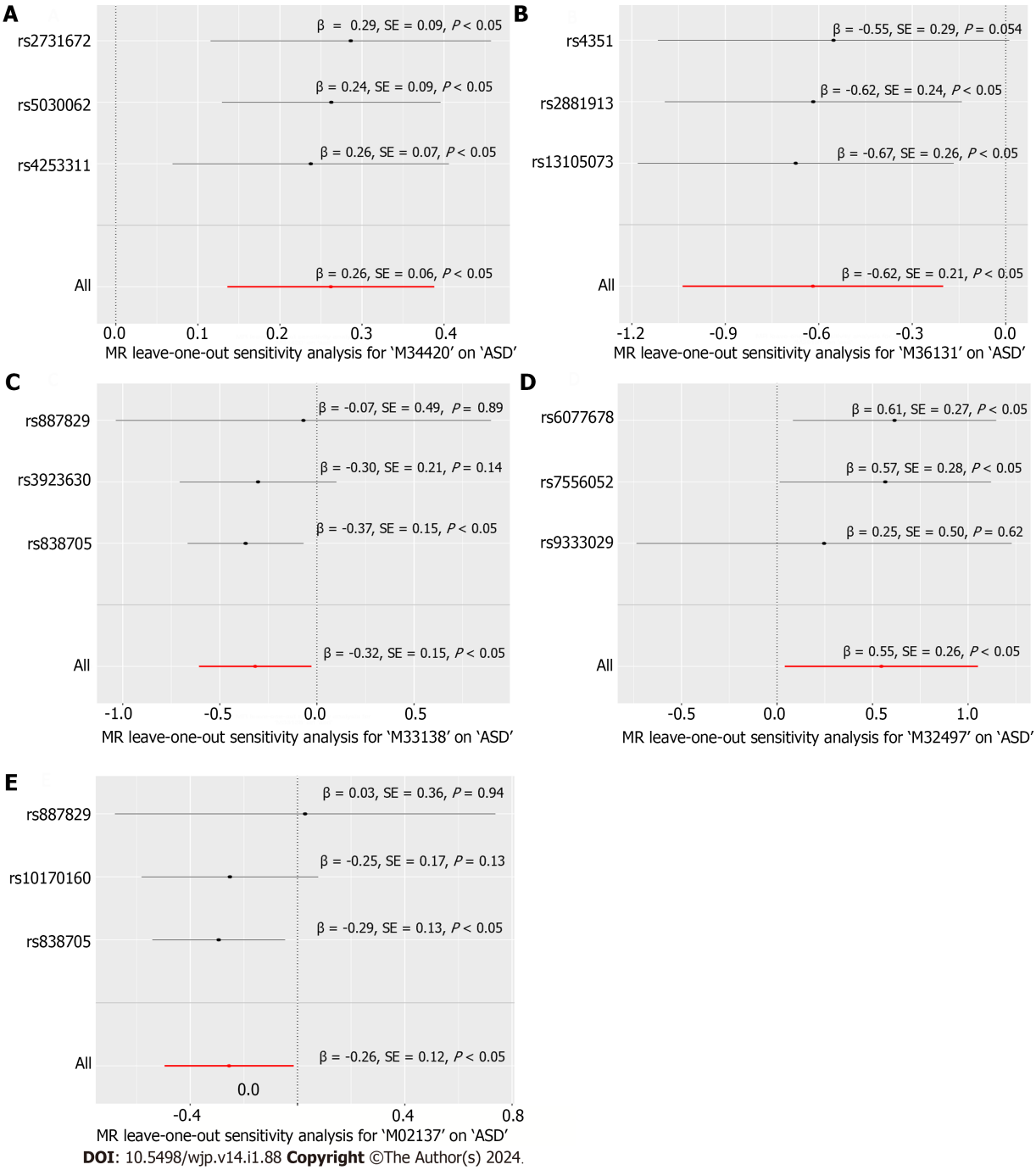

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Figure 2 Leave-one-out sensitivity plots of 5 metabolites on autism spectrum disorder. A: Mendelian randomization (MR) leave-one-out sensitivity analysis for M34420: Des-Arg(9) bradykinin on autism spectrum disorder (ASD); B: MR leave-one-out sensitivity analysis for M36131: alpha-glutamyltyrosine on ASD; C: MR leave-one-out sensitivity analysis for M33138: oxidized bilirubin on ASD; D: MR leave-one-out sensitivity analysis for M32497: 10-undecenoate (11:1n1) on ASD; E: MR leave-one-out sensitivity analysis for M02137: biliverdin on ASD. MR: Mendelian randomization.

the interaction network. These genes could play important direct or indirect roles in modulating the biological activity of other makers of the network.

To further explore the potential biological processes bridging Des-Arg(9) bradykinin and ASD, enrichment analysis was performed and the result is shown in Figure 4. Genes in the interaction network were enriched in biological processes including Peptide GPCRs, behavior, cellular senescence, multicellular organismal processes, response to

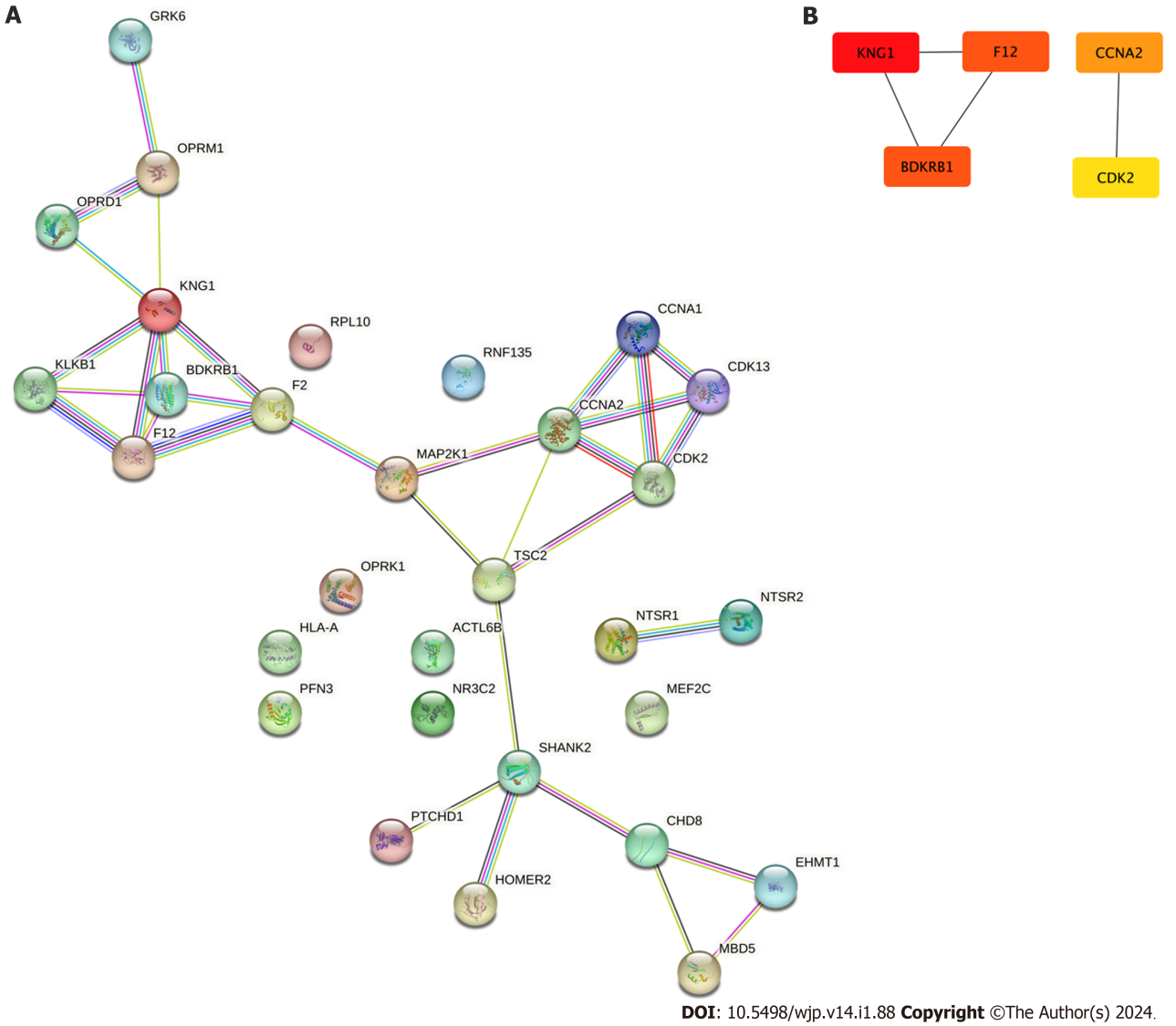

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Figure 3 Protein-protein interaction between Des-Arg(9) related targets and Austism related genes. A: Protein-protein interaction network of Des-Arg(9) bradykinin and autism spectrum disorder (ASD) related genes; B: Five hub genes of the protein-protein interaction network of Des-Arg(9) bradykinin and ASD related genes.

stimuli, metabolic processes, immune system processes, and developmental processes. These findings provide valuable insights into the potential mechanisms underlying the association between Des-Arg(9)-bradykinin and ASD, highlighting key genes and biological processes involved in this interaction.

DISCUSSION

This study used two-sample MR to investigate the causal relationship between metabolites and ASD. The analysis identified Des-Arg(9)-bradykinin as a potential risk factor for ASD($\beta = 0.262$, SE = 0.064, $P = 4.64 \times 10^{-5}$). Furthermore, an interaction network analysis revealed five hub genes associated with Des-Arg(9)-bradykinin and ASD. Enrichment analysis indicated that this association may be involved in complex biological processes, including behavior, response to stimulus, and interaction between organisms. These findings provide valuable insights into the potential mechanisms underlying the association between Des-Arg(9)-bradykinin and ASD, highlighting potential key genes and biological processes involved in the development of ASD.

The pathophysiology of ASD is believed to result from intricate interactions between environmental and genetic factors [24]. Studies have found that elevated levels of inflammatory markers, such as cytokines, were detected in the blood and brains of some individuals with autism[25]. Dysregulated neuroinflammation has been proposed as a potential contributor to ASD development, emphasizing the importance of immune-neuronal crosstalk in neuroinflammation research[26]. There is also a suggestion of possible interaction between innate immunity and neuronal activity in the etiology of autism[27]. Increased microglial activation and density, and increased proinflammatory cytokines were observed in several brain regions among ASD individuals[28]. Furthermore, certain environmental factors associated

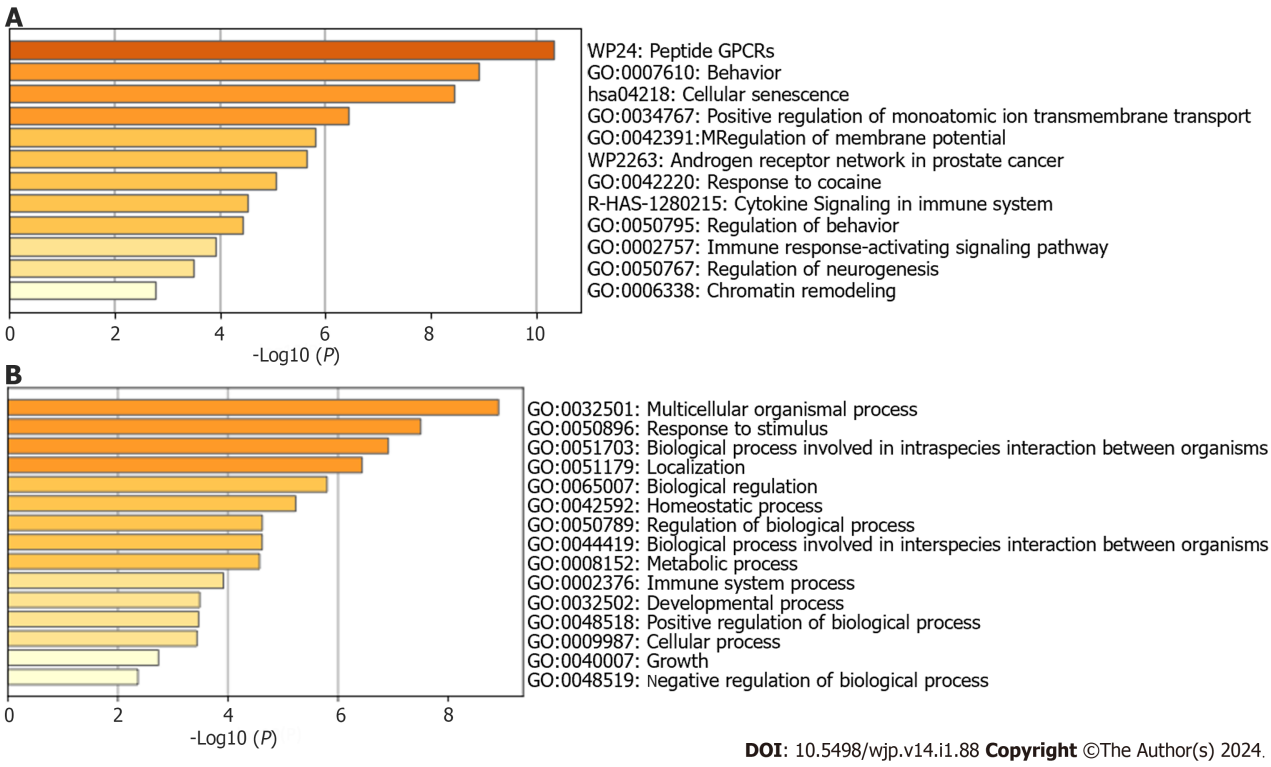

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Figure 4 Annotation of the genes in the interaction network. A: Enrichment analysis results of pathways; B: Enrichment analysis results of gene ontology biological process.

with autism, such as prenatal infection, are known to trigger immune responses and inflammation. The enrichment of behavior-related processes aligns with the core symptoms of ASD, including impaired social interaction and repetitive behaviors. Additionally, the association with the biological process of response to stimulus suggests potential sensitivities or altered sensory processing in individuals with ASD.

Current research revealing the role of Des-Arg(9)-bradykinin in the development of ASD is limited. However, there is evidence suggesting that the Des-Arg(9)-bradykinin is involved in inflammatory and neurobiological processes. As a member of the kallikrein–kinin system, bradykinin participates in the modulation of important biological activities including vasocontraction, nitric oxide release, and anti-ischemic effects *via* interaction with the renin-angiotensin system [29]. Contributing to fluid retention within cerebral tissue, bradykinin was also considered to have a pathophysiological role in the mammalian brain[30]. The *BDKRB1* and *BDKRB2* were two of the main targets of bradykinin and its metabolites. The expression of B1R is induced during injury by cytokines such as interleukin-1beta while B2R is ubiquitously expressed. As a metabolite of bradykinin mediated by carboxypeptidase N, Des-Arg(9)-bradykinin was reported as a B1 receptor agonist that increases intracellular Ca^{2+} and induces vasocontraction, cell proliferation, and collagen synthesis[31,32]. The activation of the B1 receptor was reported to participate in the inflammatory response by inducing the release of pro-inflammatory cytokines and promoting leukocyte recruitment to the site of inflammation[33]. In light of the regulatory approval of drugs targeting bradykinin receptors, notably lcatibant, there arises an interesting topic for the in-depth examination and exploration of their potential effects on neurodevelopmental diseases. This prospect warrants further observation and comprehensive investigation.

Enrichment analysis results of this study also indicated the complexity of the interactions between the metabolism of Des-Arg(9) bradykinin and ASD. Given the potential role of the B1 receptor activation in immune cell infiltration, microglia activation, and cytokine production within the central nervous system, B1 receptor-mediated signaling cascades might result in elevated neuroinflammation[31]. As predicted targets of Des-Arg(9)-bradykinin, NTSR1, and NTSR2 participates in the modulation of neurotensin signaling that has been reported to stimulate microglia to secrete IL-1beta and CXCL8[34] and affect social behavior and repetitive behaviors, which are core features of ASD[35-37]. The Mu opioid receptors have also been reported as a critical neurobiological substrate of social behavior that participate in stress response and immune processes[38]. Therefore, immune-inflammation pathways could be the potential factors mediating Des-Arg(9)-bradykinin and ASD. The exact mechanism should be further explored and validated.

Setting genetic variances as instrumental variables, the causal relationship between metabolites and diseases estimated by MR provides practical clues for exploring biomarkers for neurodevelopmental disorders, such as ASD. The bioinformatic approaches integrating multi-scale evidence also provide a novel perspective for interpreting the association between metabolite and disease. Even if the causal relationship between Des-Arg(9)-bradykinin and ASD is validated pathogenetically, further research on the pharmacological treatment targeting the metabolic pathway of bradykinin or repurposing the drug target B1R would promote the discovery of a novel approach to treating ASD.

This study identified Des-Arg(9)-bradykinin as a causal metabolite for ASD using MR analysis. However, there are several limitations to be considered in this study. Firstly, linear algorithms were used in MR analysis hypothesizing a simple interaction mode between metabolites and disease. However, the modulation of biological processes is complex and dynamic. It should be also noticed that other metabolites, though evaluated as non-significant in this study, could also participate in the modulation of inflammation condition and immune status, and further affect the development of disease. Therefore, the pathogenetic interaction between the metabolite profile and ASD needs to be further validated using GWAS data from a larger sample size over more adaptive subgrouping. This would enhance the robustness and generalizability of the findings. Secondly, while genetic variables were utilized as reliable instrument variables for causal inference between metabolic exposure and ASD, the presence of pleiotropy in SNPs can disrupt their reliability. It is important to acknowledge that the strength of the instrument variables and the sample size employed in this study may introduce potential biases in the results. Thirdly, the study is based on the hypothesis that altered gene expression leads to changes in metabolite levels, ultimately contributing to the development of ASD. However, it is important to note that not all cases of ASD can be attributed to gene expression alterations alone. Other factors and mechanisms may also play a role in the disorder. Additionally, the practicality of the analytical results may be limited as the study did not comprehensively consider actual conditions such as the dosage, duration of exposure, interindividual variation in metabolism, and the ability of metabolites to reach the target tissues. Lastly, the study predominantly involved individuals of European ancestry to mitigate potential biases stemming from population variations. However, this selection may limit the generalizability and applicability of the findings to other demographic groups. Considering the genetic and environmental heterogeneity prevalent in various ethnic groups, it is imperative to replicate these findings in diverse populations to confirm their broader applicability. The journey toward identifying valid biomarkers to aid in clinical disease diagnosis is undeniably lengthy[39]. Although this study offers valuable insights into the potential role of Des-Arg(9)-bradykinin in ASD development, further research addressing these limitations is essential to bolster the validity, reliability, and practicality of the results.

CONCLUSION

Our study suggests a potential role for Des-Arg(9)-bradykinin in the development of ASD, mediated through metabolic and immune processes. The identification of hub genes and the enrichment of relevant biological processes provide additional evidence to support the interpretation of this association. Understanding the underlying pathological mechanisms and exploring the metabolic pathway of bradykinin, including the B1 receptor, could pave the way for novel therapeutic approaches for ASD. Further research, involving larger and more diverse cohorts, is warranted to validate and extend our findings.

ARTICLE HIGHLIGHTS

Research background

This study delves into the complex landscape of autism spectrum disorder (ASD), an early-onset neurodevelopmental condition characterized by social communication deficits and repetitive behaviors. The etiology of ASD remains enigmatic, prompting a crucial need for robust diagnostic biomarkers. The study explores the potential interplay of genetic and environmental factors in ASD development, with a focus on plasma metabolites and their causal associations, providing a foundation for future advancements in diagnosis and intervention.

Research motivation

In the realm of ASD research, the pressing motivation lies in early diagnosis and effective therapeutic interventions. The study aims to tackle the pivotal challenge of identifying diagnostic biomarkers, given the intricate interplay of genetic and environmental factors in ASD etiology. A successful exploration of these causal associations can pave the way for innovative diagnostic tools and targeted interventions, offering hope for improved outcomes and quality of life for individuals with ASD.

Research objectives

This study sought to uncover the causal connections between plasma metabolites and ASD while accounting for genetic and environmental factors. The realized objective of identifying these associations carries profound implications for advancing diagnostic biomarkers and guiding future research in the field of ASD.

Research methods

This study employed a two-sample Mendelian randomization (MR) analysis, a robust method that harnessed data from large-scale genome-wide association studies on metabolites and ASD. Novelty lies in the integration of genetic variants as instrumental variables to estimate causal associations, and the innovative use of the inverse variant weight algorithm. These methods unveiled the potential role of plasma metabolites in ASD etiology, shedding new light on diagnostic biomarkers and therapeutic avenues.

Research results

Des-Arg(9)-bradykinin emerged as a compelling causal metabolite associated with an increased risk of ASD. The sensitivity analysis underscored the robustness of this association. Furthermore, the identification of five hub genes, including *KNG1*, *F12*, *BDKRB1*, *CCNA2* and *CDK2*, signifies the potential involvement of these genes in the ASD-Des-Arg(9)-bradykinin association. Enrichment analysis shed light on a multitude of biological processes, from peptide GPCRs to immune system functions, offering a comprehensive insight into the potential mechanisms linking Des-Arg(9)-bradykinin with ASD.

Research conclusions

This study contributes novel insights by proposing Des-Arg(9)-bradykinin as a potential causal metabolite for ASD. The study set metabolites as proxy of genetic and environmental factors, and leveraged two-sample MR methods to elucidate the associations. These findings introduce new diagnostic and predictive biomarker for ASD, offering a promising pathway for future research and clinical practice.

Research perspectives

The direction of future research should focus on comprehensive investigations into the complex interplay of genetic and environmental factors in ASD etiology. Expanding datasets to include diverse populations and incorporating multi-omics approaches can provide a more nuanced understanding of ASD development. Additionally, future research should explore the identification of additional biomarkers and the underlying mechanisms, potentially paving the way for innovative diagnostic tools and personalized interventions to enhance the lives of individuals with ASD.

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FOOTNOTES

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REFERENCES

1 **Yates K**, Le Couteur A. Diagnosing autism/autism spectrum disorders. *Paediatr Child Health* 2016; **26**: 513-518 [DOI: 10.1016/j.paed.2016.08.004]

2 **Hus Y**, Segal O. Challenges Surrounding the Diagnosis of Autism in Children. *Neuropsychiatr Dis Treat* 2021; **17**: 3509-3529 [PMID: 34898983 DOI: 10.2147/NDT.S282569]

3 **Dawson G**, Sapiro G. Potential for Digital Behavioral Measurement Tools to Transform the Detection and Diagnosis of Autism Spectrum Disorder. *JAMA Pediatr* 2019; **173**: 305-306 [PMID: 30715131 DOI: 10.1001/jamapediatrics.2018.5269]

4 **Frye RE**, Vassall S, Kaur G, Lewis C, Karim M, Rossignol D. Emerging biomarkers in autism spectrum disorder: a systematic review. *Ann Transl Med* 2019; **7**: 792 [PMID: 32042808 DOI: 10.21037/atm.2019.11.53]

5 **Bölte S**, Girdler S, Marschik PB. The contribution of environmental exposure to the etiology of autism spectrum disorder. *Cell Mol Life Sci* 2019; **76**: 1275-1297 [PMID: 30570672 DOI: 10.1007/s00018-018-2988-4]

6 **Kim YS**, Leventhal BL. Genetic epidemiology and insights into interactive genetic and environmental effects in autism spectrum disorders. *Biol Psychiatry* 2015; **77**: 66-74 [PMID: 25483344 DOI: 10.1016/j.biopsych.2014.11.001]

7 **Leblond CS**, Le TL, Malesys S, Cliquet F, Tabet AC, Delorme R, Rolland T, Bourgeron T. Operative list of genes associated with autism and neurodevelopmental disorders based on database review. *Mol Cell Neurosci* 2021; **113**: 103623 [PMID: 33932580 DOI: 10.1016/j.mcn.2021.103623]

8 **Li J**, Wang L, Guo H, Shi L, Zhang K, Tang M, Hu S, Dong S, Liu Y, Wang T, Yu P, He X, Hu Z, Zhao J, Liu C, Sun ZS, Xia K. Targeted sequencing and functional analysis reveal brain-size-related genes and their networks in autism spectrum disorders. *Mol Psychiatry* 2017; **22**: 1282-1290 [PMID: 28831199 DOI: 10.1038/mp.2017.140]

9 **Madore C**, Leyrolle Q, Lacabanne C, Benmamar-Badel A, Joffre C, Nadjar A, Layé S. Neuroinflammation in Autism: Plausible Role of Maternal Inflammation, Dietary Omega 3, and Microbiota. *Neural Plast* 2016; **2016**: 3597209 [PMID: 27840741 DOI: 10.1155/2016/3597209]

10 **Kwon HK**, Choi GB, Huh JR. Maternal inflammation and its ramifications on fetal neurodevelopment. *Trends Immunol* 2022; **43**: 230-244 [PMID: 35131181 DOI: 10.1016/j.it.2022.01.007]

11 **de la Torre-Ubieta L**, Won H, Stein JL, Geschwind DH. Advancing the understanding of autism disease mechanisms through genetics. *Nat Med* 2016; **22**: 345-361 [PMID: 27050589 DOI: 10.1038/nm.4071]

12 **Liu Y**, Qing H, Deng Y. Biomarkers in Alzheimer's disease analysis by mass spectrometry-based proteomics. *Int J Mol Sci* 2014; **15**: 7865-7882 [PMID: 24806343 DOI: 10.3390/ijms15057865]

13 **Glinton KE**, Elsea SH. Untargeted Metabolomics for Autism Spectrum Disorders: Current Status and Future Directions. *Front Psychiatry* 2019; **10**: 647 [PMID: 31551836 DOI: 10.3389/fpsyt.2019.00647]

14 **Ritz B**, Yan Q, Uppal K, Liew Z, Cui X, Ling C, Inoue K, von Ehrenstein O, Walker DI, Jones DP. Untargeted Metabolomics Screen of Mid-pregnancy Maternal Serum and Autism in Offspring. *Autism Res* 2020; **13**: 1258-1269 [PMID: 32496662 DOI: 10.1002/aur.2311]

15 **Liang Y**, Ke X, Xiao Z, Zhang Y, Chen Y, Li Y, Wang Z, Lin L, Yao P, Lu J. Untargeted Metabolomic Profiling Using UHPLC-QTOF/MS Reveals Metabolic Alterations Associated with Autism. *Biomed Res Int* 2020; **2020**: 6105608 [PMID: 32964039 DOI: 10.1155/2020/6105608]

16 **Likhitweerawong N**, Thonusin C, Boonchooduang N, Louthrenoo O, Nookaew I, Chattipakorn N, Chattipakorn SC. Profiles of urine and blood metabolomics in autism spectrum disorders. *Metab Brain Dis* 2021; **36**: 1641-1671 [PMID: 34338974 DOI: 10.1007/s11011-021-00788-3]

17 **Sanderson E**, Glymour MM, Holmes MV, Kang H, Morrison J, Munafò MR, Palmer T, Schooling CM, Wallace C, Zhao Q, Smith GD. Mendelian randomization. *Nat Rev Methods Primers* 2022; **2** [PMID: 37325194 DOI: 10.1038/s43586-021-00092-5]

18 **Lawlor DA**. Commentary: Two-sample Mendelian randomization: opportunities and challenges. *Int J Epidemiol* 2016; **45**: 908-915 [PMID: 27427429 DOI: 10.1093/ije/dyw127]

19 **Grover S**, Del Greco M F, Stein CM, Ziegler A. Mendelian Randomization. *Methods Mol Biol* 2017; **1666**: 581-628 [PMID: 28980266 DOI: 10.1007/978-1-4939-7274-6_29]

20 **Shin SY**, Fauman EB, Petersen AK, Krumsiek J, Santos R, Huang J, Arnold M, Erte I, Forgetta V, Yang TP, Walter K, Menni C, Chen L, Vasquez L, Valdes AM, Hyde CL, Wang V, Ziemek D, Roberts P, Xi L, Grundberg E; Multiple Tissue Human Expression Resource (MuTHER) Consortium, Waldenberger M, Richards JB, Mohney RP, Milburn MV, John SL, Trimmer J, Theis FJ, Overington JP, Suhre K, Brosnan MJ, Gieger C, Kastenmüller G, Spector TD, Soranzo N. An atlas of genetic influences on human blood metabolites. *Nat Genet* 2014; **46**: 543-550 [PMID: 24816252 DOI: 10.1038/ng.2982]

21 **Grove J**, Ripke S, Als T, Mattheisen M, Walters R, Won H, Pallesen J, Agerbo E, Andreasssen O, Anney R, Belliveau R, Bettella F, Buxbaum J, Grauholm J, Bækved-Hansen M, Cerrato F, Chambert K, Christensen J, Churchhouse C, Børglum A. Common risk variants identified in autism spectrum disorder. 2017 Preprint. Available from: bioRxiv:224774 [DOI: 10.1101/224774]

22 **Hemani G**, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, Laurin C, Burgess S, Bowden J, Langdon R, Tan VY, Yarmolinsky J, Shihab HA, Timpson NJ, Evans DM, Relton C, Martin RM, Davey Smith G, Gaunt TR, Haycock PC. The MR-Base platform supports systematic causal inference across the human phenome. *Elife* 2018; **7** [PMID: 29846171 DOI: 10.7554/eLife.34408]

23 **Verbanck M**, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet* 2018; **50**: 693-698 [PMID: 29686387 DOI: 10.1038/s41588-018-0099-7]

24 **Gevezova M**, Sarafian V, Anderson G, Maes M. Inflammation and Mitochondrial Dysfunction in Autism Spectrum Disorder. *CNS Neurol Disord Drug Targets* 2020; **19**: 320-333 [PMID: 32600237 DOI: 10.2174/1871527319666200628015039]

25 **Stavridou T**, Driga A M, Drigas A. Blood Markers in Detection of Autism. *Int J Recent Contributions Eng Sci IT* 2021; **9**: 79-86 [DOI: 10.3991/ijes.v9i2.21283]

26 **Matta SM**, Hill-Yardin EL, Crack PJ. The influence of neuroinflammation in Autism Spectrum Disorder. *Brain Behav Immun* 2019; **79**: 75-90 [PMID: 31029798 DOI: 10.1016/j.bbi.2019.04.037]

27 **Gupta S**, Ellis SE, Ashar FN, Moes A, Bader JS, Zhan J, West AB, Arking DE. Transcriptome analysis reveals dysregulation of innate immune response genes and neuronal activity-dependent genes in autism. *Nat Commun* 2014; **5**: 5748 [PMID: 25494366 DOI: 10.1038/ncomms6748]

28 **Toscano CVA**, Barros L, Lima AB, Nunes T, Carvalho HM, Gaspar JM. Neuroinflammation in autism spectrum disorders: Exercise as a "pharmacological" tool. *Neurosci Biobehav Rev* 2021; **129**: 63-74 [PMID: 34310976 DOI: 10.1016/j.neubiorev.2021.07.023]

29 **Bekassy Z**, Lopatko Fagerström I, Bader M, Karpman D. Crosstalk between the renin-angiotensin, complement and kallikrein-kinin systems in

inflammation. *Nat Rev Immunol* 2022; **22**: 411-428 [PMID: 34759348 DOI: 10.1038/s41577-021-00634-8]

30 **Dobrivojević M**, Špiranec K, Sinđić A. Involvement of bradykinin in brain edema development after ischemic stroke. *Pflugers Arch* 2015; **467**: 201-212 [PMID: 24756199 DOI: 10.1007/s00424-014-1519-x]

31 **Sriramula S**. Kinin B1 receptor: A target for neuroinflammation in hypertension. *Pharmacol Res* 2020; **155**: 104715 [PMID: 32087235 DOI: 10.1016/j.phrs.2020.104715]

32 **Sharma JN**. Does the kinin system mediate in cardiovascular abnormalities? An overview. *J Clin Pharmacol* 2003; **43**: 1187-1195 [PMID: 14551172 DOI: 10.1177/0091270003258171]

33 **Mugisho OO**, Robilliard LD, Nicholson LFB, Graham ES, O'Carroll SJ. Bradykinin receptor-1 activation induces inflammation and increases the permeability of human brain microvascular endothelial cells. *Cell Biol Int* 2020; **44**: 343-351 [PMID: 31498530 DOI: 10.1002/cbin.11232]

34 **Patel AB**, Tsilioni I, Leeman SE, Theoharides TC. Neurotensin stimulates sortilin and mTOR in human microglia inhibitable by methoxyluteolin, a potential therapeutic target for autism. *Proc Natl Acad Sci U S A* 2016; **113**: E7049-E7058 [PMID: 27663735 DOI: 10.1073/pnas.1604992113]

35 **Boules MM**, Fredrickson P, Muehlmann AM, Richelson E. Elucidating the role of neurotensin in the pathophysiology and management of major mental disorders. *Behav Sci (Basel)* 2014; **4**: 125-153 [PMID: 25379273 DOI: 10.3390/bs4020125]

36 **Angelidou A**, Francis K, Vasiadi M, Alysandratos KD, Zhang B, Theoharides A, Lykouras L, Sideri K, Kalogeromitros D, Theoharides TC. Neurotensin is increased in serum of young children with autistic disorder. *J Neuroinflammation* 2010; **7**: 48 [PMID: 20731814 DOI: 10.1186/1742-2094-7-48]

37 **Tsilioni I**, Dodman N, Petra AI, Taliou A, Francis K, Moon-Fanelli A, Shuster L, Theoharides TC. Elevated serum neurotensin and CRH levels in children with autistic spectrum disorders and tail-chasing Bull Terriers with a phenotype similar to autism. *Transl Psychiatry* 2014; **4**: e466 [PMID: 25313509 DOI: 10.1038/tp.2014.106]

38 **Pellissier LP**, Gandía J, Laboute T, Becker JAJ, Le Merrer J. μ opioid receptor, social behaviour and autism spectrum disorder: reward matters. *Br J Pharmacol* 2018; **175**: 2750-2769 [PMID: 28369738 DOI: 10.1111/bph.13808]

39 **Cortese S**, Solmi M, Michelini G, Bellato A, Blanner C, Canozzi A, Eudave L, Farhat LC, Højlund M, Köhler-Forsberg O, Leffa DT, Rohde C, de Pablo GS, Vita G, Wesselhoeft R, Martin J, Baumeister S, Bozhilova NS, Carlisi CO, Leno VC, Floris DL, Holz NE, Kraaijenvanger EJ, Sacu S, Vainieri I, Ostuzzi G, Barbui C, Correll CU. Candidate diagnostic biomarkers for neurodevelopmental disorders in children and adolescents: a systematic review. *World Psychiatry* 2023; **22**: 129-149 [PMID: 36640395 DOI: 10.1002/wps.21037]

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ORIGINAL ARTICLE

Observational Study

Performance of the walking trail making test in older adults with white matter hyperintensities

Hong-Yi Zhao, Zhi-Qiang Zhang, Yong-Hua Huang, Hong Li, Fang-Yuan Wei

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Abstract

BACKGROUND

Several studies have reported that the walking trail making test (WTMT) completion time is significantly higher in patients with developmental coordination disorders and mild cognitive impairments. We hypothesized that WTMT performance would be altered in older adults with white matter hyperintensities (WMH).

AIM

To explore the performance in the WTMT in older people with WMH.

METHODS

In this single-center, observational study, 25 elderly WMH patients admitted to our hospital from June 2019 to June 2020 served as the WMH group and 20 participants matched for age, gender, and educational level who were undergoing physical examination in our hospital during the same period served as the control group. The participants completed the WTMT-A and WTMT-B to obtain their gait parameters, including WTMT-A completion time, WTMT-B completion time,

speed, step length, cadence, and stance phase percent. White matter lesions were scored according to the Fazekas scale. Multiple neuropsychological assessments were carried out to assess cognitive function. The relationships between WTMT performance and cognition and motion in elderly patients with WMH were analyzed by partial Pearson correlation analysis.

RESULTS

Patients with WMH performed significantly worse on the choice reaction test (CRT) (0.51 ± 0.09 s *vs* 0.44 ± 0.06 s, P = 0.007), verbal fluency test (VFT, 14.2 ± 2.75 *vs* 16.65 ± 3.54, P = 0.012), and digit symbol substitution test (16.00 ± 2.75 *vs* 18.40 ± 3.27, P = 0.010) than participants in the control group. The WMH group also required significantly more time to complete the WTMT-A (93.00 ± 10.76 s *vs* 70.55 ± 11.28 s, P < 0.001) and WTMT-B (109.72 ± 12.26 s *vs* 82.85 ± 7.90 s, P < 0.001). WTMT-A completion time was positively correlated with CRT time (r = 0.460, P = 0.001), while WTMT-B completion time was negatively correlated with VFT (r = -0.391, P = 0.008). On the WTMT-A, only speed was found to statistically differ between the WMH and control groups (0.803 ± 0.096 *vs* 0.975 ± 0.050 m/s, P < 0.001), whereas on the WTMT-B, the WMH group exhibited a significantly lower speed (0.778 ± 0.111 *vs* 0.970 ± 0.053 m/s, P < 0.001) and cadence (82.600 ± 4.140 *vs* 85.500 ± 5.020 steps/m, P = 0.039), as well as a higher stance phase percentage (65.061 ± 1.813% *vs* 63.513 ± 2.465%, P = 0.019) relative to controls.

CONCLUSION

Older adults with WMH showed obviously poorer WTMT performance. WTMT could be a potential indicator for cognitive and motor deficits in patients with WMH.

Key Words: White matter hyperintensities; Cognitive dysfunction; Motor deficits; Gait analysis; Trail making test; Small vessel disease

Core Tip: A new modified trail making test [walking trail making test (WTMT)], was used to explore the cognitive and motor deficits in older adults with WMH. In addition, wearable sensors were selected firstly in the WTMT to analyze the gait features of subjects. The results implied that WTMT could be a potential indicator for the cognitive and motor deficits in WMH patients.

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INTRODUCTION

With continued advances in medical technologies and improvement in life expectancy in modern society, cognitive impairment and gait disturbance have become common symptoms negatively affecting the daily life of the growing elderly population. In the last decade, an increasing number of studies have confirmed that cognitive impairment and gait abnormalities in older adults should not to be explored in isolation[1]. On the contrary, impairments in cognitive and physical dimensions are frequently concurrent[2]. Kelaiditi *et al*[3] proposed the concept of "cognitive frailty" in 2013, and "motor cognitive risk syndrome" was reported by Verghese *et al*[4] a year later. Recent findings have even demonstrated the synergistic effects of cognitive and motor dysfunction in patients with cerebral small vessel disease (CSVD)[5].

White matter hyperintensities (WMH), together with cerebral microbleeds, recent subcortical lacunar infarcts (clinically symptomatic), lacunes (clinically silent), prominent perivascular spaces, atrophy lacunar infarcts, etc are known to be common signs of CSVD on conventional magnetic resonance imaging (MRI)[6]. WMH represent a common condition in older adults, occurring in approximately 80% adults in the general population over the age of 60 years[7]. Gait disorders and cognitive dysfunction (especially executive dysfunction) are the main symptoms of WMH[8]. Longitudinal studies revealed that WMH are associated with a high risk of falling, disability, and mortality due to the persistent deterioration of cognitive and motor function[9,10]. However, the early detection of the above symptoms is difficult in clinical practice. Recent studies inferred that a well-designed cognitive-motor dual walking task could be a useful tool for detecting cognitive and motor impairment in patients with WMH[11]. Under dual task conditions, the motor and/or cognitive task performance of older people can deteriorate due to competing demands when the available central resource capacity is exceeded[12].

The traditional trail making test (TMT) is a commonly used paper-and-pencil cognitive function test that can reflect a person's ability in terms of executive function, attention, and processing speed. Recent studies have attempted to modify the traditional TMT to create the walking TMT (WTMT)[13-15]. In contrast to the ordinary dual walking task tests based

on a cognitive task separate from a motor task, the WTMT incorporates a cognitive task into walking. In addition, recently published findings have implied that cognitive tasks involving internal interfering factors (*e.g.*, mental tracking) impair gait performance more than those involving external interfering factors (*e.g.*, reaction time)[13]. Multiple studies have reported that the WTMT completion time is significantly higher in patients with developmental coordination disorders and mild cognitive impairment[14,16]. Thus, the aim of the current study was to assess the gait characteristics of elderly individuals with WMH using the WTMT task.

MATERIALS AND METHODS

Study population

A total of 25 older adults with WMH (WMH group) and 20 healthy individuals matched for age, gender, and educational level (HE group) were recruited from the Department of Neurology, the Seventh Medical Center of PLA General Hospital (which also receives older individuals in Aged Cadre Convalescent subdepartments). These patients were recruited consecutively from June 1, 2021, to April 1, 2022. Participants in the HE group, who had no record of a WMH diagnosis and who had regular rest and recuperation plans, were recruited from the Aged Cadre Convalescent subdepartment. Each participant voluntarily signed an informed consent form to participate in the current study.

All participants underwent screening by 3.0 T MRI of the brain and were grouped based on a method previously described by our group[11]. White matter lesions were graded using the Fazekas scale, as previously described[17]. Briefly, we rated WMH severity as grade 1 (punctate lesions), grade 2 (early confluent lesions), or grade 3 (confluent lesions). Only individuals with a Fazekas score of 0 were included in the HE group.

The exclusion criteria were history of major stroke; presence of multiple lacunar infarcts, other reasons for leukoencephalopathy (including immune, demyelination, and genetic); major psychiatric disorders (diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV); use of psychotropic medications or drugs with the side effect of risk of falling (*e.g.*, tranquillizers/sedatives, diuretics, antiparkinsonian drugs); MRI contraindications; dementia (diagnosed using an International Classification of Diseases-10 code); a mini-mental state examination (MMSE) score lower than 23 points[18]; and use of walking aids.

MRI measurements

A 3.0 T MRI brain scan (Discovery MR750; GE Healthcare, United States) displayed white matter lesions, which indicated the degree of CSVD. Brain MRI (slice and interslice thicknesses of 5 mm and 1.5 mm, respectively) was carried out as follows: T1 fluid-attenuated inversion recovery (TR, 1750 ms; TE, 23 ms; TI, 780 ms; FOV, 24 cm) and T2-weighted imaging (TR, 7498 ms; TE, 105 ms; FOV, 24 cm) sequences. The researchers who assessed gait were blinded to the imaging findings.

WTMT paradigm and gait evaluation

The WTMT was conducted in a quiet and comfortable environment. For the WTMT-A, randomly distributed coins with a 30-cm diameter and labeled with Arabic numbers (1-15) were positioned in a 16 m^2 square area (4 m × 4 m). Participants were instructed to step as quickly and accurately as possible. Experimenters instructed the participants as follows: "Please walk on numbered targets in a sequential order as rapidly as possible, joining consecutive numbers (*i.e.*, 1 to 2 to 3…15) in the coins randomly distributed on the floor." When participants stepped on an incorrect number, the experimenter indicated the error, instructing them to step on the correct number as time continued to be measured. The WTMT-A was performed only once.

For the WTMT-B, the arrangement and procedure were similar to those of WTMT-A, except the Arabic numbers 1-15 were replaced with Arabic numbers (1-8) and Chinese characters (壹, 贰, 叁, 肆, 伍, 陆, 柒). Experimenters instructed the participants as follows: "Please walk on numbered targets in a sequential order as rapidly as possible joining consecutive numbers (*i.e.*, 1 to 壹 to 2 to 贰 to 3 to 叁…8) in the coins randomly distributed on the floor."

The arrangements of numbers in the WTMT are detailed in Figure 1 and were similar to the method reported by Schott *et al*[16].

Data collection

Participants' gait characteristics during the WTMT were captured and analyzed using the Intelligent Device for Energy Expenditure and Activity (IDEEA) (Minisun, United States). The IDEEA comprises five motion sensors and a microcomputer. The device was calibrated and used as indicated by the manufacturer and as depicted previously[1].

The parameters captured by the IDEEA are detailed in Figure 2 and listed below: (1) Speed (m/s), as the mean velocity for two successive strides; (2) Step length (m), representing the half distance between consecutive points of initial contact of the same foot; (3) Cadence (steps/min), representing the number of steps/stairs per minute; and (4) Stance phase percentage (%), reflecting the duration of the stance phase (starting from initial contact and ending at toe-off for a particular foot) divided by stride time.

Neuropsychological assessment

All participants completed a series of neuropsychological assessments, including the MMSE (reflecting global cognitive level), choice reaction test (CRT, reflecting attention and concentration), digit symbol substitution test (DSST, reflecting processing speed), category verbal fluency test (cVFT, reflecting psychomotor speed, attention, and semantic memory),

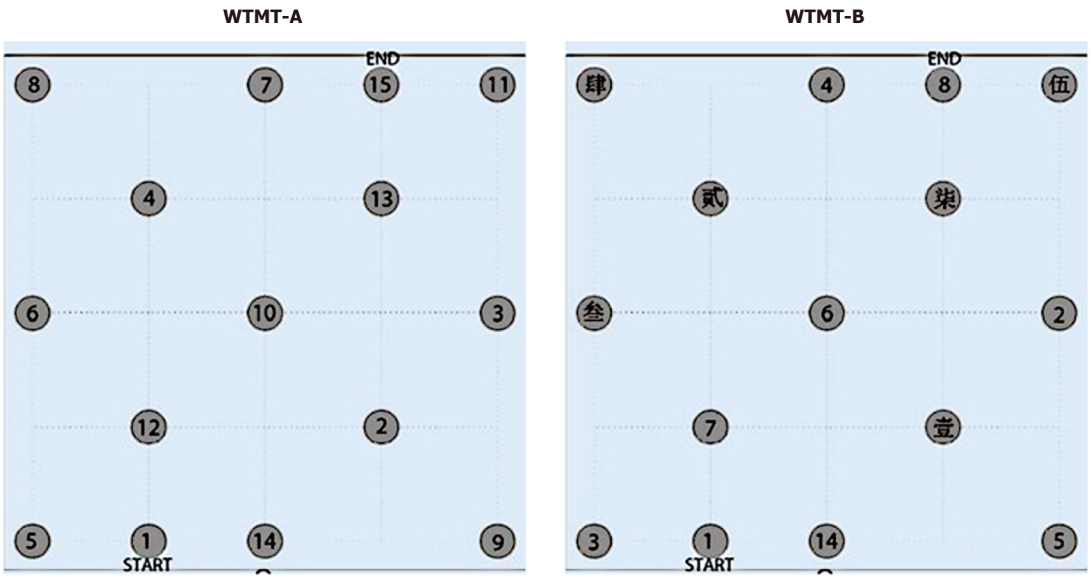

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Figure 1 The arrangements of numbers in the walking trail making test. WTMT: Walking trail making test.

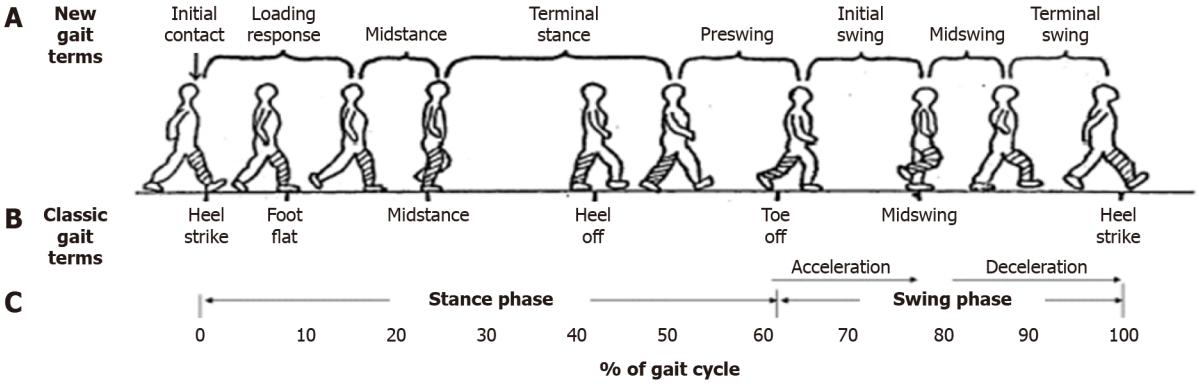

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Figure 2 The parameters captured by the Intelligent Device for Energy Expenditure and Activity. (1) Speed (m/s), as the mean velocity for two successive strides; (2) Step length (m), representing the half distance between consecutive points of initial contact of the same foot; (3) Cadence (steps/min), representing the number of steps/stairs per minute; and (4) Stance phase percentage (%), reflecting the duration of the stance phase (starting from initial contact and ending at toe-off for a particular foot) divided by stride time. A: The new gait terms of gait cycles; B: The classic gait terms of gait cycles; C: The percentage of stance/swing phase of gait cycles.

and auditory verbal learning test-huashan (AVLTh, reflecting immediate memory performance)[19].

Statistical analysis

Student's *t*-test was carried out for comparison of continuous parametric variables. Categorical variables were compared using the Chi-square or Fisher exact test. Partial Pearson correlation analysis was performed to calculate the correlation between the WTMT completion time and neuropsychological performance, controlled for age, sex, and educational level.

RESULTS

As shown in Table 1, age, sex, and educational level were similar between the WMH and HE groups ($P > 0.05$). The participants in the WMH group had an average Fazekas score of 1.52. Overall, the WMH group performed significantly worse on the CRT (0.51 ± 0.09 s *vs* 0.44 ± 0.06 s, $P = 0.007$), VFT (14.2 ± 2.75 *vs* 16.65 ± 3.54, $P = 0.012$), and DSST (16.00 ± 2.75 *vs* 18.40 ± 3.27, $P = 0.010$) than the HE group. In addition, the WHM group had significantly longer completion times for the WTMT-A (93.00 ± 10.76 s *vs* 70.55 ± 11.28 s, $P < 0.001$) and WTMT-B (109.72 ± 12.26 s *vs* 82.85 ± 7.90 s, $P < 0.001$; Table 1).

The results for the correlation between WTMT completion time and performance on neuropsychological tests for the WMH group are presented in Table 2. WTMT-A completion time was positively correlated with CRT time ($r = 0.460$, $P =$

Table 1 Clinical and demographic characteristics of the participants (mean ± SD)

	WMH group (*n* = 25)	HE group (*n* = 20)	*P* value
Age, years	74.00 ± 5.40	75.30 ± 4.26	0.385
Male, %	48%	35%	0.392
Education, years	8.00 ± 2.34	8.05 ± 2.28	0.943
MMSE, score	28.00 ± 1.15	28.10 ± 1.10	0.883
CRT, seconds	0.51 ± 0.09	0.44 ± 0.06	0.007
cVFT, words	14.20 ± 2.75	16.65 ± 3.54	0.012
DSST, counts	16.00 ± 2.75	18.40 ± 3.27	0.010
AVLTh, words	7.60 ± 1.83	8.25 ± 1.20	0.178
WTMT-A, seconds	93.00 ± 10.76	70.55 ± 11.28	< 0.001
WTMT-B, seconds	109.72 ± 12.26	82.85 ± 7.90	< 0.001
Fazekas, score	1.52 ± 0.71	0.00 ± 0.00	< 0.001

MMSE: Mini-mental state examination; CRT: Choice reaction test; cVFT: Category verbal fluency test; DSST: Digit symbol substitution test; AVLTh: Auditory verbal learning test-huashan; WTMT: Walking trail making test; WMH: White matter hyperintensities; HE: Healthy.

Table 2 Partial Pearson correlation between cognitive function and walking trail making test

	WTMT-A		WTMT-B	
	r value	*P* value	*r* value	*P* value
MMSE	0.060	0.697	0.190	0.212
CRT	0.460	0.001	0.254	0.092
cVFT	-0.157	0.303	-0.391	0.008
DSST	-0.264	0.080	-0.207	0.172
AVLTh	-0.024	0.874	-0.267	0.076

Adjustment for age, sex, and educational level. MMSE: Mini-mental state examination; CRT: Choice reaction test; cVFT: Category verbal fluency test; DSST: Digit symbol substitution test; AVLTh: Auditory verbal learning test-huashan.

0.001), while WTMT-B completion time was negatively correlated with VFT (r = -0.391, P = 0.008).

Furthermore, we explored the gait features during the WTMT, and only speed was found to differ statistically between the two groups (0.803 ± 0.096 *vs* 0.975 ± 0.050 m/s, P < 0.001). On the WTMT-B, the WMH group exhibited significantly lower speed (0.778 ± 0.111 *vs* 0.970 ± 0.053 m/s, P < 0.001) and cadence (82.600 ± 4.140 *vs* 85.500 ± 5.020 steps/m, P = 0.039), as well as a higher stance phase percentage (65.061 ± 1.813% *vs* 63.513 ± 2.465%, P = 0.019) relative to the HE group (Table 3).

DISCUSSION

The clinical presentation of WMH can be asymptomatic, silent, or covert[20] until a threshold is reached and "malignant" symptoms (such as stroke) appear[21]. Thus, much research effort has been devoted to identifying indicators for earlier recognition of WMH[19]. The present study revealed that patients with WMH exhibited remarkably worse performance on the WTMT compared with healthy individuals, as reflected in by the completion times for both the WTMT-A and WTMT-B. Considering its simplicity, non-invasiveness, and low cost, the WTMT represents a potentially useful assessment tool for patients with WMH.

Our previous studies confirmed that patients with WMH display cognitive deficits and gait abnormalities[11,22]. According to the consensus on shared measures of mobility and cognition from the Canadian Consortium on Neurodegeneration in Aging[23], both the TMT and the dual task gait speed task were included as proposed "core battery" tests. These findings, together with those of the present study, support the modification of the TMT into the WTMT, for evaluation of characteristics in aspects of gait and cognition. Furthermore, as the WTMT was designed to be an incorporated cognitive task, instead of an addition to a motor task, WTMT performance could be a better indicator of cognitive impairment than gait or cognitive tests alone[24].

Table 3 Gait analysis of the participants in walking trail making test (mean ± SD)

	WMH group (*n* = 25)	HE group (*n* = 20)	*P* value
WTMT-A			
Speed, m/s	0.803 ± 0.096	0.975 ± 0.050	< 0.001
Step length, m	0.486 ± 0.035	0.484 ± 0.038	0.820
Cadence, steps/min	86.520 ± 5.730	89.050 ± 5.671	0.127
Stance phase percentage, %	63.189 ± 1.147	63.737 ± 1.231	0.130
WTMT-B			
Speed, m/s	0.778 ± 0.111	0.970 ± 0.054	< 0.001
Step length, m	0.468 ± 0.041	0.473 ± 0.041	0.713
Cadence, steps/min	82.600 ± 4.140	85.500 ± 5.020	0.039
Stance phase percentage, %	65.061 ± 1.813	63.513 ± 2.465	0.019

WTMT: Walking trail making test; WMH: White matter hyperintensities; HE: Healthy.

The current study also investigated the relationship between WTMT completion time and cognitive function in older adults with WMH. Our analyses showed that the WTMT-A completion time was correlated with attention and concentration, while the WTMT-B completion time was correlated with psychomotor speed, attention, and semantic memory. These results should not be surprising, as the WTMT, a type of cognitive-motor dual task, is considered a useful "brain stress test" for predicting cognitive deficits[25]. For example, Perrochon and Kemoun[14] reported that poor WTMT performance is associated with executive dysfunction (in particular, mental flexibility) in patients with mid-cognitive impairment. Among community-dwelling older adults, Osuka *et al*[13] discovered that the WTMT completion time is associated with a series of executive functions, such as performance on the DSST and the traditional TMT. The disruption of crucial subcortical connections in the frontal and other lobes, as well as the basal ganglia area, following multiple pathophysiological changes could be the possible mechanism through which WMH affect cognition and WTMT performance[26,27].

To the best of our knowledge, this is the first study to assess the utility of a wearable sensor for gait analysis during the WTMT. Gait speed was not the only parameter found to be affected in the WTMT-B. Older people with WMH exhibited significantly lower speed and cadence, as well as a higher stance phase percentage. The discrepancy between the WTMT-A and WTMT-B might also imply that WTMT-B performance reflects sophisticated processing and problem solving aspects of executive functioning, which may be necessary to deal with more challenging terrain[28]. Similar trends were also reported for the traditional WTMT and other variations of the TMT[29].

Several limitations of the present study warrant consideration. First, the sample size was small. Second, some aspects, such as delayed recall of the AVLTh, were not chosen in the present study, because patients with WMH were previously found to not show deficits in this domain[30]. In addition, 3T-WMH volume should be used to quantify WMH in future research.

Notably, the TMT has been modified in different ways by multiple research groups previously (*e.g.*, WTMT, oral TMT [31], driving TMT[32]), and alternative evaluation systems for the TMT also have been reported (*e.g.*, error analysis[33], derived TMT indices[34,35]). From our point of view, delta TMT is a good indicator of executive function. Thus, delta WTMT might be another effective tool for detecting the cognitive profile of WMH and neuropsychological features of subcortical vascular dementia in the future.

CONCLUSION

In the present study, older adults with WMH showed obviously poorer WTMT performance than healthy control participants. The WTMT completion time was associated with aspects of cognitive function. Therefore, WTMT performance represents a potential indicator for early identification of the cognitive and mobility decline induced by WMH.

ARTICLE HIGHLIGHTS

Research background

The early detection of the white matter hyperintensities (WMH) is difficult in clinical practice, and dual task has been confirmed as a useful tool.

Research motivation
Trail making test (TMT), a commonly used paper-and-pencil cognitive function test, is now modified into different versions. Walking TMT (WTMT) is a modified TMT incorporates a cognitive task and concurrent walking.

Research objectives
The aim of the current study was to assess the gait characteristics of elderly individuals with WMH using the WTMT task.

Research methods
The WTMT was conducted in a 16 m^2 square area (4 m × 4 m). Each participant need to walk according to the coins randomly distributed as TMT-A and TMT-B to complete this task.

Research results
The WMH group also required significantly more time to complete the WTMT-A and WTMT-B.

Research conclusions
Older adults with WMH showed obviously poorer WTMT performance.

Research perspectives
Notably, the TMT has been modified in different ways by multiple research groups previously (*e.g.*, WTMT, oral TMT, driving TMT), and alternative evaluation systems for the TMT also have been reported (*e.g.*, error analysis, derived TMT indices). From our point of view, delta TMT is a good indicator of executive function. Thus, delta WTMT might be another effective tool for detecting the cognitive profile of WMH and neuropsychological features of subcortical vascular dementia in the future.

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FOOTNOTES

Co-first authors: Hong-Yi Zhao and Zhi-Qiang Zhang.

Author contributions: Zhao HY and Zhang ZQ were responsible for data collection, analysis and writing of the actual manuscript; Wei FY was responsible for study design; Huang YH and Li H were responsible for manuscript preparation.

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Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

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

Data sharing statement: Dataset available from the corresponding author at huangyonghua2017@126.com.

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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REFERENCES

1 **Zhào H**, Wei W, Xie H, Huang Y. Motoric Cognitive Risk Syndrome Among Chinese Older Adults with White Matter Lesions: A Cross-Sectional Observational Study. *J Alzheimers Dis* 2023; **91**: 925-931 [PMID: 36565113 DOI: 10.3233/JAD-220712]

2 **Lauretani F**, Longobucco Y, Ferrari Pellegrini F, De Iorio AM, Fazio C, Federici R, Gallini E, La Porta U, Ravazzoni G, Roberti MF, Salvi M, Zucchini I, Pelà G, Maggio M. Comprehensive Model for Physical and Cognitive Frailty: Current Organization and Unmet Needs. *Front Psychol* 2020; **11**: 569629 [PMID: 33324282 DOI: 10.3389/fpsyg.2020.569629]

3 **Kelaiditi E**, Cesari M, Canevelli M, van Kan GA, Ousset PJ, Gillette-Guyonnet S, Ritz P, Duveau F, Soto ME, Provencher V, Nourhashemi F, Salvà A, Robert P, Andrieu S, Rolland Y, Touchon J, Fitten JL, Vellas B; IANA/IAGG. Cognitive frailty: rational and definition from an (I.A.N.A./I.A.G.G.) international consensus group. *J Nutr Health Aging* 2013; **17**: 726-734 [PMID: 24154642 DOI: 10.1007/s12603-013-0367-2]

4 **Verghese J**, Ayers E, Barzilai N, Bennett DA, Buchman AS, Holtzer R, Katz MJ, Lipton RB, Wang C. Motoric cognitive risk syndrome: Multicenter incidence study. *Neurology* 2014; **83**: 2278-2284 [PMID: 25361778 DOI: 10.1212/WNL.0000000000001084]

5 **Jokinen H**, Laakso HM, Ahlström M, Arola A, Lempiäinen J, Pitkänen J, Paajanen T, Sikkes SAM, Koikkalainen J, Lötjönen J, Korvenoja A, Erkinjuntti T, Melkas S. Synergistic associations of cognitive and motor impairments with functional outcome in covert cerebral small vessel disease. *Eur J Neurol* 2022; **29**: 158-167 [PMID: 34528346 DOI: 10.1111/ene.15108]

6 **Rudilosso S**, Rodríguez-Vázquez A, Urra X, Arboix A. The Potential Impact of Neuroimaging and Translational Research on the Clinical Management of Lacunar Stroke. *Int J Mol Sci* 2022; **23** [PMID: 35163423 DOI: 10.3390/ijms23031497]

7 **Moran C**, Phan TG, Srikanth VK. Cerebral small vessel disease: a review of clinical, radiological, and histopathological phenotypes. *Int J Stroke* 2012; **7**: 36-46 [PMID: 22111922 DOI: 10.1111/j.1747-4949.2011.00725.x]

8 **Siejka TP**, Srikanth VK, Hubbard RE, Moran C, Beare R, Wood A, Phan T, Callisaya ML. Frailty and Cerebral Small Vessel Disease: A Cross-Sectional Analysis of the Tasmanian Study of Cognition and Gait (TASCOG). *J Gerontol A Biol Sci Med Sci* 2018; **73**: 255-260 [PMID: 28977392 DOI: 10.1093/gerona/glx145]

9 **Taylor ME**, Lord SR, Delbaere K, Wen W, Jiang J, Brodaty H, Kurrle SE, Stefanie Mikolaizak A, Close JCT. White matter hyperintensities are associated with falls in older people with dementia. *Brain Imaging Behav* 2019; **13**: 1265-1272 [PMID: 30145714 DOI: 10.1007/s11682-018-9943-8]

10 **Del Brutto OH**, Rumbea DA, Recalde BY, Mera RM. The association between white matter hyperintensities of presumed vascular origin and disability is mediated by age: a population-based study in stroke-free older adults. *Aging Clin Exp Res* 2023; **35**: 887-892 [PMID: 36720797 DOI: 10.1007/s40520-023-02355-5]

11 **Ma R**, Zhào H, Wei W, Liu Y, Huang Y. Gait characteristics under single-/dual-task walking conditions in elderly patients with cerebral small vessel disease: Analysis of gait variability, gait asymmetry and bilateral coordination of gait. *Gait Posture* 2022; **92**: 65-70 [PMID: 34826695 DOI: 10.1016/j.gaitpost.2021.11.007]

12 **Piche E**, Chorin F, Gerus P, Jaafar A, Guerin O, Zory R. Effects of age, sex, frailty and falls on cognitive and motor performance during dual-task walking in older adults. *Exp Gerontol* 2023; **171**: 112022 [PMID: 36371049 DOI: 10.1016/j.exger.2022.112022]

13 **Osuka Y**, Kojima N, Sakurai R, Watanabe Y, Kim H. Reliability and construct validity of a novel motor-cognitive dual-task test: A Stepping Trail Making Test. *Geriatr Gerontol Int* 2020; **20**: 291-296 [PMID: 32064719 DOI: 10.1111/ggi.13878]

14 **Perrochon A**, Kemoun G. The Walking Trail-Making Test is an early detection tool for mild cognitive impairment. *Clin Interv Aging* 2014; **9**: 111-119 [PMID: 24426778 DOI: 10.2147/CIA.S53645]

15 **Yamada M**, Ichihashi N. Predicting the probability of falls in community-dwelling elderly individuals using the trail-walking test. *Environ Health Prev Med* 2010; **15**: 386-391 [PMID: 21432571 DOI: 10.1007/s12199-010-0154-1]

16 **Schott N**, El-Rajab I, Klotzbier T. Cognitive-motor interference during fine and gross motor tasks in children with Developmental Coordination Disorder (DCD). *Res Dev Disabil* 2016; **57**: 136-148 [PMID: 27428781 DOI: 10.1016/j.ridd.2016.07.003]

17 **Fazekas F**, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR Am J Roentgenol* 1987; **149**: 351-356 [PMID: 3496763 DOI: 10.2214/ajr.149.2.351]

18 **Blumen HM**, Allali G, Beauchet O, Lipton RB, Verghese J. A Gray Matter Volume Covariance Network Associated with the Motoric Cognitive Risk Syndrome: A Multicohort MRI Study. *J Gerontol A Biol Sci Med Sci* 2019; **74**: 884-889 [PMID: 29985983 DOI: 10.1093/gerona/gly158]

19 **Zhào H**, Teulings HL, Xia C, Huang Y. Aged Patients With Severe Small Vessel Disease Exhibit Poor Bimanual Coordination During the Anti-Phase Horizontal Line Drawing Task. *Percept Mot Skills* 2023; **130**: 750-769 [PMID: 36562499 DOI: 10.1177/00315125221146230]

20 **Clancy U**, Appleton JP, Arteaga C, Doubal FN, Bath PM, Wardlaw JM. Clinical management of cerebral small vessel disease: a call for a holistic approach. *Chin Med J (Engl)* 2020; **134**: 127-142 [PMID: 33118960 DOI: 10.1097/CM9.0000000000001177]

21 **Lau AYL**, Ip BYM, Ko H, Lam BYK, Shi L, Ma KKY, Au LWC, Soo YOY, Leung TWH, Wong A, Mok VCT. Pandemic of the aging society - sporadic cerebral small vessel disease. *Chin Med J (Engl)* 2021; **134**: 143-150 [PMID: 33410627 DOI: 10.1097/CM9.0000000000001320]

22 **Zhào H**, Wei W, Do EY, Huang Y. Assessing Performance on Digital Clock Drawing Test in Aged Patients With Cerebral Small Vessel Disease. *Front Neurol* 2019; **10**: 1259 [PMID: 31849821 DOI: 10.3389/fneur.2019.01259]

23 **Montero-Odasso M**, Almeida QJ, Bherer L, Burhan AM, Camicioli R, Doyon J, Fraser S, Muir-Hunter S, Li KZH, Liu-Ambrose T, McIlroy W, Middleton L, Morais JA, Sakurai R, Speechley M, Vasudev A, Beauchet O, Hausdorff JM, Rosano C, Studenski S, Verghese J; Canadian Gait and Cognition Network. Consensus on Shared Measures of Mobility and Cognition: From the Canadian Consortium on Neurodegeneration in Aging (CCNA). *J Gerontol A Biol Sci Med Sci* 2019; **74**: 897-909 [PMID: 30101279 DOI: 10.1093/gerona/gly148]

24 **Osuka Y**, Kim H, Watanabe Y, Taniguchi Y, Kojima N, Seino S, Kawai H, Sakurai R, Inagaki H, Awata S, Shinkai S. A Stepping Trail Making Test as an Indicator of Cognitive Impairment in Older Adults. *J Clin Med* 2020; **9** [PMID: 32887235 DOI: 10.3390/jcm9092835]

25 **Osuka Y**, Kim H, Watanabe Y, Taniguchi Y, Kojima N, Seino S, Kawai H, Sakurai R, Inagaki H, Awata S, Shinkai S. A combined stepping and visual tracking task predicts cognitive decline in older adults better than gait or visual tracking tasks alone: a prospective study. *Aging Clin Exp Res* 2021; **33**: 1865-1873 [PMID: 32965610 DOI: 10.1007/s40520-020-01714-w]

26 **Biesbroek JM**, Weaver NA, Biessels GJ. Lesion location and cognitive impact of cerebral small vessel disease. *Clin Sci (Lond)* 2017; **131**: 715-728 [PMID: 28385827 DOI: 10.1042/CS20160452]

27 **Joutel A**, Chabriat H. Pathogenesis of white matter changes in cerebral small vessel diseases: beyond vessel-intrinsic mechanisms. *Clin Sci*

(Lond) 2017; **131**: 635-651 [PMID: 28351960 DOI: 10.1042/CS20160380]

28 **Alexander NB**, Ashton-Miller JA, Giordani B, Guire K, Schultz AB. Age differences in timed accurate stepping with increasing cognitive and visual demand: a walking trail making test. *J Gerontol A Biol Sci Med Sci* 2005; **60**: 1558-1562 [PMID: 16424288 DOI: 10.1093/gerona/60.12.1558]

29 **Guo Y**. A selective review of the ability for variants of the Trail Making Test to assess cognitive impairment. *Appl Neuropsychol Adult* 2022; **29**: 1634-1645 [PMID: 33625945 DOI: 10.1080/23279095.2021.1887870]

30 **Tao W**, Liu J, Ye C, Kwapong WR, Wang A, Wang Z, Chen S, Liu M. Relationships between cerebral small vessel diseases markers and cognitive performance in stroke-free patients with atrial fibrillation. *Front Aging Neurosci* 2022; **14**: 1045910 [PMID: 36688147 DOI: 10.3389/fnagi.2022.1045910]

31 **Mrazik M**, Millis S, Drane DL. The oral trail making test: effects of age and concurrent validity. *Arch Clin Neuropsychol* 2010; **25**: 236-243 [PMID: 20197294 DOI: 10.1093/arclin/acq006]

32 **Lee S**, Lee JA, Choi H. Driving Trail Making Test part B: a variant of the TMT-B. *J Phys Ther Sci* 2016; **28**: 148-153 [PMID: 26957747 DOI: 10.1589/jpts.28.148]

33 **Mahurin RK**, Velligan DI, Hazleton B, Mark Davis J, Eckert S, Miller AL. Trail making test errors and executive function in schizophrenia and depression. *Clin Neuropsychol* 2006; **20**: 271-288 [PMID: 16690547 DOI: 10.1080/13854040590947498]

34 **Drane DL**, Yuspeh RL, Huthwaite JS, Klingler LK. Demographic characteristics and normative observations for derived-trail making test indices. *Neuropsychiatry Neuropsychol Behav Neurol* 2002; **15**: 39-43 [PMID: 11877550]

35 **Hobert MA**, Meyer SI, Hasmann SE, Metzger FG, Suenkel U, Eschweiler GW, Berg D, Maetzler W. Gait Is Associated with Cognitive Flexibility: A Dual-Tasking Study in Healthy Older People. *Front Aging Neurosci* 2017; **9**: 154 [PMID: 28596731 DOI: 10.3389/fnagi.2017.00154]

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ORIGINAL ARTICLE

Observational Study

Embracing different languages and local differences: Co-constructive patient simulation strengthens host countries' clinical training in psychiatry

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Abstract

BACKGROUND

Global education in psychiatry is heavily influenced by knowledge from Western, high-income countries, which obscures local voices and expertise.

AIM

To adapt a human simulation model to psychiatric education in a context that is specific to local languages and cultures.

METHODS

We conducted an observational study consisting of six human simulation sessions with standardized patients from two host countries, speaking their native languages, and following an adaptation of the co-constructive patient simulation (CCPS) model. As local faculty became increasingly familiar with the CCPS approach, they took on the role of facilitators—in their country's native language.

RESULTS

Fifty-three learners participated: 19 child and adolescent psychiatry trainees and 3 faculty members in Türkiye (as a group that met online during 3 consecutive months); and 24 trainees and 7 faculty in Israel (divided into 3 groups, in parallel in-person sessions during a single training day). Each of the six cases reflected local realities and clinical challenges, and was associated with specific learning goals identified by each case-writing trainee.

CONCLUSION

Human simulation has not been fully incorporated into psychiatric education: The creation of immersive clinical experiences and the strengthening of reflective practice are two areas ripe for development. Our adaptations of CCPS can also strengthen local and regional networks and psychiatric communities of practice. Finally, the model can help question and press against hegemonies in psychiatric training that overshadow local expertise.

Key Words: Human simulation; Standardized patients; Medical education; Psychiatric education; Capacity building; Local languages

Core Tip: The co-constructive patient simulation (CCPS) model harnesses human simulation as a novel way of psychiatric education and training that is immersive, experiential, and uniquely tailored to (and by) its intended learners. For a globally under-resourced field like psychiatry, developing and strengthening vibrant communities of practice can have enduring and long-lasting returns, including in workforce recruitment and retention. The adaptations of CCPS that we describe, through their train-the-trainer components, have the potential to sustain and even replicate themselves; they can become vehicles of local capacity building.

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INTRODUCTION

Psychiatric education worldwide is heavily—often exclusively—influenced by the prevailing paradigms of Western, high-income countries. As a result, local voices and expertise are often obscured or ignored altogether. The discrepancy between local and "expert" knowledge can be particularly jarring around the granularities of clinical care embedded in the specificities of place and language[1]. For example, the norm is for books, scholarly articles, and training manuals to be translated into local languages, with only a minority of countries having a robust native language literature of its own. In an age of artificial intelligence and powerful software such as DeepL, Google Translate, and Chat GPT, translation into local languages is easier than could have been imagined just a decade ago-arguably too easy, in that it may have stifled the development of local resources. Moreover, the ubiquity of the Internet has made access to up-to-date literature easily available to global users.

Despite these remarkable advances, challenges and limitations remain. For one, translation, no matter how precise, does not necessarily imply relevance or applicability to local realities. For another, theoretical knowledge is hard to apply at a practical, clinical, "on the ground" level. Making scientific knowledge clinically applicable, moving it from development into practice (the T3 transformation)[2] is challenging enough within languages and countries; translation, cultural adaptation, and geographic distance all add significant layers of complexity.

We have taken on these challenges by harnessing two innovations: First, we have used simulation using standardized patients (alternatively named simulated participants, hereafter SPs). We have used SPs from host countries, speaking their native languages, and following an adaptation of a high-fidelity simulation model we recently developed, co-constructive patient simulation (CCPS)[3]. Second, we used synchronized videoconferencing with Zoom to describe the model to our partners, to prepare the initial sessions together, and at one site, to conduct the experiential sessions virtually. Local capacity building was our ultimate goal in sharing the model[4]: For each of the sites to be able to continue using the adapted model of learning and supervision without further external help. In brief, to use local knowledge, local realities and language, and the texture of their unique expertise, to improve on their reflective clinical practice, and to help train their next generation of mental health practitioners.

We go on to describe our application of the CCPS model as conducted in the native language of two Middle Eastern countries (Turkish and Hebrew, respectively, for Türkiye and Israel). Our goals were to: (1) Prove the feasibility of conducting the model overseas and in a native language; (2) Use the model flexibly, during either consecutive months or on a single day; and (3) Explore barriers and opportunities for the replication and self-sustainability of the approach.

MATERIALS AND METHODS

Participants, settings, planning, and sessions

We conducted six CCPS sessions between January and June 2023.

Three sessions took place online in Türkiye, separated six weeks from each other. For those sessions, we worked in collaboration with the training director of child and adolescent psychiatry (CAP) at Bursa University. All first and second year fellows and faculty members actively involved in training were invited to participate.

In the case of Israel, we conducted three sessions simultaneously, in parallel groups, each with a different case, facilitator, and scriptwriter. The three sessions were part of a training retreat held on June 19, 2023 at the Eitanim psychiatric hospital for children and adolescents, in Jerusalem. The retreat was sponsored by the Israel Psychiatric Society, which convened and supported the attendance of all trainees in CAP from throughout the country.

Each of the six sessions was planned well in advance, typically two to four weeks ahead of time. To that end, each of the volunteer learners (hereafter scriptwriters) was provided with background literature[3,5,6] and sample scripts. They were encouraged to think back to a case (or cases) that had proven emotionally challenging, frustrating, or taxing in some way. In fostering their writing, we encouraged scriptwriters with a gentle editing hand to identify something that was personally meaningful, and to generally steer away from technical aspects such as diagnostic or treatment details. Once they created a first draft, we regrouped together with the scriptwriter and their designated SP (scriptwriters knew in advance the gender, age, and basic demographic characteristics of their SP). As local faculty became familiar and increasingly comfortable with the CCPS model, they went to take on the role of facilitators—in their native language. Case writing included a role-play with the scriptwriter standing in the "hot seat" in order to try out the emotional legitimacy of the case, and to adapt as needed until reaching its verisimilitude.

On the day of the session, participants knew nothing about the case, except for a brief "door note," which set the stage for the encounter. Two participants interviewed the SP-in-role, each for 20 min, and transitioning without interruption between one another. They did not re-introduce themselves at the transition point: Both doctors in Türkiye were "Dr. Korkmaz", and both in Israel were "Dr. Cohen", just as in the United States they are a generic "Dr. Jones". The point is to make the action seamless and continuous, and for the interviewers to scaffold clinically on each other. Following the session, the entire group debriefed for an hour, following best practices in healthcare[7-9].

Adaptations to the CCPS model

We applied CCPS adhering to our original description of the model and in keeping with our experience during its first three years of implementation, representing over twenty unique sessions. Still, in order to conduct the experience across distance, language, and cultural differences, we had to make several adjustments. In Table 1 we summarize highlights of the adaptations we found necessary to make.

Theoretical framework

We conducted the two CCPS series in the context of Design-Based Research (DBR), an approach that seeks to bridge the gap between practice and research, and in which real-life settings (or clinical interactions) take place[10]. It can tackle clinical problems and advance theoretical knowledge; critically, it is intended to "unleash the power of reflection[11]. Three of DBR's key components[12] are particularly well aligned with those of CCPS and of reflective functioning: (1) *Culture:* Building collaborations in a psychologically supportive setting; (2) *Connecting contexts:* Making participants understand each other's worldviews and activities; and (3) *Making the implicit explicit:* Having supervisors as fellow participants (of note, CCPS emphasizes the non-hierarchical relationship between trainees and supervisors).

Ethics approval

This study was approved by the Yale University Institutional Review Board (Protocol # 2000026241). All actors were 18 years or older and compensated for their performance. In three cases, young adult actors were able to realistically "pass" for adolescents 15-17 years of age.

RESULTS

Fifty-three learners participated: 19 CAP trainees and 3 faculty members in Türkiye (as a single group); 24 trainees and 7 faculty in Israel (divided into 3 groups). The same local facilitator participated in the three Turkish sessions; after planning the first one in English, she was comfortable planning the next two in Turkish; all three sessions and debriefings took place in Turkish. In the case of Israel, two facilitators planned their sessions and conducted their simulations in Hebrew. The third facilitator planned and conducted the session in English. Given that the three sessions in Hebrew took place simultaneously, we allocated an extra half hour for a rapporteur from each of the three groups to share their case and debriefing highlights with their peers; that final debriefing spanned both Hebrew and English, depending on

Table 1 Adapting co-constructive patient simulation to a native language and local setting

Components	Possible adaptations
Actors/standardized patients/SPs	Hire actors through local drama schools or theater programs when no SP programs are available
	Adjust compensation to local market fees (averaging in the US approximately $ 25 per hour per actor, 4-h minimum)
	Consider alternatives to professional actors, *e.g.*, non-professional actors, other mental health professionals who are not part of the same peer group
Delivery *via* synchronized videoconferencing	Chat feature in Zoom can be useful for a bilingual native speaker to translate key points to any outside guests, particularly during early stages of CCPS development
	Geographic distance can result in wide time zone variance, an added logistic challenge during early planning stages
	Consider that some international and non-academic Zoom accounts can limit session time or number of participants
Facilitation	Transition of leadership as sessions progress: From an outside "guest" to a local "host" facilitator

SPs: Simulated participants; CCPS: Co-constructive patient simulation.

participants' preference and comfort.

In Table 2 we summarize the six cases, including each clinical scenario, their associated learning objectives, and salient statements made by their participants.

Developed independently of each other—within and between countries—the scripted scenarios evinced notable similarities. For example, comparable clinical challenges faced by trainees included the conveying of difficult news, such as an unanticipated diagnoses, or the forestalling of an inpatient discharge; the complexities of being a mandated reporter in the context of interfamilial sexual abuse and an active police investigation; or survivor guilt, whether in the setting of a natural disaster or of the unexpected recent death of a spouse. Alternatively, the local specificities of certain cases made them uniquely culture- or setting-bound. For example, in one of the Turkish cases, much of the background familial tension revolved around the competition between two siblings attending a Quran memorialization school; in one of the Israeli cases, a teenager's inability to leave the hospital for a visit home for the Sabbath set many of the cases' challenges in motion. The specifics of time were also relevant, most notably in one of the Turkish cases: Its script had been nearly finalized by February 6, 2023, the date of a devastating 7.8-magnitude earthquake that affected Southeastern Türkiye. In the weeks that followed, as the participants and the entire country responded and adapted to the calamity, the script was adjusted as well: Incorporating relevant daily realities, such as the massive loss of life, the influx of refugees, and the lack of sufficient material and human resources to address the population's needs and mitigate the trauma.

DISCUSSION

In this study we replicated and expanded the use of a new approach to human simulation in a CAP training context. Specifically, we changed the CCPS model from its original use at a single site into one encompassing various locations (*e.g.*, Bursa, Istanbul, and New Haven for the Turkish series); from the exclusive use of English into two local languages (Turkish and Hebrew); from reliance on in-person meetings to using synchronized videoconferencing; and from consecutive sessions over months to several sessions running in parallel at the same time and place (in the Israeli series). Notwithstanding these logistic differences from the model as originally described, most of the educational benefits carried over from the original to the adapted versions. Moreover, the adapted versions had unique educational benefits, mostly around upending and challenging traditional modes of post-graduate medical education.

We go on to describe the benefits and pedagogic innovations that ensued from these six, locally adapted, language-specific CCPS sessions.

Creation, immersion, reflection: Simulation in psychiatric education. The CCPS model harnesses human simulation as a novel way of psychiatric education and training that is immersive, experiential, and uniquely tailored to (and by) its intended learners. Insofar as its participants are at once its developers and its target beneficiaries, the model can be considered a form of participatory action research (PAR)[13-15].

Human simulation has had a limited, but far from trivial role in psychiatric education and training[16,17]. However, in most instances it is used to depict certain types of psychopathology or clinical interactions, and used on an *ad hoc* basis rather than as a standing curricular component associated with specific competencies. We are not aware of other instances in which learners take an active role in crafting their cases and learning objectives. Another feature that sets CCPS apart is its emphasis on structured debriefing, with the explicit goal of enhancing and refining reflective practice. Specifically, the model follows the tenets set forth by Donald Schön in *The Reflective Practitioner*[18], adapting them to the psychiatric context: Reflection *in* action ("while doing"); *on* action ("having done"); and *for* action ("toward doing"). Stated alternatively, learners—like all session participants—exercise self-awareness by hovering between their own

Table 2 Application of co-constructive patient simulation in two Middle Eastern countries

Country	Session	Clinical scenario	Salient quote(s)	Learning objective(s)
Türkiye (online)	1	A 17-year-old young woman overdoses after being denied access to her phone when her deeply religious parents find out she has been having unsupervised contact with boys her age	"We love you, but not more than God. So, if you oppose our faith, we understand if you decide to end your life"	Navigate divergent religious world views in the context of their impact on a family member's acute psychiatric emergency
	2	A 15-year-old adolescent girl is met with disbelief and anger by her mother when confiding details of long-standing sexual abuse by her brother, the family's breadwinner and "man of the house"	"She said, 'his hand might have accidentally touched [my] body,' and so I might have misunderstood his love for me. Besides, as far as she knows, 'he has a girlfriend already and so he wouldn't *need* me'"	(1) Lead patient to understand that as a clinician you need to contact the authorities (today, as she is still at active risk), and to do so in as collaborative a fashion as possible with her mother; and (2) Ensure the patient's safety and notify the authorities, while not alienating the child and her family in the process
	3	A 16-year-old gender fluid adolescent struggles with suicidality in the context of rejection by peers and non-acceptance by their family. As a major earthquake affects the country and their immediate family, they blame themselves for the natural disaster	"My grandma kept saying that the earthquake happened because of rebels and godless people like me, that wherever there are degenerates, bad things like this happen"	(1) Appreciate challenges affecting non-binary youth developing in culturally conservative settings; and (2) Explore the roots and psychological function of pathological and survivor guilt
Israel (in person)	1	The mother of a hospitalized adolescent is confronted with the news that, for reasons unknown, her weekend pass and forthcoming discharge are being put on hold. Unbeknownst to the mother is her daughter's revelation of having been recently assaulted sexually at home, by her brother. As the police investigation proceeds, the physician is forbidden from sharing information with the family	"We gave you our perfect daughter and now you have broken her completely. As if cutting herself was not bad enough, she won't even come home to us for *Shabbat* (the Sabbath)"	On being unable to tell the "whole story," balance the competing demands of sharing limited information with providing sufficient support and not sacrificing the therapeutic alliance along the way
	2	A young widow is informed that her 4-year-old son has autism. Although she had long suspected something was amiss given differences from her normally developing older child, this is the first time she is informed of her "worst fear"	"At such a young age, his father's death was a tragedy. This news feels like another tragedy, a compounded catastrophe"	(1) Convey a realistic sense of hope, optimism, and a path forward in the face of challenging information; (2) Disentangle losses, and disambiguate permanent, from addressable losses (death, from a chronic diagnosis); and (3) Start mourning the loss of the expected/idealized/anticipated child in order to permit accepting and loving the realities of the actual child
	3	A young father is informed that his 15-old-son's loud ways, provocative comments, lack of sleep, and concerning behaviors landing him in increasing troubles with family, school, and now the legal system, are neither due to his extroverted personality or possible use of drugs. Rather, the doctor is now certain of a diagnosis of bipolar disorder and is recommending treatment with mood stabilizers	"Is this my doing? Bipolar disorder runs in my family." "He was always the liveliest, literally the life of the party. How did I not see this coming, this liveliness having a dark side?" "He is now doomed to take medicines forever, isn't he?"	(1) Consider spontaneous *vs* more structured ways (*e.g.*, SPIKES[28]) of sharing difficult news; and (2) Address uncertainty about lifelong questions and prognosis; provide hopefulness without trivializing unknowns or dismissing concerns

thoughts, feelings, and actions and those of their interlocutors, refining their interactions in real time, and when confronted with a similar clinical situation in the future.

Geolocation: Strengthening local and regional networks: By design, we approached the two CCPS applications in different ways, each exemplifying variations of similar goals. In the case of Türkiye, our aim was to strengthen a local training program (in Bursa) and to link it to regional resources and expertise (in Istanbul). For its initial iteration it was conducted through videoconferencing, though in moving forward it could be delivered in person or through hybrid approaches as well, whether in Türkiye or any other location. By contrast, the Israel approach took advantage of the very specific availability of a resident training day. Such single-day opportunities can be well-suited to disseminate new information or clinical skills through this novel training approach—one that comes closer to the day-to-day granularity of practitioners in general, and of trainees in particular. Alternatively, to a date set aside for training, with all the attendant logistic challenges, a CCPS sample session(s) can be embedded into local or regional society meetings.

Despite their differences in timing and delivery, both approaches have as a common goal the strengthening of CAP professional networks, whether at the hyperlocal (*e.g.*, single site), local (*e.g.*, citywide), national, or regional levels. We originally designed CCPS as a way to develop and strengthen not just individual clinical skills, but communities of practice (CoP) as well[19-21]. As such, the goal of CCPS is just as much to gain hands-on reflective practice, as it is to foster the development of a group of like-minded learners supporting one another, developing and growing professionally together, and becoming comfortable in sharing with one another their vulnerabilities as much as their strengths. For an under-resourced field like CAP, developing and strengthening vibrant CoPs can have enduring and long-lasting

returns. The models that we describe, through their train-the-trainer components, have the potential to sustain and even replicate themselves; they could become vehicles of local capacity building. Longer term replication is needed to determine the feasibility of these optimistic projections.

Celebrating differences: Questioning hegemonies in psychiatric training: We conceptualize these two applications of the CCPS model as a way to welcome, celebrate, foster, and learn from local realities and innovations in clinical practice. By resisting, or at the very least by questioning, an over-reliance on models of psychopathology, diagnostic paradigms, and treatment interventions developed by high-income countries in the West, learners can proudly lean into the heterogeneity of their own practices. In this way, participants can value and stand to gain by learning from their (near-) experience rather than by mostly relying on (distant-) expertise. Fostering partnerships based on equity and mutual benefit, such as those exemplified by CCPS, can support local capacity-building, and promote culturally sensitive care in CAP.

Our experience with CCPS in two very different international settings can be viewed through the lens of anti-neocolonialism in medical education[22-26]. Clinicians are often subject to curricular and knowledge biases, ones in which goals and curricula are solely designed based on Western standards and perspectives, often neglecting local context and healthcare needs of specific regions or countries. Such biased approaches can marginalize local medical knowledge and practices, reinforcing the dominance of Western medical models. CCPS is not intended to invite "either or" but rather "both and" thinking: It seeks to become a pedagogic vehicle to welcome and foster local innovations in clinical practice, benefit from hard-earned and important sources of information, while at the same time resisting neocolonial approaches that privilege over-reliance on hegemonic models of education.

Limitations

We recognize four main limitations to this work. First, our colleagues lived and practiced in high- and middle-upper-income countries (Israel and Türkiye, respectively). Important inroads as these partnerships represent, we also consider them as proofs-of-principle that can pave the way for work with low-resource and high-demand areas, particularly in the Global South, where most of the world's children live. Adaptations of the CCPS model is such locations could benefit from welcoming a wide array of child-facing professional and lay participants. Second, we have no follow up data on the self-sustainability, replicability, or longer-term adoption of the CCPS model. Similarly, we have no outcome data from individual participants' experiences; qualitative methods may prove useful in addressing this limitation in future studies. Third, the number of sessions was small toward the goal of strengthening a CoP. For example, in our previous experience, the same group of participants attended six sessions in as many months—compared to three sessions in the case of Türkiye and only one in that of Israel. Despite this difference, our anecdotal experience from informal "exit interviews" in this and previous studies[27] is that even a single session of CCPS was able to provide something pedagogically unique and clinically helpful. Finally, cost is a potential limitation. Even as professional actors can be relatively costly, the major expense to consider with CCPS are time and opportunity costs, *e.g.*, what responsibilities will trainees need to forego, or who will cover for relevant clinical services.

CONCLUSION

Despite these and other shortcomings we demonstrated the feasibility of adapting the CCPS model in two different countries and languages, and to use the model flexibly, whether during consecutive months or on a single day, in person or *via* videoconferencing. Next steps include the replication of the model in these and/or other sites; we are currently exploring the adaptation of the CCPS model into international partnerships and global partnerships.

ARTICLE HIGHLIGHTS

Research background

Human simulation has a long tradition in medical education, but has made limited inroads in psychiatric education, particularly as pertaining to child and adolescent clinical scenarios.

Research motivation

We sought to expand human simulation applications in child psychiatry. Specifically, we explored the adaptation of simulation in two international settings by embracing different languages and local differences.

Research objectives

We examined: (1) The replicability of a simulation model into international settings; (2) The ability to develop a train-the-trainer approach toward local capacity building in child and adolescent psychiatry (CAP) simulation; and (3) The feasibility of conducting sessions using synchronized videoconferencing.

Research methods

We conducted six human simulation sessions with standardized patients from two host countries, using their native languages (Turkish and Hebrew), and adapting the co-constructive patient simulation (CCPS) model. As local participants became increasingly familiar with the CCPS approach, they took on the role of facilitator—in the country's

native language. We conceptualize these two applications of the CCPS model as a way to welcome, celebrate, foster, and learn from local realities and innovations in clinical practice.

Research results

Fifty-three learners participated: 19 in Türkiye and 24 in Israel. Through the CCPS model we were able to harness human simulation as a novel way of psychiatric education and training that is immersive, experiential, and uniquely tailored to (and by) its intended learners. We were able to approach the two CCPS applications in different ways, each exemplifying regional variations of similar goals.

Research conclusions

Our approach describes a pedagogic vehicle to welcome and foster local innovations in clinical practice, benefit from hard-earned and important sources of local and regional expertise, while at the same time resisting neocolonial approaches that privilege over-reliance on hegemonic models of education.

Research perspectives

Human simulation is a powerful pedagogic approach to improve reflective practice and enhance clinical care. It provides a safe and risk-free environment in which to practice and refine skills. By involving learners in the creation of learning goals and associated scenarios, the CCPS approach is particularly relevant to psychiatry in general, and to CAP in particular.

FOOTNOTES

Author contributions: All authors made substantial contributions to the conception and design of the work; as acquisition and interpretation of the data for the work; they all were part of drafting the work and revising it critically for important intellectual content; they all provided final approval of the version to be published. The corresponding author takes final responsibility for the accuracy and integrity of the work.

Institutional review board statement: This study was approved by the Yale University Institutional Review Board, No. 2000026241.

Informed consent statement: All study participants provided informed written consent prior to study enrollment.

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Data sharing statement: The data that support the findings of this study are available from the corresponding author (Andrés Martin), upon reasonable request.

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REFERENCES

1 **Stein DJ**, Shoptaw SJ, Vigo DV, Lund C, Cuijpers P, Bantjes J, Sartorius N, Maj M. Psychiatric diagnosis and treatment in the 21st century: paradigm shifts versus incremental integration. *World Psychiatry* 2022; **21**: 393-414 [PMID: 36073709 DOI: 10.1002/wps.20998]

2 **Vukotich Jr CJ**. Challenges of T3 and T4 translational research. *J Res Pract* 2016; **12**: 2

3 **Martin A**, Weller I, Amsalem D, Duvivier R, Jaarsma D, de Carvalho Filho MA. Co-constructive Patient Simulation: A Learner-Centered Method to Enhance Communication and Reflection Skills. *Simul Healthc* 2021; **16**: e129-e135 [PMID: 33273424 DOI: 10.1097/SIH.0000000000000528]

4 **Danieli PP**, Hanson MD, VanRiper L, van Hoof MJ, Thomas I, Sibeoni J, Raats P, Prins C, Porter S, Piot MA, Nair B, Mian I, Leung K, Hibbard K, Billon G, Benoit L, Baker JD, Alleyne S, de Carvalho-Filho MA, Amsalem D, Martin A. Psychiatric Clinical Training Across

Borders: Developing Virtual Communities of Practice Through International Co-constructive Patient Simulation. *Acad Psychiatry* 2023 [PMID: 37789233 DOI: 10.1007/s40596-023-01880-9]

5 **de Carvalho Filho MA**, Sehlbach C, Martin A. Co-Constructive Patient Simulation as an Experiential Tool for Continuing Professional Development in Healthcare. *J CME* 2023; **12**: 2192378 [PMID: 37006384 DOI: 10.1080/28338073.2023.2192378]

6 **Martin A**, Weller I, Amsalem D, Adigun A, Jaarsma D, Duvivier R, de Carvalho-Filho MA. From Learning Psychiatry to Becoming Psychiatrists: A Qualitative Study of Co-constructive Patient Simulation. *Front Psychiatry* 2020; **11**: 616239 [PMID: 33488433 DOI: 10.3389/fpsyt.2020.616239]

7 **Eppich W**, Cheng A. Promoting Excellence and Reflective Learning in Simulation (PEARLS): development and rationale for a blended approach to health care simulation debriefing. *Simul Healthc* 2015; **10**: 106-115 [PMID: 25710312 DOI: 10.1097/SIH.0000000000000072]

8 **Bajaj K**, Meguerdichian M, Thoma B, Huang S, Eppich W, Cheng A. The PEARLS Healthcare Debriefing Tool. *Acad Med* 2018; **93**: 336 [PMID: 29381495 DOI: 10.1097/ACM.0000000000002035]

9 **Cheng A**, Eppich W, Kolbe M, Meguerdichian M, Bajaj K, Grant V. A Conceptual Framework for the Development of Debriefing Skills: A Journey of Discovery, Growth, and Maturity. *Simul Healthc* 2020; **15**: 55-60 [PMID: 31743312 DOI: 10.1097/SIH.0000000000000398]

10 **Dolmans DH**, Tigelaar D. Building bridges between theory and practice in medical education using a design-based research approach: AMEE Guide No. 60. *Med Teach* 2012; **34**: 1-10 [PMID: 22250671 DOI: 10.3109/0142159X.2011.595437]

11 **Chen W**, Reeves TC. Twelve tips for conducting educational design research in medical education. *Med Teach* 2020; **42**: 980-986 [PMID: 31498719 DOI: 10.1080/0142159X.2019.1657231]

12 **Looman N**, de Graaf J, Thoonen B, van Asselt D, de Groot E, Kramer A, Scherpbier N, Fluit C. Designing the learning of intraprofessional collaboration among medical residents. *Med Educ* 2022; **56**: 1017-1031 [PMID: 35791303 DOI: 10.1111/medu.14868]

13 **Baum F**, MacDougall C, Smith D. Participatory action research. *J Epidemiol Community Health* 2006; **60**: 854-857 [PMID: 16973531 DOI: 10.1136/jech.2004.028662]

14 **Bergold J**, Thomas S. Participatory research methods: a methodological approach in motion. *Hist Soc Res* 2012; **37**: 191-222 [DOI: 10.17169/fqs-13.1.1801]

15 **McTaggart R**. Principles for participatory action research. *Adult Educ Q* 1991; **41**: 168-187 [DOI: 10.1177/0001848191041003003]

16 **Piot MA**, Dechartres A, Attoe C, Jollant F, Lemogne C, Layat Burn C, Rethans JJ, Michelet D, Cross S, Billon G, Guerrier G, Tesniere A, Falissard B. Simulation in psychiatry for medical doctors: A systematic review and meta-analysis. *Med Educ* 2020; **54**: 696-708 [PMID: 32242966 DOI: 10.1111/medu.14166]

17 **Piot MA**, Attoe C, Billon G, Cross S, Rethans JJ, Falissard B. Simulation Training in Psychiatry for Medical Education: A Review. *Front Psychiatry* 2021; **12**: 658967 [PMID: 34093275 DOI: 10.3389/fpsyt.2021.658967]

18 **Schön DA**. The Reflective Practitioner: How Professionals Think in Action. New York: Basic Books; 1983

19 **Nicolini D**, Scarbrough H, Gracheva J. Communities of Practice and Situated Learning in Health Care. In: The Oxford Handbook of Health Care Management. Oxford: Oxford University Press Oxford; 2016: 255-278

20 **Wenger E**, McDermott R, Snyder WM. Cultivating Communities of Practice: A Guide to Managing Knowledge. Cambridge: Harvard Business Review Press; 2012

21 **de Carvalho-Filho MA**, Tio RA, Steinert Y. Twelve tips for implementing a community of practice for faculty development. *Med Teach* 2020; **42**: 143-149 [PMID: 30707855 DOI: 10.1080/0142159X.2018.1552782]

22 **Rashid MA**, Ali SM, Dharanipragada K. Decolonising medical education regulation: a global view. *BMJ Glob Health* 2023; **8** [PMID: 37311579 DOI: 10.1136/bmjgh-2022-011622]

23 **Kulesa J**, Brantuo NA. Barriers to decolonising educational partnerships in global health. *BMJ Glob Health* 2021; **6** [PMID: 34789513 DOI: 10.1136/bmjgh-2021-006964]

24 **Bleakley A**, Bligh J, Browne J. Global Medical Education—A Post-Colonial Dilemma BT - Medical Education for the Future: Identity, Power and Location. In: Bleakley A, Bligh J, Browne J, eds. Dordrecht: Springer Netherlands; 2011: 171-184

25 **Karle H**, Christensen L, Gordon D, Nystrup J. Neo-colonialism versus sound globalization policy in medical education. *Med Educ* 2008; **42**: 956-958 [PMID: 18823513 DOI: 10.1111/j.1365-2923.2008.03155.x]

26 **Gosselin K**, Norris JL, Ho MJ. Beyond homogenization discourse: Reconsidering the cultural consequences of globalized medical education. *Med Teach* 2016; **38**: 691-699 [PMID: 26571353 DOI: 10.3109/0142159X.2015.1105941]

27 **Spruijt A**, Prins-Aardema CC, Antonio de Carvalho-Filho M, Jaarsma D, Martin A. Co-constructive Veterinary Simulation: A Novel Approach to Enhancing Clinical Communication and Reflection Skills. *J Vet Med Educ* 2023; **50**: 134-139 [PMID: 35452374 DOI: 10.3138/jvme-2021-0160]

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ORIGINAL ARTICLE

Observational Study

Postpartum depression and partner support during the period of lactation: Correlation research and its influencing factors

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Abstract

BACKGROUND

Postpartum depression (PPD) not only affects the psychological and physiological aspects of maternal health but can also affect neonatal growth and development. Partners who are in close contact with parturient women play a key role in communication and emotional support. This study explores the PPD support relationship with partners and its influencing factors, which is believed to establish psychological well-being and improve maternal partner support.

AIM

To explore the correlation between PPD and partner support during breastfeeding and its influencing factors.

METHODS

Convenience sampling was used to select lactating women (200 women) who underwent postpartum examinations at the Huzhou Maternity and Child Health Care Hospital from July 2022 to December 2022. A cross-sectional survey was conducted on the basic information (general information questionnaire), depression level [edinburgh postnatal depression scale (EPDS)], and partner support score [dyadic coping inventory (DCI)] of the selected subjects. Pearson's correlation analysis was used to analyze the correlation between PPD and DCI in lactating women. Factors affecting PPD levels during lactation were analyzed using multiple linear regression.

RESULTS

The total average score of EPDS in 200 lactating women was (9.52 ± 1.53), and the total average score of DCI was (115.78 ± 14.90). Dividing the EPDS, the dimension scores were: emotional loss (1.91 ± 0.52), anxiety (3.84 ± 1.05), and depression (3.76 ± 0.96). Each dimension of the DCI was subdivided into: Pressure communication (26.79±6.71), mutual support (39.76 ± 9.63), negative support (24.97 ± 6.68), agent support (6.87 ± 1.92), and joint support (17.39 ± 4.19). Pearson's correlation

analysis demonstrated that the total mean score and individual dimension scores of EPDS during breastfeeding were inversely correlated with the total score of partner support, stress communication, mutual support, and co-support ($P < 0.05$). The total mean score of the EPDS and its dimensions were positively correlated with negative support ($P < 0.05$). Multiple linear regression analysis showed that the main factors affecting PPD during breastfeeding were marital harmony, newborn health, stress communication, mutual support, negative support, co-support, and the total score of partner support ($P < 0.05$).

CONCLUSION

PPD during breastfeeding was associated with marital harmony, newborn health, stress communication, mutual support, negative support, joint support, and the total DCI score.

Key Words: Lactation period; Puerpera; Postpartum depression; Partner support; Correlation

Core Tip: Lactating women face both physical and psychological pressures and are prone to postpartum depression (PPD), bipolar disorder, and other mental disorders. The partner is a close contact for the mother during this time, and their communication with the mother or behavioral decisions are crucial. Through this study, we found that during breastfeeding, mothers' PPD, degree of marital harmony, newborn health situation, and partner support were associated.

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INTRODUCTION

Given the implementation of China's three-child policy, women's mental health status is of great significance to family and social development. Postpartum depression (PPD) is a common non-psychotic depression in women that persists for a certain period after childbirth. Studies have reported that the incidence of PPD in China is approximately 10.9%-18.6% [1,2]. In addition, there is evidence that PPD may impair infant development, increase children's distraction and antisocial or neurotic behaviors, and affect their cognition and play choices[3]. Moreover, by comparing the incidence of depression in women at 35-60 d and 18-30 mo postpartum, it was found that PPD continues to affect women's mental health[4]. As a unique physiological period for women, lactation is accompanied by changes in personal factors, such as role conversion, irregular work and rest, decreased resistance, and abnormal hormone secretion. In addition, there may be negative external factors such as a shift in the family's attention, preference for the baby's gender, a lack of understanding, and disrespect caused by differences in the perceptions of relatives and elders. Therefore, breastfeeding women are faced with both physical and psychological pressures and are prone to PPD, bipolar disorder, and other mental diseases[5,6]. For lactating women who lack the daily attention of relatives and friends as well as normal social interactions, the need for care from relatives and friends as well as social support, social trust, and partner support is critical.

As a close contact of lactating women, the partner's communication with the women and their behavioral decisions are crucial. Supportive coping is an effective way for partners to relieve individual stress through a series of measures, such as providing emotional support or helping solve problems after receiving specific stress signals[7]. Good partner support can not only help postpartum women physically but also provide psychological support, help them gain positive strength and a sense of hope about PPD, and prevent the deterioration of the marriage[8,9]. Currently, there are few studies on the factors influencing PPD among breastfeeding mothers in China, and the correlation between PPD and dyadic coping inventory (DCI) remains unclear. This study analyzed the correlation between PPD and DCI in women during lactation and explored the influencing factors to provide evidence for improving the mental health status of postpartum women.

MATERIALS AND METHODS

Object

Convenience sampling was used to select lactating women (200 women) who underwent postpartum examinations at the Huzhou Maternity and Child Health Care Hospital from July 2022 to December 2022. The inclusion criteria were as follows: Women who were: (1) Lactating; (2) between 18 and 40 years of age; (3) in a legal marriage or de facto marriage; and (4) willing to voluntarily participate in the investigation. The exclusion criteria were as follows: (1) Serious physical disease or disability, (2) accompanied by malignant tumors and mental abnormalities, and (3) dyslexia.

Methods

The relevant questionnaires were completed under the guidance of professional investigators trained in the hospital, who explained the purpose and significance of the study to the postpartum women and their families and informed them of the matters that needed attention. The questionnaire could only be issued with the consent of the postpartum woman and her family. The questionnaire was completed after on-site verification and retrieval.

Survey tool

(1) General information questionnaire: This included age, education level, planned pregnancy, parity, prenatal sleep, marital harmony, newborn health status, and mode of delivery; (2) The edinburgh postnatal depression scale (EPDS): This scale was developed by Cox *et al*[10] and translated into Chinese by Lee *et al*[11] at the Chinese University of Hong Kong. The scale includes three independent structural subscales (10 items in total): The affective deficit, anxiety, and depression subscales. Each item was scored on a scale of 0-3 points, with a total score of 0-30, which was proportional to depression; (3) DCI: The DCI compiled by Randall and Bodenmann[12] was used in this study. The questionnaire has five dimensions (35 items in total): Stress communication, negative coping, agent coping, mutual support, and joint support. All entries are self-assessed on a scale of 1-5, and the total score ranging from 35-175 for negative support responses is reversed. The score was proportional to partner-supportive coping.

Statistical analysis

The Chinese version of the Epi Data 3.1 was used for two-person input of the scale data. SPSS Statistics for Windows, version 26.0 (Armonk: NY, IBM Corp), was used to analyze the project data. Counting variables are expressed as [n (%)] and compared using the χ^2 test. Continuous variables are reported as mean ± SD. Comparisons were performed using the t-test or one-way analysis of variance (ANOVA). This study employed multiple regression analysis to explore the factors influencing lactating women's PPD score; inspection level $\alpha = 0.05$. Statistical significance was set at $P < 0.05$, on behalf of the difference was statistically significant.

RESULTS

Single factor analysis of EPDS scores of women during lactation and EPDS scores of women with different characteristics

The total score of EPDS in 200 lactating women was (9.52 ± 1.53). Dividing the EPDS for all dimensions resulted in the following scores for emotional loss (1.91 ± 0.52), anxiety (3.84 ± 1.05), and depression (3.76 ± 0.96). The results are presented in Table 1. There were significant differences in PPD scores among those with different marital harmony and newborn health conditions ($P < 0.05$). The results are presented in Table 2.

Maternal DCI score

The average DCI score of 200 lactating women was (115.78 ± 14.90). Each dimension of the DCI was separated into pressure communication (26.79 ± 6.71), mutual support (39.76 ± 9.63), negative support (24.97 ± 6.68), agent support (6.87 ± 1.92), and joint support (17.39 ± 4.19) scores. The results are presented in Table 3.

Correlation analysis of PPD and DCI during lactation

Pearson's correlation analysis showed that the total average score of the EPDS and its dimensions during lactation were inversely proportional to the total scores of partner support, stress communication, mutual support, and common support of lactating women ($P < 0.05$). The total average score and each dimension of the EPDS were positively correlated with negative support ($P < 0.05$). The results are presented in Table 4. Among them, the relationship between the EPDS total mean score and each dimension and the total DCI mean score is shown in Figure 1.

Stepwise regression analysis of different characteristics and DCI on PPD during lactation

Multivariate linear regression analysis was undertaken with the total mean score of PPD as the dependent variable, and the characteristics of puerpera and each dimension and the total score of the DCI as the independent variables (Table 5). The selected variable $\alpha = 0.05$, and the excluded variable $\alpha = 0.10$ were used for multiple linear regression analysis, the results showed that the main factors affecting PPD in lactating women were marital harmony, newborn health, pressure communication, mutual support, negative support, common support, and the total average score of the DCI ($P < 0.05$). The results are presented in Table 6.

DISCUSSION

PPD refers to mothers with no previous history of mental disorders showing symptoms of depression, postpartum within six weeks of the first onset; depression, boredom, crying and emotional irritability are the main characteristics of PPD. Severe cases may manifest as hallucinations and even self-harm, harming the baby, and other violent episodes[13]. PPD is a common abnormal psychological behavior in gynecology that seriously endangers the physical and mental health of pregnant women and affects the growth and development of infants. The incidence of PPD is slightly different between

Table 1 Edinburgh postnatal depression scale scores during lactation

Item	Dimension score (points)
Lack of emotion	1.91 ± 0.52
Anxiety	3.84 ± 1.05
Depression	3.76 ± 0.96
Total EPDS mean score	9.52 ± 1.53

EPDS: Edinburgh postnatal depression scale.

Table 2 Univariate analysis of edinburgh postnatal depression scale scores of parturients with different characteristics

Item	Number of cases	EPDS (scores)	*t*/F value	*P* value
Age (yr)			-1.904	0.058
≤ 30	95	9.31 ± 1.36		
> 30	105	9.71 ± 1.65		
Education level (yr)			0.246	0.864
Junior high school and below	41	9.63 ± 1.55		
Secondary school or high school	72	9.51 ± 1.51		
Junior college	62	9.40 ± 1.73		
Bachelor's degree or above	25	9.64 ± 1.53		
Plan a pregnancy			-1.170	0.243
Yes	129	9.43 ± 1.55		
No	71	9.69 ± 1.49		
Number of births				
Primary birth	118	9.38 ± 1.52	-1.450	0.149
Multiparous	82	9.71 ± 1.53		
Prenatal sleep status			1.030	0.380
Good	84	9.57 ± 1.63		
General	48	9.21 ± 1.50		
Occasional insomnia	46	9.61 ± 1.18		
Frequent insomnia	22	9.82 ± 1.79		
Marriage harmony situation			-4.804	< 0.001
Harmonious	126	9.14 ± 1.35		
Disharmonious	74	10.16 ± 1.59		
Mode of delivery			1.759	0.080
Natural childbirth	110	9.69 ± 1.49		
Cesarean section	90	9.31 ± 1.56		
Neonatal health			-10.051	< 0.001
Healthy	137	8.92 ± 1.25		
Unhealthy	63	10.83 ± 1.24		

EPDS: Edinburgh postnatal depression scale.

Table 3 Dyadic coping inventory scores during lactation

Item	Dimension score (points)
Stress communication	26.79 ± 6.71
Mutual support	39.76 ± 9.63
Negative support	24.97 ± 6.68
Agent support	6.87 ± 1.92
Joint support	17.39 ± 4.19
DCI total average	115.78 ± 14.90

DCI: Dyadic coping inventory.

Table 4 Correlation between edinburgh postnatal depression scale and dyadic coping inventory during lactation

Dimensions	Lack of emotion	Anxiety	Depression	Total EPDS mean score
Stress communication	-0.150[a]	-0.252[c]	-0.163[a]	-0.327[c]
Mutual support	-0.282[c]	-0.165[a]	-0.185[b]	-0.326[c]
Negative support	0.178[a]	0.157[a]	0.205[b]	0.298[c]
Agent support	-0.087	0.117	0.046	0.080
Joint support	-0.238[b]	-0.158[a]	-0.301[c]	-0.357[c]
DCI total average	-0.248[c]	-0.172[a]	-0.167[a]	-0.308[c]

[a]$P < 0.05$.
[b]$P < 0.001$.
[c]$P < 0.0001$.
EPDS: Edinburgh postnatal depression scale; DCI: Dyadic coping inventory.

Table 5 Variable assignment

Item	Assignment mode
Age	≤ 30 yr = 0, > 30 yr = 1
Education level	Junior high school and below = 0, secondary school or high school = 1, junior college = 2, Bachelor's degree or above = 3
Plan a pregnancy	Yes = 0, no = 1
Number of births	Primary birth = 0, produce = 1
Prenatal sleep status	Good = 0, general = 1, occasional insomnia = 2, frequent insomnia = 3
Marriage harmony situation	Harmonious = 0, disharmonious = 1
Mode of delivery	Natural childbirth = 0, cesarean section = 1
Neonatal health	Healthy = 0, unhealthy = 1
Stress communication	-
Mutual support	-
Negative support	-
Agent support	-
Joint support	-
DCI total average	-

DCI: Dyadic coping inventory.

Table 6 Multiple stepwise regression analysis of postpartum depression during lactation by different characteristics and dyadic coping inventory.

Independent variable	Partial regression coefficient	Standard regression coefficient	*t*	*P* value
Marital harmony	0.903	0.190	4.765	< 0.001
Newborn health	1.069	0.194	5.524	< 0.001
Stress communication	-0.129	0.032	-4.074	< 0.001
Mutual support	-0.099	0.029	-3.389	0.001
Negative support	-0.061	0.030	-2.015	0.045
Joint support	-0.143	0.033	-4.361	< 0.001
DCI total average	0.085	0.029	4.765	0.004

$R = 0.744$, $R^2 = 0.553$, after the adjustment $R^2 = 0.537$, $F = 33.957$, $P < 0.001$. DCI: Dyadic coping inventory.

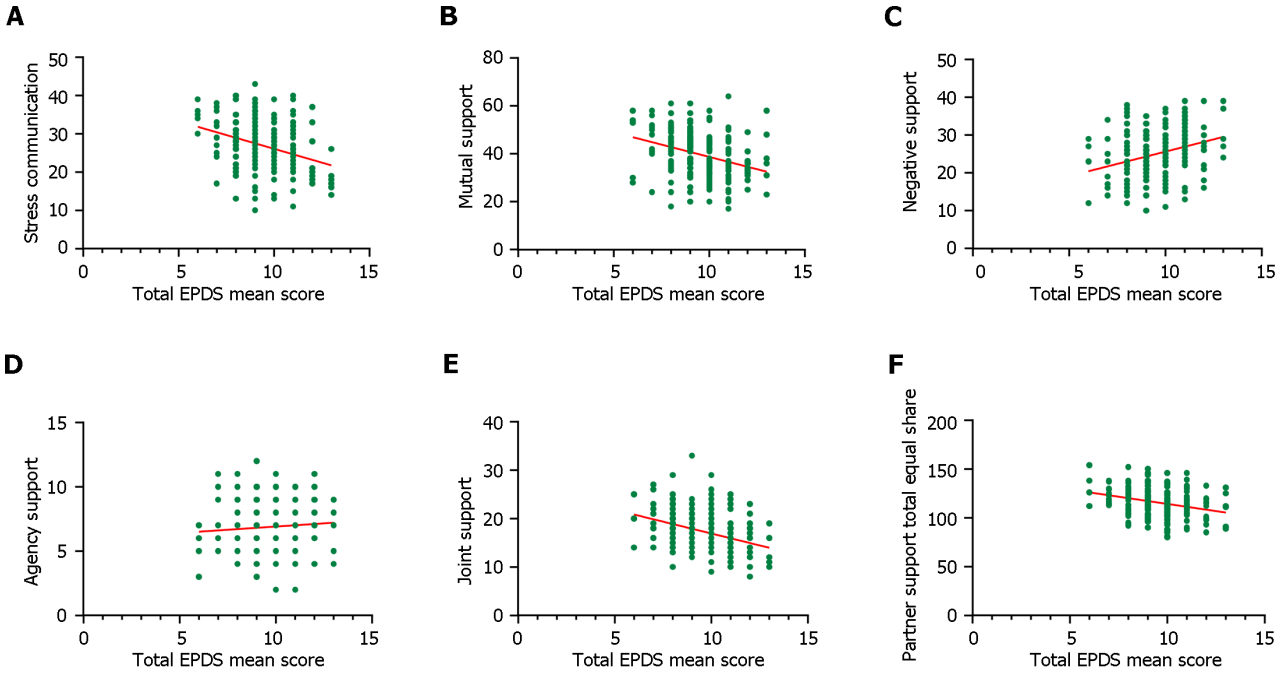

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Figure 1 The relationship between the total mean score of edinburgh postnatal depression scale and each dimension and total mean score of dyadic coping inventory. A: Edinburgh postnatal depression scale (EPDS) total split and pressure relationship; B: EPDS always divides relationships with mutual support; C: Relationship between total EPDS mean score and negative support; D: Relationship between EPDS general sharing and agency support; E: Relationship between total EPDS sharing and joint support; F: Relationship between the total mean EPDS score and the total mean dyadic coping inventory score. EPDS: Edinburgh postnatal depression scale.

countries, with a prevalence of more than 20% in Western countries and 10%-20% in China[14,15]. The total average score of EPDS in 200 lactating women in this study was (9.52 ± 1.53), indicating that the EPDS of lactating women were at a moderate level. This may have been affected by different PPD evaluation time points and different evaluation tools. In addition, PPD is related to other factors such as regional economic development, population structure, cultural background, and so on.

The total partner support score of 200 cases during lactation was (115.78 ± 14.90), and the partner support level for PPD during lactation was moderate. This indicated that women were more willing to face the illness with their partners. Regarding communication and mutual support pressure, the score was relatively high, showing that mothers with PPD tend to communicate and take the initiative to talk about their psychological problems to obtain their partner's support and understanding, when facing pressure. By encouraging and supporting each other, both parties can reduce psychological pressure and create a good spiritual environment[16,17]. Korotkin *et al*[18] believed that the expression of emotions in the process of patients seeking social support can significantly improve their psychological pressure of patients. Studies have found that a good family atmosphere can provide sufficient material and spiritual support, enhance patients' sense of self-esteem, and reduce pressure when they are ill[19]. These findings provide guidelines for

interventions in PPD.

This study found that the total average score and each dimension of the postpartum EPDS were inversely related to the total score of partner support, pressure communication, mutual support, and common support, and positively related to negative support ($P < 0.05$), suggesting that good relationships with the partner can lower the mother's bad mood. Eastwood[20] found that emotional support from a partner was closely associated with PPD and was an important indicator to measure partnerships. Razurel and Kaiser[21] noted that pregnant women had different expectations and requirements from family members. Partners can provide strong support for lactating women with depression in terms of their financial and psychological well-being as well as disease-related care, which can reduce their psychological burden, relieve patients' negative emotions, and greatly improve their quality of life[22,23].

The effect of influential factors of PPD are relatively complex. Multiple linear regression analysis results show that the influence degree of the factors in lactating mothers' PPD include marital harmony, newborn health condition, communication, mutual support, negative pressure support, mutual support, and partner support total score ($P < 0.05$). According to existing literature, marital disharmony is also a risk factor for PPD[24,25]. Analysis suggests that the capacity of lactating parturients to bear psychological stress is weak, and marital disharmony can increase their psychological burden. Additionally, when newborn health is poor, pregnant women will not only find it difficult to accept, but also have a large psychological gap, and are therefore prone to serious negative mental well-being, thus inducing PPD[26,27]. Therefore, clinical attention should be paid to postpartum psychological changes and corresponding measures should be taken to reduce PPD as much as possible. Partners are the most important source of social support for patients and an important aspect that affects patients' perceptions of illness. Good partner support can be reflected in the care and understanding of patients' physical and mental well-being and is a positive and strong source of hope for patients[28]. The positive support and communication of partners can alleviate postpartum women's negative emotions and improve the negative cognition of the patients. Contrastingly, negative support can increase a patients' negative awareness, and negative support and awareness promote each other[29].

CONCLUSION

In summary, PPD during lactation was associated with marital harmony, newborn health, stress communication, mutual support, negative support, co-support, and partner support. Hospitals and relevant departments should pay attention to the level of PPD in parturients, guide them to correctly recognize and understand the disease, carry out targeted individualized nursing interventions for patients and their partners, and improve the support level of their partners to improve the mental health of parturients with PPD.

ARTICLE HIGHLIGHTS

Research background

Postpartum depression (PPD) not only causes anxiety, lower self-image, self-guilt, and other conditions in lactating women but also has adverse effects on the health of the baby. PPD can appear in normal life circumstances and negative life events such as marital discord. Good partner support can not only help patients physically but also provide psychological support. Exploring the relationship between PPD and dyadic coping inventory (DCI) in lactating women and analyzing the related influencing factors of PPD are helpful for clinical interventions from related factors to prevent and alleviate the occurrence of PPD.

Research motivation

Negative partner support, marital disharmony, and unhealthy newborns were associated with PPD in lactating women.

Research objectives

By exploring the relationship between PPD and partner support and the factors affecting PPD in lactating women, it is helpful to provide a reference for the clinical construction of PPD intervention programs and partner support strategies.

Research methods

A general information questionnaire, edinburgh postnatal depression scale (EPDS) scale, and DCI scale were used to investigate the correlation between PPD and partner support during lactation, and to further analyze the factors affecting the level of PPD.

Research results

The total average score of EPDS of 200 women during lactation was (9.52 ± 1.53), and the total average score of partner support was (115.78 ± 14.90), both of which were at the medium level. The degree of marital harmony, neonatal health, stress communication, mutual support, negative support, common support, and total partner support score were factors influencing PPD in lactating women.

Research conclusions

Through research, we found that the poor psychological health of lactating women is significantly related to their partner support. By analyzing the influencing factors of women's PPD, providing timely psychological help and encouraging partners to provide maternal support and care will help to improve the PPD level of lactating women.

Research perspectives

Future research should establish a predictive model based on the factors influencing PPD in lactating women.

FOOTNOTES

Author contributions: Ruan JM acquired the data and drafted the first version of the paper; Wu LJ acquired and interpreted the data, and critically appraised the paper; all authors have approved the version to be published.

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

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REFERENCES

1 **Liu X**, Wang S, Wang G. Prevalence and Risk Factors of Postpartum Depression in Women: A Systematic Review and Meta-analysis. *J Clin Nurs* 2022; **31**: 2665-2677 [PMID: 34750904 DOI: 10.1111/jocn.16121]
2 **Nisar A**, Yin J, Waqas A, Bai X, Wang D, Rahman A, Li X. Prevalence of perinatal depression and its determinants in Mainland China: A systematic review and meta-analysis. *J Affect Disord* 2020; **277**: 1022-1037 [PMID: 33065811 DOI: 10.1016/j.jad.2020.07.046]
3 **Grace SL**, Evindar A, Stewart DE. The effect of postpartum depression on child cognitive development and behavior: a review and critical analysis of the literature. *Arch Womens Ment Health* 2003; **6**: 263-274 [PMID: 14628179 DOI: 10.1007/s00737-003-0024-6]
4 **Gopalan P**, Spada ML, Shenai N, Brockman I, Keil M, Livingston S, Moses-Kolko E, Nichols N, O'Toole K, Quinn B, Glance JB. Postpartum Depression-Identifying Risk and Access to Intervention. *Curr Psychiatry Rep* 2022; **24**: 889-896 [PMID: 36422834 DOI: 10.1007/s11920-022-01392-7]
5 **Silva CS**, Lima MC, Sequeira-de-Andrade LAS, Oliveira JS, Monteiro JS, Lima NMS, Santos RMAB, Lira PIC. Association between postpartum depression and the practice of exclusive breastfeeding in the first three months of life. *J Pediatr (Rio J)* 2017; **93**: 356-364 [PMID: 28034730 DOI: 10.1016/j.jped.2016.08.005]
6 **Becker M**, Weinberger T, Chandy A, Schmukler S. Depression During Pregnancy and Postpartum. *Curr Psychiatry Rep* 2016; **18**: 32 [PMID: 26879925 DOI: 10.1007/s11920-016-0664-7]
7 **Varner S**, Lloyd G, Ranby KW, Callan S, Robertson C, Lipkus IM. Illness uncertainty, partner support, and quality of life: A dyadic longitudinal investigation of couples facing prostate cancer. *Psychooncology* 2019; **28**: 2188-2194 [PMID: 31418505 DOI: 10.1002/pon.5205]
8 **Hinnen C**, Ranchor AV, Baas PC, Sanderman R, Hagedoorn M. Partner support and distress in women with breast cancer: The role of patients' awareness of support and level of mastery. *Psychol Health* 2009; **24**: 439-455 [PMID: 20205004 DOI: 10.1080/08870440801919513]
9 **Gil N**, Fisher A, Beeken RJ, Pini S, Miller N, Buck C, Lally P, Conway R. The role of partner support for health behaviours in people living with and beyond cancer: A qualitative study. *Psychooncology* 2022; **31**: 1997-2006 [PMID: 36097392 DOI: 10.1002/pon.6032]
10 **Cox JL**, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. *Br J*

Psychiatry 1987; **150**: 782-786 [PMID: 3651732 DOI: 10.1192/bjp.150.6.782]

11 **Lee DT**, Yip SK, Chiu HF, Leung TY, Chan KP, Chau IO, Leung HC, Chung TK. Detecting postnatal depression in Chinese women. Validation of the Chinese version of the Edinburgh Postnatal Depression Scale. *Br J Psychiatry* 1998; **172**: 433-437 [PMID: 9747407 DOI: 10.1192/bjp.172.5.433]

12 **Randall AK**, Bodenmann G. The role of stress on close relationships and marital satisfaction. *Clin Psychol Rev* 2009; **29**: 105-115 [PMID: 19167139 DOI: 10.1016/j.cpr.2008.10.004]

13 **Pearlstein T**, Howard M, Salisbury A, Zlotnick C. Postpartum depression. *Am J Obstet Gynecol* 2009; **200**: 357-364 [PMID: 19318144 DOI: 10.1016/j.ajog.2008.11.033]

14 **Sockol LE**, Epperson CN, Barber JP. Preventing postpartum depression: a meta-analytic review. *Clin Psychol Rev* 2013; **33**: 1205-1217 [PMID: 24211712 DOI: 10.1016/j.cpr.2013.10.004]

15 **Ceriani Cernadas JM**. Postpartum depression: Risks and early detection. *Arch Argent Pediatr* 2020; **118**: 154-155 [PMID: 32470247 DOI: 10.5546/aap.2020.eng.154]

16 **Kroska EB**, Stowe ZN. Postpartum Depression: Identification and Treatment in the Clinic Setting. *Obstet Gynecol Clin North Am* 2020; **47**: 409-419 [PMID: 32762926 DOI: 10.1016/j.ogc.2020.05.001]

17 **Traa MJ**, De Vries J, Bodenmann G, Den Oudsten BL. Dyadic coping and relationship functioning in couples coping with cancer: a systematic review. *Br J Health Psychol* 2015; **20**: 85-114 [PMID: 24628822 DOI: 10.1111/bjhp.12094]

18 **Korotkin BD**, Hoerger M, Voorhees S, Allen CO, Robinson WR, Duberstein PR. Social support in cancer: How do patients want us to help? *J Psychosoc Oncol* 2019; **37**: 699-712 [PMID: 30929593 DOI: 10.1080/07347332.2019.1580331]

19 **Yamada A**, Isumi A, Fujiwara T. Association between Lack of Social Support from Partner or Others and Postpartum Depression among Japanese Mothers: A Population-Based Cross-Sectional Study. *Int J Environ Res Public Health* 2020; **17** [PMID: 32549294 DOI: 10.3390/ijerph17124270]

20 **Eastwood JG**, Jalaludin BB, Kemp LA, Phung HN, Barnett BE. Relationship of postnatal depressive symptoms to infant temperament, maternal expectations, social support and other potential risk factors: findings from a large Australian cross-sectional study. *BMC Pregnancy Childbirth* 2012; **12**: 148 [PMID: 23234239 DOI: 10.1186/1471-2393-12-148]

21 **Razurel C**, Kaiser B. The role of satisfaction with social support on the psychological health of primiparous mothers in the perinatal period. *Women Health* 2015; **55**: 167-186 [PMID: 25775391 DOI: 10.1080/03630242.2014.979969]

22 **Pilkington P**, Milne L, Cairns K, Whelan T. Enhancing reciprocal partner support to prevent perinatal depression and anxiety: a Delphi consensus study. *BMC Psychiatry* 2016; **16**: 23 [PMID: 26842065 DOI: 10.1186/s12888-016-0721-0]

23 **Lal A**, Bartle-Haring S. Relationship among differentiation of self, relationship satisfaction, partner support, and depression in patients with chronic lung disease and their partners. *J Marital Fam Ther* 2011; **37**: 169-181 [PMID: 21457282 DOI: 10.1111/j.1752-0606.2009.00167.x]

24 **Qi W**, Zhao F, Liu Y, Li Q, Hu J. Psychosocial risk factors for postpartum depression in Chinese women: a meta-analysis. *BMC Pregnancy Childbirth* 2021; **21**: 174 [PMID: 33653288 DOI: 10.1186/s12884-021-03657-0]

25 **Shi P**, Ren H, Li H, Dai Q. Maternal depression and suicide at immediate prenatal and early postpartum periods and psychosocial risk factors. *Psychiatry Res* 2018; **261**: 298-306 [PMID: 29331710 DOI: 10.1016/j.psychres.2017.12.085]

26 **Slomian J**, Honvo G, Emonts P, Reginster JY, Bruyère O. Consequences of maternal postpartum depression: A systematic review of maternal and infant outcomes. *Womens Health (Lond)* 2019; **15**: 1745506519844044 [PMID: 31035856 DOI: 10.1177/1745506519844044]

27 **McPeak KE**, Sandrock D, Spector ND, Pattishall AE. Important determinants of newborn health: postpartum depression, teen parenting, and breast-feeding. *Curr Opin Pediatr* 2015; **27**: 138-144 [PMID: 25564189 DOI: 10.1097/MOP.0000000000000185]

28 **Goldzweig G**, Baider L, Andritsch E, Rottenberg Y. Hope and social support in elderly patients with cancer and their partners: an actor-partner interdependence model. *Future Oncol* 2016; **12**: 2801-2809 [PMID: 27712084 DOI: 10.2217/fon-2016-0267]

29 **Desta M**, Memiah P, Kassie B, Ketema DB, Amha H, Getaneh T, Sintayehu M. Postpartum depression and its association with intimate partner violence and inadequate social support in Ethiopia: a systematic review and meta-analysis. *J Affect Disord* 2021; **279**: 737-748 [PMID: 33234282 DOI: 10.1016/j.jad.2020.11.053]

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ORIGINAL ARTICLE

Observational Study

Abnormalities of electroencephalography microstates in patients with depression and their association with cognitive function

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Abstract

BACKGROUND

A growing number of recent studies have explored underlying activity in the brain by measuring electroencephalography (EEG) in people with depression. However, the consistency of findings on EEG microstates in patients with depression is poor, and few studies have reported the relationship between EEG microstates, cognitive scales, and depression severity scales.

AIM

To investigate the EEG microstate characteristics of patients with depression and their association with cognitive functions.

METHODS

A total of 24 patients diagnosed with depression and 32 healthy controls were included in this study using the Structured Clinical Interview for Disease for The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. We collected information relating to demographic and clinical characteristics, as well as data from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Chinese version) and EEG.

RESULTS

Compared with the controls, the duration, occurrence, and contribution of microstate C were significantly higher [depression (DEP): Duration 84.58 ± 24.35, occurrence 3.72 ± 0.56, contribution 30.39 ± 8.59; CON: Duration 72.77 ± 10.23, occurrence 3.41 ± 0.36, contribution 24.46 ± 4.66; Duration $F = 6.02$, $P = 0.049$; Occurrence $F = 6.19$, $P = 0.049$; Contribution $F = 10.82$, $P = 0.011$] while the duration, occurrence, and contribution of microstate D were significantly lower

(DEP: Duration 70.00 ± 15.92, occurrence 3.18 ± 0.71, contribution 22.48 ± 8.12; CON: Duration 85.46 ± 10.23, occurrence 3.54 ± 0.41, contribution 28.25 ± 5.85; Duration $F = 19.18$, $P < 0.001$; Occurrence $F = 5.79$, $P = 0.050$; Contribution $F = 9.41$, $P = 0.013$) in patients with depression. A positive correlation was observed between the visuospatial/constructional scores of the RBANS scale and the transition probability of microstate class C to B ($r = 0.405$, $P = 0.049$).

CONCLUSION

EEG microstate, especially C and D, is a possible biomarker in depression. Patients with depression had a more frequent transition from microstate C to B, which may relate to more negative rumination and visual processing.

Key Words: Depression; Electroencephalography; Microstates; Cognitive functions

Core Tip: This study aims to explore electroencephalography microstates in patients with depression and the correlation between microstates and cognitive scales. Through statistical analyses, we found parameters of the microstate C were higher while microstate D were lower in patients with depression compared with the controls. A positive correlation was observed between the visuospatial/constructional scores and the transition probability of microstate C to B. Therefore, we speculate that microstates C and D, is a possible biomarker in depression. Patients with depression had a more frequent transition from microstate C to B, which may relate to more negative rumination and visual processing.

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INTRODUCTION

Depression is a chronic and debilitating disease that is characterized by depressed mood, diminished interests, and cognitive deficits manifested as low self-esteem, sleep disturbance, weight loss, and even disability[1,2]. In the Global Burden of Disease Study 2013 (GBD 2013), depression is the second-largest contributor to the burden of chronic disease as measured by years lived with disability[3]. Several characteristics of depression are consistent across countries, such as higher lifetime prevalence, lifelong chronic–recurrent persistence, and increased risk of early death due to somatic illness and suicide[4]. There is growing evidence that depression is associated with neural activity and connectivity[5], while our understanding of the neurobiology of depression continues to progress. However, there is still no definitive explanation for the pathophysiological mechanisms of the disease.

Electroencephalography (EEG), commonly used to study electrophysiological processes in the cerebral cortex, is capable of describing local and global neuronal activity in the brain neural networks[6]. Compared with other neuroimaging modalities such as functional magnetic resonance imaging (fMRI), EEG has the advantages of high temporal resolution, ease of measurement, and lower cost. Recently, a growing number of studies have attempted to explore possible abnormal potential activity in the brain neural networks of patients with depression by measuring EEG. For example, quantitative EEG was used to predict and monitor the response to depression treatment. Arns *et al*[7] found that depressed patients with low theta waves in the frontal cortex and the rostral anterior cingulate were more responsive to medication. Another study showed that those with increased quantitative EEG theta cordance had significant improvement in depressive symptoms after 6 weeks of repetitive transcranial magnetic stimulation (rTMS) treatment[8]. This suggests that changes in EEG theta cordance could be a potential clinical predictor of outcome of depression treatment.

In early studies based on resting-state EEG analyses, Lehmann *et al*[9] found that the alpha frequency band (8-12 Hz) of the EEG signal can be broken down into several quasi-stable states called EEG microstates, which can be recorded as four quasi-stable topographic maps to represent global brain activity[10], remaining stable for 80-120 ms and rapidly transitioning to the next microstate. Different information and data transmitted to the brain elicit different neurophysiological responses and correspond to individual EEG microstates. These four classical maps of EEG microstates are: (A) States associated with auditory processing; (B) States associated with visual processing; (C) States associated with cognitive control networks; and (D) States associated with dorsal attention networks[11]. EEG microstate analysis has been widely used in studies related to psychiatric disorders, showing schizophrenia[12-14], bipolar disorders[15,16], anxiety disorders [17], panic disorders[18], and insomnia[19]. For example, increases in microstate C and decreases in microstate D have been consistently identified as characteristic changes in individuals with schizophrenia. These microstates, C and D, have emerged as potential endophenotypes for schizophrenia[20]. The utilization of these microstates in the clinical diagnosis and treatment of schizophrenia has reached a significant level of consensus among various studies[21,22].

However, many studies found significant but less consistent results regarding EEG microstate features in patients with depression. Some studies found increased occurrence and contribution of microstate B and decreased occurrence and contribution of microstate D in patients with depression compared to healthy controls[23,24]. However, another study suggested that students with depression had lower duration of microstate C[25]. Qin *et al*[26] demonstrated a positive correlation between the occurrence of microstate B and Beck Depression Inventory-II (BDI-II) scores, and the occurrence of microstates D and E were negatively correlated with BDI-II scores. In contrast, several experimental studies have found no association between severity of depression and EEG microstate[23]. Lei *et al*[27] found that shorter durations of microstate D, higher frequencies of microstate C, and lower probabilities of transition from microstate D to B were associated with better treatment effects in patients with depression. Additionally, several studies have proposed that EEG microstate can predict the treatment outcomes of selective serotonin reuptake inhibitors (SSRI) or rTMS[27,28]. The discrepancy among the results of studies may be attributed to differences in the severity of depression or differences in microstate analysis methods. Therefore, there is a need to conduct a more comprehensive study of EEG microstates in patients with depression.

According to The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), cognitive dysfunction is well established as a core diagnostic criterion of depression. Current research suggests that cognitive dysfunction reduces occupational productivity and interferes with social function in patients with depression[29]. In 2016, the United States Food and Drug Administration recommended cognitive symptoms as a target for intervention in the treatment of depressive disorder[30]. Thus, there is a need to emphasize the impairment of cognitive function in patients with and to include this in the diagnosis and treatment. A growing number of scientists are demonstrating that individual EEG microstates may correspond to specific mental states, which consistently influence the processing of and response to incoming information[31,32]. Taken together, we can collect data on global neuronal activity in the brain through EEG, quantify the cognitive cuts through neurocognitive assessment, and analyze multidimensional data in order to find biological markers that more accurately assess the condition of patients with depression.

We collected 128-lead resting-state EEG data from patients with depression and healthy controls to investigate their EEG microstate characteristics. The results were calibrated through statistical methods, attempting to find more realistic and reliable characterizations of EEG microstates. In addition, we also analyzed the correlation between EEG microstate characteristics and cognitive scales, which has rarely been studied before. Third, we correlated EEG microstate parameters with the Hamilton Depression Scale (HAMD) to figure out possible relationships between depression severity and EEG microstates.

MATERIALS AND METHODS

Participants

Participants were recruited from January 2016 to December 2018 at Suzhou Guangji Hospital, in adherence with the Helsinki Declaration. Written informed consent was obtained from all individuals, and the study received approval from the Ethics Committee of Suzhou Guangji Hospital. Demographic and clinical characteristics, as well as data from the repeatable battery for the assessment of neuropsychological status (RBANS; Chinese version)[33] and EEG, were collected from a sample of 24 patients diagnosed with depression (DEP) and 32 healthy controls (CON). Patients who exhibited stable depression were deemed suitable for inclusion. Each patient underwent an interview utilizing the Structured Clinical Interview for DSM Disorders (SCID) to ascertain their compliance with the criteria for a depressive episode. Control participants, who were in good health, possessed no prior psychiatric afflictions, had no immediate family members with psychiatric disorders, and had not previously utilized psychotropic medications. All participants, regardless of their depression status, underwent the SCID for diagnostic validation, as well as the HAMD to evaluate the extent of their depressive symptoms. All individuals classified with depression satisfied the inclusion criteria: (1) Age 18-60 years; (2) Right-handed; (3) All participants who were clinically stable did not have a history of neurological disorders or head trauma; and (4) None of the participants had undergone electroconvulsive therapy within the past 6 mo. Participants with a history of alcohol or drug dependence or abuse, with the exception of tobacco, were excluded from the study.

The CON group was comprised of individuals who were matched to the DEP group in terms of gender, age, and years of education.

Neurocognitive assessments

The neurocognitive functions of the participants were evaluated using the RBANS. RBANS is a standardized assessment tool that measures five specific cognitive domains, namely immediate memory (IMM), delayed memory (DEM), visuo-spatial/constructional (VC), attention (ATT), and language (LAN).

EEG recording and preprocessing

Participants were seated comfortably in a reclining chair and instructed to close their eyes and maintain a relaxed and quiet state for a duration of 3 min. The continuous EEG data were digitized at a sampling rate of 1000 Hz using the EGI EEG system (Electrical Geodesics, Eugene, OR, United States) with a 128-electrode HydroCelnet referenced to the vertex (Cz). Offline preprocessing of the EEG data was performed using the EEGLAB (v2021.1)[34] and HAPPE[35] toolboxes in MATLAB (Release 2022b; MathWorks). The raw EEG data were initially resampled to a sampling rate of 500 Hz. A band-pass filter with a range of 0.5-45 Hz was applied. Subsequently, the EEG data for each participant was preprocessed using the HAPPE toolkit. Following this, a manual inspection of the EEG data was conducted to confirm the removal of

artifacts. Lastly, all electrodes were re-referenced to an average reference.

Microstate analysis

A band-pass filtering ranging from 2 to 20 Hz was executed. Microstate analysis was conducted utilizing the EEGLAB microstate plugin[36]. The global field power was used to measure the collective alteration in potential across the electrode set, thereby indicating the electric field intensity throughout the brain at each moment. The atomize and agglomerate hierarchical clustering (AAHC) algorithm[37] was used to compute four optimal microstate topographies.

Cluster analyses were conducted on a series of EEGs at the individual level, referred to as first-level clustering. The clustering was performed at the group level, known as second-level clustering. And clusters were rearranged based on normative microstate template maps. This process involved clustering across all subjects to generate a comprehensive set of global maps representing all participants. Lastly, a new dataset was generated, and each temporal parameter of the microstate was extracted for subsequent statistical analysis. Figure 1 shows the topographic distributions of global maps. Based on earlier studies' spatial patterns[27,38], we classified the spatial patterns as microstates A/B/C/D. We used the duration, occurrence, contribution and transition probability of microstates as our parameters. Duration denoted the mean steady duration of a microstate; occurrence denoted the mean frequency of observation of each microstate; contribution denoted the proportion of the total time spent in each microstate; and transition probability denoted the proportion of all observed microstate transitions that went from X to Y.

Statistical analysis

Statistics were performed in RStudio (Version 2023.06.1, Boston, MA, United States) with R software (Version 4.3.1). The independent sample *t*-test, chi-square test and Wilcox Mann-Whitney test were conducted to evaluate potential differences in demographic and clinical characteristics between the DEP and CON groups. The analysis of covariance (ANCOVA, education was controlled) was conducted to calculate *P* value in RBANS score and EEG microstate features between the DEP and CON groups, and the false discovery rate (FDR) was calculated to adjust *P* values for multiple testing based on the Benjamini-Hochberg method[39]. $P < 0.05$ (two-tailed) was considered as indicative of statistical significance. Within the DEP group, Pearson correlation analysis were performed for neurocognitive RBANS score and EEG microstate parameters. To account for multiple testing, *P* values were calculated using a permutation test with 100000 replicates.

RESULTS

Demographic, clinical and neurocognitive RBANS characteristics

The demographic and primary clinical data include gender, age, years of education, HAMD score, duration of illness, and age at onset. Age and education were expressed as means and SDs, HAMD score, duration of illness and age at onset were expressed as median and range. The demographic and clinical characteristics of the DEP and CON groups are shown in Table 1. There were no significant differences in age or gender between the two groups. Only years of education and HAMD score showed significant differences in the two groups (education: $t = 2.056$, $P = 0.045$; HAMD score: $W = 83$, $P < 0.001$). ANCOVA and FDR were used to analyze participant RBANS characteristics, but no significant differences were found in the two groups (Table 2).

Differences in EEG microstate between the DEP and CON groups

The ANCOVA (education was controlled) and FDR results are shown in Figure 2 and Table 3. Regarding the duration of all four EEG microstates, the duration of microstate C (DEP: 84.58 ± 24.35; CON: 72.77 ± 10.23; $F = 6.02$, $P = 0.049$) in the DEP group was higher than in the CON group. The duration of microstate D (DEP: 70.0 ± 15.92; CON: 85.46 ± 10.23; $F = 19.18$, $P < 0.001$) in the DEP group was lower than in the CON group. The occurrence and contribution of microstate C (DEP: Occurrence 3.72 ± 0.56, contribution 30.39 ± 8.59; CON: Occurrence 3.41 ± 0.36, contribution 24.46 ± 4.66; Occurrence $F = 6.19$, $P = 0.049$; Contribution $F = 10.82$, $P = 0.011$) in the DEP group was significantly higher than in the CON group. The occurrence and contribution of microstate D (DEP: Occurrence 3.18 ± 0.71, contribution 22.48 ± 8.12; CON: Occurrence 3.54 ± 0.41, contribution 28.25 ± 5.85; Occurrence $F = 5.79$, $P = 0.050$; Contribution $F = 9.41$, $P = 0.013$) in the DEP group was significantly lower than in the CON group.

The result of EEG microstate transition probability (%) showed that the transition probability of class A to C (DEP: 9.17 ± 2.23; CON: 8.01 ± 1.42; $F = 5.94$, $P = 0.049$), class B to C (DEP: 9.18 ± 2.69; CON: 7.45 ± 1.68; $F = 8.58$, $P = 0.017$) and class C to B (DEP: 9.28 ± 2.89; CON: 7.39 ± 1.75; $F = 9.12$, $P = 0.015$) was significantly higher in the DEP group compared to the CON group. The transition probability of class A to D (DEP: 7.00 ± 2.43; CON: 8.93 ± 1.91; $F = 11.01$, $P = 0.011$) and class D to A (DEP: 7.08 ± 2.38; CON: 8.89 ± 1.91; $F = 9.95$, $P = 0.013$) was significantly lower in the DEP group than in the CON group. No statistically significant differences were found in other EEG microstate parameters.

Relationships among the EEG microstate parameters, HAMD score, and RBANS score in DEP group

Correlation analysis showed no significant correlation between the HAMD score and EEG microstate parameters in the DEP group. Considering the findings from EEG microstate analysis conducted on the DEP group, our attention was directed towards examining the relationship between microstate parameters and neurocognitive RBANS score. Pearson correlation analysis revealed a negative correlation between immediate memory scores and the frequency of microstate class A ($r = -0.406$, $P = 0.049$). Additionally, a positive correlation was observed between visuospatial/constructional

Table 1 Demographic and clinical characteristics of depression group and healthy control

Variables	DEP (*n* = 24)	CON (*n* = 32)	$\chi^2/t/W$	*P* value
Gender (female/male)	8/16	15/17	0.555	0.456[1]
Age (yr)	32.4 ± 11.3	33.8 ± 10.5	0.490	0.626[1]
Education (years of schooling)[a]	13.3 ± 2.8	14.8 ± 2.7	2.056	0.045[2]
HAMD score[c]	10 (0-23)	0 (0-6)	83	< 0.001[3]
Duration of illness (mo)	48.0 (24.5-195.0)			
Age at onset (yr)	25.5 (16.8- 27.3)			

[1]Indicates *P*-value for Chi-square test.
[2]Indicates *P*-value for independent sample *t*-test.
[3]Indicates *P*-value for Wilcox Mann–Whitney test.
[a]$P < 0.05$.
[c]$P < 0.001$.
mean ± SD are reported for age, education; Median (interquartile range) are reported duration of illness, age at onset, HAMD score. DEP: Depression group; CON: Healthy control group; HAMD: Hamilton Depression Scale.

Table 2 Neurocognitive RBANS score of depression group and healthy control

Variables	DEP (*n* = 24)	CON (*n* = 32)	*F*	*P* value[1]
RBANS score				
Immediate memory	85.92 ± 21.07	94.78 ± 15.57	3.559	0.145
Visuospatial/constructional	98.50 ± 17.92	94.44 ± 17.60	0.893	0.428
Language	92.92 ± 13.42	99.38 ± 14.23	3.204	0.167
Attention	104.54 ± 11.64	109.3 ± 11.74	2.755	0.196
Delayed memory	90.42 ± 18.13	94.25 ± 11.32	1.05	0.393
Total score	92.79 ± 17.66	97.78 ± 13.56	1.824	0.302

[1]Indicates *P* value for analysis of covariance, education was controlled, and false discovery rate was used to adjust *P* value.
mean ± SD are reported for all variables. DEP: Depression group; CON: Healthy control group.

scores and the transition probability of microstate class C to B ($r = 0.405$, $P = 0.049$). Nevertheless, no significant disparities were found in relation to other microstates. Subsequently, in order to mitigate the likelihood of erroneous positive results, a permutation test employing 100,000 random permutations was employed to ascertain the statistical significance of the two correlations. Notably, the correlation between the visuospatial/constructional score and the microstate transition probability from class C to B remained significant at $P < 0.050$ (Figure 3). Conversely, no significant correlation was observed between the immediate memory scores and the incidence of microstate class A.

DISCUSSION

This study sought to explore the dynamic activity of global brain resting-state networks (RSNs) among patients with depressive disorder and investigate their EEG microstate characteristics. This study showed significant differences in microstate analysis in the DEP group compared with the CON group, and EEG microstates can be characteristic indicators of depression. Especially, we showed that increased occurrence, duration, and contribution of microstate C and decreased occurrence, duration, and contribution of microstate D were depression characteristics. Another finding of our study was that patients with depression had a higher transition probability from C to B, which might be related to their cognitive function and visual processing.

EEG microstates in patients with depression

Our results indicate that the duration, occurrence, and contribution of microstate C increased while the duration, occurrence, and contribution of microstate D decreased. These results were generally consistent with previous studies. In a study exploring EEG microstates in adolescents with depression, the occurrence and contribution of microstate D were reduced compared with in healthy controls[23], which were also found among adults with depression[40]. Enhanced

Table 3 Electroencephalography microstate features of depression group and healthy control

Variables	DEP (*n* = 24)	CON (*n* = 32)	*F*	*P* value[1]
Duration (millisecond)				
Class A	70.01 ± 11.40	73.19 ± 7.35	1.70	0.314
Class B	72.20 ± 12.25	69.28 ± 6.37	1.38	0.36
Class C[a]	84.58 ± 24.35	72.77 ± 10.23	6.02	0.049
Class D[c]	70.00 ± 15.92	85.46 ± 10.23	19.18	< 0.001
Occurrence (Hz)				
Class A	3.30 ± 0.69	3.45 ± 0.41	1.13	0.393
Class B	3.36 ± 0.50	3.24 ± 0.25	1.31	0.363
Class C[a]	3.72 ± 0.56	3.41 ± 0.36	6.19	0.049
Class D[a]	3.18 ± 0.71	3.54 ± 0.41	5.79	0.050
Contribution (%)				
Class A	23.08 ± 7.06	25.25 ± 4.70	1.96	0.292
Class B	24.05 ± 5.68	22.04 ± 3.01	3.09	0.168
Class C[a]	30.39 ± 8.59	24.46 ± 4.66	10.82	0.011
Class D[a]	22.48 ± 8.12	28.25 ± 5.85	9.41	0.013
Transition probability (%)				
Class A to B	6.94 ± 1.82	7.22 ± 1.02	0.50	0.525
Class A to C[a]	9.17 ± 2.23	8.01 ± 1.42	5.94	0.049
Class A to D[a]	7.00 ± 2.43	8.93 ± 1.91	11.01	0.011
Class B to A	7.21 ± 1.88	7.55 ± 0.98	0.73	0.458
Class B to C[a]	9.18 ± 2.69	7.45 ± 1.68	8.58	0.017
Class B to D	7.16 ± 2.88	7.49 ± 1.31	0.34	0.578
Class C to A	8.83 ± 2.05	7.77 ± 1.41	5.40	0.057
Class C to B[a]	9.28 ± 2.89	7.39 ± 1.75	9.12	0.015
Class C to D	8.31 ± 2.31	8.60 ± 1.33	0.34	0.578
Class D to A[a]	7.08 ± 2.38	8.89 ± 1.91	9.95	0.013
Class D to B	7.30 ± 2.84	7.99 ± 1.54	1.38	0.360
Class D to C	8.08 ± 2.40	8.30 ± 1.20	0.21	0.650

[1]Indicates *P* value for analysis of covariance, education was controlled, and false discovery rate was used to adjust *P* value.
[a]$P < 0.05$.
[c]$P < 0.001$.
mean ± SD are reported for all variables. DEP: Depression group; CON: Healthy control group.

microstate D activity was found in the right superior parietal lobules, the right inferior parietal lobules, the right middle and superior frontal gyri[11,41], which was associated with the dorsal attention network. In a study combining fMRI and EEG to capture global brain activity, reduced microstate D associated with decreases in connectivity of the dorsal attention network may manifest as rumination and predict attention deficits among patients with depression[23,42]. Meanwhile, another study showed that duration of microstate C was significantly higher in patients with depression compared with the control group[43], which was also consistent with our results. However, some studies take different views; reduced duration of microstate C was found in students with depression[25]. Other studies found a result that we did not observe, which was the increased occurrence of microstate B[26,27].

There can be a number of possible reasons for these inconsistencies. Firstly, different frequency bands were studied; early experiments examined 8-12 Hz, but recently, most microstate studies were based on larger bandwidths such as 2-20 Hz or 1-40 Hz[32]. Secondly, the methods of analyzing EEG microstates varied, such as different clustering algorithms. Thirdly, the subjects included were different; for example, Liang's study[25] included college students with depressive symptoms and only screened the students with depression according to the Beck Depression Inventory-II (BDI-II) and

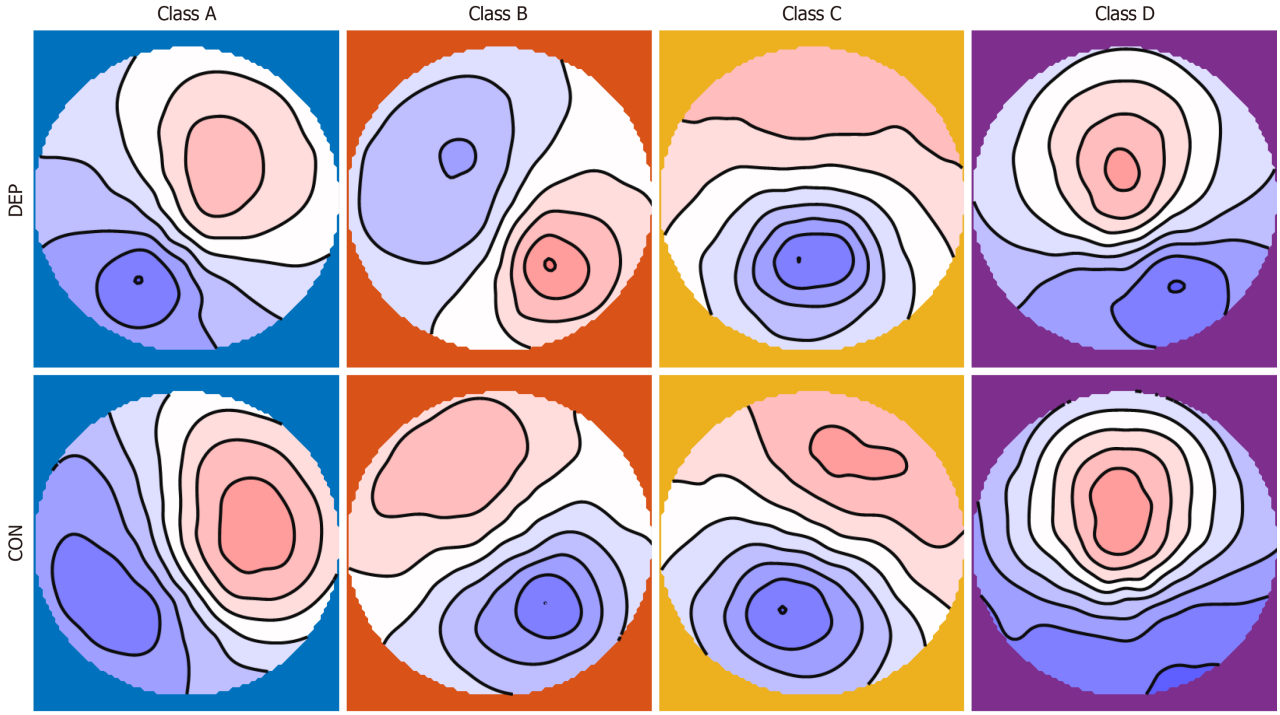

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Figure 1 Illustrates a comparison of scalp topographies between the depression group and healthy control group. According to previous literature, microstates are represented by the classes A to D. DEP: Depression group; CON: Healthy control group.

Depression Self-Rating Scale scores, but it did not fully meet the diagnostic criteria of the DSM-V. However, the decreased duration, occurrence, and contribution of microstate D have been found in most studies examining EEG microstates in patients with depression. We applied the FDR to adjust the *P* value to obtain more reliable results. Thus, possibly, microstate D is a potential biomarker for patients with depressive disorder.

From the transition probability among the EEG microstates, we found that the transition probability of microstates A to C, C to B, and B to C increased, while the transition probability of microstates A to D and D to A decreased. The fast transition probabilities among EEG microstates had a relationship with the quick switching in brain functional networks [44]. Patients with depression had significantly more transition from A to C, which explained the increase in microstate C among patients with depression compared with the controls. Some previous studies reported that microstate C was correlated with memory and rest recovery capabilities, and increased occurrence of microstate C and higher transition probability of A to C was related to the better therapeutic effect in patients with depression[27,42]. These results suggested that microstate C may be a protective factor and that the higher occurrence of microstate C was associated with better prognosis and treatment outcomes in depression. However, our study is a cross-sectional study, and in the future, we will follow up the EEG microstates of patients with depression after treatment to examine whether microstate C is an antidepressive factor.

Relationship between EEG microstates and cognitive function

Using RBANS, we found there were no significant differences in cognitive function among patients with depressive disorders compared to the controls, which is in contrast to the findings of previous studies[45-47]. The large discrepancy may be attributed to the following reasons. First, the subjects included were different in that the patients with depression in our study had lower HAMD scores (10.04 ± 8.06), whereas most of the other studies included patients with major depressive disorder, and thus the differences in cognitive dysfunction were not significant between our DEP and CON groups. Second, the tools of clinical and neuropsychological tests used to detect cognitive function were different. Our experiment used RBANS to detect cognitive functions, whereas other studies assessed them with the Sheehan Disability Scale[45], CogState Research Battery[46], or MATRICS Consensus Cognitive Battery[47], and different scales may produce different results.

From the EEG microstates, a significantly higher transition probability of microstates C to B was observed in patients with depression. Microstate B activity was found in the left and right occipital cortices (cuneus), including Brodmann areas 17 and 18 (primary visual cortex), the right insular cortex extending to the right claustrum, and the right frontal eye field[41], and was associated with visual processing[11]. Microstate C activity was found in the precuneus, posterior cingulate cortex, and left angular gyrus[41], and was associated with cognitive control networks[11]. In addition to this, from the RBANS scores of the DEP and CON groups in Table 2, patients with depression had a higher score of visuospatial/constructional compared with the CON group, which was the only item of the RBANS that scored higher than in the CON group, with all other items showing a downward trend. Furthermore, the increased transition probability of microstates C to B significantly correlated with the visuospatial/constructional of RBANS in Figure 3, so,

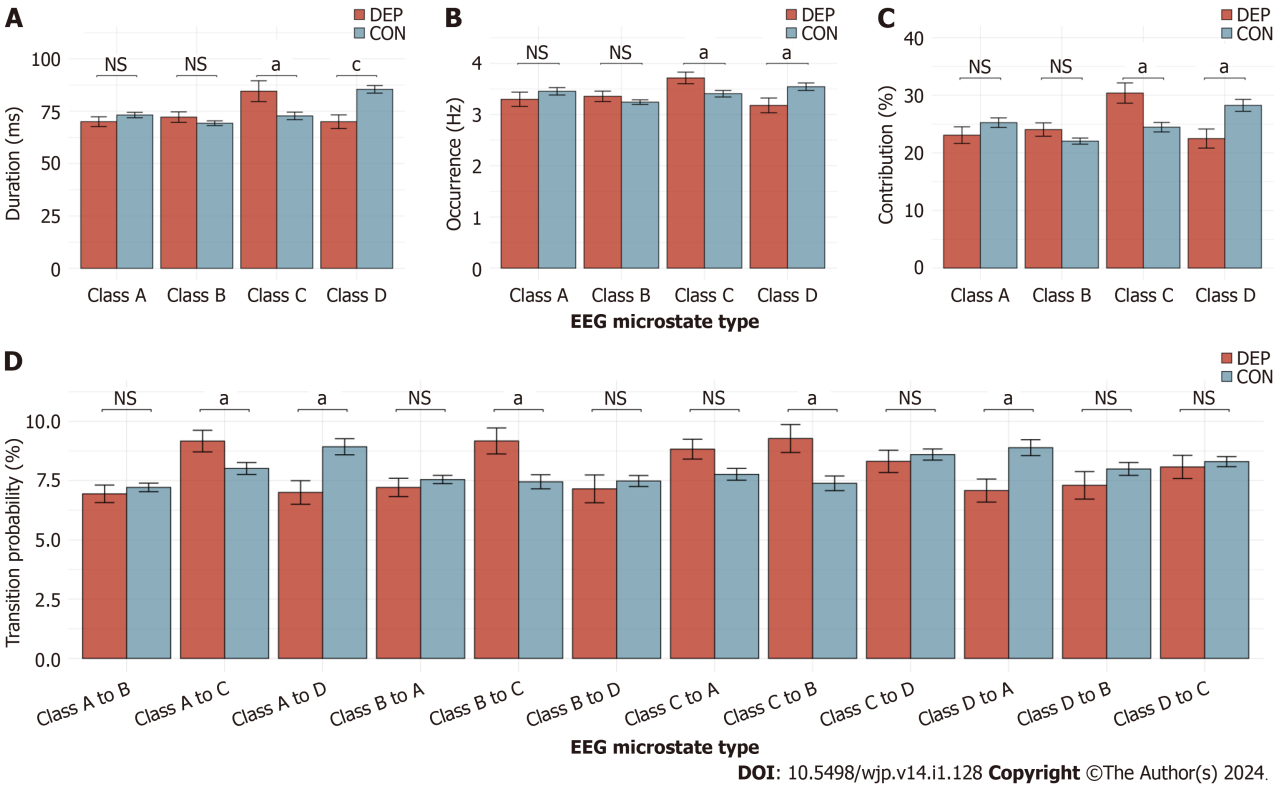

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Figure 2 Bar diagrams show the parameters of each microstate of the two groups. A: Duration; B: Occurrence; C: contribution. Horizontal coordinate axis represents four microstates A, B, C, and D; D: Transition probability; horizontal coordinate axis represents microstate transition type. $^{a}P < 0.05$; $^{c}P < 0.001$. DEP: Depression group; CON: Healthy control group; NS: Not significant.

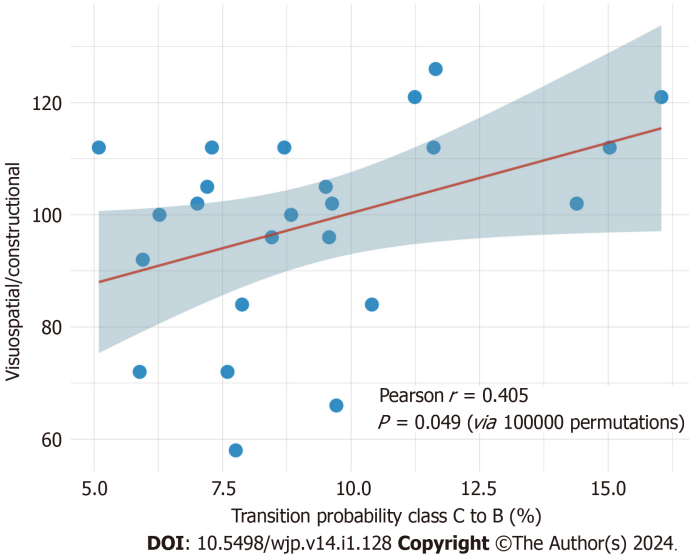

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Figure 3 Correlation between the repeatable battery for the assessment of neuropsychological status visuospatial/constructional function scores and transition probability microstate class C to class B in the depression group. *P* values were generated by permutation tests with 100000 replicates.

we were able to hypothesize that the increased transition probability of microstates C to B in patients with depression was related to more visual processing. Previous studies found that depression was associated with negative rumination [48], such as the constant recollection of replaying negative events in the mind, which involved visual processing[49], cognition[50], and the default mode network (DMN)[51], with visual processing being associated with microstate B and the activated regions of microstate C being part of the DMN. Consequently, the more frequent transition from C to B may imply that patients with depressive disorders had more frequent negative rumination as well as more and longer visual processing.

Correlations between EEG microstates and depressive severity

From the correlation analysis of HAMD and EEG microstates, our study did not identify a strong association between the severity of depression and EEG microstates, which was consistent with previous studies[23,27]. However, many studies have also found a strong relationship between the severity of depressive symptoms and EEG microstates. For example, some studies found that more severe depressive symptoms were positively correlated with microstate B and negatively correlated with microstate D[26,40], while other studies found that more severe depressive symptoms were associated with higher occurrence of microstate A[52]. Differences in results may be due to the following. First, different methodological approaches may have led to different conclusions regarding EEG microstate data in this and previous studies, such as different clustering algorithms applied and different numbers of maps recorded (4-6 types of maps were recorded in EEG microstate). Second, a variety of scales was used to assess the severity of depressive symptoms, including the Montgomery–Åsberg Depression Rating Scale, BDI-II, and HAMD.

CONCLUSION

we examined the temporal dynamics of resting-state EEG microstates in patients with depression and healthy controls. Our study demonstrated that, compared with controls, the occurrence, duration, and contribution of microstate C increased while the occurrence, duration, and contribution of microstate D decreased in patients with depression. Several alterations in EEG microstate transition probabilities were related to the fast switching in brain functional networks, including the increased transition probability of microstates A to C, C to B, and B to C, while the transition probability of microstates A to D and D to A decreased. In addition, we found that patients with depression had a more frequent transition from microstate C to B, which may be related to more negative rumination and visual processing. Therefore, EEG microstate analyzed the possible changes in neurons in the brain of patients with depression from the perspective of sub-second brain dynamics and was a possible biomarker in depression. In future clinical practice, comprehensive clinical examinations from multiple angles and dimensions should be performed to assess and diagnose depression.

This study had some limitations. First, the sample size was small, only 24 people were included in the DEP group and they only had mild or moderate depression. Subsequently, more studies with larger numbers of patients with depression and normal controls should be conducted to assess more accurately the relationship between depressive disorders and EEG microstates. Second, this study was only a cross-sectional study, and no longitudinal follow-up assessment was performed to explore the changes in EEG microstates after treatment. So, we will further perform a longitudinal interventional cohort study on therapy in the DEP group to find any possible associations between EEG microstates and prognosis through regular follow-up. Third, there was no sex difference between the two groups in our study, but other studies have found that there are differences in EEG microstates across age and sex[53]. In the future, we will study a broader age group and investigate possible sex differences in EEG microstates. Finally, future studies could combine EEG data with resting-state fMRI data from patients with depression to study brain neural network changes through both temporal and spatial dimensions in an integrated manner.

ARTICLE HIGHLIGHTS

Research background

Depression is a chronic and debilitating disease that is characterized by depressed mood, diminished interests, and cognitive deficits manifested as low self-esteem, sleep disturbance, weight loss, and even disability. Electroencephalography (EEG), commonly used to study electrophysiological processes in the cerebral cortex, is capable of describing local and global neuronal activity in the brain neural networks. Therefore, there is a need to conduct a more comprehensive study of EEG microstates in patients with depression.

Research motivation

The results were calibrated through statistical methods, attempting to find more realistic and reliable characterizations of EEG microstates. In addition, we also analyzed the correlation between EEG microstate characteristics and cognitive scales, which has rarely been studied before. Third, we correlated EEG microstate parameters with the Hamilton Depression Scale (HAMD) to figure out possible relationships between depression severity and EEG microstates.

Research objectives

This study was to investigate the EEG microstate characteristics of patients with depression and their association with cognitive functions. Our study demonstrated that, EEG microstate, especially C and D, is a possible biomarker in depression. In addition, we found that patients with depression had a more frequent transition from microstate C to B, which may be related to more negative rumination and visual processing. In future clinical practice, healthcare professionals can combine with clinical examination to assess and diagnose depression comprehensively from multiple angles and dimensions.

Research methods

Demographic and clinical characteristics, as well as data from the repeatable battery for the assessment of neuropsycho-

logical status (RBANS; Chinese version) and EEG, were collected from a sample of 24 patients diagnosed with depression (DEP) and 32 healthy controls (CON). Participants were seated comfortably in a reclining chair and instructed to close their eyes and maintain a relaxed and quiet state for a duration of 3 min. Microstate analysis was conducted utilizing the EEGLAB microstate plugin and the atomize and agglomerate hierarchical clustering algorithm was used to compute four optimal microstate topographies.

Research results

Our study found that years of education and HAMD score showed significant differences in the two groups (education: $t = 2.056$, $P = 0.045$; HAMD score: $W = 83$, $P < 0.001$). Compared with the controls, the duration, occurrence, and contribution of microstate C were significantly higher (duration $F = 6.02$, $P = 0.049$; Occurrence $F = 6.19$, $P = 0.049$; contribution $F = 10.82$, $P = 0.011$) while the duration, occurrence, and contribution of microstate D were significantly lower (duration $F = 19.18$, $P < 0.001$; Occurrence $F = 5.79$, $P = 0.050$; Contribution $F = 9.41$, $P = 0.013$) in depressed patients. Additionally, a positive correlation was observed between visuospatial/constructional scores and the transition probability of microstate class C to B ($r = 0.405$, $P = 0.049$).

Research conclusions

We examined the temporal dynamics of resting-state EEG microstates in patients with depression and healthy controls. EEG microstate analyzed the possible changes in neurons in the brain of patients with depression from the perspective of sub-second brain dynamics and was a possible biomarker (especially microstate C and D) in depression. Furthermore, the more frequent transition from microstate C to B, which may be related to more negative rumination and visual processing.

Research perspectives

In the future, more studies with larger numbers of patients with depression and normal controls should be conducted to assess more accurately the relationship between depressive disorders and electroencephalography EEG microstates. Furthermore, we will further perform a longitudinal interventional cohort study on therapy in the DEP group to find any possible associations between EEG microstates and prognosis through regular follow-up. Finally, future studies could combine EEG data with resting-state fMRI data from patients with depression to study brain neural network changes through both temporal and spatial dimensions in an integrated manner.

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FOOTNOTES

Co-first authors: Rui-Jie Peng and Yu Fan.

Co-corresponding authors: Qing Tian and Xiao-Bin Zhang.

Author contributions: Peng RJ and Fan Y were responsible for data collection, data curation, and writing original draft; Li J and Zhu F were involved in supervision and review; Tian Q and Zhang XB as co-corresponding author, participated in conceptualization, funding acquisition, supervision and editing; all authors reviewed the manuscript.

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REFERENCES

1 **Otte C**, Gold SM, Penninx BW, Pariante CM, Etkin A, Fava M, Mohr DC, Schatzberg AF. Major depressive disorder. *Nat Rev Dis Primers* 2016; **2**: 16065 [PMID: 27629598 DOI: 10.1038/nrdp.2016.65]

2 **Burrows K**, Stewart JL, Kuplicki R, Figueroa-Hall L, Spechler PA, Zheng H, Guinjoan SM; Tulsa 1000 Investigators, Savitz JB, Kent Teague T, Paulus MP. Elevated peripheral inflammation is associated with attenuated striatal reward anticipation in major depressive disorder. *Brain Behav Immun* 2021; **93**: 214-225 [PMID: 33508469 DOI: 10.1016/j.bbi.2021.01.016]

3 **Global Burden of Disease Study 2013 Collaborators**. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; **386**: 743-800 [PMID: 26063472 DOI: 10.1016/S0140-6736(15)60692-4]

4 **Kessler RC**, Bromet EJ. The epidemiology of depression across cultures. *Annu Rev Public Health* 2013; **34**: 119-138 [PMID: 23514317 DOI: 10.1146/annurev-publhealth-031912-114409]

5 **Etkin A**, Büchel C, Gross JJ. The neural bases of emotion regulation. *Nat Rev Neurosci* 2015; **16**: 693-700 [PMID: 26481098 DOI: 10.1038/nrn4044]

6 **Ingber L**, Nunez PL. Neocortical dynamics at multiple scales: EEG standing waves, statistical mechanics, and physical analogs. *Math Biosci* 2011; **229**: 160-173 [PMID: 21167841 DOI: 10.1016/j.mbs.2010.12.003]

7 **Arns M**, Etkin A, Hegerl U, Williams LM, DeBattista C, Palmer DM, Fitzgerald PB, Harris A, deBeuss R, Gordon E. Frontal and rostral anterior cingulate (rACC) theta EEG in depression: implications for treatment outcome? *Eur Neuropsychopharmacol* 2015; **25**: 1190-1200 [PMID: 25936227 DOI: 10.1016/j.euroneuro.2015.03.007]

8 **Hunter AM**, Nghiem TX, Cook IA, Krantz DE, Minzenberg MJ, Leuchter AF. Change in Quantitative EEG Theta Cordance as a Potential Predictor of Repetitive Transcranial Magnetic Stimulation Clinical Outcome in Major Depressive Disorder. *Clin EEG Neurosci* 2018; **49**: 306-315 [PMID: 29224411 DOI: 10.1177/1550059417746212]

9 **Lehmann D**, Ozaki H, Pal I. EEG alpha map series: brain micro-states by space-oriented adaptive segmentation. *Electroencephalogr Clin Neurophysiol* 1987; **67**: 271-288 [PMID: 2441961 DOI: 10.1016/0013-4694(87)90025-3]

10 **Lehmann D**, Pascual-Marqui RD, Michel CJS. EEG microstates. 2009; 4: 7632 [DOI: 10.4249/scholarpedia.7632]

11 **Britz J**, Van De Ville D, Michel CM. BOLD correlates of EEG topography reveal rapid resting-state network dynamics. *Neuroimage* 2010; **52**: 1162-1170 [PMID: 20188188 DOI: 10.1016/j.neuroimage.2010.02.052]

12 **Sun Q**, Zhou J, Guo H, Gou N, Lin R, Huang Y, Guo W, Wang X. EEG Microstates and Its Relationship With Clinical Symptoms in Patients With Schizophrenia. *Front Psychiatry* 2021; **12**: 761203 [PMID: 34777062 DOI: 10.3389/fpsyt.2021.761203]

13 **Soni S**, Muthukrishnan SP, Samanchi R, Sood M, Kaur S, Sharma R. Pre-trial and pre-response EEG microstates in schizophrenia: An endophenotypic marker. *Behav Brain Res* 2019; **371**: 111964 [PMID: 31129232 DOI: 10.1016/j.bbr.2019.111964]

14 **Tomescu MI**, Rihs TA, Roinishvili M, Karahanoglu FI, Schneider M, Menghetti S, Van De Ville D, Brand A, Chkonia E, Eliez S, Herzog MH, Michel CM, Cappe C. Schizophrenia patients and 22q11.2 deletion syndrome adolescents at risk express the same deviant patterns of resting state EEG microstates: A candidate endophenotype of schizophrenia. *Schizophr Res Cogn* 2015; **2**: 159-165 [PMID: 29379765 DOI: 10.1016/j.scog.2015.04.005]

15 **Damborská A**, Piguet C, Aubry JM, Dayer AG, Michel CM, Berchio C. Altered Electroencephalographic Resting-State Large-Scale Brain Network Dynamics in Euthymic Bipolar Disorder Patients. *Front Psychiatry* 2019; **10**: 826 [PMID: 31803082 DOI: 10.3389/fpsyt.2019.00826]

16 **Vellante F**, Ferri F, Baroni G, Croce P, Migliorati D, Pettoruso M, De Berardis D, Martinotti G, Zappasodi F, Giannantonio MD. Euthymic bipolar disorder patients and EEG microstates: a neural signature of their abnormal self experience? *J Affect Disord* 2020; **272**: 326-334 [PMID: 32553374 DOI: 10.1016/j.jad.2020.03.175]

17 **Al Zoubi O**, Mayeli A, Tsuchiyagaito A, Misaki M, Zotev V, Refai H, Paulus M, Bodurka J; Tulsa 1000 Investigators. EEG Microstates Temporal Dynamics Differentiate Individuals with Mood and Anxiety Disorders From Healthy Subjects. *Front Hum Neurosci* 2019; **13**: 56 [PMID: 30863294 DOI: 10.3389/fnhum.2019.00056]

18 **Wiedemann G**, Stevens A, Pauli P, Dengler W. Decreased duration and altered topography of electroencephalographic microstates in patients with panic disorder. *Psychiatry Res* 1998; **84**: 37-48 [PMID: 9870416 DOI: 10.1016/s0925-4927(98)00044-4]

19 **Wei Y**, Ramautar JR, Colombo MA, Te Lindert BHW, Van Someren EJW. EEG Microstates Indicate Heightened Somatic Awareness in Insomnia: Toward Objective Assessment of Subjective Mental Content. *Front Psychiatry* 2018; **9**: 395 [PMID: 30237769 DOI: 10.3389/fpsyt.2018.00395]

20 **da Cruz JR**, Favrod O, Roinishvili M, Chkonia E, Brand A, Mohr C, Figueiredo P, Herzog MH. EEG microstates are a candidate endophenotype for schizophrenia. *Nat Commun* 2020; **11**: 3089 [PMID: 32555168 DOI: 10.1038/s41467-020-16914-1]

21 **Pan Z**, Xiong D, Xiao H, Li J, Huang Y, Zhou J, Chen J, Li X, Ning Y, Wu F, Wu K. The Effects of Repetitive Transcranial Magnetic Stimulation in Patients with Chronic Schizophrenia: Insights from EEG Microstates. *Psychiatry Res* 2021; **299**: 113866 [PMID: 33735740 DOI: 10.1016/j.psychres.2021.113866]

22 **Keihani A**, Sajadi SS, Hasani M, Ferrarelli F. Bayesian Optimization of Machine Learning Classification of Resting-State EEG Microstates in Schizophrenia: A Proof-of-Concept Preliminary Study Based on Secondary Analysis. *Brain Sci* 2022; **12** [PMID: 36358423 DOI: 10.3390/brainsci12111497]

23 **He Y**, Yu Q, Yang T, Zhang Y, Zhang K, Jin X, Wu S, Gao X, Huang C, Cui X, Luo X. Abnormalities in Electroencephalographic Microstates Among Adolescents With First Episode Major Depressive Disorder. *Front Psychiatry* 2021; **12**: 775156 [PMID: 34975577 DOI: 10.3389/fpsyt.2021.775156]

24 **Yan D**, Liu J, Liao M, Liu B, Wu S, Li X, Li H, Ou W, Zhang L, Li Z, Zhang Y, Li L. Prediction of Clinical Outcomes With EEG Microstate in Patients With Major Depressive Disorder. *Front Psychiatry* 2021; **12**: 695272 [PMID: 34483990 DOI: 10.3389/fpsyt.2021.695272]

25 **Liang A,** Zhao S, Song J, Zhang Y, Zhang Y, Niu X, Xiao T, Chi A. Treatment Effect of Exercise Intervention for Female College Students with Depression: Analysis of Electroencephalogram Microstates and Power Spectrum. *Sustainability* 2021; **13**: 6822 [DOI: 10.3390/su13126822]

26 **Qin X**, Xiong J, Cui R, Zou G, Long C, Lei X. EEG microstate temporal Dynamics Predict depressive symptoms in College Students. *Brain Topogr* 2022; **35**: 481-494 [PMID: 35790705 DOI: 10.1007/s10548-022-00905-0]

27 **Lei L**, Liu Z, Zhang Y, Guo M, Liu P, Hu X, Yang C, Zhang A, Sun N, Wang Y, Zhang K. EEG microstates as markers of major depressive disorder and predictors of response to SSRIs therapy. *Prog Neuropsychopharmacol Biol Psychiatry* 2022; **116**: 110514 [PMID: 35085607 DOI: 10.1016/j.pnpbp.2022.110514]

28 **Gold MC**, Yuan S, Tirrell E, Kronenberg EF, Kang JWD, Hindley L, Sherif M, Brown JC, Carpenter LL. Large-scale EEG neural network changes in response to therapeutic TMS. *Brain Stimul* 2022; **15**: 316-325 [PMID: 35051642 DOI: 10.1016/j.brs.2022.01.007]

29 **Knight MJ**, Baune BT. Cognitive dysfunction in major depressive disorder. *Curr Opin Psychiatry* 2018; **31**: 26-31 [PMID: 29076892 DOI: 10.1097/YCO.0000000000000378]

30 **Mattingly G**, Anderson RH, Mattingly SG, Anderson EQ. The impact of cognitive challenges in major depression: the role of the primary care physician. *Postgrad Med* 2016; **128**: 665-671 [PMID: 27500820 DOI: 10.1080/00325481.2016.1221318]

31 **Britz J**, Díaz Hernàndez L, Ro T, Michel CM. EEG-microstate dependent emergence of perceptual awareness. *Front Behav Neurosci* 2014; **8**: 163 [PMID: 24860450 DOI: 10.3389/fnbeh.2014.00163]

32 **Khanna A**, Pascual-Leone A, Michel CM, Farzan F. Microstates in resting-state EEG: current status and future directions. *Neurosci Biobehav Rev* 2015; **49**: 105-113 [PMID: 25526823 DOI: 10.1016/j.neubiorev.2014.12.010]

33 **Wang J**, Li C, Cheng Y, Yi Z, Long B, Wang JJ. Reliability and validity of repeatable battery for the assessment of neuropsychological status (RBANS) in schizophrenic patients: a preliminary study. *Shanghai Jingshen Yixue* 2009; **21**: 265-268

34 **Delorme A**, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods* 2004; **134**: 9-21 [PMID: 15102499 DOI: 10.1016/j.jneumeth.2003.10.009]

35 **Monachino AD**, Lopez KL, Pierce LJ, Gabard-Durnam LJ. The HAPPE plus Event-Related (HAPPE+ER) software: A standardized preprocessing pipeline for event-related potential analyses. *Dev Cogn Neurosci* 2022; **57**: 101140 [PMID: 35926469 DOI: 10.1016/j.dcn.2022.101140]

36 **Nagabhushan Kalburgi S**, Kleinert T, Aryan D, Nash K, Schiller B, Koenig T. Microstatelab: The EEGLAB Toolbox for Resting-State Microstate Analysis. *Brain Topogr* 2023 [DOI: 10.1007/s10548-023-01003-5]

37 **Murray MM**, Brunet D, Michel CM. Topographic ERP analyses: a step-by-step tutorial review. *Brain Topogr* 2008; **20**: 249-264 [PMID: 18347966 DOI: 10.1007/s10548-008-0054-5]

38 **Koenig T**, Prichep L, Lehmann D, Sosa PV, Braeker E, Kleinlogel H, Isenhart R, John ER. Millisecond by millisecond, year by year: normative EEG microstates and developmental stages. *Neuroimage* 2002; **16**: 41-48 [PMID: 11969316 DOI: 10.1006/nimg.2002.1070]

39 **Benjamini Y**, Hochberg Y. Controlling the False Discovery Rate - a Practical and Powerful Approach to Multiple Testing. *J R Stat Soc* **57**: 289-300 [DOI: 10.1111/j.2517-6161.1995.tb02031.x]

40 **Murphy M**, Whitton AE, Deccy S, Ironside ML, Rutherford A, Beltzer M, Sacchet M, Pizzagalli DA. Abnormalities in electroencephalographic microstates are state and trait markers of major depressive disorder. *Neuropsychopharmacology* 2020; **45**: 2030-2037 [PMID: 32590838 DOI: 10.1038/s41386-020-0749-1]

41 **Custo A**, Van De Ville D, Wells WM, Tomescu MI, Brunet D, Michel CM. Electroencephalographic Resting-State Networks: Source Localization of Microstates. *Brain Connect* 2017; **7**: 671-682 [PMID: 28938855 DOI: 10.1089/brain.2016.0476]

42 **Bréchet L**, Brunet D, Birot G, Gruetter R, Michel CM, Jorge J. Capturing the spatiotemporal dynamics of self-generated, task-initiated thoughts with EEG and fMRI. *Neuroimage* 2019; **194**: 82-92 [PMID: 30902640 DOI: 10.1016/j.neuroimage.2019.03.029]

43 **Zhao YN**, He JK, Wang Y, Li SY, Jia BH, Zhang S, Guo CL, Zhang JL, Zhang GL, Hu B, Fang JL, Rong PJ. The pro-inflammatory factors contribute to the EEG microstate abnormalities in patients with major depressive disorder. *Brain Behav Immun Health* 2022; **26**: 100523 [PMID: 36267834 DOI: 10.1016/j.bbih.2022.100523]

44 **Michel CM**, Koenig T. EEG microstates as a tool for studying the temporal dynamics of whole-brain neuronal networks: A review. *Neuroimage* 2018; **180**: 577-593 [PMID: 29196270 DOI: 10.1016/j.neuroimage.2017.11.062]

45 **Papalexi E**, Galanopoulos A, Roukas D, Argyropoulos I, Michopoulos I, Douzenis A, Gkolia I, Fotiadis P, Kontis D, Zervas IM. Residual cognitive and psychosocial functional impairment in outpatients in Greece who responded to conventional antidepressant monotherapy treatments for major depressive disorder (MDD). *J Affect Disord* 2022; **314**: 185-192 [PMID: 35817305 DOI: 10.1016/j.jad.2022.07.009]

46 **Zazula R**, Mohebbi M, Dodd S, Dean OM, Berk M, Vargas HO, Nunes SOV. Cognitive Profile and Relationship with Quality of Life and Psychosocial Functioning in Mood Disorders. *Arch Clin Neuropsychol* 2022; **37**: 376-389 [PMID: 34259318 DOI: 10.1093/arclin/acab054]

47 **Zhang X**, Zhang R, Lv L, Qi X, Shi J, Xie S. Correlation between cognitive deficits and dorsolateral prefrontal cortex functional connectivity in first-episode depression. *J Affect Disord* 2022; **312**: 152-158 [PMID: 35752217 DOI: 10.1016/j.jad.2022.06.024]

48 **Disner SG**, Beevers CG, Haigh EA, Beck AT. Neural mechanisms of the cognitive model of depression. *Nat Rev Neurosci* 2011; **12**: 467-477 [PMID: 21731066 DOI: 10.1038/nrn3027]

49 **Michl LC**, McLaughlin KA, Shepherd K, Nolen-Hoeksema S. Rumination as a mechanism linking stressful life events to symptoms of depression and anxiety: longitudinal evidence in early adolescents and adults. *J Abnorm Psychol* 2013; **122**: 339-352 [PMID: 23713497 DOI: 10.1037/a0031994]

50 **Petrošanec M**, Brekalo M, Nakić Radoš S. The metacognitive model of rumination and depression in postpartum women. *Psychol Psychother* 2022; **95**: 838-852 [PMID: 35638223 DOI: 10.1111/papt.12405]

51 **Zhou HX**, Chen X, Shen YQ, Li L, Chen NX, Zhu ZC, Castellanos FX, Yan CG. Rumination and the default mode network: Meta-analysis of brain imaging studies and implications for depression. *Neuroimage* 2020; **206**: 116287 [PMID: 31655111 DOI: 10.1016/j.neuroimage.2019.116287]

52 **Damborská A**, Tomescu MI, Honzírková E, Barteček R, Hořínková J, Fedorová S, Ondruš Š, Michel CM. EEG Resting-State Large-Scale Brain Network Dynamics Are Related to Depressive Symptoms. *Front Psychiatry* 2019; **10**: 548 [PMID: 31474881 DOI:

10.3389/fpsyt.2019.00548]

53 **Tomescu MI**, Rihs TA, Rochas V, Hardmeier M, Britz J, Allali G, Fuhr P, Eliez S, Michel CM. From swing to cane: Sex differences of EEG resting-state temporal patterns during maturation and aging. *Dev Cogn Neurosci* 2018; **31**: 58-66 [PMID: 29742488 DOI: 10.1016/j.dcn.2018.04.011]

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Analysis of influencing factors of anxiety and depression in patients with periodontitis

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Abstract

BACKGROUND

Periodontitis is a chronic oral disease caused by pathogenic microorganisms that corrode tooth tissue, form periodontal pockets, absorb alveolar bone, and finally lead to tooth loss. During treatment, patients are prone to anxiety, tension, and other negative emotions, which affect their ability to face the disease and may also lead to aggravation of the original condition and affect oral health. Therefore, it is important to improve the negative psychology of patients with periodontitis to clarify the factors that may lead to negative psychological emotions.

AIM

To investigate the risk factors that may lead to anxiety and depression in patients with periodontitis.

METHODS

One hundred patients with periodontitis were selected between March 2022 and March 2023 at our hospital. All patients were assessed with the Zung Self-rating Depression Scale (SDS) (≥ 53 points indicate a depressive state) and Zung Self-rating Anxiety Scale (SAS) (≥ 50 points indicates an anxious state). In this study, patients who experienced anxiety or depression were included in the occurrence group and those without anxiety or depression were included in the non-occurrence group. The baseline data of the two groups were compared to explore the risk factors for anxiety and depression in patients with periodontitis.

RESULTS

A total of 100 patients with periodontitis were included in this study. According to the SDS, 38 patients (38.00%) developed depression, with an average SDS score of (68.52 ± 5.85) points. According to the SAS, 40 patients (40.00%) developed anxiety, and the average SAS score was (72.15 ± 4.15) points. In this study, 56 patients with anxiety or depression were included. Compared with the non-occurrence group, the occurrence group had higher ages (≥ 60 years), lower level

of hope (low level), educational level (high school or below), disease perception (poor), and sleep disorder (yes). The negative coping dimension scores of the simplified coping style questionnaire (SCSQ) and Dental Fear Scale (DFS) in the occurrence group were higher, whereas the score of the positive coping dimension of the SCSQ was significantly lower ($P < 0.05$). There were no significant differences in the other data between the groups ($P > 0.05$). The results of multiple logistics regression analysis showed that age (≥ 60 years), level of hope (low level), educational level (high school or below), disease perception (poor), sleep disorder (yes), high negative coping dimension scores of SCSQ, high score of DFS, and low positive coping dimension scores of SCSQ were all factors contributing to the anxiety and depression in patients with periodontitis (odds ratio > 1, $P < 0.05$).

CONCLUSION

Age, hope level, educational level, disease perception, sleep disorders, coping style, and dental fear were all associated with anxiety and depression in patients with periodontitis.

Key Words: Periodontitis; Anxiety; Depression; Mental state; Influencing factor

Core Tip: Patients with periodontitis experience a vicious cycle of depression and anxiety due to repeated diseases and a long treatment cycle, which leads to aggravation of the original condition and affects oral health. Therefore, it is important to identify the key factors that may affect anxiety and depression in patients with periodontitis to improve their prognosis.

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INTRODUCTION

Periodontitis is a chronic oral disease caused by the corrosion of dental tissues by pathogenic microorganisms that form periodontal pockets and are absorbed by the alveolar bone, eventually leading to tooth loss. Epidemiological studies have shown that the incidence of periodontitis is increasing and that the elderly account for a relatively high proportion of the population with periodontitis[1,2]. Anxiety and depression are adverse emotions such as tension and fear that occur in patients with periodontitis during treatment and are prevalent in patients of all ages, mainly manifested as fear and avoidance of dental treatment. The unpleasant emotional experience directly affects patients' ability to face diseases. In addition, adverse emotions can aggravate the stress reactions of patients, leading to the aggravation of their original condition and affecting their oral health. Increasingly aggravating oral diseases cause patients to fall into a vicious cycle of depression, anxiety, and avoidance. Therefore, it is important to clarify the current state of depression and anxiety in patients with periodontitis and the factors that may lead to adverse psychological emotions in patients[3-5]. To date, many clinical studies have mainly focused on the treatment of patients with periodontitis and anxiety and depression, whereas related studies on factors that may lead to anxiety and depression in patients with periodontitis are rare. In view of this, this study focused on observing the status of anxiety and depression in patients with periodontitis and analyzing the risk factors that may lead to anxiety and depression in these patients, in order to improve their negative psychology and overall health.

MATERIALS AND METHODS

General data

The subjects were selected from 100 patients with periodontitis who were admitted to our hospital between March 2022 and March 2023. All subjects met the following inclusion criteria: (1) Periodontitis was diagnosed by referring to the relevant diagnosis in the 2018 World New Classification of Periodontal and Peri-Implant Diseases and Conditions[6]; (2) Initial illness; and (3) The enrolled subjects and their families knew the purpose of the study and signed the consent form. Exclusion criteria were: (1) Comorbid with other diseases, such as immune system diseases and diabetes mellitus; (2) Comorbid with other oral diseases; (3) History of previous psychological illnesses, such as anxiety and depression; and (4) Poor compliance and trouble cooperating with the researchers. This study was performed after the approval of the medical ethics committee of our hospital.

Assessment criteria for anxiety and depression

The patients included in the study were assessed using the Zung Self-Rating Depression Scale (SDS)[7] and the Zung Self-rating Anxiety Scale (SAS)[8]. There are 20 items in the SDS, and each item was assigned a score of 1-4; a score of ≥ 53 indicated that the patient had depression. There are 20 items in the SAS, and each item was assigned a score of 1-4; a score of ≥ 50 indicated that the patient had anxiety. Patients who developed anxiety or depression were included in the occurrence group.

Baseline data collection

The baseline data of patients were collected, including sex, age and disease perception (evaluation by Brief Illness Perception Questionnaire[9]: The questionnaire included 8 items, with a scores of 0-10 for each item, and a total score of 80 points; 0-48 points indicated poor disease perception and 49-80 points indicated good disease perception), sleep disorder (Pittsburgh Sleep Quality Index[10]: 18 items including sleep latency, sleep time, sleep disorder, sleep quality, *etc.*, were scored according to 0-3 points, with a total score of 21 points; ≥ 7 points indicated sleep disorder and a higher score indicated more severe sleep disorder), the level of hope (Herth Hope Scale[11]; the scale included 12 items in three dimensions: taking active action, maintaining close relationship with others, and current and future positive attitude; each item was assigned according to a 1-4 score system, with a total score of 12-48 points; 12-23 points indicated low level, 24-35 points medium level, and ≥ 36 points high level), coping styles [simplified coping style questionnaire (SCSQ)[12], which included 20 items of positive response (1-12 items) and negative response (13-20 items), according to the 0-3 score system; the higher the score of negative coping dimension, the more negative the surface coping style, and the higher the score of positive coping dimension, the more positive the surface coping style], and dental fear [Dental Fear Scale (DFS) [13]; the 20 items in the scale were all scored according to the 5-grade method with full scores of 20-100 points; a higher score indicated that dental fear was more serious].

Statistical methods

SPSS25.0 software was used to analyze the data. Shapiro-Wilk normal distribution was used to test the normality of measurement data, and mean ± SD meant the measurement data conformed to the normal distribution. An independent sample t test was used for intergroup comparisons. n (%) represented the count data, and χ^2 test was used. Logistic regression analysis was used to test factors influencing anxiety and depression in patients with periodontitis. The significance level was set at $\alpha = 0.05$.

RESULTS

Analysis of depression and anxiety status in patients with periodontitis

Among the 100 patients with periodontitis included in the study, 38 cases (38.00%) developed depression according to the SDS; the average SDS score was (68.52 ± 5.85) points. According to the SAS, there were 40 patients with anxiety, the incidence rate was 40.00%, and the average SAS score was (72.15 ± 4.15) points. A total of 56 patients with anxiety or depression were included in the study.

Comparison of baseline data

Compared with the non-occurrence group, the age (≥ 60 years), hope level (low), education level (high school or below), disease perception (poor), and sleep disorder (yes) were higher in the occurrence group. The negative coping dimension score of the SCSQ and DFS score in the occurrence group were higher, the positive coping dimension score of the SCSQ was lower, and the difference was statistically significant ($P < 0.05$). There were no significant differences in the other data between the groups ($P > 0.05$) (Table 1).

Logistic regression analysis of anxiety and depression in patients with periodontitis

Whether patients with periodontitis had anxiety or depression was the dependent variable (1 = yes, 0 = no). The results of multiple logistics regression analysis showed that: age (≥ 60 years old), level of hope (low level), educational level (high school or below), disease perception (poor), sleep disorder (yes), high negative coping dimension scores of SCSQ, high score of DFS, and low positive coping dimension scores of SCSQ were all factors contributing to anxiety and depression in patients with periodontitis (odds ratio > 1, $P < 0.05$) (Tables 2 and 3).

DISCUSSION

Oral cavity-related diseases not only affect the function of oral organs, but also affect the whole-body health of patients and their psychological development. With the development of the "biological-psychological-social medicine" model in clinical medicine, clinical treatment is increasingly not only for the diagnosis and treatment of the disease itself, but also for holistic medical treatment[14-16].

The results of this study showed that among the 100 included patients with periodontitis, 38 (38.00%) developed depression according to the SDS score, and the average SDS score was (68.52 ± 5.85) points. According to the SAS, there were 40 patients with anxiety, and the incidence rate was 40.00%; the average score of the SAS was (72.15 ± 4.15) points,

Table 1 Comparison of baseline information

Factor		Occurrence group (*n* = 56)	Non-occurrence group (*n* = 44)	Statistical values	*P* value
Age, *n* (%)	≥ 60	38 (67.86)	12 (27.27)	16.234	< 0.001
	< 60	18 (32.14)	32 (72.73)		
Sex, *n* (%)	Male	28 (50.00)	25 (56.82)	0.460	0.500
	Female	28 (50.00)	19 (43.18)		
Hope level n, *n* (%)	Low level	40 (71.43)	12 (27.27)	19.247	< 0.001
	Medium and high level	16 (28.57)	32 (72.73)		
Educational level, *n* (%)	High school and below	45 (80.36)	15 (34.09)	21.977	< 0.001
	College and above	11 (19.64)	29 (65.91)		
Disease perception, *n* (%)	Be poor	40 (71.43)	10 (22.73)	23.377	< 0.001
	Good	16 (28.56)	34 (77.27)		
Sleep disorders, *n* (%)	Be	35 (62.50)	11 (25.00)	13.949	< 0.001
	No	21 (37.50)	33 (75.00)		
coping style (mean ± SD, points)	SCSQ negative coping dimension score	17.25 ± 1.52	8.25 ± 0.85	35.169	< 0.001
	SCSQ positive coping dimension score	15.12 ± 1.58	25.12 ± 2.05	27.556	< 0.001
Dental fear (DFS scale) (mean ± SD, points)		60.25 ± 5.25	30.12 ± 4.15	31.168	< 0.001

SCSQ: Simplified coping style questionnaire; DFS: Dental Fear Scale.

Table 2 Description of main independent variables

Independent variable	Variable declaration	Assignment condition
Age	Binary variable	0 ≤ 60 yr, 1 ≥ 60 yr
Hope level	Binary variable	0 = medium high level, 1 = low level
Education level	Binary variable	0 = high school and below, 1 = college and above
Disease perception	Binary variable	0 = poor, 1 = good
Sleep disorder	Binary variable	0 = yes, 1 = no
SCSQ negative coping dimension score	Continuous variable	-
SCSQ positive coping dimension score	Continuous variable	-
Dental fears	Continuous variable	-

SCSQ: Simplified coping style questionnaire.

indicating that anxiety and depression were common in patients with periodontitis. The related mechanisms of clinical anxiety and depressive negative emotions affecting periodontitis are relatively complex and mainly manifest in two aspects. The first is pituitary-adrenal axis dysfunction, neuroendocrine changes, and increased secretion of glucocorticoids in patients with periodontitis combined with anxiety and depression, as well as the inhibition of the immune response of the body and increased susceptibility of the body to pathogenic bacteria of periodontitis. Second, the life attitudes of patients with periodontitis and anxiety and depression are mainly pessimistic. Gingival swelling, bleeding, and even loss in patients with periodontitis are likely to increase their negative emotions, thus forming a vicious circle that is a negative factor for both negative emotions and disease control[17-19]. Therefore, it is necessary to explore factors that may lead to anxiety and depression in patients with periodontitis.

The results of this study showed that compared with the non-occurrence group, the occurrence group had relatively high ages (≥ 60 years old), hope level (low level), education level (high school or below), disease perception (poor), and sleep disorder (yes). The negative coping dimension score of the SCSQ and DFS score in the occurrence group were higher, while the score of positive coping dimension of the SCSQ was lower. The results of multiple logistics regression

Table 3 Logistic regression analysis of anxiety and depression in patients with periodontitis

Correlative factor	*β*	Standard error	*Wald*	*P* value	OR	95% confidence interval
Age	1.728	0.443	15.200	< 0.001	5.630	2.362-13.420
Hope level	1.897	0.450	17.810	< 0.001	6.667	2.762-16.090
Education level	2.062	0.463	19.958	< 0.001	7.909	3.192-19.595
Disease perception	2.140	0.466	21.114	< 0.001	8.500	3.412-21.177
Sleep disorder	1.609	0.444	13.122	< 0.001	5.000	2.093-11.944
SCSQ negative coping dimension score	0.886	0.179	24.424	< 0.001	2.427	1.707-3.449
SCSQ positive coping dimension score	0.956	0.222	18.489	< 0.001	2.601	1.683-4.022
Dental fears	0.267	0.054	24.152	< 0.001	1.306	1.174-1.452

OR: Odds ratio; SCSQ: Simplified coping style questionnaire.

analysis showed the influencing factors leading to anxiety and depression in patients with periodontitis were as follows: (1) Age: Elderly patients with periodontitis have a relatively low quality of life, and such patients bear a heavy burden of worry about the prognosis of the disease, that they will impose a burden on their children and loved ones and affect the quality of life of themselves and their families. Consequently, patients experience severe negative emotions related to anxiety and depression[20]; (2) Hope level: The lower the hope level, the more negative and pessimistic patients would be when facing the stressors, unable to face the disease squarely, unwilling or rejecting cooperative treatment, lacking confidence in disease recovery, feeling helpless when facing the disease, and trapped in negative emotions such as anxiety and depression for a long time, which are not conducive to disease diagnosis and treatment[21]; (3) Education level: For patients with low education level, the knowledge level is relatively low, the learning ability is not high, and the understanding of the disease cognition is not thorough. In addition, the erroneous understanding of the disease leads to the occurrence or even aggravation of anxiety and depression in patients[22]; (4) Disease perception: Patients with poor disease perception have no correct cognition of the occurrence, development, and prognosis of the disease and have incomplete disease understanding, which leads to patients not fully comprehending disease diagnosis and treatment and unable to make a reasonable judgment on the prognosis. Patients had a stronger sense of abnormal experiences of the disease and were excessively concerned about its negative effects. Consequently, anxiety and depression are more prominent in these patients[23]; (5) Sleep disorder: In patients with sleep disorder, the body immunity will decrease, the inflammatory pathways will be activated, and the inflammatory reaction will be aggravated. The increasingly aggravated inflammatory reaction leads to the aggravation of the psychological burden on patients and causes them to worry more about the treatment effect and development of the disease after treatment. In addition, negative emotions, such as anxiety and depression, act on the body and affect sleep quality, thus forming a negative cycle that is not conducive to the recovery of the patient's condition[24]; (6) Coping styles: There were two kinds of coping styles: negative and positive. A positive coping style can weaken the psychological burden and promote disease recovery, whereas a negative coping style strengthens the psychological burden and delays disease recovery. The reason that patients with periodontitis mostly adopted a negative coping style was related to persistent toothache and bad breath, which led to an inferiority complex. Second, fear of operating instruments during oral treatment, high treatment costs, and uncomfortable treatment experiences were also related. Moreover, anxiety and depression resulting from negative coping styles gradually increase and persist over time[25]; and (7) Dental fear: The treatment cycle of periodontitis is long, and during the treatment process, patients experience severe discomfort. Therefore, patients with periodontitis generally experience dental fear, which leads to poor compliance in patients receiving the diagnosis and treatment. Whether patients still have phenomena such as delayed treatment and a prolonged treatment cycle, which will cause unsatisfactory diagnosis and treatment effects, is more likely to aggravate patients' rejection psychology, and negative emotions of anxiety and depression are generated and gradually strengthened[26].

However, due to the limited number of samples included and the retrospective nature of this study, there are limitations with regard to the inclusion of relevant indicators, and the credibility of the study needs to be verified by expanding the sample size in the future.

CONCLUSION

In summary, age, hope level, education level, disease perception, sleep disorders, coping style, and dental fear were all associated with anxiety and depression in patients with periodontitis.

ARTICLE HIGHLIGHTS

Research background

Periodontitis is a chronic oral disease caused by pathogenic microorganisms that corrode tooth tissue, form periodontal pockets, absorb alveolar bone, and finally lead to tooth loss. During treatment, patients are prone to anxiety, tension, and other negative emotions, which affect their ability to face the disease and may also lead to aggravation of the original condition and affect oral health. Therefore, it is important to improve the negative psychology of patients with periodontitis to clarify the factors that may lead to negative psychological emotions.

Research motivation

To observe the status of anxiety and depression in patients with periodontitis and analyze the risk factors that may lead to anxiety and depression to improve the negative psychology of patients with periodontitis and the overall benefit level of patients.

Research objectives

Improve the negative psychology of patients with periodontitis and the overall benefit level for patients.

Research methods

Logistic regression analysis was used to analyze the data in this article.

Research results

The results of multiple logistics regression analysis showed that age (≥ 60 years), level of hope (low level), educational level (high school or below), disease perception (poor), sleep disorder (yes), high negative coping dimension scores of simplified coping style questionnaire (SCSQ), high score of Dental Fear Scale, and low positive coping dimension scores of SCSQ were all factors contributing to the anxiety and depression in patients with periodontitis.

Research conclusions

Age, hope level, educational level, disease perception, sleep disorders, coping style, and dental fear were all associated with anxiety and depression in patients with periodontitis.

Research perspectives

This study shows that age, hope level, education level, disease perception, sleep disorders, coping style, and dental fear can all lead to anxiety and depression in patients with periodontitis, and clinical treatment should consider formulating reasonable countermeasures against these factors.

FOOTNOTES

Author contributions: Kong Y designed the research study; Kong Y performed the research; Kong Y contributed new reagents and analytic tools; Kong Y analyzed the data and wrote the manuscript; all authors have read and approve the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Xinxiang Central Hospital, The Fourth Clinical College of Xinxiang Medical University Institutional Review Board.

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.

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REFERENCES

1 **Nana Nana AR**, Tsobgny Tsague NF, Lontchi-Yimagou E, Bengondo Messanga C, Tankeu A, Katte JC, Balti Vounsia E, Dehayem M, Sobngwi E. Effects of non-surgical treatment of chronic periodontitis on insulin resistance and glucose tolerance in subjects without diabetes (PARODIA 2 study). *J Investig Med* 2021; **69**: 1377-1381 [PMID: 34261767 DOI: 10.1136/jim-2021-001831]
2 **Li W**, Zhang Z, Li Y, Wang Z. Abnormal hsa_circ_0003948 expression affects chronic periodontitis development by regulating miR-144-3p/NR2F2/PTEN signaling. *J Periodontal Res* 2022; **57**: 316-323 [PMID: 34910830 DOI: 10.1111/jre.12961]
3 **Martínez M**, Postolache TT, García-Bueno B, Leza JC, Figuero E, Lowry CA, Malan-Müller S. The Role of the Oral Microbiota Related to Periodontal Diseases in Anxiety, Mood and Trauma- and Stress-Related Disorders. *Front Psychiatry* 2021; **12**: 814177 [PMID: 35153869 DOI: 10.3389/fpsyt.2021.814177]
4 **Aragão WAB**, Souza-Monteiro D, Frazão DR, Né YGS, Ferreira RO, Rivera LFS, Saito MT, Rösing CK, Fagundes NCF, Maia LC, Lima RR. Is There Any Association Between Chronic Periodontitis and Anxiety in Adults? A Systematic Review. *Front Psychiatry* 2021; **12**: 710606 [PMID: 34413802 DOI: 10.3389/fpsyt.2021.710606]
5 **Cataldo D**, Mourão LC, Gonçalves LS, Canabarro A. Association of anxiety, age and oral health-related quality of life with periodontitis: A case-control study. *Int J Dent Hyg* 2023 [PMID: 37122131 DOI: 10.1111/idh.12687]
6 **Meng HX**. 2018 world new classification of periodontal and peri-implant diseases and conditions. *Zhonghua Kou Qiang Yi Xue Za Zhi* 2019; **54**: 73-78 [PMID: 30695907 DOI: 10.3760/cma.j.issn.1002-0098.2019.02.001]
7 **Campbell MH**, Maynard D, Roberti JW, Emmanuel MK. A comparison of the psychometric strengths of the public-domain Zung Self-rating Depression Scale with the proprietary Beck Depression Inventory-II in Barbados. *West Indian Med J* 2012; **61**: 483-488 [PMID: 23441369 DOI: 10.7727/wimj.2010.145]
8 **Samakouri M**, Bouhos G, Kadoglou M, Giantzelidou A, Tsolaki K, Livaditis M. [Standardization of the Greek version of Zung's Self-rating Anxiety Scale (SAS)]. *Psychiatriki* 2012; **23**: 212-220 [PMID: 23073544]
9 **Broadbent E**, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. *J Psychosom Res* 2006; **60**: 631-637 [PMID: 16731240 DOI: 10.1016/j.jpsychores.2005.10.020]
10 **Hashmi AM**, Khawaja IS, Butt Z, Umair M, Naqvi SH, Jawad-Ul-Haq. The Pittsburgh Sleep Quality Index: validation of the Urdu translation. *J Coll Physicians Surg Pak* 2014; **24**: 123-126 [PMID: 24491008]
11 **Wang YH**. Study on feasibility of Chinese version of Herth hope index for cancer patients. *Huli Yanjiu* 2010; **24**: 20-21 [DOI: 10.3969/j.issn.1009-6493.2010.01.008]
12 **Wang DW**, Zhang JX. Factor analysis of the simplified coping style questionnaire. *Shandongdaxue Xuebao (Yixueban)* 2014; **52**: 96-100 [DOI: 10.6040/j.issn.1671-7554.0.2013.380]
13 **Qin Q**. Development of scale for dental phobia in China and validation of its application. M.M. Thesis, Fourth Military Medical University. 2011. Available from: https://d.wanfangdata.com.cn/thesis/ChJUaGVzaXNOZXdTMjAyMzA5MDESB0QyMjA2MTkaCGR3emh1OTh5
14 **Aggarwal K**, Gupta J, Kaur RK, Bansal D, Jain A. Effect of anxiety and psychologic stress on periodontal health: a systematic review and meta-analysis. *Quintessence Int* 2022; **53**: 144-154 [PMID: 34595909 DOI: 10.3290/j.qi.b2091191]
15 **Deng Y**, He S, Wang J. Validation of the Hospital Anxiety and Depression Scale and the Perceived Stress Scale and psychological features in patients with periodontitis. *J Periodontol* 2021; **92**: 1601-1612 [PMID: 33386608 DOI: 10.1002/JPER.20-0756]
16 **Piedra-Hernández L**, Batista-Cárdenas D, Gómez-Fernández A, Ramírez K. Dental anxiety and oral health-related quality of life before and after non-surgical periodontal treatment. *Clin Oral Investig* 2023; **27**: 5459-5474 [PMID: 37488334 DOI: 10.1007/s00784-023-05165-1]
17 **Petit C**, Anadon-Rosinach V, Tuzin N, Davideau JL, Huck O. Influence of Depression and Anxiety on Non-Surgical Periodontal Treatment Outcomes: A 6-Month Prospective Study. *Int J Environ Res Public Health* 2021; **18** [PMID: 34501984 DOI: 10.3390/ijerph18179394]
18 **Varotto BLR**, Martinez RCR, Gouveia FV, Antunes GF, Fabri GMC, Ballester G, Antequera R, de Siqueira SRDT, Fonoff ET, Teixeira MJ, de Siqueira JTT. Increased Anxiety-Like Behavior in the Acute Phase of a Preclinical Model of Periodontal Disease. *Front Neurol* 2020; **11**: 598851 [PMID: 33414759 DOI: 10.3389/fneur.2020.598851]
19 **Kavarthapu A**, Gurumoorthy K. Linking chronic periodontitis and oral cancer: A review. *Oral Oncol* 2021; **121**: 105375 [PMID: 34140233 DOI: 10.1016/j.oraloncology.2021.105375]
20 **Vohra F**, Bukhari IA, Sheikh SA, Albaijan R, Naseem M, Hussain M. Effectiveness of scaling and root planing with and without adjunct probiotic therapy in the treatment of chronic periodontitis among shamma users and non-users: A randomized controlled trial. *J Periodontol* 2020; **91**: 1177-1185 [PMID: 31985066 DOI: 10.1002/JPER.19-0464]
21 **Nascimento GG**, Gastal MT, Leite FRM, Quevedo LA, Peres KG, Peres MA, Horta BL, Barros FC, Demarco FF. Is there an association between depression and periodontitis? A birth cohort study. *J Clin Periodontol* 2019; **46**: 31-39 [PMID: 30499588 DOI: 10.1111/jcpe.13039]
22 **Jiang Y**, Feng J, Du J, Fu J, Liu Y, Guo L. Clinical and biochemical effect of laser as an adjunct to non-surgical treatment of chronic periodontitis. *Oral Dis* 2022; **28**: 1042-1057 [PMID: 33715262 DOI: 10.1111/odi.13847]
23 **Akram Z**, Alqahtani F, Alqahtani M, Al-Kheraif AA, Javed F. Levels of advanced glycation end products in gingival crevicular fluid of chronic periodontitis patients with and without type-2 diabetes mellitus. *J Periodontol* 2020; **91**: 396-402 [PMID: 31389020 DOI: 10.1002/JPER.19-0209]
24 **Emampanahi M**, Masoudi Rad S, Saghaeian Jazi M, Mansour Samaei N, Behnampour N, Mohammadi S, Fakhari E. Association between interleukin-10 gene polymorphisms and severe chronic periodontitis. *Oral Dis* 2019; **25**: 1619-1626 [PMID: 31055876 DOI: 10.1111/odi.13114]
25 **Bhattarai B**, Gupta S, Dahal S, Roy DK, Pant S, Karki R, Thakuri T. Anxiety among Patients Visiting for Periodontal Therapy in a Tertiary Care Dental Hospital: A Descriptive Cross-sectional Study. *JNMA J Nepal Med Assoc* 2021; **59**: 697-702 [PMID: 34508513 DOI: 10.31729/jnma.6109]
26 **Singh A**, Shrestha A, Bhagat T. Pain perception and dental anxiety during periodontal probing in patients visiting community oral health programme: a cross sectional study. *BMC Oral Health* 2021; **21**: 82 [PMID: 33622321 DOI: 10.1186/s12903-021-01437-y]

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ORIGINAL ARTICLE

Observational Study

Relationship between physical activity and specific working memory indicators of depressive symptoms in university students

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Abstract

BACKGROUND

The detection rate of depression among university students has been increasing in recent years, becoming one of the main psychological diseases that endangers their physical and mental health. According to statistics, self-harm and suicide, for which there is no effective intervention, are the second leading causes of death.

AIM

To explore the relationship between different elements and levels of physical activity and college students' depression-symptom-specific working memory indicators.

METHODS

Of 143 college students were analyzed using the Beck Depression Self-Rating Scale, the Physical Activity Rating Scale, and the Working Memory Task.

RESULTS

There was a significant difference between college students with depressive symptoms and healthy college students in completing verbal and spatial working memory (SWM) tasks correctly (all $P < 0.01$). Physical Activity Scale-3 scores were significantly and positively correlated with the correct rate of the verbal working memory task ($r = 0.166$) and the correct rate of the SWM task ($r = 0.210$) (all $P < 0.05$). There were significant differences in the correct rates of verbal and SWM tasks according to different exercise intensities (all $P < 0.05$) and different exercise durations (all $P < 0.05$), and no significant differences in the correct rates of verbal and SWM tasks by exercise frequency (all $P > 0.05$).

CONCLUSION
An increase in physical exercise among college students, particularly medium- and high-intensity exercise and exercise of 30 min or more, can improve the correct rate of completing working memory tasks.

Key Words: Physical activity; Depression symptoms; University students; Working memory

Core Tip: This study discusses physical exercise in university students with depression and the specificity of their working memory. In addition, this study analyzes the relationships between the three variables through cross-sectional research, the relationship between different factors, performance of physical exercise, and working memory of university students with depression.

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INTRODUCTION

The World Health Organization predicts that depression will become the leading contributor to the global burden of disease by 2030[1]. Early adulthood is a critical period for the physiological and psychological development of individuals, and is also a high-risk period for developing depression[2]. College students are generally in the early adulthood stage from 18 to 25 years of age, and because of their immature physical and mental development, they are prone to internal conflicts when facing multiple pressures, such as complicated study tasks and life events, which can induce depression and other undesirable emotions, and in severe cases, can lead to suicide and other crisis events[3,4]. Some studies have shown that the detection rate of depression among Chinese college students ranges from 21.6% to 37.6%, with an increasing trend year by year[5-7]. Therefore, the prevention and intervention of depressive symptoms in college students is of great significance.

Working memory impairment occurs in patients with depressive symptoms. Working memory, a capacity-limited cognitive system that temporarily stores relevant information[8,9], is one of the core elements of the human cognitive system and plays an important role in learning, reasoning, and completing complex tasks. Typical symptoms of depression (*e.g.*, pleasure deficit) are highly correlated with impairment of working memory[8,10-12]. Related brain imaging studies have found that depressed individuals show greater activation in the cingulate cortex and prefrontal lobe when completing *N*-back tasks compared to healthy individuals[13-17], suggesting that to achieve the same level of performance on working memory tasks as healthy individuals, depressed individuals need to mobilize more cognitive resources and exert greater cognitive effort. Comparisons were made between depressed and non-depressed college students on a working memory task, and it was found that the correct rate of depressed subjects was lower than that of healthy subjects, and the reaction time was higher than that of healthy subjects, both of which were statistically significant [18]. The working memory model proposed by Baddeley includes the Central Executive, Visuo- spatial Sketchpad, and Phonological Loop[19]. According to the manner in which information is processed and handled, working memory can be divided into visuospatial and verbal working memory (VWM)[20]. People with depressive symptoms may experience impairments in different dimensions of working memory.

Physical exercise is closely associated with depressive symptoms and working memory. Physical exercise is an effective means of alleviating negative mood in depressed patients, with the advantages of high adherence, low adverse effects, and stable effects[21,22]. Previous cross-sectional studies have found that physical activity is significantly negatively correlated with depressive symptoms[23,24], and the higher the level of participation in sports, the lower the risk of depression detection[25]; Physical activity can also improve depressive symptoms by improving working memory. Weuve *et al*[26] found that those with higher weekly physical activity had better performance in reverse-order memory breadth, and the decline in homework performance was lower than the decline in physical activity performance in the second test two years later. The decline in homework performance was lower in this group than that of those with low physical activity; and the findings of Szabo *et al*[27] suggest that cardiorespiratory fitness levels in older adults can directly influence hippocampal gyrus volume, which in turn promotes overall correctness and speed of response in spatial working memory (SWM). Depressive disorder severity significantly affects working memory and may be related to altered frontal executive control circuit functioning in patients[28], who show consistent abnormalities in limbic-subcortical calcium cycle functioning during working memory processing[29]; disruption of working memory updating is mainly characterized by altered activity in the connections between visual association areas and the prefrontal cortex[30], and physical activity can significantly affect prefrontal activation, which in turn affects performance on working memory tasks, thereby ameliorating depressive symptoms.

Previous studies have shown that physical exercise, working memory, and depressive symptoms are closely related to each other, and that impairment of working memory is a prominent manifestation of cognitive impairment in patients with depression. There is a basic consensus that physical exercise improves working memory, and that improvement of working memory alleviates depressive symptoms. We found that previous studies did not clarify whether there was a difference in working memory task performance between healthy college students and college students with depressive symptoms, nor did they mention the relationship between the elements of physical exercise and working memory. The present study thus adopted a cross-sectional design paradigm to explore the correlation between various elements of physical activity and working memory-specific indicators, as well as the relationship between different levels of physical activity and working memory under each element, to clarify the indicators of depression-symptom-specific working memory in college students with a view to provide evidence for future clinical practice.

MATERIALS AND METHODS

Participants

Based on the principle of voluntariness, university students were randomly recruited from Songjiang University in Shanghai. All subjects were required to be 18-26 years old; have no mental illness; have never taken barbiturates, benzodiazepines, or chloral hydrate; be non-sports majors or high-level athletes; and have no sports contraindications. All participants signed informed consent forms, and the study was approved by the Ethics Committee of Shanghai University of Sport, with an ethical code of 102772023RT075. The recruitment process for the participants is shown in Figure 1.

Measures

General information questionnaire: Participants' basic information, such as age, sex, height, weight, and family status was obtained, as well as information on any mental illness, on the use of barbiturates, benzodiazepines, and chloral hydrate, whether they were professional athletes, and whether they had sports contraindications.

Beck Depression Inventory-II: This widely used 21-item self-assessment scale was used to assess depressive symptoms. Responses were rated on a 4-point Likert scale ranging from 0 (no symptoms) to 3 (severe symptoms). Total scores of 0-13, 14-19, 20–28, and 29–63 indicate no, mild, moderate, and severe depression, respectively. The internal consistency coefficient was 0.948[16].

The Physical Activity Scale-3: The Physical Activity Scale-3 (PARS-3), translated and revised by Liang *et al*[31] is currently recognized as an effective adult physical activity measurement questionnaire. This scale defines the amount of exercise = intensity × duration × frequency. The intensity and frequency are divided into five grades, with 1-5 points respectively. The five grades of duration are 0-4 points respectively, and the score range is 0-100 points. The evaluation criteria are: ≤ 19 means a small amount of exercise, 20-42 a moderate amount of exercise, and ≥ 43 a large amount of exercise. In this study, Cronbach α coefficient of the scale is 0.740.

Working memory task: A verbal *n*-back spatial *n*-back task paradigm was used to measure the refreshing ability of the participants' working memory, where *n* was 2. VWM and SWM were tested according to different processing levels of working memory. The experimental procedure was completed using the subjects' keystrokes on a computer, and the verbal and spatial *n*-back tasks used the same experimental materials and procedures but differentiated between the two experimental procedures using different experimental instructions. Eight distinct uppercase letters-B, D, H, K, M, P, S, and Y-were chosen for the experimental material to avoid confusion in the subjects. The screen background was black and eight letters were randomly presented at eight positions on the screen.

The verbal *n*-back task required participants to memorize the letters themselves, ignoring their spatial location, and consisted of 55 trials, including 5 practice trials and 50 formal trials. After completing the 5 practice trials, the participant was asked whether he/she was familiar with the task and the procedure, and if he/she did not receive an affirmative answer, he/she was given the option of pressing the "Q" key to practice again; if he/she received an affirmative answer, he/she was given the option of pressing the "Enter" key to enter the formal experiment. Each experiment consisted of 50 trials. There were 50 trials in the formal experiment, and the specific experimental procedure was as follows: first, a gaze point "+" was presented for 3000 ms, and then a picture with a letter was presented sequentially for 2000 ms, with a stimulus interval of 1000 ms. Participants were asked to memorize the letter itself, ignore the spatial location of the letter, and remember the letter if it was different from the second letter. If the currently presented letter was the same as the second letter in the previous interval, the "J" key was pressed, and if it was different, the "F" key was pressed. The statistics show the response times and correct rates for the verbal *n*-back task (Figure 2).

The spatial *n*-back task was the same as the verbal *n*-back task in terms of the number of trials and the complete experimental procedure, with the difference that participants were required to memorize the spatial position of the letter, ignoring the letter itself. Participants were asked to press the "J" key to respond if the position of the currently presented letter was the same as that of the previous penultimate letter (in this case, there would be a situation in which the letters are different, but the spatial position of the letter is the same), and press the "F" key if they are different. The statistics represent the response times, press the "J" key to respond, and if they are different, press the "F" key. The statistics represent the response times and correct rates for the spatial *N*-back task (Figure 3).

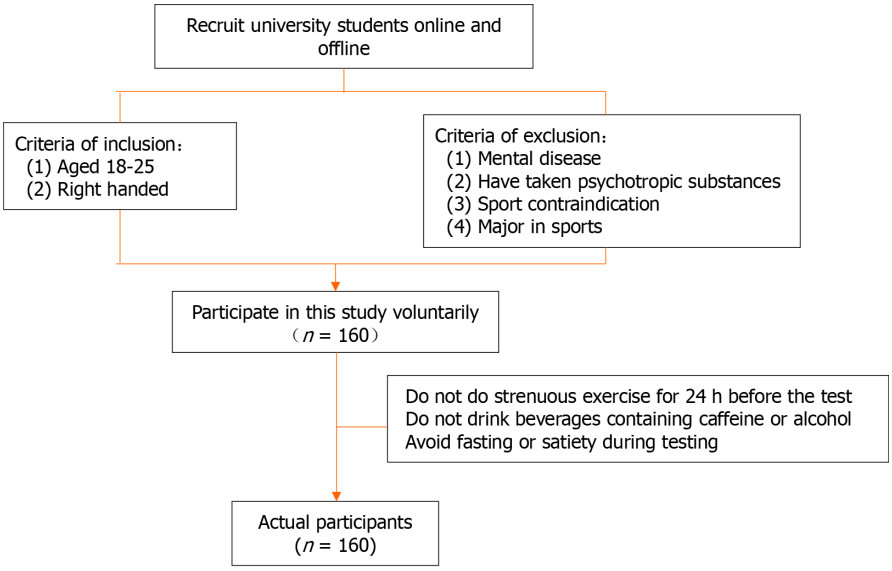

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Figure 1 Flow chart of subject recruiting.

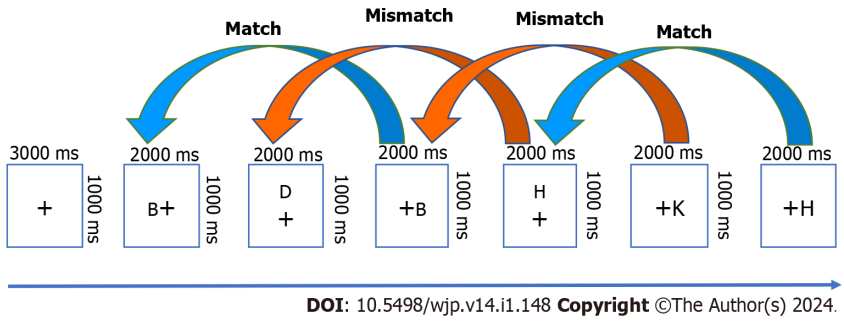

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Figure 2 Flowchart of speech 2-back task.

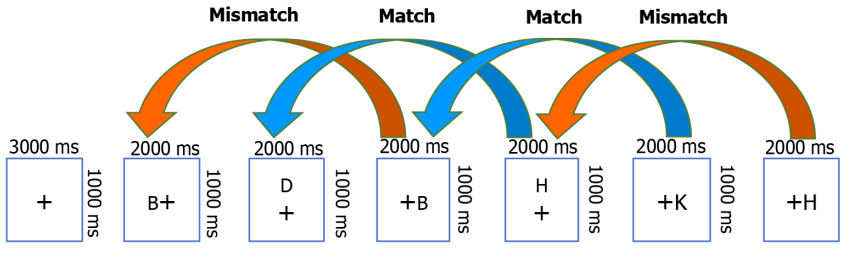

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Figure 3 Flowchart of the space 2-back mission.

Test procedure

Questionnaires (basic information form, Beck Depression Inventory-II, and PARS-3) were distributed to the participants. Before filling in the questionnaires, the chief examiner read out the guidelines and explained the entries, making it clear that the data obtained were only used for scientific research, and emphasizing that the answers were true, independent and voluntary. In the process of filling in the questionnaires, the subjects were prompted to answer the questionnaires according to the requirements. After filling in the questionnaires, the chief examiner checked the questionnaires that had omitted any item or whose responses were against common sense, and ensured the completeness of the information through filling and re-filling the questionnaires (Figure 4).

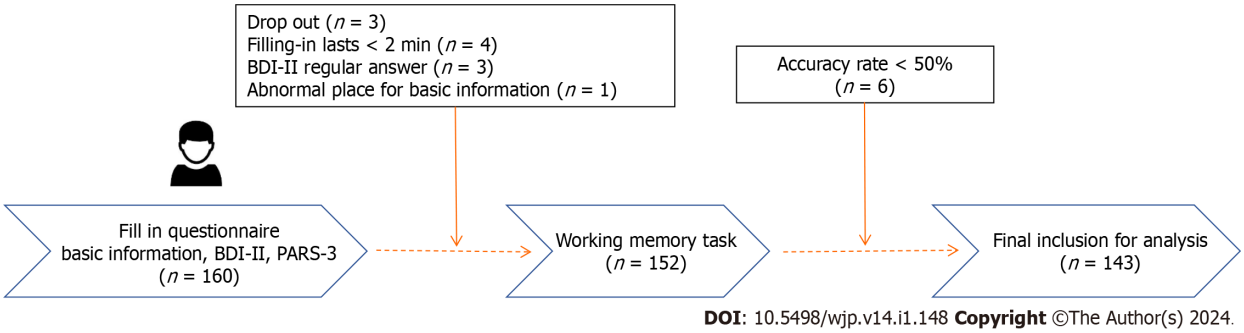

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Figure 4 Flow chart of measurement. BDI-II: Beck depression inventory-II; PARS-3: The physical activity scale-3.

Data processing

IBM SPSS Statistics 26.0 software was used to statistically analyze the data. For the questionnaire, there was a non-random lack of data to avoid the use of a simple deletion method to make the estimated coefficients biased; then the same kind of mean interpolation processing was performed. The common method bias test was conducted by using the Harman one-way test; the data distribution was observed through frequency histograms, and the independent sample *t*-test was used for comparison between groups of the measured data that conformed to normal distribution or nearly normal distribution; the Mann-Whitney *U* nonparametric test was used for comparison of the measured data that were obviously skewed; the count data were described by *n* (%), and the χ^2 test was used for comparison between groups. One-way analysis of variance (ANOVA) and least significant difference post-hoc multiple tests were used to compare the effects of different exercise intensities, times, and frequencies on the correct rate of verbal and SWM tasks, and Pearson correlation analysis and linear regression analysis were used to explore the relationship between physical exercise, depressive symptoms, and working memory. One-way ANOVA was used to investigate the relationship between physical exercise (intensity and duration) and working memory.

RESULTS

Demographic information of university students with/without depression

Overall, 143 participants were included, with age 19.53 ± 1.149 year-old, and a 21.68% detection rate of depression. Comparing the demographic features between depressed and non-depressed university students, as shown in Table 1, we discovered significant differences in the groups in terms of registered households, only children, study pressure, interpersonal relationships, and social activities. Further analysis found that compared to non-depressed university students, depressed university students had significantly higher study pressure, a lower proportion of only children, more tense interpersonal relationships, and fewer social activities. This result shows that being in a senior grade, not being an only child, high study pressure, more tense interpersonal relationships, and fewer social activities are indicators of depressive symptoms in the high-risk groups.

Specificity of working memory of university students with different depressive symptoms

As shown in Table 2 and Figure 5, there was a significant difference in the rate of correct completion of both verbal and SWM tasks between college students with depressive symptoms and healthy college students (all $P < 0.01$).

Relationship between different elements and levels of physical exercise and college students' depressive symptom-specific working memory indicators

To facilitate the analysis of different physical exercise elements and levels, the participants were divided into different exercise intensities, durations, and frequencies according to the PARS-3 questionnaire. Exercise intensity was classified as light exercise (level 1), medium-low intensity (levels 2 and 3), and high intensity (levels 4 and 5), exercise duration was classified as < 30 min (levels 1-3), 30-59 min (level 4), and ≥ 60 min (level 5), and exercise frequency was classified as ≤ 1 time/mo (level 1), 2 times/mon-2 times/wk (levels 2 and 3), and ≥ 3 times/wk (levels 4 and 5).

Characteristics of working memory of university students with different exercise intensity, duration, and frequency

In order to analyze the characteristics of working memory in students with different exercise intensity, duration, and frequency according to the PARS-3 questionnaire, exercise intensity was divided into light exercise (level 1), medium and low intensity (levels 2 and 3), and high intensity (levels 4 and 5), and exercise duration was divided into < 30 min (levels 1-3), 30–59 min (levels 4) and ≥ 60 min (level 5), frequency of exercise was divided into ≤ once/month (level 1, twice/month-twice/week (level 2 and 3) and ≥ three times/week (level 4 and 5).

As shown in Table 3, there were significant differences in VWM and SWM accuracies among the different exercise intensities (all $P < 0.05$). After multiple comparisons, significant differences were found between high-intensity and medium-intensity physical exercise and low-intensity physical exercise (all $P < 0.05$), suggesting that medium intensity

Table 1 Basic information of university students with different depression symptoms, (%)

Demographic indicators	Overall	Without depression	With depression	Comparison among groups	
	(*n* = 143)	(*n* = 112)	(*n* = 31)	χ^2/t	*P* value
Gender (male)	47.55	48.21	45.16	0.091	0.763
Age (yr)	19.53 ± 1.149	19.52 ± 1.139	19.58 ± 1.205	0.959	0.789
BMI (kg/m²)	21.483 ± 3.939	21.729 ± 4.039	20.592 ± 3.468	0.245	0.156
Registered household (city)	52.45	58.04	32.26	6.469	0.011[a]
Only child (yes)	46.15	50.89	29.03	4.669	0.031[a]
Single-parent family (yes)	9.09	9.82	6.45	0.334	0.564
Average education year of parents (yr)	11.119 ± 3.598	11.371 ± 3.370	10.210 ± 4.260	0.117	0.112
Drinking habit (yes)	20.28	18.75	25.81	0.748	0.387
Smoking habit (yes)	2.10	2.68	0	0.848	0.357
Family relations					
Amiable	50.35	53.57	38.71	3.466	0.177
General	47.55	43.75	61.29		
Many conflicts	2.10	2.68	0		
Study pressure					
Easy	22.38	25.89	9.68	7.107	0.029[a]
General	54.55	55.36	51.61		
Difficult	23.08	18.75	38.71		
Interpersonal relationship					
Good	74.13	83.04	41.94	22.009	< 0.001[b]
General	23.78	16.07	51.61		
Bad	2.10	0.89	6.45		
Social activities					
> Three times/wk	2.80	1.79	6.45	13.625	0.001[b]
≤ Three times/wk	83.22	89.29	61.29		
Hardly	13.99	8.93	32.26		

[a]$P < 0.05$.
[b]$P < 0.01$.
BMI: Body mass index.

Table 2 Differences in working memory among college students with different depressive symptoms (mean ± SD)

Variable	Without depression, (*n* = 134)	With depression, (*n* = 31)	*F* value	*P* value
VWM accuracy	0.868 ± 0.080	0.762 ± 0.170	50.963	0.002
VWM reaction time	995.18 ± 146.27	913.45 ± 290.846	42.502	0.14
SWM accuracy	0.875 ± 0.084	0.773 ± 0.187	73.121	0.006
SWM reaction time	955.41 ± 168.20	880.81 ± 249.87	10.484	0.125

VWM: Verbal working memory; SWM: spatial working memory.

Table 3 Characteristics of working memory of university students with different exercise intensity

Variable	Overall	Different intensity			F value	P value	Multiple comparisons		
	(*n* = 143)	Low (*n* = 27)	Medium (*n* = 94)	High (*n* = 22)			Low *vs* medium	Low *vs* high	Medium *vs* high
Accuracy rate of VWM	0.845 ± 0.114	0.795 ± 0.102	0.849 ± 0.104	0.889±0.048	4.45	0.013	0.028	0.004	0.137
Accuracy rate of SWM	0.853 ± 0.121	0.786 ± 0.171	0.862 ± 0.106	0.894±0.069	6.008	0.003	0.004	0.002	0.241

VWM: Verbal working memory; SWM: Spatial working memory.

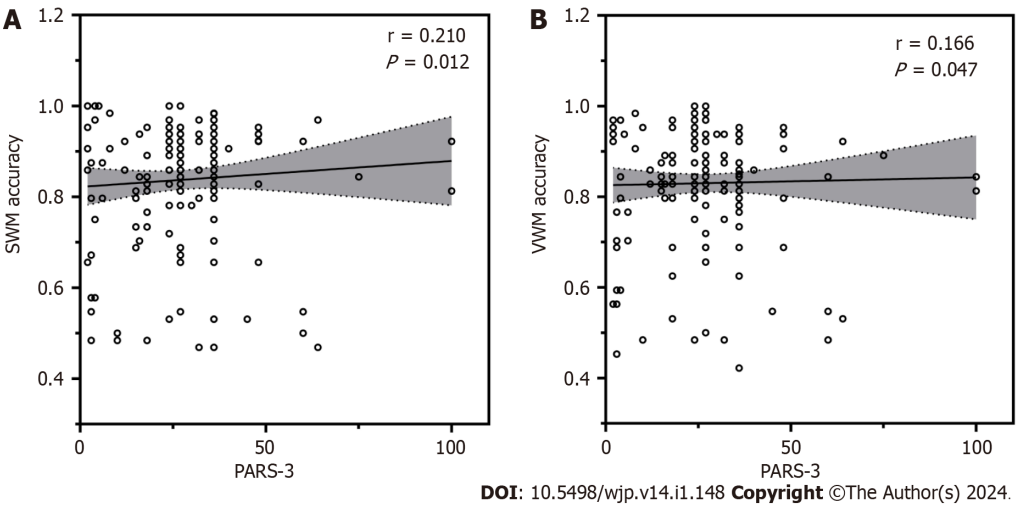

Figure 5 The relationship between physical activity and task-specific indicators of working memory. A: Physical activity was significantly and positively correlated with correctness of spatial working memory; B: Physical activity was significantly and positively correlated with correctness of verbal working memory. PARS-3: The physical activity scale-3.

had already taken effect, and there was little difference between medium and high intensity.

As shown in Table 4, there were significant differences in the VWM and SWM accuracy rates for different exercise durations (all $P < 0.05$). After multiple comparisons, significant differences were found in the VWM accuracy rate between physical exercise of middle- and low duration ($P < 0.05$). In terms of the accuracy rate of SWM, there were significant differences between the group of low-duration and the groups of high-duration and medium-duration (all $P < 0.05$), suggesting that the exercise duration takes effect when it exceeds 30 min, and there is little difference between medium-duration and high-duration physical exercise.

As shown in Table 5, there was no significant difference in the VWM and SWM accuracy rates for different exercise frequencies (all $P > 0.05$), suggesting that different exercise frequencies pose no effect on the completion of working memory tasks.

DISCUSSION

The results of this study showed that the correct rate when completing a working memory task is a depression-symptom-specific working memory indicator for college students and that physical activity participation has a positive correlation with the correct rate when completing a working memory task, which is consistent with the results of previous studies. The results of previous studies found[32,33] that depressed individuals had lower rates of correctness and slower responses when completing tasks compared to healthy individuals, and the severity of working memory impairment was positively correlated with the severity of symptoms in depressed patients[34]. In terms of research on physical exercise to improve working memory in depressed groups, previous researchers have found through cross-sectional studies[35] that there is a positive correlation between physical activity and cognition and a significant positive correlation between physical activity and its rate of correctness in completing working memory[36-38]. Overseas studies have found that depressed patients all have abnormal activation of the frontal and parietal lobes when performing working memory tasks and also have failure of inhibition of the limbic system[39,40].

Table 4 Characteristics of working memory of university students with different exercise duration.

Variable	Overall	Duration			*F* value	*P* value	Multiple comparisons		
	(*n* = 143)	< 30 min (*n* = 33)	30-59 min (*n* = 63)	≥ 60 min (*n* = 47)			Low *vs* medium	Low *vs* high	Medium *vs* high
Accuracy rate of VWM	0.845 ± 0.114	0.808 ± 0.165	0.869 ± 0.084	0.838 ± 0.114	3.344	0.038	0.012	0.243	0.151
Accuracy rate of SWM	0.853 ± 0.121	0.798 ± 0.172	0.874 ± 0.084	0.862 ± 0.111	4.675	0.011	0.003	0.018	0.608

VWM: Verbal working memory; SWM: Spatial working memory.

Table 5 Characteristics of working memory of university students with different exercise frequency

Variable	Overall	Frequency			*F* value	*P* value
	(*n* = 143)	≤ Once/mo (*n* = 1)	Twice/month-twice/week (*n* = 103)	≥ Three times/week (*n* = 39)		
Accuracy rate of VWM	0.845 ± 0.114	0.766 ± 0.000	0.840 ± 0.117	0.861 ± 0.114	0.709	0.494
Accuracy rate of SWM	0.853 ± 0.121	0.797 ± 0.000	0.847 ± 0.114	0.870 ± 0.139	0.623	0.538

VWM: Verbal working memory; SWM: Spatial working memory.

This study found that the higher the exercise intensity and longer the duration of physical exercise for college students, the better their performance in working memory tasks, whereas the positive facilitation effect of exercise frequency on working memory task performance was not significant. Evidence shows[41] that physical exercise can provide sufficient nutrition and energy to the brain by increasing neurotransmitter content, promoting glial cell regeneration, improving synaptic plasticity, effectively regulating neurotrophic factor concentration, glucocorticoid hormone levels, morphology and structure of specific parts of the central nervous system, as well as the release of pro-inflammatory cytokines, and at the same time increasing brain plasticity and improving working memory. Furthermore, physical exercise increases the area of grey and white matter in the prefrontal, parietal and temporal lobes[42], induces structural changes in the hippocampal volume and the vascular system[43], and significantly increases the number of newborn neurons[44], which, in turn, improves working memory capacity. Vazou *et al*[45] conducted a cross-sectional cognitive test on and showed that subjects who exercised more performed better. Sibley *et al*[46] and Griffin *et al*[47] found that both moderate- and high-intensity exercise resulted in a significant increase in working memory capacity in university students.

We also found that depressive symptoms were significantly negatively correlated with the correct rate of completion of the working memory task, but not with the response time of completing the working memory task, which is inconsistent with the results of previous studies[17,48], which may be due to the difference in task paradigms, as previous studies of working memory used both the 1-back and 2-back working memory tasks, whereas the present study used only the 2-back task. This result may be due to the difference in task paradigms, as the 1-back task is simpler for college students, and a "ceiling effect" may occur[49]. Another inconsistent result is that there is no significant difference in college students' performance on the working memory task between different exercise frequencies[50]. This may be due to the difference in the study population; previous researchers selected healthy college students, whereas the present study included college students with depressive symptoms. Cross-sectional studies on the effect of physical activity frequency on working memory have rarely been reported at home and abroad, and high-quality studies are still necessary in the future to supplemented these findings.

Limitations: This study used a cross-sectional design, which needs to be confirmed by longitudinal studies in the future. The physical activity scale, as a subjective report, may have some bias, and some objective indicators such as accelerometers and heart rate bands can be used to measure physical activity data in future studies. Larger samples are required for future investigations.

CONCLUSION

The more physical exercise college students engage in, the higher is the correct rate of completing working memory tasks. Among the elements of physical exercise, exercise intensity of medium intensity or more and exercise duration of more than 30 minutes can improve the correct rate of working memory tasks. Therefore, college students with depressive symptoms should be encouraged to increase their physical activity to improve their working memory and pay attention to changes in working memory, which may reduce scores on depressive symptoms.

ARTICLE HIGHLIGHTS

Research background

Depression is an important factor contributing to the global burden of disease, and the detection rate of depressed mood among Chinese university students ranges from 21.6 per cent to 37.6 percent, with a tendency to increase year by year.

Research motivation

Reduce the prevalence of depressive symptoms in college students.

Research objectives

This paper aims to discuss the relationship between different factors, the performance of sports exercises, and the working memory of university students with depression.

Research methods

One-way analysis of variance and Pearson's correlation were used to explore the correlations and interaction pathways between variables.

Research results

There was a significant difference between depressive symptomatic and healthy college students in the completion of both verbal and spatial working memory tasks correctly. Physical Activity Scale-3 scores were significantly and positively correlated with verbal working memory (VWM) correctness and spatial working memory (SWM) correctness. High- and moderate-intensity physical exercise were significantly different from low-intensity physical exercise. In terms of VWM correctness, there was a significant difference between medium-duration compared with low-duration physical exercise; in terms of SWM correctness, there was a significant difference between high-duration and medium-duration physical exercise compared with low-duration physical exercise. There was no significant difference in the correct VWM and SWM rates between the different exercise frequencies.

Research conclusions

Colleges and universities should encourage students with depressive symptoms to increase their physical activity and improve their working memory. This is particularly evident with increased intensity and duration of physical activity, which may reduce the incidence of depressive symptoms.

Research perspectives

The use of objective measurement tools is recommended for future studies, and longitudinal studies are necessary to further define the course of action.

FOOTNOTES

Author contributions: Zhao Q wrote the original manuscript and collected the data; Wang X collected and analyzed the data; Wang P wrote part of the manuscript; Xin X and Yin ZS collected the data; Li SF curated the data; Wang X and Yin SW curated the data; Mao LJ reviewed and edited.

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REFERENCES

1 **Lépine JP**, Briley M. The increasing burden of depression. *Neuropsychiatr Dis Treat* 2011; **7**: 3-7 [PMID: 21750622 DOI: 10.2147/NDT.S19617]
2 **Hayley AC**, Skogen JC, Sivertsen B, Wold B, Berk M, Pasco JA, Øverland S. Symptoms of Depression and Difficulty Initiating Sleep from Early Adolescence to Early Adulthood: A Longitudinal Study. *Sleep* 2015; **38**: 1599-1606 [PMID: 26194578 DOI: 10.5665/sleep.5056]
3 **Zhang R**, Yang CY, Zhang YD. Influencing Factors of Depression in Chinese College Students: A Meta-analysis. *Zhongguo Quanke Yixue* 2020; **23**: 4497-4502 [DOI: 10.12114/j.issn.1007-9572.2020.00.135]
4 **Cao C**, Wang MP, JI LQ, Wei X, Cao YN, Zhang WX. The MAOA rs6323 polymorphism interacts with maternal supportive parenting in predicting adolescent depression:Testing the diathesis-stress and differential susceptibility hypotheses. *Xinli Xuebao* 2016; **48**: 22-35 [DOI: 10.3724/SP.J.1041.2016.00022]
5 **Tang H**, Ding LL, Song XL, Huang ZW, Qi Q, He LP, Yao YS. Meta-analysis of detection rate of depressed mood among Chinese college students from 2002 to 2011. *Jilin Daxue Xuebao (Yixueban)* 2013; **39**: 965-969
6 **Hu YQ**, Liu ZH. An Intervention Study of Psychological Health of Depressed College Students:the Different Effects of Different Types of School Support. *Huan Shifan Daxue Jiaoyu Kexue Xuebao* 2019; **18**: 120-125 [DOI: 10.19503/j.cnki.1671-6124.2019.05.018]
7 **Wang MY**, Liu J, Wu X, Li L, Hao XD, Shen Q, Huang MT, Sun RH. The prevalence of depression among students in Chinese universities over the past decade: A Me-ta-analysis. *Hainan Yixueyuan Xuebao* 2020; **26**: 686-93+99 [DOI: 10.13210/j.cnki.jhmu.20200218.001]
8 **Chen NT**, Clarke PJ, Watson TL, MacLeod C, Guastella AJ. Attentional bias modification facilitates attentional control mechanisms: evidence from eye tracking. *Biol Psychol* 2015; **104**: 139-146 [PMID: 25527400 DOI: 10.1016/j.biopsycho.2014.12.002]
9 **Eriksson J**, Vogel EK, Lansner A, Bergström F, Nyberg L. Neurocognitive Architecture of Working Memory. *Neuron* 2015; **88**: 33-46 [PMID: 26447571 DOI: 10.1016/j.neuron.2015.09.020]
10 **Joormann J**, Gotlib IH. Emotion regulation in depression: relation to cognitive inhibition. *Cogn Emot* 2010; **24**: 281-298 [PMID: 20300538 DOI: 10.1080/02699930903407948]
11 **LeMoult J**, Gotlib IH. Depression: A cognitive perspective. *Clin Psychol Rev* 2019; **69**: 51-66 [PMID: 29961601 DOI: 10.1016/j.cpr.2018.06.008]
12 **Rock PL**, Roiser JP, Riedel WJ, Blackwell AD. Cognitive impairment in depression: a systematic review and meta-analysis. *Psychol Med* 2014; **44**: 2029-2040 [PMID: 24168753 DOI: 10.1017/S0033291713002535]
13 **Harvey PO**, Fossati P, Pochon JB, Levy R, Lebastard G, Lehéricy S, Allilaire JF, Dubois B. Cognitive control and brain resources in major depression: an fMRI study using the n-back task. *Neuroimage* 2005; **26**: 860-869 [PMID: 15955496 DOI: 10.1016/j.neuroimage.2005.02.048]
14 **Rose EJ**, Simonotto E, Ebmeier KP. Limbic over-activity in depression during preserved performance on the n-back task. *Neuroimage* 2006; **29**: 203-215 [PMID: 16157491 DOI: 10.1016/j.neuroimage.2005.07.002]
15 **Matsuo K**, Glahn DC, Peluso MA, Hatch JP, Monkul ES, Najt P, Sanches M, Zamarripa F, Li J, Lancaster JL, Fox PT, Gao JH, Soares JC. Prefrontal hyperactivation during working memory task in untreated individuals with major depressive disorder. *Mol Psychiatry* 2007; **12**: 158-166 [PMID: 16983390 DOI: 10.1038/sj.mp.4001894]
16 **Fitzgerald PB**, Srithiran A, Benitez J, Daskalakis ZZ, Oxley TJ, Kulkarni J, Egan GF. An fMRI study of prefrontal brain activation during multiple tasks in patients with major depressive disorder. *Hum Brain Mapp* 2008; **29**: 490-501 [PMID: 17525987 DOI: 10.1002/hbm.20414]
17 **Nikolin S**, Tan YY, Martin D, Moffa A, Loo CK, Boonstra TW. Behavioural and neurophysiological differences in working memory function of depressed patients and healthy controls. *J Affect Disord* 2021; **295**: 559-568 [PMID: 34509071 DOI: 10.1016/j.jad.2021.08.083]
18 **Wang X**. A study of the effects of depressed mood on working memory in college students. M.Sc. Thesis, Dalian Maritime University. 2017. [DOI: 10.7666/d.Y3264735]
19 **Baddeley AD**, Hitch GJ, Allen RJ. From short-term store to multicomponent working memory: The role of the modal model. *Mem Cognit* 2019; **47**: 575-588 [PMID: 30478520 DOI: 10.3758/s13421-018-0878-5]
20 **Wang Z**, Jia DM. Evolution of a theoretical model of working memory and its application. *Changji Xueyuan Xuebao* 2009; 98-101 [DOI: 10.3969/j.issn.1671-6469.2009.05.024]
21 **Wang P**, Wang J, Zhao JL, Wang X, Xin X, Qiu SL, Zang YH. Relationship Between Physical Activity Level and Depressive Symptoms in College Students:A Pathway Analysis Based on EEG. *Shanghai Tiyu Xueyuan Xuebao* 2023; **47**: 51-60 [DOI: 10.16099/j.sus.2022.07.30.0003]
22 **Hallgren M**, Stubbs B, Vancampfort D, Lundin A, Jääkallio P, Forsell Y. Treatment guidelines for depression: Greater emphasis on physical activity is needed. *Eur Psychiatry* 2017; **40**: 1-3 [PMID: 27837666 DOI: 10.1016/j.eurpsy.2016.08.011]
23 **da Costa BGG**, Chaput JP, Lopes MVV, Malheiros LEA, Silva KS. Movement behaviors and their association with depressive symptoms in Brazilian adolescents: A cross-sectional study. *J Sport Health Sci* 2022; **11**: 252-259 [PMID: 32791204 DOI: 10.1016/j.jshs.2020.08.003]
24 **Sun WX**, Wang X, Yu MX, Zhao QY, Zhou XJ. Physical activity participation levels and depressive symptoms among college students: the mediating role of social support. *Zhongguo Weisheng Tongji* 2023; **40**: 421-4+8 [DOI: 10.11783/j.issn.1002-3674.2023.03.025]
25 **Zhang SH**, Dai YX, Zhang XH, Li YJ, Zhang JX. Impact of social sports activities on depression among junior middle school students. *Zhongguo Xuexiao Weisheng* 2020; **41**: 551-3+7 [DOI: 10.16835/j.cnki.1000-9817.2020.04.019]
26 **Weuve J**, Kang JH, Manson JE, Breteler MM, Ware JH, Grodstein F. Physical activity, including walking, and cognitive function in older women. *JAMA* 2004; **292**: 1454-1461 [PMID: 15383516 DOI: 10.1001/jama.292.12.1454]
27 **Szabo AN**, McAuley E, Erickson KI, Voss M, Prakash RS, Mailey EL, Wójcicki TR, White SM, Gothe N, Olson EA, Kramer AF. Cardiorespiratory fitness, hippocampal volume, and frequency of forgetting in older adults. *Neuropsychology* 2011; **25**: 545-553 [PMID: 21500917 DOI: 10.1037/a0022733]
28 **Watters AJ**, Carpenter JS, Harris AWF, Korgaonkar MS, Williams LM. Characterizing neurocognitive markers of familial risk for depression using multi-modal imaging, behavioral and self-report measures. *J Affect Disord* 2019; **253**: 336-342 [PMID: 31078833 DOI:

10.1016/j.jad.2019.04.078]
29 **Wang XL**, Du MY, Chen TL, Chen ZQ, Huang XQ, Luo Y, Zhao YJ, Kumar P, Gong QY. Neural correlates during working memory processing in major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2015; **56**: 101-108 [PMID: 25174680 DOI: 10.1016/j.pnpbp.2014.08.011]
30 **Le TM**, Borghi JA, Kujawa AJ, Klein DN, Leung HC. Alterations in visual cortical activation and connectivity with prefrontal cortex during working memory updating in major depressive disorder. *Neuroimage Clin* 2017; **14**: 43-53 [PMID: 28138426 DOI: 10.1016/j.nicl.2017.01.004]
31 **Liang DQ**. Stress levels and their relationship with physical activity among university students. *Zhongguo Xinli Weisheng Zazhi* 1994; 8: 5-6
32 **Li M**, Feng L, Liu X, Zhang M, Fu B, Wang G, Lu S, Zhong N, Hu B. Emotional working memory in patients with major depressive disorder. *J Int Med Res* 2018; **46**: 1734-1746 [PMID: 29529905 DOI: 10.1177/0300060518758225]
33 **Nikolin S**, Tan YY, Schwaab A, Moffa A, Loo CK, Martin D. An investigation of working memory deficits in depression using the n-back task: A systematic review and meta-analysis. *J Affect Disord* 2021; **284**: 1-8 [PMID: 33581489 DOI: 10.1016/j.jad.2021.01.084]
34 **Friedman NP**, Miyake A, Corley RP, Young SE, Defries JC, Hewitt JK. Not all executive functions are related to intelligence. *Psychol Sci* 2006; **17**: 172-179 [PMID: 16466426 DOI: 10.1111/j.1467-9280.2006.01681.x]
35 **Fedewa AL**, Ahn S. The effects of physical activity and physical fitness on children's achievement and cognitive outcomes: a meta-analysis. *Res Q Exerc Sport* 2011; **82**: 521-535 [PMID: 21957711 DOI: 10.1515/ijsl.2000.143.183]
36 **Weng TB**, Pierce GL, Darling WG, Voss MW. Differential Effects of Acute Exercise on Distinct Aspects of Executive Function. *Med Sci Sports Exerc* 2015; **47**: 1460-1469 [PMID: 25304335 DOI: 10.1249/MSS.0000000000000542]
37 **Gothe N**, Pontifex MB, Hillman C, McAuley E. The acute effects of yoga on executive function. *J Phys Act Health* 2013; **10**: 488-495 [PMID: 22820158 DOI: 10.1123/jpah.10.4.488]
38 **Shi H**. Time-course effects of high-intensity interval exercise on executive function in young people with high and low cardiorespiratory fitness. M.Sc. Thesis, Shandong Tiyu Xueyuan. 2022. [DOI: 10.27725/d.cnki.gsdty.2021.000108]
39 **Rodríguez-Cano E**, Sarró S, Monté GC, Maristany T, Salvador R, McKenna PJ, Pomarol-Clotet E. Evidence for structural and functional abnormality in the subgenual anterior cingulate cortex in major depressive disorder. *Psychol Med* 2014; **44**: 3263-3273 [PMID: 25066663 DOI: 10.1017/S0033291714000841]
40 **Lee TW**, Liu HL, Wai YY, Ko HJ, Lee SH. Abnormal neural activity in partially remitted late-onset depression: an fMRI study of one-back working memory task. *Psychiatry Res* 2013; **213**: 133-141 [PMID: 23154094 DOI: 10.1016/j.pscychresns.2012.04.010]
41 **Voss MW**, Vivar C, Kramer AF, van Praag H. Bridging animal and human models of exercise-induced brain plasticity. *Trends Cogn Sci* 2013; **17**: 525-544 [PMID: 24029446 DOI: 10.1016/j.tics.2013.08.001]
42 **Hillman CH**, Pontifex MB, Castelli DM, Khan NA, Raine LB, Scudder MR, Drollette ES, Moore RD, Wu CT, Kamijo K. Effects of the FITKids randomized controlled trial on executive control and brain function. *Pediatrics* 2014; **134**: e1063-e1071 [PMID: 25266425 DOI: 10.1542/peds.2013-3219]
43 **Thomas AG**, Dennis A, Bandettini PA, Johansen-Berg H. The effects of aerobic activity on brain structure. *Front Psychol* 2012; **3**: 86 [PMID: 22470361 DOI: 10.3389/fpsyg.2012.00086]
44 **van Praag H**, Christie BR, Sejnowski TJ, Gage FH. Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proc Natl Acad Sci U S A* 1999; **96**: 13427-13431 [PMID: 10557337 DOI: 10.1073/pnas.96.23.13427]
45 **Vazou S**, Pesce C, Lakes K, Smiley-Oyen A. More than one road leads to Rome: A narrative review and meta-analysis of physical activity intervention effects on cognition in youth. *Int J Sport Exerc Psychol* 2019; **17**: 153-178 [PMID: 31289454 DOI: 10.1080/1612197X.2016.1223423]
46 **Sibley BA**, Beilock SL. Exercise and working memory: an individual differences investigation. *J Sport Exerc Psychol* 2007; **29**: 783-791 [PMID: 18089904 DOI: 10.1123/jsep.29.6.783]
47 **Griffin ÉW**, Mullally S, Foley C, Warmington SA, O'Mara SM, Kelly AM. Aerobic exercise improves hippocampal function and increases BDNF in the serum of young adult males. *Physiol Behav* 2011; **104**: 934-941 [PMID: 21722657 DOI: 10.1016/j.physbeh.2011.06.005]
48 **Ren LJ**, Han MF, Li YS, Xia J, Long X. Working Memory in Depression Patients : a fMRI Study. *Hangtian Yixue Yu Yixue Gongcheng* 2013; **26**: 402-404 [DOI: 10.16289/j.cnki.1002-0837.2013.05.014]
49 **Wang YL**, Chen CX, Ma SH, Dou N, Li D. The ceiling effects and correlation of three balance scales in stroke patients. *Zhongguo Kangfu Yixue Zazhi* 2015; **30**: 679-683
50 **Liu JY**. "Dosage Effect" of the Relationship Between Aerobic Exercise and College Students' Executive Function. *Beijing Tiyu Daxue Xuebao* 2017; **40**: 58-64 [DOI: 10.19582/j.cnki.11-3785/g8.2017.01.010]

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ORIGINAL ARTICLE

Basic Study

Nutritional epigenetics education improves diet and attitude of parents of children with autism or attention deficit/hyperactivity disorder

Renee J Dufault, Katherine M Adler, David O Carpenter, Steven G Gilbert, Raquel A Crider

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Abstract

BACKGROUND

Unhealthy maternal diet leads to heavy metal exposures from the consumption of ultra-processed foods that may impact gene behavior across generations, creating conditions for the neurodevelopmental disorders known as autism and attention deficit/hyperactivity disorder (ADHD). Children with these disorders have difficulty metabolizing and excreting heavy metals from their bloodstream, and the severity of their symptoms correlates with the heavy metal levels measured in their blood. Psychiatrists may play a key role in helping parents reduce their ultra-processed food and dietary heavy metal intake by providing access to effective nutritional epigenetics education.

AIM

To test the efficacy of nutritional epigenetics instruction in reducing parental

ultra-processed food intake.

METHODS

The study utilized a semi-randomized test and control group pretest-posttest pilot study design with participants recruited from parents having a learning-disabled child with autism or ADHD. Twenty-two parents who met the inclusion criteria were randomly selected to serve in the test (n = 11) or control (n = 11) group. The test group participated in the six-week online nutritional epigenetics tutorial, while the control group did not. The efficacy of the nutritional epigenetics instruction was determined by measuring changes in parent diet and attitude using data derived from an online diet survey administered to the participants during the pre and post intervention periods. Diet intake scores were derived for both ultra-processed and whole/organic foods. Paired sample t-tests were conducted to determine any differences in mean diet scores within each group.

RESULTS

There was a significant difference in the diet scores of the test group between the pre- and post-intervention periods. The parents in the test group significantly reduced their intake of ultra-processed foods with a pre-intervention diet score of 70 (mean = 5.385, SD = 2.534) and a post-intervention diet score of 113 (mean = 8.692, SD = 1.750) and the paired t-test analysis showing a significance of $P < 0.001$. The test group also significantly increased their consumption of whole and/or organic foods with a pre-intervention diet score of 100 (mean = 5.882, SD = 2.472) and post-intervention diet score of 121 (mean = 7.118, SD = 2.390) and the paired t-test analysis showing a significance of $P < 0.05$.

CONCLUSION

Here we show nutritional epigenetics education can be used to reduce ultra-processed food intake and improve attitude among parents having learning-disabled children with autism or ADHD.

Key Words: Epigenomics; Parenteral nutrition; Autism; Attention deficit/hyperactivity disorder; Ultra-processed foods; Heavy metals

Core Tip: Ultra-processed foods remain a source of heavy metal exposure in American families. The bioaccumulation of inorganic mercury and lead in the blood increases the severity of symptoms in children with autism and attention deficit/hyperactivity disorder *via* paraoxonase-1 gene modulation. Providing parents with nutritional epigenetics instruction may reduce their intake of ultra-processed foods and empower them to influence their child's behavior through dietary changes.

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INTRODUCTION

Excessive consumption of ultra-processed foods is a characteristic of unhealthy diet due to the increased intake of saturated fats and added sugars and decreased intake of essential micronutrients zinc (Zn), calcium (Ca), magnesium, vitamins A, C, D, E, B12, and niacin[1,2]. Increasing evidence links consumption of ultra-processed foods to the development of various disease conditions including obesity, type-2 diabetes, cardiovascular disease[3], and adverse child neurodevelopment[4,5]. In a recent diet study involving 2377 pairs of pregnant women and their offspring, Puig-Vallverdú *et al*[4] found an adverse association between maternal prenatal consumption of ultra-processed foods and verbal functioning in the offspring during early childhood. Zupo *et al*[5] performed a literature review of the evidence showing an association between maternal pre-natal diet and adverse neurodevelopmental outcomes in offspring and found a positive association between maternal prenatal diet high in ultra-processed foods and adverse verbal intelligence and executive functioning in the offspring during middle childhood. While the health problems associated with the consumption of ultra-processed foods are indisputable, the precise factors (*e.g.*, food ingredients, contaminants, additives, nutrient profiles) that cause the problems are not yet fully understood[3].

A few food ingredients have been studied by researchers and their role in the development of disease is becoming clearer. Ward was the first to report the health problems of hyperactive children affected by the consumption of yellow food colors including the development of eczema and/or asthma, respiratory and/or ear infections, poor speech, and poor coordination[6]. In a behavioral response study of hyperactive children and an age and gender matched control group, Ward determined only hyperactive children showed significant losses in serum Zn levels along with increased

levels of overactivity and aggression following the consumption of yellow food colors #5 and #6[7]. Milne and Neilsen[8] reported significant losses in Ca from the consumption of high fructose corn syrup (HFCS) in a small study of men and cautioned that a high fructose containing diet could lead to bone loss and the development of osteoporosis over time. Food colors yellow #5 and #6 and HFCS are a few examples of food ingredients commonly found in ultra-processed foods that are suspected of causing health problems by creating nutritional deficit and/or mineral imbalance. Numerous studies now indicate that reducing ultra-processed food intake will help eliminate the nutritional deficits that lead to poor health outcomes[2,3]. In a recent review, Touvier *et al*[3] stated "public health policies to reduce the consumption of ultra-processed food cannot wait". This statement especially applies to birth outcomes. In a recent scoping review, Cortés-Albornoz *et al*[9] found nutritional deficits during pregnancy are the recognized cause of some adverse birth outcomes and contribute to increased risk of several neuropsychiatric disorders, including those found in the autism spectrum, and attention deficit/hyperactivity disorder (ADHD).

In addition to the problem of creating nutritional deficits, excessive consumption of ultra-processed foods results in dietary heavy metal exposures[10,11]. Heavy metal exposures *via* the consumption of ultra-processed foods are allowed by food safety laws that regulate contaminant concentrations in various food ingredients. For example, in the case of synthetic petroleum-based food coloring, the United States Food and Drug Administration requires manufacturers to test and certify each batch of coloring to ensure the concentration of heavy metals does not exceed the levels permitted by law (≤ 1 ppm mercury (Hg), ≤ 10 ppm lead (Pb), and ≤ 3 ppm arsenic (As)[12]. These "certified" food colors (*e.g.*, yellow #5, yellow #6, red #40) are found in many ultra-processed food products consumed by both children[13] and adults in the United States and remain a significant health concern[14,15].

In addition to petroleum-based food coloring, heavy metal contaminants may be found in other highly consumed food ingredients such as high fructose corn syrup which is used by beverage companies as an added sweetener in soft drinks. Dufault *et al*[16] was the first to publish findings of Hg in HFCS. In subsequent studies, Rideout *et al*[17] and Wallinga *et al*[18] also reported finding low levels of (Hg in food products containing corn syrup or HFCS. Corn sweeteners, including HFCS, are at risk of inorganic-Hg (I-Hg) contamination due to their manufacturing process which involves the application of mercuric chloride to the corn starch at the beginning of the process to prevent starch degrading enzymes [19] and the use of Hg-grade chlor-alkali chemicals throughout the manufacturing process to adjust the pH of the various corn products[16].

Heavy metal contaminants are found throughout the food supply. Emerging evidence suggests prenatal exposure to heavy metals can influence the development of the child's immune system and contribute to the development of various disease conditions[20]. Prenatal exposures to cadmium (Cd), Pb, and/or Hg have been linked to the development of asthma, eczema, food allergy, and adverse respiratory outcomes in children[20-22]. Heavy metals may be transmitted to the fetus during pregnancy *via* cord blood. In a birth cohort study of 1751 pregnant women, Jeong *et al*[23] found maternal blood Pb and Hg concentrations correlated with the levels found in cord blood and in children up to age 5 years. In a more recent birth cohort study of children diagnosed with autism and/or ADHD in Norway, Skogheim *et al* [24] determined prenatal exposures to different heavy metals during gestation could adversely impact child neurodevelopment[24]. Hg, Pb, Cd, and As were among the notable heavy metals found to be involved in the development of autism and ADHD.

Heavy metals are detoxified in the body by metallothionein (MT) metal carrier proteins that must bind with Zn and copper (Cu) which are the elements required to regulate MT gene expression[25,26]. MT proteins play a vital role in metal trace element homeostasis within cells and tissues as heavy metals are detoxified and eliminated from the body[25]. In this capacity, MTs serve the immune system as potent antioxidant proteins because they protect DNA against oxidative stress that may occur if heavy metals accumulate in the body[25]. Dietary elements that reduce Zn availability or deplete Zn stores may disable MT functioning creating conditions for the bioaccumulation of heavy metals in cells and the buildup of oxidative stress which destroys cell membranes and tissues[27]. Dietary elements or contaminants known to reduce or deplete Zn include excessive exposures to heavy metals Hg[27,28], Pb, Cu, Cd, silver (Ag), Bismuth (Bi)[28], HFCS[27,29], yellow #5 and yellow#6[7], alcohol and some drugs[29]. Recent studies suggest the synaptic pathway for the development of autism may be the disruption of glutamatergic synapses which can be influenced by prenatal Zn deficiency and MT dysfunction both of which affect brain tissue metal-ion homeostasis[30].

Prenatal Zn deficiency arising from the maternal consumption of ultra-processed foods is one example of how reproductive risk occurs and can lead to behavioral abnormalities and impaired immunocompetence in children[31]. Uriu-Adams and Keen[31] found poor diet leading to Zn deficiency, for even a short period of time, can present a risk to the developing fetus. More recent literature reviews indicate prenatal and offspring Zn deficiency are now strongly associated with the development of autism and ADHD[32,33]. Heavy metal exposures from consumption of ultra-processed foods compromise maternal and child Zn status and cause MT gene malfunction which leads to the bioaccumulation of heavy metals in blood[27]. Multiple studies indicate the heavy metal levels found in the blood of children with autism or ADHD correlate with the severity of their symptoms[34-39]. Recent rat studies demonstrate the toxic and synergistic effects of low dose combined exposures to Hg, Pb, and Cd on hippocampal neurons[40,41]. These studies show dietary co-exposures to Hg, Pb, and Cd correlate to Hg, Pb, and Cd levels in blood and the intensity of oxidative stress in brain tissue with impacts on rat learning and memory impairment[40,41].

Evidence suggests nutritional deficits and heavy metal exposures associated with poor diet (*e.g.*, excessive consumption of ultra-processed foods) are the primary epigenetic factors responsible for the development of autism and ADHD *via* MT gene dysfunction[27] and paraoxonase-1 (PON1) gene suppression[11]. The field of science that studies the effects of heavy metal exposures and diet on gene behavior is nutritional epigenetics. Figure 1 shows the constructs of the nutritional epigenetics model for autism and ADHD that explains how dietary factors (*e.g.*, HFCS, yellow #5, yellow #6, Hg and Pb exposures) from the consumption of ultra-processed foods lead to the development of nutritional deficits and mineral imbalances that disrupt MT gene function. MT gene disruption leads to the bioaccumulation of heavy metals in

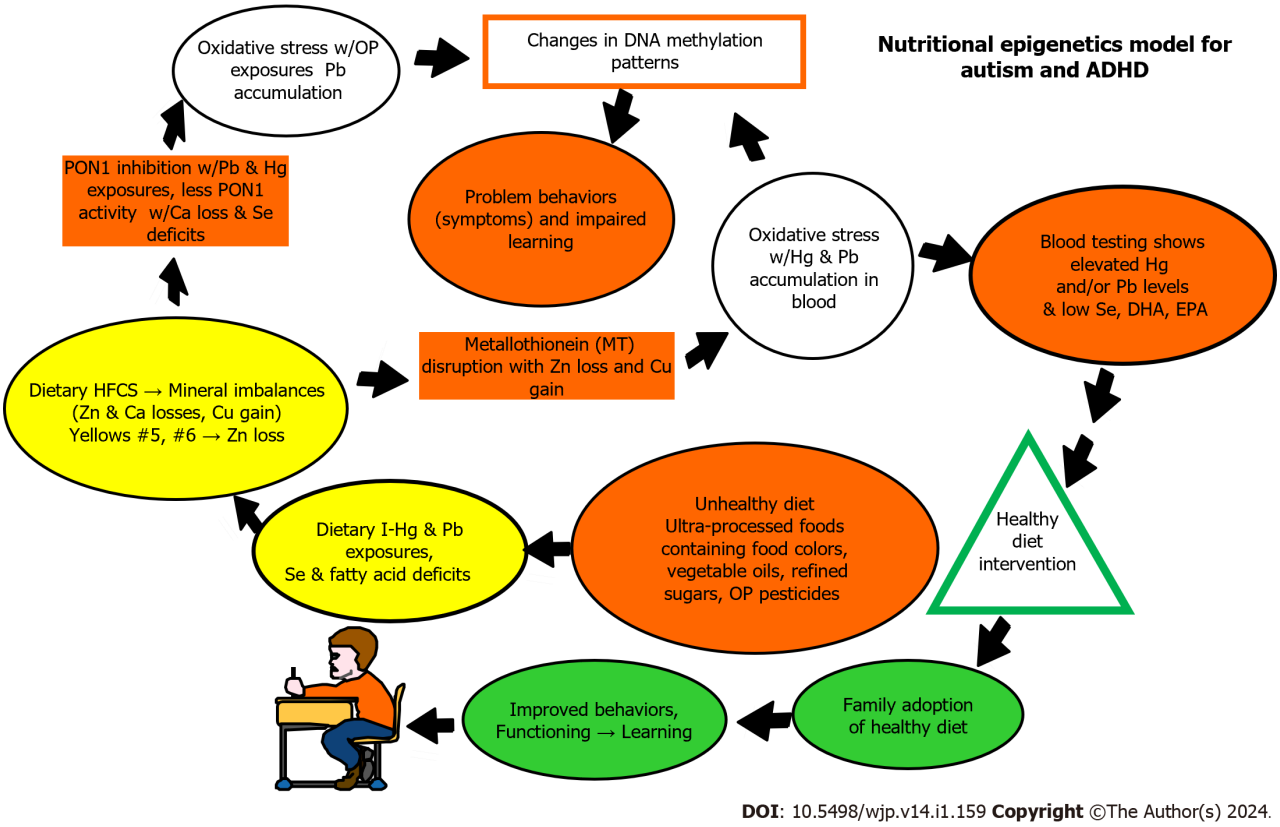

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Figure 1 Nutritional epigenetics model for autism and attention deficit hyperactivity/disorder. Ultra-processed foods contain food colors, vegetable oils, refined sugars such as high fructose corn syrup (HFCS), and organophosphate (OP) and other pesticide residues. Consumption of ultra-processed foods leads to inorganic mercury and lead (Pb) exposures and dietary deficits in fatty acids (*e.g.*, docosahexaenoic acid, eicosapentaenoic acid) and micronutrients such as selenium. Dietary consumption of HFCS and food colors, yellow #5 and yellow #6, leads to mineral imbalances such as zinc and/or calcium losses and copper gain. Inadequate zinc stores and copper gain can disrupt metallothionein gene function and result in the bioaccumulation of heavy metals in the blood stream which creates oxidative stress and changes in DNA methylation patterns that may impact child health and learning across generations. Inadequate calcium stores can lead to the bioaccumulation of Pb in the bloodstream and inhibit paraoxonase-1 (PON-1) gene function which is needed to detoxify the neurotoxic OP residues in the food supply. Without adequate PON1 gene activity, dietary exposures to OP pesticide residues result in oxidative stress and changes in DNA methylation patterns that impact child health and learning across generations. ADHD: Attention deficit hyperactivity/disorder; OP: Organophosphate; DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; I-Hg: Inorganic mercury; PON-1: Paraoxonase-1.

the blood and problem behaviors and impaired learning in offspring. Maternal exposures to Pb and Hg *via* unhealthy or poor diet, lifestyle, and environment are transmitted to the child *via* cord blood[23] and are likely responsible for the development of autism and ADHD in children[24,42], especially in the case of PON1 gene suppression[10,11,43] which can result in oxidative stress[44] and changes in DNA methylation patterns[45]. Expression of the PON1 gene results in the body's production of the Ca dependent paraoxonase enzyme that detoxifies organophosphate (OP) pesticide residues [46] found widely in the United States food supply[47]. Prenatal OP pesticide exposures are neurotoxic, producing lasting effects on the behavioral health of children[48] and may impact their ability to learn when PON1 gene activity levels are low[11]. Inhibitors of PON1 gene activity include dietary exposures to fructose (*e.g.*, HFCS), Hg and Pb, and nutritional deficits in fatty acids, Ca, and selenium (Se)[10]. Diet interventions aimed at educating parents on each of the constructs that form this model may lead to the adoption of healthier diets.

MATERIALS AND METHODS

The study utilized a semi-randomized test and control group pretest-posttest pilot study design with participants recruited from parents having a learning-disabled child with autism or ADHD. Prior to participant recruitment, the curriculum for the tutorial intervention was developed and built online at the non-profit Food Ingredient and Health Research Institute[49]. The online curriculum was modeled after a previous online nutritional epigenetics course that was focused on teaching college students how to reduce their intake of ultra-processed foods and improve their intake of whole and organic foods while reducing their blood I-Hg and glucose levels[50]. For this diet intervention study, we focused the curriculum on the known factors of the western diet that contribute to heavy metal exposures and nutritional deficits that may impact gene behaviors in children with autism and ADHD. In learning how specific food ingredients contribute to heavy metal exposures, impact nutrient status and/or gene behavior (Figure 1), and child health and learning outcomes, parents may then have the knowledge they need to feed themselves and their children a healthy diet.

Curriculum and tutorial development

The curriculum consisted of a textbook titled, "The Toxic Western Diet: What Parents Must Know to Protect Their Family," that was written by the principal investigator for use in conjunction with six online modules of instruction[51]. There were learning objectives posted online for each module of instruction along with four assigned activities. Every week each participant was expected to complete four activities which included a reading assignment from the textbook, three discussion questions to be answered in a discussion group setting, and two other activities which varied depending on the topic (*e.g.*, video assignment, kitchen cupboard survey, online scavenger hunt for facts, meal preparation assignment). The hands-on activity and video assignments for each chapter are provided in the textbook which accompanies this article as Supplementary material in PDF file format for the purpose of study duplication.

The textbook chapters and associated modules of instruction are titled as follows: (1) Chapter 1: How food regulates and supports gene function; (2) Chapter 2: What we eat or don't eat leads to disease; (3) Chapter 3: Ingredients that add heavy metals to your body; (4) Chapter 4: What we know about corn sweeteners; (5) Chapter 5: What we know about pesticides; and (6) Chapter 6: How we can create a safe food environment. Each textbook chapter provides at least 42 science-based references to support the content. During the study, all references were accessible online at the tutorial web page. Each chapter presented several lessons that helped improve parent understanding of the role diet plays on their child's behavior and health. Table 1 provides detailed information on the content covered in each module of instruction.

The textbook has been updated[52] and the tutorial is now available in a study guide hardcopy format[53]. Supplementary material provides an example of one module of instruction in the tutorial/study guide[53]. It may be used in conjunction with Chapter 4 of the current textbook which is titled, "Ingredients that add heavy metals to your body"[52]. In this chapter, parents read the results of previous studies that show consumption of food colors yellow #5 and yellow #6 by hyperactive children leads to Zn losses and increased hyperactivity[6,7]. Parents learn that products with these food colors sold in the European Union must carry the following mandatory warning on their labels: "May have an adverse effect on activity and attention in children[54,55]." A hands-on activity in the study guide involves the parent conducting a survey while using the tables in this chapter to find and list all the food products in their kitchen that contain yellow #5, yellow #6, and other ingredients with allowable heavy metal residues. Another hands-on activity involves the parent finding a recipe to prepare a Zn rich meal for the family. Parents learn that Zn is needed by the body to build the MT transporter protein that supports heavy metal excretion. The textbook is geared to teach parents how to avoid consuming ultra-processed food products known or likely to contain ingredients with heavy metal or pesticide residues while increasing consumption of whole foods that contain the essential nutrients required by the body to support gene function so that it can build the proteins needed to improve child health, behavior, and learning outcomes.

Study design for evaluating tutorial

The study was a semi-randomized test and control group pretest-posttest pilot study design. The tutorial intervention lasted six weeks, and participants were surveyed online at baseline and post intervention. In accordance with the protocol, all the participants provided written informed consent to participate in the study. The protocol for the study was approved and found to be exempt from further review by the A.T. Still University Institutional Review Board (IRB).

Sample size calculation

The required sample size was calculated before the start of the study. A prior study using the same survey instrument[50] produced mean diet scores at pre and post intervention of 16.0 and 23.2 with the standard deviations of 1.72 and 2.83, with n = 10. Based on calculation procedures provided by Kirkwood and Stein[56], a sample size of less than 10 was determined to be adequate for this study. The variables for the sample size analysis are shown in Table 2. The formula used to determine the sample size for each group (test and control) is provided by Kirkwood and Sterne[56] as follows:

$$\frac{(u + v)^2 (\sigma 1^2 + \sigma 0^2)}{(\mu 1 - \mu 0)^2} > n$$

n (number required for each group), assuming power = 90%, u = 1.28; assuming significance level = 5%, v = 1.96. Substituting estimated values for the means and standard deviations outlined in Table 2 results in the following:

$$\frac{(1.28 + 1.96)^2 (1.72^2 + 2.83)^2}{(23.2 - 16.0)^2} > 2.2 \text{ (number required for each group)}$$

According to the calculation, at least three participants were needed in each group (test and control) for this study. If 20 participants were recruited to enroll in the study with 10 participants serving in the test group and 10 participants serving in the control group, there would be enough data to include in the final analysis even with a few dropouts.

Participant recruitment and eligibility

Participants were chosen from a population of parents who have learning-disabled children with behavior problems commonly associated with autism, developmental delay, and ADHD. Recruitment was primarily conducted using a Facebook[57] web page announcement hosted by the non-profit Food Ingredient and Health Research Institute[49]. The recruitment web page was "shared" with various organizations across the United States with a mission to serve parents with learning-disabled children. Approximately 250 parents responded to the recruitment web page by sending inquiry emails with most being excluded due to their child's existing diet. Parents with children on special diets (*e.g.*, Feingold, gluten free, or casein free) were excluded from the study.

Eligibility for participation in the tutorial project was determined using the protocol approved by the A.T. Still University IRB, which included the use of a screening questionnaire. Supplementary material provides a copy of the

Table 1 Content of each module of instruction

Module	Title/book chapter	Topics covered	Activities	Films
One	How food regulates and supports gene function	Genes, epigenetics, gene regulation, methylation, hypomethylation, methyl donating nutrients, micronutrients to support PON1, BDNF, and MT	3	Ghost in your genes (BBC television)
Two	What we eat or don't eat leads to disease	Characteristics of SAD, obesity, malnutrition, nutritional deficits, gene malfunction, USDA food availability system, refined sugar and vegetable oil consumption trends	3	Super size me (streaming documentary)
Three	Ingredients that add heavy metals to your body	Allowable heavy metal levels in food ingredients (*e.g.*, food coloring, preservatives), food manufacturing, chlor-alkali refining, known contaminants (*e.g.*, vegetable oils), zinc deficiency in autism and ADHD	4	The medicine of food (Smithsonian Institute)
Four	What we know about corn sweeteners	Corn sweeteners, manufacturing process, contamination, ultra-processed foods, heavy metal bioaccumulation, western diet - > western disease	2	King corn (streaming)
Five	What we know about pesticides	Chlorine, USDA Pesticide Data Program, OP, *PON1* gene function in autism/ADHD, symptoms of OP poisoning	3	The autism revolution: Thinking about environment and food (IATP)
Six	How we can create a safe food environment	Current food regulations (*e.g.*, ingredient safety and labeling), history of FDA, food allergies, dietary supplements, Hg in fish issues, healthy food labels	4	No video

ADHD: Attention deficit hyperactivity/disorder; OP: Organophosphate; PON-1: Paraoxonase-1; MT: Metallothionein; FDA: Food and Drug Administration; IATP: Institute for Agriculture and Trade Policy.

Table 2 Change in diet scores for each participant (for sample size calculation)

	Intervention	Control	*P* value (*t*-test)
N	10	10	
Mean diet score			
Baseline	16.0 (2.83)	16	
6 wk	23.2 (1.72)	16	
Change	7.2	0	< 0.05

Data are means with SD and *t*-test.

screening questionnaire. Parents of learning-disabled children demonstrating the most severe behavior problems were given priority for enrollment in the tutorial. Severity was determined by the number of child behaviors observed by the parents within the last 24 h as recorded on the screening questionnaire checklist. Observed child behaviors included any of the following: Frequent tantrums, hyperactivity, self-injury (head banging), pica (chewing on objects), running away, and aggression (hitting, name-calling). Of the 93 parents who filled out and submitted the screening questionnaire, 23 met the inclusion criteria for the study and were invited to participate in the tutorial project. Prior to their enrollment in the study, all parents interviewed face to face *via* Skype or by phone with the investigator and were provided with the opportunity to ask questions about their participation in the study before signing the informed consent form. Participants were alternately assigned to the test or control group when eligibility was confirmed and after receipt of the signed informed consent form.

Eligible parents had a learning-disabled child between the age of 34 mo and 8 years, daily access to the internet, and documentation of their child's disability. All participants reported having a minimum educational level equivalent to a high school diploma. For this basic study, only the test group received nutritional epigenetics instruction *via* the online tutorial intervention. The participants in the test group began the tutorial on the same date and had the flexibility of any other online course. They were able to access the tutorial at any time anywhere in the world if they had internet access. One parent dropped out of the study before the tutorial began, which left 11 parents serving in the test group and 11 parents serving in the control group. Pre and post intervention, all participants completed the online diet survey questionnaire comprised of 30 dietary habit questions and 10 participant characteristic questions.

Survey instrument design and use

A survey questionnaire was developed using the Survey Monkey[58] website. The survey consisted of one item to determine parental belief about the role of diet in child behavior, several items to collect qualitative demographic data to characterize the family units (*e.g.*, highest level of education, race or ethnicity, age of learning-disabled child, parent observation of child behavior in past 24 h), and food frequency questions to characterize parental dietary intake. The food

frequency questions were modeled after those used by the National Cancer Institute[59] to measure dietary intake in the past month and designed to determine the proportion of time specific whole foods or ultra-processed foods were eaten by the parent. There were seventeen questions for measuring whole and/or organic food intake and thirteen questions for measuring ultra-processed food intake. Food products were considered ultra-processed if they contained more than one ingredient along with at least one ingredient known, or likely, to contain heavy metal residues. Products made from conventional flour with pesticide residues or bleached flour were considered ultra-processed foods. Whole foods, originating from a farm (one ingredient) were considered less processed and healthier to consume.

All food frequency questions used a similar structure. For example, an item used to measure the intake of dark green vegetables, a whole food, was written as follows: During the past month, how many times did you eat dark green vegetables (romaine lettuce, spinach, broccoli, kale, Swiss chard, collard, or other greens)? The possible responses included: Never, rarely (once or twice a month), once a week, several times a week, daily (1-2 servings), several times a day (3 or more servings). An example of a question used to measure the intake of cereal, an ultra-processed food, was written as follows: During the past month, how many times did you eat ready to eat cereal (corn flakes, rice crisp, corn squares, fruity o's, oat circles, *etc.*)? The same set of responses were used for each question. A question used to measure the intake of swordfish or tuna was included in the ultra-processed food category because their consumption can lead to Hg exposure, and one purpose of the tutorial was to decrease consumption of foods that may contain heavy metal or pesticide residues.

The food frequency questions did not follow any specified order in the survey (whole food *vs* ultra-processed food), so parents were not aware of their significance. Item design was intentional and tracked back to lessons learned about the importance of certain nutrients in modulating gene function and child behavior. For example, some items used to measure intake of ultra-processed foods were associated with food ingredient labels containing corn sweeteners and food colors that may lead to heavy metal exposures and Zn losses. All the food frequency questions are provided in Tables 3 and 4.

The food frequency questions had been pilot tested successfully and validated in a previous clinical trial that involved the delivery of an online nutritional epigenetics course to students at a tribal college located on an Indian reservation[50]. The diet survey utilized during that trial was comprised of the same food frequency questions used for the diet survey administered during this study. The survey was validated to correctly measure intake of ultra-processed and whole foods through biomarker collection (*e.g.,* blood) and analyses[50]. College students who significantly reduced their intake of ultra-processed foods and increased their intake of whole and/or organic foods had lower inorganic blood Hg levels compared to students who did not participate in the online nutritional epigenetics course[50]. During this study, parents in the test and control groups were administered the survey online pre and post intervention during a specified period. Each parent received a link to the confidential survey *via* email.

Data analysis

The qualitative demographic data was analyzed to determine the percent of family units with or without college, percent of family units in each ethnic group, percent of participants observing specific problem behaviors in the last 24 h, and percent of families having learning-disabled children in different age groups.

Quantitative data in ratio form (proportion) was analyzed to determine how many times in the past month different foods were eaten by the parent. The data was coded and each response in the healthier range was awarded a score of 1. Less healthy responses received a score of 0. For example, more frequent consumption of whole and/or organic foods achieved a higher score, as did less frequent consumption of ultra-processed foods. Each item was scored positively with a 1 if the participant reported a diet habit consistent with the instruction. A diet behavior score was calculated for each participant as the sum of the 1's across all questions. The mean diet score for each group (test and control) was also calculated for each period (pre and post intervention). The scoring procedure for this study was the same procedure used for the tribal college study[50]. A two-sample paired *t*-test was conducted to determine any significant difference in parental diet behavior between the pre and post periods.

Comparisons of pre- and post-intervention diet scores for test and control groups were performed using a two-sample paired *t*-test, with two tails and alpha = 0.05. All *t*-tests were conducted in R. Version 4.3.0 (2023-04-21ucrt). The following four assumptions of the *t*-test are met: (1) No outliers - outliers were tested in two stages using box plots and Grubbs test. Stage 1: Each of the distributions were examined for outliers using box plots in R. Outliers were noted for the distribution of process - post-intervention test group and the distribution of process - post-intervention control group. Both these outliers were for the item, "eat grain products made of wheat such as macaroni, bread, hamburger or hot dog buns, or spaghetti". Another outlier was found for the distribution of process - pre-intervention control group for the item, "eat foods prepared with organic flour". Stage 2: The outliers found in stage 1 were not found to be outliers when tested using the Grubbs test with alpha = 0.01. The Grubbs test is known as the maximum normed residual test or the extreme studentized deviate test[60,61]; (2) Normality: The Shapiro-Wilk normality test in R showed no distributions with a *P*-value < 0.01. All distributions were found to be normally distributed; (3) Random: Subjects were assigned randomly to test and control groups as described in the participant recruitment and eligibility section above; and (4) Equal variance: R does not assume equal variance between the samples for the *t*-test. The default status in R for the *t*-test is unequal variance. The Welch's *t*-test was performed for all *t*-tests in R. The statistical methods of this study were reviewed and verified by Dr. Raquel Crider of the Food Ingredient and Health Research Institute.

Table 3 Changes in intake of ultra-processed food pre- and post-intervention

Survey questions (questions begin with "During the past month, how many times did you …?"	Pre-intervention		Post-intervention	
	Test	Control	Test	Control
…drink a sugar sweetened beverage such as ginger ale, orange soda, fruit punch, root beer, or other soft drink (do not include diet drinks)[1]	5	8	9	8
…eat canned fruit with syrup or added sugar (applesauce, apricot halves, mixed fruit, pears, cling peaches)?[1]	9	8	11	10
…eat canned meals (soup, re-fried beans, chili, spaghetti, beef stew, *etc.*…)?[2]	8	10	10	11
…eat processed cheese (American, yellow cheddar)?[1]	3	5	9	6
…eat sweetened or flavored milk products (fruity or sweetened yogurt, pudding cups, chocolate flavored milk, *etc.*…)?[1]	8	7	9	7
…eat processed meat (lunch meat, hotdogs, bacon, ham in a can, sausage, beef jerky, *etc.*)?[2]	4	7	10	8
…eat ready to eat cereal (corn flakes, rice crisp, corn squares, fruity o's, oat circles, *etc.*)?[2]	3	5	7	3
…eat swordfish or tuna (canned, fresh, or frozen)?[1]	8	7	9	7
…eat foods fried in vegetable oil such as potato or corn chips, popcorn, French fries, hash browns, fry bread, fast food fried chicken, fish sticks, doughnuts?[2]	5	6	10	5
…eat food purchased from a drive thru taco or hamburger restaurant, pizza parlor, other chain?[1]	4	5	9	7
…eat sweet snacks such as candy, cookies, ice cream, popsicle, other sugar sweetened treat (do not include diet)?[2]	1	6	8	8
…eat grain products made of wheat such as macaroni, bread, hamburger or hotdog buns, or spaghetti?[2]	4	3	4	2
…eat white rice?[2]	8	9	8	10
Total diet score	70	86	113	92
mean ± SD	5.385 ± 2.534	6.615 ± 1.895	8.692 ± 1.750	7.077 ± 2.629

[1]Score = 1 if "never, rarely (once or twice a month)".
[2]Score = 1 if "never, rarely, once a week".

RESULTS

Participant demographic characteristics

Table 5 shows the demographic characteristics of the parents who participated in the nutritional epigenetics tutorial study. All (100%) of the participants reported having some college. Participant race or ethnic group only varied slightly between test and control groups. The age distribution for the learning-disabled children in the family units was the same for both groups. Although the gender of the parents was not determined by the questionnaire, pre-intervention interviews confirmed all participants were female. Problem child behaviors observed by parents in the last 24 h varied only slightly between groups.

Efficacy of tutorial on parent diet

Table 3 shows the changes in dietary intake of ultra-processed foods among the parents between the pre and post intervention period. The unit of analysis is the item of the online diet survey. The processed food section of the diet survey had 13 items. Each participant that responded with a healthy response to a single item was awarded a score of 1. For example, during the pre-intervention period, one person in the test group gave a healthy response (*e.g.*, "never, rarely, once a week") to the question "during the past month, how many times did you eat sweet snacks such as candy, cookies, ice cream……?" After undergoing the intervention, 8 participants in the test group gave a healthy response to the same question so the score for this item on sweet snack intake increased from 1 to 8. After participating in the intervention, parents in the test group adopted a healthier eating pattern for sweet snacks. The only items in this part of the survey for which scores did not change for the test group were the questions asking about grain products made of wheat and white rice.

Table 4 shows the dietary intake of whole and/or organic food among the parents between the pre and post intervention period. The unit of analysis is the item of the online diet survey. The whole and/or organic food section of the diet survey had 17 items. Each participant that responded with a healthy response to a single item was awarded a score of 1. For example, during the pre-intervention period, four participants in the test group each received a score of 1 because each gave a healthy response (*e.g.*, "rarely, once a week, several times a week, every day") to the question "during the past month, how many times did you eat foods prepared with organic flour……?" After undergoing the intervention, 9 participants in the test group gave a healthy response to the same question so the score for this item on

Table 4 Changes in intake of whole and/or organic food pre- and post-intervention

Survey questions (questions begin with "During the past month, how many times did you …?"	Pre-intervention		Post-intervention	
	Test	Control	Test	Control
…eat crab or oyster (fresh, frozen, or canned)?[1]	4	2	6	1
…drink unflavored milk (non-fat, 2%, or whole)?[2]	7	5	7	4
…eat product made from unsweetened, unflavored milk (plain yogurt, cottage cheese, white cheese)?[3]	9	9	10	8
….eat fresh or frozen fruit (bananas, oranges, apples, strawberries, blueberries, *etc.*)?[2]	10	10	10	10
…eat canned vegetables (spinach, green beans, corn, peas, mixed vegetables, tomato, *etc.*)?[4]	5	5	2	4
…eat frozen vegetables (spinach, green beans, corn, peas, carrots, mixed vegetables, *etc.*)?[2]	3	5	3	3
…drink 100% fruit or vegetable juice (apple, orange, grape, tomato, *etc.*)?[3]	4	5	6	6
…eat salmon or sardines (frozen, fresh or canned)?[3]	3	1	4	1
…eat poultry (chicken or turkey)?[2]	9	7	8	9
…eat red meat (hamburger, beef, pork, lamb, *etc.*)?[3]	10	10	8	10
…eat nuts or seeds (Brazil, sunflower, pine, almonds, sesame seeds, peanuts, pecans)?[3]	4	6	6	5
…eat dark green vegetables (romaine lettuce, spinach, broccoli, kale, Swiss chard, collard or other greens)?[2]	7	5	7	3
….eat brown rice?[1]	7	5	9	6
…eat oatmeal?[1]	6	8	8	7
….eat foods prepared with organic flour?[1]	4	3	9	4
…eat organic produce?[1]	5	10	10	10
….eat organic processed foods (bread, cereal, *etc.*)?[1]	3	9	8	10
Total diet score	100	105	121	101
mean	5.88	6.176	7.12	5.941
SD	2.47	2.811	2.39	3.152

[1]Score = 1 if "rarely (once or twice a month), once a week, several times a week, pretty much every day (1-2 servings)".
[2]Score = 1 if "several times a week, pretty much every day (1-2 servings), several times a day (3 or more servings)"[45].
[3]Score = 1 if "once a week, several times a week, pretty much every day (1-2 servings)".
[4]Score = 1 if "once a week, rarely (once or twice a month)".

"foods prepared with the organic flour" increased from 4 to 9. After participating in the intervention, parents in the test group adopted a healthier eating pattern by eating more organic foods thus reducing their pesticide exposure. Their intake of organic flour, organic produce and organic bread showed impressive post-intervention scores, with each item increasing 5 to 6 points. The participants likely also reduced their I-Hg exposure because organic flour is unbleached and does not contain the allowable Hg residue that may be found in the bleached flour products[62].

Table 6 presents an analysis of changes in parent dietary intake within both the test and control groups pre- and post-intervention. Paired sample *t*-tests were conducted to determine any differences in mean diet scores within each group, test, and control. While there were no significant differences in the consumption of ultra-processed or whole foods by control group participants between the pre- and post-intervention periods, there were significant differences in the dietary habits of the test group participants. The test group diet score for avoiding ultra-processed food increased from 70 to 113 between the pre- and post-intervention periods. The paired *t*-test analysis was significant with $P < 0.001$. For the whole and/or organic food category, the total pre-intervention diet score is 100, and the post-intervention score is 121 for the test group. The paired *t*-test analysis was significant with $P < 0.05$. The findings presented in Table 6 indicate the parents in the test group who completed the tutorial significantly increased their consumption of whole and/or organic foods and significantly decreased their consumption of ultra-processed foods.

Table 7 presents a summary with the key findings of the *t*-test results showing changes in parental dietary intake within groups pre- *vs* post-intervention. The summary shows all the important statistical information along with the tested hypotheses and the effect size for each of the *t*-tests.

Table 8 presents the data collected to measure the changes in the parents' attitude about their ability to control their child's behavior through diet. The survey item was worded "To what extent do you agree with the following statement: I have the ability to control the behavior of my family's learning-disabled child through diet". The data was coded "1" if a parent responded with "strongly agree" or "agree" and "0" for all other responses. The total and mean score for each group was calculated along with the standard deviation. During the pre-intervention period, three parents in the test group and four parents in the control group responded in agreement to the item statement. During the post-intervention

Table 5 Characteristics of participants in nutritional epigenetics tutorial study

	Test group, *n* = 11	Control group, *n* = 11
Race or ethnic group (%)		
White - not Hispanic	7 (63.6)	8 (72.7)
Black or African American	1 (9.1)	
Asian	3 (27.3)	1 (9.1)
Mixed - more than one race		2 (18.2)
Educational level of parent (%)		
High school diploma or GED		
Some college or college degree	11 (100)	11 (100)
Age of learning-disabled child (%)		
34 mo - 4 yr of age	2 (18.2)	2 (18.2)
5-6 yr of age	3 (27.3)	3 (27.3)
7-8 yr of age	6 (54.5)	6 (54.5)
Problem child behaviors observed by parent in the last 24 h (%)		
Tantrum	7 (63.6)	5 (45.4)
Hyperactivity	9 (81.8)	7 (63.6)
Self-injury (head banging)		2 (18.2)
Pica (chewing on objects)	5 (45.4)	5 (45.4)
Aggression (name calling, hitting)	4 (36.4)	2 (18.2)
Running away	5 (45.4)	4 (36.4)

Data are frequency (%).

Table 6 Changes in parent dietary intake within groups pre- *vs* post-intervention

Food category	Pre *vs* post-intervention		Paired sample *t*-test	Pre *vs* post-intervention		Paired sample *t*-test
	Test (*n* = 11)	Test (*n* = 11)	*P* value	Control (*n* = 11)	Control (*n* = 11)	*P* value
Ultra-processed food						
Total diet score	70	113		86	92	
mean	5.385	8.692	0.0001	6.615	7.077	0.107
SD	2.534	1.750	< 0.001	1.895	2.629	> 0.05
Whole and/or organic food						
Total diet score	100	121		105	101	
mean	5.882	7.118	0.021	6.176	5.941	0.205
SD	2.472	2.390	< 0.05	2.395	3.152	> 0.05

period, ten parents in the test group and three parents in the control group responded in agreement to the item indicating a change in attitude had occurred among the parents who participated in the tutorial.

Feedback was collected from the parents who completed the online nutritional epigenetics tutorial. Table 9 shows the feedback provided by the test group. The feedback indicates the hands-on activities helped parents learn to read food ingredient labels. The kitchen cupboard survey activities helped parents differentiate between ultra-processed and minimally processed foods. Parents indicated they changed their shopping habits by reducing or eliminating toxic food ingredients from their family's diet.

The study results showed the use of an online nutritional epigenetics tutorial could facilitate and influence healthy dietary changes in parents of children with autism and ADHD. The parents in the test group significantly reduced their consumption of ultra-processed foods and increased their consumption of whole and organic food after participating in the tutorial. Parents who participated in the tutorial became more confident in their ability to control their child's

Table 7 Within group summary with key findings of *t*-test results showing changes in parental dietary intake within groups pre- *vs* post-intervention

Ultra-processed food, test group, pre *vs* post	Ultra-processed food, control group, pre *vs* post	Whole and/or organic food, test group, pre *vs* post	Whole and/or organic food, control group, pre *vs* post
$P < 0.001$	$P > 0.05$	$P < 0.05$	$P > 0.05$
$t = -4.9109$, df = 12	$t = -1.3145$, df = 12	$t = -2.209$, df = 16	$t = 0.84563$, df = 16
P-value = 0.0003592	*P*-value = 0.2132	*P*-value = 0.0421	*P*-value = 0.4102
Effect size = 1.36	Effect size = 0.36	Effect size = 0.54	Effect size = 0.21
Cohen's d - large	Cohen's d - small	Cohen's d - medium	Cohen's d - small
H0: Mean pre-intervention group = mean post intervention group	H0: Mean pre-intervention group = mean post intervention group	H0: Mean pre-intervention group = mean post intervention group	H0: Mean pre-intervention group = mean post intervention group
H1: Mean pre intervention group ≠ mean of post intervention group	H1: Mean pre intervention group ≠ mean of post intervention group	H1: Mean pre intervention group ≠ mean of post intervention group	H1: Mean pre intervention group ≠ mean of post intervention group
H0 rejected	H0 supported	H0 rejected	H0 supported
Significant difference between pre and post intervention for test group. Mean of test group was greater than the mean of the control group	No significant difference between pre and post intervention for control group	Significant difference between pre and post intervention for test group. Mean of the test group was greater than the mean of the control group	No significant difference between pre and post intervention for control group

Table 8 Differences in attitude about behavioral control pre- and post-intervention

Survey question	Pre-intervention		Post-intervention	
	Test (*n* = 11)	Control (*n* = 11)	Test (*n* = 11)	Control (*n* = 11)
To what extent do you agree with the following statement: "I have the ability to control the behavior of my family's learning-disabled child through diet"?				
Total score	3	4	10	3
mean	0.273	0.364	0.909	0.273
SD	0.467	0.505	0.302	0.467

Data were coded "1" if participant responded with "strongly agree" or "agree" and "0" for all other responses.

problem behaviors through dietary changes. The feedback from the parents in the test group indicates they became better able to manage their family's dietary environment and eating behavior at home. During the online discussions, some parents reported seeing improvements in their child's behavior with the changes in family diet.

DISCUSSION

Parents play a crucial role in shaping a child's food preferences because they choose what foods to feed their children [63]. Food preferences begin developing in the fetus in utero and continue after birth during breast feeding and/or formula feeding[64-66]. There is evidence to suggest children eat, or learn to eat, what their parents eat. Dolwick and Persky[67] found an unhealthy dietary pattern of excessive ultra-processed food intake by parents is associated with unhealthy child feeding behaviors, including the excessive intake of ultra-processed foods. An *et al*[68] conducted a cross-sectional study of caregivers of children (n = 408) in China to determine whether caregiver feeding behaviors were associated with child ultra-processed food intake. Caregiver feeding habits were positively associated with children's consumption of ultra-processed foods including a higher frequency, and larger amount, of ultra-processed food intake [68]. Nutrition interventions aimed at parent education are recommended because such instruction may create a healthier home food environment and improve child feeding and health outcomes[67,68].

Few studies have been conducted to test the efficacy of parent education programs aimed at improving the diet of parents of learning-disabled children. In a sample of 356 parents of children with autism, spina bifida or Down syndrome, Polfuss *et al*[69] found parent feeding behaviors are significantly related to the child's weight but there was no attempt to provide a nutrition intervention. To address the feeding problems of food aversion and selectivity in children with autism, Sharp *et al*[70] conducted a pilot study to determine the feasibility of two separate parent education programs:

Table 9 Feedback from parents who completed online nutritional epigenetics tutorial

Survey questions	Feedback
Did you find the cupboard surveys and other activities helpful in preparing healthy meals for your family? Why or why not?	Yes. I'm trying to buy more organic foods after the tutorial. I was in denial before the tutorial
	Yes. Learned to pay attention to food ingredient labels
	Yes, it made me look at what I currently have and evaluate it. A lot of the items I had in my pantry I had no idea had some of the "toxic" ingredients. It made me look at it immediately instead of just thinking, "I'll look at it later."
	Yes, it is very helpful because I learned that I need to check the contents of the food before serving it to my family
	I thought it was a good way to really 'see' what you've been buying
	Yes! It forced me to take a difficult look at what I was feeding myself and my family. It's one thing to understand a concept in a book, entirely different thing to see it in real time in your own kitchen and on your children's dinner plates
	Yes, it makes you accountable for what is in your pantry
	Yes, the surveys/activities made me take the time to go through my food items and see how good/bad they were for my family
	Yes, the cupboard surveys were very helpful. The surveys allowed me to take an inventory of what I was feeding my family. It has also helped me be more aware of the food labels when purchasing food from the grocery store
	Yes. It made me really look at the things I was feeding my kids
What did you learn? How did the tutorial change you or your family's diet?	I should purchase organic grains and avoid cereals. I'm considering purchasing a bread machine so that I can make my own organic bread
	We changed to an organic more Mediterranean type diet
	I learned specifically what toxic foods/ingredients are put into our foods and then what foods will help counteract the negative effects of them. It changed our diet by making me change not only what I take out of our diet (like as much HFCS as I can, and processed foods in general), but also what I can add to improve negative reactions (like how Brazil nuts have selenium)
	This helped me a lot especially when it comes to serving food to my child with autism. He's a very picky eater but thank God he's improving right now
	This really opened my eyes to things that should have been obvious but weren't
	I learned so much! It has absolutely changed the way I buy and prepare foods. I'm also inspired to live more sustainably, growing and preserving our own foods
	As a family we have become more aware of what we eat and the ingredients in our food. We are trying to make more health choices, including not choosing flavored milk at school
	I learned that most processed/packaged food contains ingredients that are detrimental to our bodies, regardless of what the nutrition label says. Eating fresh-grown, organic produce and meats seems to be the only way to go
	I learned that the food available for consumption, although it may taste good, is not always good for us. The tutorial has taught me more about the dangers of certain food ingredients. As a result of the tutorial I have changed my family's diet by serving less of those ingredients and in most cases eliminating many of them
	I learned a lot, and I have made modest changes along with changing my husband's views, which is big

HFCS: High fructose corn syrup.

one focused on the management of eating aversions *via* behavioral interventions and the other focused on providing nutrition education with strategies for meal structure and diet expansion. The nutrition parent education program proved to be more promising at alleviating the problematic mealtime behaviors among the children but required further study [70]. Thorsteinsdottir *et al*[71] conducted a seven-week intervention trial to determine the effect of taste education on problematic mealtime behaviors in children with autism or ADHD and their parents. Children and parents received separate nutrition instruction and then combined family instruction[71]. The combined family instruction involved six kitchen sessions, each lasting 90 min, and focused on building food preparation skills using games as a base for delivering sensory and taste education[71]. The results of the study showed superior outcomes with stable effects after six months in the family groups that underwent the taste education[71].

The aim of this basic study was to test the efficacy of a six-week nutrition intervention aimed at educating parents of learning-disabled children on the role ultra-processed foods play in creating conditions for the development of autism and ADHD. The nutrition intervention was delivered online *via* tutorial and focused on teaching parents the constructs of the nutritional epigenetics model for autism and ADHD (Figure 1). Parents learned which food ingredients in ultra-processed foods contribute to heavy metal exposures, impact nutrient status, and/or gene behavior. Through the

instruction, parents became aware of the fact that they could choose to create a healthy and safe home food environment for their children (Chapter 6 of textbook, Module 6 of tutorial). The outcome measure we chose to assess the efficacy of the nutrition intervention was change in parent diet, including ultra-processed food intake and organic/whole food intake. We demonstrated that in six weeks, with nutritional epigenetics instruction, you could significantly change parent diet. The expected outcome (H1) was that parents would reduce their intake of ultra-processed foods and they did.

One limitation of this study is that we did not collect pre- and post-intervention food frequency data for the learning-disabled children. We did not ask the parents if they changed their children's diet because of the instruction they received during the nutrition intervention, so we do not know if the parental changes in diet affected the diets of the children. We do have the parent feedback data in Table 8 that indicates parents did change the way they shop for food and plan their family's meals. There is little evidence to suggest that learning disabled children will mirror their parents' dietary pattern aside from the observations made by Thorsteinsdottir *et al*[71]. For follow up studies, we recommend that hands-on parent-child cooking and meal preparation activities be incorporated into the existing nutritional epigenetics curriculum along with the collection of pre- and post-intervention child food frequency data so that researchers can measure any changes in child dietary intake patterns.

Another limitation of this study may be the relatively small sample size. However, we did use the calculation procedures provided by Kirkwood and Sterne[56] to determine the minimum sample size for each group (test and control). A prior study using the same survey instrument[50] produced mean diet scores at pre and post intervention of 16.0 and 23.2 with the standard deviations of 1.72 and 2.83, with n = 10. Based on calculation procedures provided by Kirkwood and Stein[56], a sample size less than 10 was determined to be adequate for this study. According to our calculations, at least three participants would be needed for each group; we ended up with eleven participants in each group (test and control) for this study. Each of the H0 and H1 hypotheses in this study were supported using the classical t-test.

Another limitation of this study could be the introduction of selection bias from the participant recruitment process. We used social media (Facebook) to recruit the participants. The underlying assumption of using social media is parents who use social media have access to the internet. Because we required participants to have at least a high school education and internet access, lower income parents may not have been able to participate. There is a digital divide in the United States where lower income and less educated parents are less likely to own a computer, or use social media and the internet[72,73]. Minorities are underrepresented in our study as 68% of our participants were predominantly white and non-Hispanic. Out of the twenty-two participants in this study, only 32% were members of a minority group. This type of selection bias is known as demographic bias. Because a higher proportion of black children in the United States are classified as having intellectual disability[74] and lower income is an important factor associated with receiving a diagnosis of autism/ADHD[75], follow up studies will need to be adequately funded to ensure the nutritional epigenetics curriculum is designed to be effective at teaching less educated and lower income parents from minority backgrounds. Future studies involving low-income families will also need to ensure that parents have access to whole and/or organic foods especially if they live in food deserts.

The need to implement nutrition education interventions focused on teaching parents the constructs of the nutritional epigenetics model for autism and ADHD is now critical in the United States. At a minimum, parents must learn to avoid feeding their children the ingredients in ultra-processed foods that contribute to heavy metal exposures, impact nutrient status, and/or gene behavior. Trends in ultra-processed food consumption among youth in the United States are increasing at an alarming rate. Wang *et al*[76] found ultra-processed food consumption among United States youth aged 2-19 increased from 61.4% to 67% while the total caloric intake of whole or minimally processed foods decreased from 28.8% to 23.5% between 1999 and 2018. The increasing trends in ultra-processed food consumption among youth are alarming because strong evidence now suggests the consumption of ultra-processed foods is associated with heavy metal and pesticide exposures and the development of autism, developmental delay, and/or ADHD[42]. With the increasing ultra-processed food intake, we see increasing trends in the number of children struggling with these neurodevelopmental disorders. Dufault *et al*[42] reported a 242% increase in the number of children ages 6-21 in the United States receiving special education services under the autism category while student enrollment remained flat between 2006 and 2021. The need for special education services for children under the other health impaired (including ADHD) and developmental delay categories increased 83% and 184%, respectively, during the same period[42]. Parent nutrition education programs focused on facilitating reductions in ultra-processed food intake are key to preventing the learning disabilities that are increasing in prevalence with each passing year: autism, developmental delay, and ADHD.

Children with autism and ADHD are routinely diagnosed by healthcare providers using criteria specified by the American Psychiatric Association in the Diagnostic and Statistical Manual of Mental Disorders[77]. The current diagnostic criteria do not include recommendations for biomarker analyses, even though children with autism and ADHD have elevated levels of Pb and/or I-Hg in their blood compared to their neurotypical peers[10]. Baj *et al*[78] concluded in a recent review that the analysis of trace elements as biomarkers could be relevant tools in the diagnosis, prevention, and treatment of children with autism and neurological disorders associated with heavy metal exposures. Guidelines for selecting analytical methods for the measurement of blood Pb and Hg in children with autism or ADHD are already available[10]. Because the severity of symptoms in autism and ADHD correlate directly to the heavy metal levels in their blood[10,38,78,79], it may be beneficial to utilize these biomarker tools to monitor treatment strategies[78], especially in the case of dietary interventions which may decrease heavy metal exposures. One final limitation of this study is that we did not have funding to collect biomarker data. In addition to educating parents on the role ultra-processed foods play in the development of autism and ADHD, future research efforts could include the collection of blood samples from afflicted children pre- and post-intervention (parent education) to determine any changes in the heavy metal levels.

Due to their inability to excrete heavy metals[10], a common co-morbid condition of autism and ADHD is gut dysbiosis [80,81]. It is not surprising that one of the toxic effects of heavy metals, in single or multi-metallic combination, is the alteration of metabolic profiles that lead to gut dysbiosis[82]. In a recent review, Zafar and Habib[83] found the following bacteria to be greatly decreased in the gastrointestinal tract of children with autism: Bacteroides, bifodobacterium, lactobacillus, and prevotella. In a separate review, Boonchooduang *et al*[81] found bifodobacterium and bacteroides to be the best candidates for analyses in stool samples of children and adolescents with ADHD. Dietary co-exposure to heavy metals is the least studied area of gut health; however, Mangalam *et al*[84] found a decline in Prevotella in response to heavy metal mixtures in the gut. Studying the impact of dietary heavy metal exposures on gut microbiota may also be of value when children and parents consume a western diet comprised mostly of ultra-processed foods. Future research efforts could be focused on developing guidelines for collecting and analyzing stool samples to determine the makeup of the gut biome in children with autism and ADHD.

With respect to the prevention of these neurodevelopment disorders, to date, only one study has attempted to determine a relationship between prenatal dietary heavy metal exposure and the offspring's gut microbiome: Midya *et al* [85] found prenatal Pb exposure is associated with reductions in Bifidobacterium within the gut microbiota of children at 9-11 years of age. In their conclusion, Midya *et al*[85] stated that the current Pb exposure guidelines in the United States and Mexico are not sufficient to protect the human gut microbiome from the deleterious effect of dietary Pb exposure. More research needs to be conducted to determine how prenatal exposures to the heavy metal mixtures found in ultra-processed foods may impact the child's gut microbiome.

Future research could also focus on determining whether diet can be modulated to reduce heavy metal exposures associated with gut dysbiosis in children with autism or ADHD. Emerging evidence suggests that diet does have a moderating influence on the gut microbiome and the pathophysiology of neurodevelopmental disorders such as those found in the autism spectrum[86]. The role of diet as a modulator of neuroinflammation is presented clearly in a recent review conducted by Kurowska *et al*[87]. Several studies show that consuming a diet rich in whole foods (*e.g.*, fruits, nuts, vegetables, herbs, legumes) while avoiding foods that promote inflammation (*e.g.*, ultra processed foods) results in reduced risk of neurological disease associated with gut dsybiosis[87]. In designing our nutrition education intervention for parents of children with ADHD or autism, we thought it foremost to provide instruction on how to avoid consuming ultra-processed foods that contain ingredients with allowable heavy metal residues or increase the risk of heavy metal exposure. In conducting future studies, it may also be useful to measure any changes that may occur in the gut microbiota in children with autism and ADHD in response to changes in diet that reduce heavy metal exposures.

The risk of heavy metal exposure from eating ultra-processed foods has been clearly demonstrated in studies conducted by Khan *et al*[88], Wells *et al*[89], and Raehsler *et al*[90]. Khan *et al*[88] found heavy metal concentrations in food products significantly correlated with the heavy metal levels detected in human blood samples. Wells *et al*[89] verified Hg exposure from non-fish food occurs through the consumption of vegetable oil, an ingredient commonly found in ultra-processed foodstuffs. Raehsler *et al*[90] determined excessive intake of ultra-processed "gluten-free" food may lead to significantly higher levels of Cd, Pb, and Hg in the blood. The heavy metal exposures from drinking contaminated water, or eating ultra-processed food, will destroy the metabolic processes in the human body *via* oxidative stress [91]. The nutritional epigenetics model for autism and ADHD shows how this oxidative stress occurs (Figure 1) and may thus be a useful tool for understanding other pathologies associated with heavy metal exposures.

In addition to autism and ADHD, heavy metal exposures, especially Cd, Pb, and Hg, are positively associated with the development of atherosclerotic cardiovascular disease[92] and non-alcoholic fatty liver disease[93]. From a toxicological perspective, it is interesting to note that non-alcoholic fatty liver disease is associated with ultra-processed food intake in a dose-response manner similar to the dose-response relationship showing heavy metal toxicity[94]. Not surprisingly, numerous pathologies are associated with ultra-processed food intake[95]. In a recent review, Elizabeth *et al*[95] examined forty-three articles to determine any associations between ultra-processed food intake and adverse health outcomes. Of the forty-three articles, thirty-seven found excessive ultra-processed food intake was associated with at least one of the following pathologies: Obesity, overweight, cancer, type-2 diabetes, depression, irritable bowel syndrome, cardiovascular disease, and all-cause mortality[95]. Any nutrition education program that helps individuals significantly reduce their intake of ultra-processed foods will be useful because evidence suggests that switching to a healthy diet will prevent disease and/or improve health outcomes[96].

The pre- and post-intervention outcomes presented in Table 6 show the nutrition education program used in this study was an effective tool because parents who received the nutritional epigenetics instruction significantly decreased their ultra-processed food intake ($P < 0.001$) and significantly increased their whole and/organic food intake ($P < 0.05$). Table 7 provides details on the reliability of our outcome measurements from a statistical perspective. Parent nutritional epigenetics instruction is a novel nutrition education intervention because evidence suggests that if parents reduce their consumption of ultra-processed foods, then their children will also reduce their consumption of ultra-processed foods[67, 68]. Using the nutritional epigenetics model as a teaching tool for helping parents reduce their consumption of ultra-processed foods may lead to healthier home food environments and subsequent improvements in child diet by reducing the heavy metal exposures associated with autism and ADHD. More research is needed to verify the reductions in heavy metal exposures that may be associated with reducing ultra-processed food intake.

Meanwhile heavy metal residues continue to be a problem in the American food supply. The United States Congress recently released two reports on the problem of heavy metals, including I-Hg and Pb, in baby foods sold in America[97, 98]. Dietary heavy metal exposures, I-Hg and Pb, are an important construct in the nutritional epigenetic model for autism and ADHD (Figure 1). In addition to collecting and analyzing blood samples for Hg and Pb, changes in MT and PON1 gene activity levels could also be measured in children with autism and ADHD pre- and post-parental nutritional epigenetics instruction. Meguid *et al*[99] successfully measured changes in the genetic expression of MT-1 in children with autism after Zn supplementation. Numerous studies have already been conducted successfully to measure PON1 gene

activity in response to changes in diet[100]. Further studies that use nutritional epigenetics instruction to modulate diet could shed light on the role ultra-processed foods (and heavy metal exposures) play in the development of autism and ADHD *via* MT gene disruption or PON1 gene suppression[101].

CONCLUSION

The aim of this basic study was to test the efficacy of a six-week nutritional epigenetics tutorial in improving dietary behavior patterns and attitudes of parents having a learning-disabled child with autism or ADHD. Evaluation of the tutorial showed it was an effective tool because it provided parents with the instruction and information needed to reduce poor dietary habits and facilitate healthy dietary changes over a 6-wk period. The parents who completed the tutorial significantly reduced their intake of highly processed foods, increased their intake of whole and/or organic foods, and changed their attitude about their ability to influence their child's behavior through diet. Nutritional epigenetics instruction can be used to facilitate healthy changes in diet and attitude among parents of learning-disabled children within a six-week period.

ARTICLE HIGHLIGHTS

Research background

Ultra-processed foods contain heavy metal and pesticide residues. Specific food ingredients and heavy metal contaminants found in ultra-processed foods may result in mineral imbalances that impact or disrupt gene expression. Evidence suggests prenatal nutritional deficits and heavy metal exposures associated with poor diet are the primary epigenetic factors responsible for the development of autism and attention deficit/hyperactivity disorder (ADHD) *via* metallothionein gene dysfunction and paraoxonase-1 gene suppression. The excess consumption of ultra-processed foods by parents is associated with the development of these neurodevelopmental disorders.

Research motivation

The prevalence of autism and ADHD is increasing in the United States. The key problem to be solved is the excess consumption of ultra-processed foods by parents. Parents must be encouraged to reduce their consumption of ultra-processed foods. In educating parents on the role ultra-processed foods play in the development of autism and ADHD, they may become empowered to change their diets.

Research objectives

The aim of this basic study was to test the efficacy of a six-week nutritional epigenetics tutorial in reducing parental ultra-processed food intake.

Research methods

The parent education intervention we created was novel as it is the first ever to provide instruction focused on the constructs of the nutritional epigenetics model for autism and ADHD. In learning how what they eat determines how their genes behave, parents in the test group chose to change their diets. We measured their dietary changes pre- and post-intervention using a novel, pre-tested and validated, diet survey with questions designed to measure ultra-processed or whole/organic food intake. Ultra-processed foods are characterized as having more than one ingredient along with at least one ingredient known, or likely, to contain heavy metal residues.

Research results

The literature review conducted for this basic study revealed maternal ultra-processed food consumption is associated with adverse child neurodevelopment. This new finding further strengthens the nutritional epigenetics model for autism and ADHD that was initially published in 2009 as the Mercury Toxicity Model. The literature review also revealed the role of dietary heavy metals in creating the co-morbid condition of gut dysbiosis that is found in children with autism and ADHD. Dietary heavy metal exposures continue to be a problem in the United States ultra-processed food supply.

Research conclusions

The nutritional epigenetics model for autism and ADHD that this study uses as the basis for the nutritional epigenetics instruction is not new but is further refined by the results of this study. The success of the nutritional epigenetics tutorial in helping parents reduce their intake of ultra-processed foods may be attributed to the parents' acceptance of the model constructs. They know the ultra-processed food supply is contaminated with heavy metal and pesticide residues. Two reports issued by the United States Congress in 2021 confirm there is a heavy metal problem in the ultra-processed food supply.

Research perspectives

In conducting future research, it may be useful to collect blood samples from the children and parents for heavy metal analyses pre- and post-six-week intervention that includes nutritional epigenetics instruction. If the children present with

symptoms associated with autism and/or ADHD, then blood mercury and lead levels are important to measure. Pre- and post-intervention stool samples could also be collected to measure any changes in the gut biome, especially if a child presents with symptoms of gut dysbiosis.

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FOOTNOTES

Author contributions: Dufault RJ developed the nutritional epigenetics model for autism and attention deficit/hyperactivity disorder, developed the curriculum for the intervention, designed and conducted the intervention study, acquired, analyzed, and interpreted the pre- and post-intervention data, wrote the draft manuscript; Crider RA provided guidance on statistical analysis, presented the summary of results in table 7, and reviewed and approved the analytical results; Adler KM served as primary advisor for experimental design; Carpenter DO and Gilbert SG provided feedback on data interpretation; and all authors approved the final version of the article.

Institutional review board statement: The study was reviewed, approved, and found to be exempt from further review by the Institutional Review Board at A.T. Still University.

Informed consent statement: Participants were alternately assigned to the test or control group when eligibility was confirmed and after receipt of the signed informed consent form.

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REFERENCES

1 **Martínez Steele E**, Popkin BM, Swinburn B, Monteiro CA. The share of ultra-processed foods and the overall nutritional quality of diets in the US: evidence from a nationally representative cross-sectional study. *Popul Health Metr* 2017; **15**: 6 [PMID: 28193285 DOI: 10.1186/s12963-017-0119-3]

2 **Martini D**, Godos J, Bonaccio M, Vitaglione P, Grosso G. Ultra-Processed Foods and Nutritional Dietary Profile: A Meta-Analysis of Nationally Representative Samples. *Nutrients* 2021; **13** [PMID: 34684391 DOI: 10.3390/nu13103390]

3 **Touvier M**, da Costa Louzada ML, Mozaffarian D, Baker P, Juul F, Srour B. Ultra-processed foods and cardiometabolic health: public health policies to reduce consumption cannot wait. *BMJ* 2023; **383**: e075294 [PMID: 37813465 DOI: 10.1136/bmj-2023-075294]

4 **Puig-Vallverdú J**, Romaguera D, Fernández-Barrés S, Gignac F, Ibarluzea J, Santa-Maria L, Llop S, Gonzalez S, Vioque J, Riaño-Galán I, Fernández-Tardón G, Pinar A, Turner MC, Arija V, Salas-Savadó J, Vrijheid M, Julvez J. The association between maternal ultra-processed food consumption during pregnancy and child neuropsychological development: A population-based birth cohort study. *Clin Nutr* 2022; **41**: 2275-2283 [PMID: 36087519 DOI: 10.1016/j.clnu.2022.08.005]

5 **Zupo R**, Castellana F, Boero G, Matera E, Colacicco G, Piscitelli P, Clodoveo ML, Rondanelli M, Panza F, Lozupone M, Sardone R. Processed foods and diet quality in pregnancy may affect child neurodevelopment disorders: a narrative review. *Nutr Neurosci* 2023; 1-21 [PMID: 37039128 DOI: 10.1080/1028415X.2023.2197709]

6 **Ward NI**. Assessment of chemical factors in relation to child hyperactivity. *J Nutr Environ Med* 2009; **7**: 333-342 [DOI: 10.1080/13590849762466]

7 **Ward NI**, Soulsbury KA, Zettel VH, Colquhoun ID, Bunday S, Barnes B. The influence of the chemical additive tartrazine on the zinc status of hyperactive children: A double-blind placebo-controlled study. *J Nutr Environ Med* 2009; **1**: 51-57 [DOI: 10.3109/13590849009003134]

8 **Milne DB**, Nielsen FH. The interaction between dietary fructose and magnesium adversely affects macromineral homeostasis in men. *J Am Coll Nutr* 2000; **19**: 31-37 [PMID: 10682873 DOI: 10.1080/07315724.2000.10718911]

9 **Cortés-Albornoz MC**, García-Guáqueta DP, Velez-van-Meerbeke A, Talero-Gutiérrez C. Maternal Nutrition and Neurodevelopment: A Scoping Review. *Nutrients* 2021; **13** [PMID: 34684531 DOI: 10.3390/nu13103530]

10 **Dufault RJ**, Wolle MM, Kingston HMS, Gilbert SG, Murray JA. Connecting inorganic mercury and lead measurements in blood to dietary sources of exposure that may impact child development. *World J Methodol* 2021; **11**: 144-159 [PMID: 34322366 DOI: 10.5662/wjm.v11.i4.144]

11 **Dufault R**, Lukiw WJ, Crider R, Schnoll R, Wallinga D, Deth R. A macroepigenetic approach to identify factors responsible for the autism epidemic in the United States. *Clin Epigenetics* 2012; **4**: 6 [PMID: 22490277 DOI: 10.1186/1868-7083-4-6]

12 **Code of Federal Regulations**. Part 74: Listing of color additives subject to certification. [cited 5 August 2023]. Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-74

13 **Batada A**, Jacobson MF. Prevalence of Artificial Food Colors in Grocery Store Products Marketed to Children. *Clin Pediatr (Phila)* 2016; **55**: 1113-1119 [PMID: 27270961 DOI: 10.1177/0009922816651621]

14 **Oplatowska-Stachowiak M**, Elliott CT. Food colors: Existing and emerging food safety concerns. *Crit Rev Food Sci Nutr* 2017; **57**: 524-548 [PMID: 25849411 DOI: 10.1080/10408398.2014.889652]

15 **Miller MD**, Steinmaus C, Golub MS, Castorina R, Thilakartne R, Bradman A, Marty MA. Potential impacts of synthetic food dyes on activity and attention in children: a review of the human and animal evidence. *Environ Health* 2022; **21**: 45 [PMID: 35484553 DOI: 10.1186/s12940-022-00849-9]

16 **Dufault R**, LeBlanc B, Schnoll R, Cornett C, Schweitzer L, Wallinga D, Hightower J, Patrick L, Lukiw WJ. Mercury from chlor-alkali plants: measured concentrations in food product sugar. *Environ Health* 2009; **8**: 2 [PMID: 19171026 DOI: 10.1186/1476-069X-8-2]

17 **Rideout K**, Sahni V, Copes R, Wylie M, Kosatsky T. Comments on the paper by Dufault et al: Mercury in foods containing high fructose corn syrup in Canada. Environ Health 2010; [cited 31 October 2023]. Available from: https://ehjournal.biomedcentral.com/articles/10.1186/1476-069X-8-2/comments

18 **Wallinga D**, Sorensen J, Mottl P, Yablon B. Not so sweet: missing mercury and high fructose corn syrup. Institute for Agriculture and Trade Policy (IATP). 2009 [cited 31 October 2023]. Available from: https://www.iatp.org/sites/default/files/421_2_105026.pdf

19 **Guzmán-Maldonado H**, Paredes-López O. Amylolytic enzymes and products derived from starch: a review. *Crit Rev Food Sci Nutr* 1995; **35**: 373-403 [PMID: 8573280 DOI: 10.1080/10408399509527706]

20 **Pesce G**, Sesé L, Calciano L, Travert B, Dessimond B, Maesano CN, Ferrante G, Huel G, Prud'homme J, Guinot M, Soomro MH, Baloch RM, Lhote R, Annesi-Maesano I. Foetal exposure to heavy metals and risk of atopic diseases in early childhood. *Pediatr Allergy Immunol* 2021; **32**: 242-250 [PMID: 33091176 DOI: 10.1111/pai.13397]

21 **McRae N**, Gennings C, Rivera Rivera N, Tamayo-Ortiz M, Pantic I, Amarasiriwardena C, Schnaas L, Wright R, Tellez-Rojo MM, Wright RO, Rosa MJ. Association between prenatal metal exposure and adverse respiratory symptoms in childhood. *Environ Res* 2022; **205**: 112448 [PMID: 34848207 DOI: 10.1016/j.envres.2021.112448]

22 **Emeny RT**, Korrick SA, Li Z, Nadeau K, Madan J, Jackson B, Baker E, Karagas MR. Prenatal exposure to mercury in relation to infant infections and respiratory symptoms in the New Hampshire Birth Cohort Study. *Environ Res* 2019; **171**: 523-529 [PMID: 30743244 DOI: 10.1016/j.envres.2019.01.026]

23 **Jeong KS**, Ha E, Shin JY, Park H, Hong YC, Ha M, Kim S, Lee SJ, Lee KY, Kim JH, Kim Y. Blood heavy metal concentrations in pregnant Korean women and their children up to age 5years: Mothers' and Children's Environmental Health (MOCEH) birth cohort study. *Sci Total Environ* 2017; **605-606**: 784-791 [PMID: 28679122 DOI: 10.1016/j.scitotenv.2017.06.007]

24 **Skogheim TS**, Weyde KVF, Engel SM, Aase H, Surén P, Øie MG, Biele G, Reichborn-Kjennerud T, Caspersen IH, Hornig M, Haug LS, Villanger GD. Metal and essential element concentrations during pregnancy and associations with autism spectrum disorder and attention-deficit/hyperactivity disorder in children. *Environ Int* 2021; **152**: 106468 [PMID: 33765546 DOI: 10.1016/j.envint.2021.106468]

25 **Chiaverini N**, De Ley M. Protective effect of metallothionein on oxidative stress-induced DNA damage. *Free Radic Res* 2010; **44**: 605-613 [PMID: 20380594 DOI: 10.3109/10715761003692511]

26 **Awadh SM**, Yaseen ZM, Al-Suwaiyan MS. The role of environmental trace element toxicants on autism: A medical biogeochemistry perspective. *Ecotoxicol Environ Saf* 2023; **251**: 114561 [PMID: 36696851 DOI: 10.1016/j.ecoenv.2023.114561]

27 **Dufault R**, Schnoll R, Lukiw WJ, Leblanc B, Cornett C, Patrick L, Wallinga D, Gilbert SG, Crider R. Mercury exposure, nutritional deficiencies and metabolic disruptions may affect learning in children. *Behav Brain Funct* 2009; **5**: 44 [PMID: 19860886 DOI: 10.1186/1744-9081-5-44]

28 **Coyle P**, Philcox JC, Carey LC, Rofe AM. Metallothionein: the multipurpose protein. *Cell Mol Life Sci* 2002; **59**: 627-647 [PMID: 12022471 DOI: 10.1007/s00018-002-8454-2]

29 **Vela G**, Stark P, Socha M, Sauer AK, Hagmeyer S, Grabrucker AM. Zinc in gut-brain interaction in autism and neurological disorders. *Neural Plast* 2015; **2015**: 972791 [PMID: 25878905 DOI: 10.1155/2015/972791]

30 **Baecker T**, Mangus K, Pfaender S, Chhabra R, Boeckers TM, Grabrucker AM. Loss of COMMD1 and copper overload disrupt zinc homeostasis and influence an autism-associated pathway at glutamatergic synapses. *Biometals* 2014; **27**: 715-730 [PMID: 25007851 DOI: 10.1007/s10534-014-9764-1]

31 **Uriu-Adams JY**, Keen CL. Zinc and reproduction: effects of zinc deficiency on prenatal and early postnatal development. *Birth Defects Res B Dev Reprod Toxicol* 2010; **89**: 313-325 [PMID: 20803691 DOI: 10.1002/bdrb.20264]

32 **Skalny AV**, Aschner M, Tinkov AA. Zinc. *Adv Food Nutr Res* 2021; **96**: 251-310 [PMID: 34112355 DOI: 10.1016/bs.afnr.2021.01.003]

33 **Ross MM**, Hernandez-Espinosa DR, Aizenman E. Neurodevelopmental Consequences of Dietary Zinc Deficiency: A Status Report. *Biol Trace Elem Res* 2023; **201**: 5616-5639 [PMID: 36964812 DOI: 10.1007/s12011-023-03630-2]

34 **Daneshparvar M**, Mostafavi SA, Zare Jeddi M, Yunesian M, Mesdaghinia A, Mahvi AH, Akhondzadeh S. The Role of Lead Exposure on Attention-Deficit/ Hyperactivity Disorder in Children: A Systematic Review. *Iran J Psychiatry* 2016; **11**: 1-14 [PMID: 27252763]

35 **Sears CG**, Lanphear BP, Xu Y, Chen A, Yolton K, Braun JM. Identifying periods of heightened susceptibility to lead exposure in relation to behavioral problems. *J Expo Sci Environ Epidemiol* 2022; **32**: 1-9 [PMID: 34728761 DOI: 10.1038/s41370-021-00389-3]

36 **Bernardina Dalla MD**, Ayala CO, Cristina de Abreu Quintela Castro F, Neto FK, Zanirati G, Cañon-Montañez W, Mattiello R.

Environmental pollution and attention deficit hyperactivity disorder: A meta-analysis of cohort studies. *Environ Pollut* 2022; **315**: 120351 [PMID: 36216185 DOI: 10.1016/j.envpol.2022.120351]

37 **Mostafa GA**, Bjørklund G, Urbina MA, Al-Ayadhi LY. The levels of blood mercury and inflammatory-related neuropeptides in the serum are correlated in children with autism spectrum disorder. *Metab Brain Dis* 2016; **31**: 593-599 [PMID: 26738726 DOI: 10.1007/s11011-015-9784-8]

38 **Alabdali A**, Al-Ayadhi L, El-Ansary A. A key role for an impaired detoxification mechanism in the etiology and severity of autism spectrum disorders. *Behav Brain Funct* 2014; **10**: 14 [PMID: 24776096 DOI: 10.1186/1744-9081-10-14]

39 **Hassan MH**, Desoky T, Sakhr HM, Gabra RH, Bakri AH. Possible Metabolic Alterations among Autistic Male Children: Clinical and Biochemical Approaches. *J Mol Neurosci* 2019; **67**: 204-216 [PMID: 30600432 DOI: 10.1007/s12031-018-1225-9]

40 **Li ZG**, Zhou FK, Yin AM, Gao YY, Jiang X, Liu SS, Zhang YY, Bo DD, Xie J, Jia QY, Feng JG, Feng C, Fan GQ. [Cellular damage of low-dose combined exposure to mercury, lead and cadmium on hippocampal neurons in rats]. *Zhonghua Yu Fang Yi Xue Za Zhi* 2018; **52**: 976-982 [PMID: 30392313 DOI: 10.3760/cma.j.issn.0253-9624.2018.10.003]

41 **Zhou F**, Ouyang L, Li Q, Yang S, Liu S, Yu H, Jia Q, Rao S, Xie J, Du G, Feng C, Fan G. Hippocampal LIMK1-mediated Structural Synaptic Plasticity in Neurobehavioral Deficits Induced by a Low-dose Heavy Metal Mixture. *Mol Neurobiol* 2023; **60**: 6029-6042 [PMID: 37407880 DOI: 10.1007/s12035-023-03458-w]

42 **Dufault RJ**, Crider RA, Deth RC, Schnoll R, Gilbert SG, Lukiw WJ, Hitt AL. Higher rates of autism and attention deficit/hyperactivity disorder in American children: Are food quality issues impacting epigenetic inheritance? *World J Clin Pediatr* 2023; **12**: 25-37 [PMID: 37034430 DOI: 10.5409/wjcp.v12.i2.25]

43 **Cardenas A**, Rifas-Shiman SL, Agha G, Hivert MF, Litonjua AA, DeMeo DL, Lin X, Amarasiriwardena CJ, Oken E, Gillman MW, Baccarelli AA. Persistent DNA methylation changes associated with prenatal mercury exposure and cognitive performance during childhood. *Sci Rep* 2017; **7**: 288 [PMID: 28325913 DOI: 10.1038/s41598-017-00384-5]

44 **Costa LG**, Cole TB, Garrick JM, Marsillach J, Furlong CE. Metals and Paraoxonases. *Adv Neurobiol* 2017; **18**: 85-111 [PMID: 28889264 DOI: 10.1007/978-3-319-60189-2_5]

45 **Scarpato R**, Testi S, Colosimo V, Garcia Crespo C, Micheli C, Azzarà A, Tozzi MG, Ghirri P. Role of oxidative stress, genome damage and DNA methylation as determinants of pathological conditions in the newborn: an overview from conception to early neonatal stage. *Mutat Res Rev Mutat Res* 2020; **783**: 108295 [PMID: 32192649 DOI: 10.1016/j.mrrev.2019.108295]

46 **Josse D**, Xie W, Renault F, Rochu D, Schopfer LM, Masson P, Lockridge O. Identification of residues essential for human paraoxonase (PON1) arylesterase/organophosphatase activities. *Biochemistry* 1999; **38**: 2816-2825 [PMID: 10052953 DOI: 10.1021/bi982281h]

47 **Hu Y**, Chiu YH, Hauser R, Chavarro J, Sun Q. Overall and class-specific scores of pesticide residues from fruits and vegetables as a tool to rank intake of pesticide residues in United States: A validation study. *Environ Int* 2016; **92-93**: 294-300 [PMID: 27128714 DOI: 10.1016/j.envint.2016.04.028]

48 **Sagiv SK**, Mora AM, Rauch S, Kogut KR, Hyland C, Gunier RB, Bradman A, Deardorff J, Eskenazi B. Prenatal and Childhood Exposure to Organophosphate Pesticides and Behavior Problems in Adolescents and Young Adults in the CHAMACOS Study. *Environ Health Perspect* 2023; **131**: 67008 [PMID: 37307167 DOI: 10.1289/EHP11380]

49 **Food Ingredient and Health Research Institute**. Our mission. 2023 [cited 13 August 2023]. Available from: http://www.foodingredient.info/whatandwhoweare/ourmissionstatement.html

50 **Dufault R**, Berg Z, Crider R, Schnoll R, Wetsit L, Bulls WT, Gilbert SG, Kingston HMS, Wolle MM, Rahman GMM, Laks DR. Blood inorganic mercury is directly associated with glucose levels in the human population and may be linked to processed food intake. *Integr Mol Med* 2015; **2** [PMID: 33889422 DOI: 10.15761/imm.1000134]

51 **Dufault R**. The toxic western diet what parents must know to protect their family. 2018

52 **Dufault R**. Unsafe at any meal: what the FDA does not want you to know about the foods you eat. Garden City Park, New York: Square One Pub, 2017

53 **Dufault RJ**. Nutritional epigenetics: unsafe at any meal study guide. 2023

54 **Lehto S**, Buchweitz M, Klimm A, Straßburger R, Bechtold C, Ulberth F. Comparison of food colour regulations in the EU and the US: a review of current provisions. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* 2017; **34**: 335-355 [PMID: 28004607 DOI: 10.1080/19440049.2016.1274431]

55 **Food Commission**. Warning labels for coloured foods to become EU law. 2008 [cited 13 August 2023]. Available from: http://www.foodcomm.org.uk/press/warning_labels/

56 **Kirkwood BR**, Sterne JAC. Essential medical statistics (2nd edition). Malden: Wiley-Blackwell, 2001

57 **Meta**. Give people the power to build community and bring the world closer together. 2023 [cited 13 August 2023]. Available from: https://about.fb.com/company--info/

58 **Survey Monkey**. Create surveys, get answers. [cited 13 August 2023]. Available from: http://www.surveymonkey.com/

59 **National Cancer Institute**. Diet History Questionnaire II (DHQ II) for U.S. & Canada. [cited 13 August 2023]. Available from: https://epi.grants.cancer.gov/dhq2/

60 **Grubbs FE**. Procedures for detecting outlying observations in samples. *Technometrics* 1969; **11**: 1-21 [DOI: 10.1080/00401706.1969.10490657]

61 **Graph Pad**. Outlier Calculator. [cited 2 November 2023]. Available from: https://www.graphpad.com/quickcalcs/Grubbs1.cfm

62 **Food and Agriculture Organization of the United Nations**. Online Edition: "Combined compendium of food additive specifications". 2006. [cited 11 November 2023]. Available from: https://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/detail/en/c/61/

63 **Beckerman JP**, Alike Q, Lovin E, Tamez M, Mattei J. The Development and Public Health Implications of Food Preferences in Children. *Front Nutr* 2017; **4**: 66 [PMID: 29326942 DOI: 10.3389/fnut.2017.00066]

64 **Breslin PA**. An evolutionary perspective on food and human taste. *Curr Biol* 2013; **23**: R409-R418 [PMID: 23660364 DOI: 10.1016/j.cub.2013.04.010]

65 **Mennella JA**. Ontogeny of taste preferences: basic biology and implications for health. *Am J Clin Nutr* 2014; **99**: 704S-711S [PMID: 24452237 DOI: 10.3945/ajcn.113.067694]

66 **Beauchamp GK**, Mennella JA. Early flavor learning and its impact on later feeding behavior. *J Pediatr Gastroenterol Nutr* 2009; **48** Suppl 1: S25-S30 [PMID: 19214055 DOI: 10.1097/MPG.0b013e31819774a5]

67 **Dolwick AP**, Persky S. Parental reward-based eating drive predicts parents' feeding behaviors and Children's ultra-processed food intake.

Appetite 2021; **164**: 105241 [PMID: 33839147 DOI: 10.1016/j.appet.2021.105241]

68 **An M**, Liu X, Guo H, Zhou Q. The Associations between Caregivers' Emotional and Instrumental Feeding, Children's Emotional Eating, and Children's Consumption of Ultra-Processed Foods in China. *Int J Environ Res Public Health* 2022; **19** [PMID: 35457306 DOI: 10.3390/ijerph19084439]

69 **Polfuss M**, Simpson P, Neff Greenley R, Zhang L, Sawin KJ. Parental Feeding Behaviors and Weight-Related Concerns in Children With Special Needs. *West J Nurs Res* 2017; **39**: 1070-1093 [PMID: 28322650 DOI: 10.1177/0193945916687994]

70 **Sharp WG**, Burrell TL, Berry RC, Stubbs KH, McCracken CE, Gillespie SE, Scahill L. The Autism Managing Eating Aversions and Limited Variety Plan *vs* Parent Education: A Randomized Clinical Trial. *J Pediatr* 2019; **211**: 185-192.e1 [PMID: 31056202 DOI: 10.1016/j.jpeds.2019.03.046]

71 **Thorsteinsdottir S**, Njardvik U, Bjarnason R, Olafsdottir AS. Changes in Eating Behaviors Following Taste Education Intervention: Focusing on Children with and without Neurodevelopmental Disorders and Their Families: A Randomized Controlled Trial. *Nutrients* 2022; **14** [PMID: 36235654 DOI: 10.3390/nu14194000]

72 **Perrin A**. Social media usage: 2005-2015. Pew Research Center. [cited 10 November 2023]. Available from: https://www.pewresearch.org/internet/2015/10/08/social-networking-usage-2005-2015/

73 **Zickuhr K**, Smith A. Digital differences. [Cited 10 November 2023]. Available from: https://www.ris.org/uploadi/editor/1339774693PIP_Digital_differences_041312.pdf

74 **Maenner MJ**, Shaw KA, Bakian AV, Bilder DA, Durkin MS, Esler A, Furnier SM, Hallas L, Hall-Lande J, Hudson A, Hughes MM, Patrick M, Pierce K, Poynter JN, Salinas A, Shenouda J, Vehorn A, Warren Z, Constantino JN, DiRienzo M, Fitzgerald RT, Grzybowski A, Spivey MH, Pettygrove S, Zahorodny W, Ali A, Andrews JG, Baroud T, Gutierrez J, Hewitt A, Lee LC, Lopez M, Mancilla KC, McArthur D, Schwenk YD, Washington A, Williams S, Cogswell ME. Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2018. *MMWR Surveill Summ* 2021; **70**: 1-16 [PMID: 34855725 DOI: 10.15585/mmwr.ss7011a1]

75 **Federico A**, Zgodic A, Flory K, Hantman RM, Eberth JM, Mclain AC, Bradshaw J. Predictors of Autism Spectrum Disorder and ADHD: Results from the National Survey of Children's Health. *Disabil Health J* 2023; 101512 [PMID: 37838574 DOI: 10.1016/j.dhjo.2023.101512]

76 **Wang L**, Martínez Steele E, Du M, Pomeranz JL, O'Connor LE, Herrick KA, Luo H, Zhang X, Mozaffarian D, Zhang FF. Trends in Consumption of Ultraprocessed Foods Among US Youths Aged 2-19 Years, 1999-2018. *JAMA* 2021; **326**: 519-530 [PMID: 34374722 DOI: 10.1001/jama.2021.10238]

77 **American Psychiatric Association**. Diagnostic and statistical manual of mental disorders: DSM-5™, 5th ed. Washington: American Psychiatric Publishing, 2013

78 **Baj J**, Flieger W, Flieger M, Forma A, Sitarz E, Skórzyńska-Dziduszko K, Grochowski C, Maciejewski R, Karakuła-Juchnowicz H. Autism spectrum disorder: Trace elements imbalances and the pathogenesis and severity of autistic symptoms. *Neurosci Biobehav Rev* 2021; **129**: 117-132 [PMID: 34339708 DOI: 10.1016/j.neubiorev.2021.07.029]

79 **He J**, Ning H, Huang R. Low blood lead levels and attention-deficit hyperactivity disorder in children: a systematic review and meta-analysis. *Environ Sci Pollut Res Int* 2019; **26**: 17875-17884 [PMID: 28780688 DOI: 10.1007/s11356-017-9799-2]

80 **Hughes HK**, Rose D, Ashwood P. The Gut Microbiota and Dysbiosis in Autism Spectrum Disorders. *Curr Neurol Neurosci Rep* 2018; **18**: 81 [PMID: 30251184 DOI: 10.1007/s11910-018-0887-6]

81 **Boonchooduang N**, Louthrenoo O, Chattipakorn N, Chattipakorn SC. Possible links between gut-microbiota and attention-deficit/hyperactivity disorders in children and adolescents. *Eur J Nutr* 2020; **59**: 3391-3403 [PMID: 32918136 DOI: 10.1007/s00394-020-02383-1]

82 **Bist P**, Choudhary S. Impact of Heavy Metal Toxicity on the Gut Microbiota and Its Relationship with Metabolites and Future Probiotics Strategy: a Review. *Biol Trace Elem Res* 2022; **200**: 5328-5350 [PMID: 34994948 DOI: 10.1007/s12011-021-03092-4]

83 **Zafar U**, Habib H. The Link Between Autism Spectrum Disorder And Gastrointestinal Microbiota. *J Ayub Med Coll Abbottabad* 2021; **33**: 513-518 [PMID: 34487668]

84 **Mangalam A**, Shahi SK, Luckey D, Karau M, Marietta E, Luo N, Choung RS, Ju J, Sompallae R, Gibson-Corley K, Patel R, Rodriguez M, David C, Taneja V, Murray J. Human Gut-Derived Commensal Bacteria Suppress CNS Inflammatory and Demyelinating Disease. *Cell Rep* 2017; **20**: 1269-1277 [PMID: 28793252 DOI: 10.1016/j.celrep.2017.07.031]

85 **Midya V**, Lane JM, Gennings C, Torres-Olascoaga LA, Wright RO, Arora M, Téllez-Rojo MM, Eggers S. Prenatal Pb exposure is associated with reduced abundance of beneficial gut microbial cliques in late childhood: an investigation using Microbial Co-occurrence Analysis (MiCA). *medRxiv* 2023 [PMID: 37293091 DOI: 10.1101/2023.05.18.23290127]

86 **Horn J**, Mayer DE, Chen S, Mayer EA. Role of diet and its effects on the gut microbiome in the pathophysiology of mental disorders. *Transl Psychiatry* 2022; **12**: 164 [PMID: 35443740 DOI: 10.1038/s41398-022-01922-0]

87 **Kurowska A**, Ziemichód W, Herbet M, Piątkowska-Chmiel I. The Role of Diet as a Modulator of the Inflammatory Process in the Neurological Diseases. *Nutrients* 2023; **15** [PMID: 36986165 DOI: 10.3390/nu15061436]

88 **Khan K**, Khan H, Lu Y, Ihsanullah I, Nawab J, Khan S, Shah NS, Shamshad I, Maryam A. Evaluation of toxicological risk of foodstuffs contaminated with heavy metals in Swat, Pakistan. *Ecotoxicol Environ Saf* 2014; **108**: 224-232 [PMID: 25086826 DOI: 10.1016/j.ecoenv.2014.05.014]

89 **Wells EM**, Kopylev L, Nachman R, Radke EG, Segal D. Seafood, wine, rice, vegetables, and other food items associated with mercury biomarkers among seafood and non-seafood consumers: NHANES 2011-2012. *J Expo Sci Environ Epidemiol* 2020; **30**: 504-514 [PMID: 32015433 DOI: 10.1038/s41370-020-0206-6]

90 **Raehsler SL**, Choung RS, Marietta EV, Murray JA. Accumulation of Heavy Metals in People on a Gluten-Free Diet. *Clin Gastroenterol Hepatol* 2018; **16**: 244-251 [PMID: 28223206 DOI: 10.1016/j.cgh.2017.01.034]

91 **Fu Z**, Xi S. The effects of heavy metals on human metabolism. *Toxicol Mech Methods* 2020; **30**: 167-176 [PMID: 31818169 DOI: 10.1080/15376516.2019.1701594]

92 **Wang K**, Mao Y, Liu Z, Li Y, Li Z, Sun Y, Ding Y, Liu X, Hong J, Xu D, Zhang J. Association of Blood Heavy Metal Exposure with Atherosclerotic Cardiovascular Disease (ASCVD) Among White Adults: Evidence from NHANES 1999-2018. *Biol Trace Elem Res* 2023; **201**: 4321-4333 [PMID: 36542304 DOI: 10.1007/s12011-022-03537-4]

93 **Sadighara P**, Abedini AH, Irshad N, Ghazi-Khansari M, Esrafili A, Yousefi M. Association Between Non-alcoholic Fatty Liver Disease and Heavy Metal Exposure: a Systematic Review. *Biol Trace Elem Res* 2023; **201**: 5607-5615 [PMID: 36929113 DOI: 10.1007/s12011-023-03629-9]

94 **Henney AE**, Gillespie CS, Alam U, Hydes TJ, Cuthbertson DJ. Ultra-Processed Food Intake Is Associated with Non-Alcoholic Fatty Liver

Disease in Adults: A Systematic Review and Meta-Analysis. *Nutrients* 2023; **15** [PMID: 37242149 DOI: 10.3390/nu15102266]

95 **Elizabeth L**, Machado P, Zinöcker M, Baker P, Lawrence M. Ultra-Processed Foods and Health Outcomes: A Narrative Review. *Nutrients* 2020; **12** [PMID: 32630022 DOI: 10.3390/nu12071955]

96 **Cena H**, Calder PC. Defining a Healthy Diet: Evidence for The Role of Contemporary Dietary Patterns in Health and Disease. *Nutrients* 2020; **12** [PMID: 32012681 DOI: 10.3390/nu12020334]

97 **United States House of Representatives**. Baby foods are tainted with dangerous levels of arsenic, lead, cadmium, and mercury. [cited 15 August 2023]. Available from: https://oversightdemocrats.house.gov/sites/democrats.oversight.house.gov/files/2021-02-04%20ECP%20Baby%20Food%20Staff%20Report.pdf

98 **United States House of Representatives**. New disclosures show dangerous levels of toxic metals in even more baby foods. [cited 29 September 2023]. Available from: https://oversightdemocrats.house.gov/sites/democrats.oversight.house.gov/files/ECP%20Second%20Baby%20Food%20Report%209.29.21%20FINAL.pdf

99 **Meguid NA**, Bjørklund G, Gebril OH, Doşa MD, Anwar M, Elsaeid A, Gaber A, Chirumbolo S. The role of zinc supplementation on the metallothionein system in children with autism spectrum disorder. *Acta Neurol Belg* 2019; **119**: 577-583 [PMID: 31302864 DOI: 10.1007/s13760-019-01181-9]

100 **Lou-Bonafonte JM**, Gabás-Rivera C, Navarro MA, Osada J. PON1 and Mediterranean Diet. *Nutrients* 2015; **7**: 4068-4092 [PMID: 26024295 DOI: 10.3390/nu7064068]

101 **Banhela N**, Naidoo P, Naidoo S. Association between pesticide exposure and paraoxonase-1 (PON1) polymorphisms, and neurobehavioural outcomes in children: a systematic review. *Syst Rev* 2020; **9**: 109 [PMID: 32386510 DOI: 10.1186/s13643-020-01330-9]

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META-ANALYSIS

Global epidemiology of mental disorder in atrial fibrillation between 1998-2021: A systematic review and meta-analysis

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Abstract

BACKGROUND

As the burden of mental disorders among patients with atrial fibrillation (AF) increases, researchers are beginning to pay close attention to the risk and prevalence of these comorbidities. Although studies have independently analyzed the risk of comorbidity with depression and anxiety in patients with AF, no study has systematically focused on the global epidemiology of these two mental disorders.

AIM

To explore the prevalence of depression and anxiety in patients with AF.

METHODS

Five databases were searched from their date of establishment until January 2023. Observational studies reporting the comorbidity of AF with depression and anxiety, were included in this study. Basic information, such as the first author/publication year, study year, study type, and prevalence of depression and anxiety, were extracted. STATA SE 15.1 was used to analyze the data. Subgroup, meta-regression, and sensitivity analyses were performed to estimate study heterogeneity.

RESULTS

After a thorough search, 26 studies were identified and included in this meta-analysis. The prevalence rates of depression and anxiety in adults with AF were 24.3% and 14.5%, respectively. Among adult males with AF, the prevalence was 11.7% and 8.7%, respectively, whereas in females it was 19.8% and 10.1%,

respectively. In older adults with AF, the prevalence rates of depression and anxiety were 40.3% and 33.6%, respectively. The highest regional prevalence of depression and anxiety was observed in European (30.2%) and North American (19.8%) patients with AF.

CONCLUSION
In this study, we found that the prevalence of depression and anxiety among patients with AF varies with sex, region, and evaluation scales, suggesting the need for psychological interventions for patients with AF in clinical practice.

Key Words: Atrial fibrillation; Depression; Anxiety; Prevalence

Core Tip: Mental disorders are risk factors for the development of atrial fibrillation (AF). The global prevalence of AF comorbidity with depression and anxiety is not clear. This is the first study to evaluate the global prevalence of two types of psychiatric disorders (depression and anxiety) in patients with AF from the aspects of age, sex, country, and evaluation scale for depression and anxiety.

Citation: Zhang S, Zhang N, Liu L, Zheng W, Ma ZL, Qiao SY, Zhao YL, Wei YH, Wu G, Yu QT, Deng B, Shen L. Global epidemiology of mental disorder in atrial fibrillation between 1998-2021: A systematic review and meta-analysis. *World J Psychiatry* 2024; 14(1): 179-193
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INTRODUCTION

Atrial fibrillation (AF), an irregular and rapid heart rate, is one of the most common cardiac arrhythmias[1,2]. The prevalence of AF has increased steadily over the past three decades, with approximately 60 million people worldwide currently suffering from it[3]. It has been demonstrated that age, gender, smoking, alcohol consumption, hypertension, diabetes, and genetic predisposition are all recognized risk factors for the development and progression of AF[4,5]. The continued increase in AF prevalence and mortality adversely affects patients' quality of life with a significant burden on health and economic development[6].

Recently, mental disorders have become a serious concern worldwide. As reported by WHO in 2019, 970 million people worldwide have mental disorders, with anxiety and depression being the two most common categories[7]. Emerging evidence has shown that patients with acute and chronic cardiovascular diseases are at a higher risk of developing mental disorders[8]. Mental disorders are also on the agenda for patients with AF. Studies have shown that patients with AF have a poorer quality of life than patients with other cardiovascular diseases, regardless of disease symptoms[9], which directly affects their psychological well-being. In another study, several factors affecting Health-related quality of life in patients with AF included depression and anxiety[10]. Although studies have independently analyzed the risk of comorbidity with depression and anxiety in patients with AF[11], no study has systematically focused on the global epidemiology of these two mental disorders. Therefore, we aimed to analyze the epidemiology of AF's co-morbidity with depression and anxiety.

MATERIALS AND METHODS

This study was conducted according to the PRISMA 2009 statement and Meta-analysis of Observational Studies in Epidemiology guidelines (Supplementary Table 1). This study was registered in the PROSPERO (No. CRD42023405975) database.

Search strategy

Two researchers (Zhang S and Zhang N) independently searched the PubMed, Embase, CNKI, Wanfang, and Sinomed databases from their construction date to January 2023 using a combination of subject and free words. The primary search terms were: "AF", "mental health", "depression", "anxiety", "affective symptoms", "psychological distress", "epidemiology", "prevalence", and "incidence". The details are shown in Supplementary Tables 2-6.

Inclusion and exclusion criteria

The criteria for inclusion in this study were as follows: (1) Epidemiological studies reporting co-morbidity of AF with depression and anxiety; (2) observational studies, including cohort studies and cross-sectional studies; (3) studies

published in Chinese or English; and (4) no restrictions for age, gender, and country.

The exclusion criteria were as follows: (1) Literature not relevant to the topic of the study; (2) duplicate studies; (3) case-control studies and non-observational studies; and (4) unavailability of full texts.

Data extraction

Two investigators (Zheng W and Ma ZL) separately extracted the key constituents for inclusion in the study. The following information was retrieved: first author/publication year, study year, study type, age, region (country), type of mental health, diagnostic criteria for mental health, generation, number of cases of AF, and prevalence of comorbidities. If the prevalence was not stated in the study or if the study was cross-sectional, we used the following formula: Cases/total number of subjects in the observational group × 100%.

Study quality

Two researchers (Zhao YL and Qiao SY) evaluated the quality of the pooled research. The Agency for Healthcare Research and Quality tool was used to estimate the risk of bias in cross-sectional studies. Additionally, the Newcastle-Ottawa Scale was used to assess the cohort studies. The researchers graded each study based on the entries of the scale and classified them as high (8-11), moderate (4-7), and low (0-3) quality.

Statistical analysis

We used STATA SE 15.1 for data analysis, and the I^2 test was used to evaluate heterogeneity. A fixed-effects model was used if the I^2 value was < 50%; otherwise, a random-effects model was applied. Heterogeneity was assessed by subgroup, meta-regression, and sensitivity analyses. Publication bias was determined using Egger's and Begg's linear tests. If there was a publication bias, the trim-and-fill method was used to estimate the number of missing studies to rectify it. We used the R 4.2.2 software to visualize world maps for the prevalence of depression and anxiety in patients with AF.

RESULTS

Characteristics of the included studies

We identified 2681 studies. A total of 2391 studies remained after removing duplicates, of which 1851 were thematic discrepancies, 370 were reviews, and 29 were duplicates. Subsequently, 141 full-text articles were assessed for eligibility. From these, 115 studies were removed due to irrelevant topics, missing data, or other study types. Finally, 26 studies[12-37] were used in the meta-analysis (Figure 1).

Of the included studies, 25 and 14 analyzed the prevalence of depression and anxiety in patients with AF, respectively. One study reported the prevalence of AF in patients with depression[14]. Details were shown in Table 1.

Study quality

After evaluating and scoring the studies, we found that they had scores ranging from 4 to 7, all of which were of moderate quality. The details are listed in Supplementary Tables 7 and 8.

Outcomes

Depression: The aggregated prevalence of depression in patients with AF was 22.0% (95%CI: 0.207-0.233). the prevalence was 24.3% (95%CI: 0.228-0.257) in adults and 40.3% (95%CI: 0.264-0.541) in patients ≥ 60 years. Additionally, the prevalence of depression in patients with AF differed between men [11.7% (95%CI: 0.088-0.147)] and women [19.8% (95%CI: 0.1494-0.252)] (Table 2, Supplementary Figures 1-4). We found in the study that evaluated the prevalence of AF in patients with depression that 46.37% of 6055 patients with depression had AF (Supplementary Table 9).

In terms of continents, the prevalence of AF co-morbidity with depression in Europe, Asia, North America, and Oceania was 30.2% (95%CI: 0.274-0.330), 8.6% (95%CI: 0.072-0.100), 28.8% (95%CI: 0.145-0.431), and 29.0% (95%CI: 0.242-0.341), respectively (Table 2, Supplementary Figure 5). European countries such as Poland, Greece, Russia, United Kingdom, Germany, Norway, Sweden and Denmark had a prevalence of 54.5% (95%CI: 0.390-0.700), 35.3% (95%CI: 0.281-0.430), 43.8% (95%CI: 0.295-0.588), 38.6% (95%CI: 0.291-0.488), 37.9% (95%CI: 0.356-0.401), 2.2% (95%CI: 0.021-0.024), 4.0% (95%CI: 0.039-0.040), and12.0% (95%CI: 0.118-0.122), respectively. Similarly, in Asia, countries such China and Korea had a prevalence of 27.8% (95%CI: 0.143-0.412) and 3.0% (95%CI: 0.030-0.030), respectively. The prevalence rates in Oceania and North America were consistent with those in Australia and the United States (Table 2, Supplementary Figure 6). The worldwide prevalence of depression among patients with AF is shown in Figure 2.

We analyzed the impact of different study types on prevalence and found a 58.2% (95%CI: 0.468-0.695) prevalence in cross-sectional, 15.3% (95%CI: 0.124-0.182) in cohort and 24.4% (95%CI: 0.217-0.271) in other studies (Table 2, Supplementary Figure 7). We subsequently analyzed the comorbidity rate of depression in patients with AF using various depression evaluation scales such as beck depression inventory, hospital anxiety and depression scale (HADS), patient health questionnaire (PHQ-9), the major depression inventory, center for epidemiological studies depression scale, international classification of diseases (ICD), and the geriatric depression scale with rates of 43.4% (95%CI: 0.370-0.499), 32.3% (95%CI: 0.187-0.459), 34.4% (95%CI: 0.225-0.463), 72.8% (95%CI: 0.693-0.761), 29.0% (95%CI: 0.242-0.341), 6.3% (95%CI: 0.039-0.087), and 44.1% (95%CI: 0.380-0.503), respectively (Table 2, Supplementary Figure 8).

Anxiety: In estimating the prevalence of anxiety in patients with AF, the meta-analysis identified an overall prevalence of

Table 1 Characteristic of included studies

Ref.	Study year	Study type	Region (country)	Type of MH	Diagnostic criteria of MH	Age (mean ± SD) (yr)[1]	Generation (yr)	AF (*n*)	*P* (MH in AF); Total (M/F) (%)
Thrall *et al*[20]	-	-	Europe (United Kingdom)	D and A	Depression-BDI; anxiety-STAI	66.30 11	Adult (≥ 18 y)	101	D (38.00); A (28.00/38.00)
Ariansen *et al*[35]	-	-	Europe (Norway)	D	HADS	-	Adult (≥ 75 y)	27	11.10
Gehi *et al*[32]	2008-2011	Cohort study	North America (United States)	D and A	Depression-PHQ-9; anxiety-HADS	61.70 13.50	Adult (≥ 18 y)	300	D (50.00); A (17.00)
Ball *et al*[31]		SAFETY	Oceania (Austria)	D	CES-D	75 13	Adult (≥ 45 y)	335	29.00
Schnabel *et al*[30]	2007	Population-based Gutenberg Health Study	Europe (Germany)	D	PHQ-9	64.8 8.2	Adult (35-74 y)	309	8.00
Thompson *et al*[19]	2009-2012	Cohort study	North America (United States)	D and A	Anxiety-HADS-A Depression-PHQ-9	61.60 13.30	Adult (≥ 18 y)	378	D (39.40/16.9); A (17.72)
von Eisenhart Rothe *et al*[21]	2005-2008	Cross-sectional study	Europe (Germany)	D	MDI scale	-	Adult (≥ 18 y)	702	73.00
Hsu *et al*[29]	-	Population based community health survey	Asia (China)	D and A	HADS	74.90 6.90	Adult (≥ 65 y)	1732	D (14.00); A (36.00)
Wändell *et al*[28]	2001-2007	Cohort study	Europe (Sweden)	D and A	ICD-10	-	Adult (≥ 45 y)	12283 (6702/5750)	D (8.50) (6.10/10.90); A (4.03) (2.70/5.40)
Hu *et al*[12]	2000-2010	Cohort study	Asia (China)	D and A	ICD-9-CM	72.70 13.40	Adult (≥ 18 y)	88259	D (1.57); A (1.06)
Rewiuk *et al*[13]	2007-2012	Population-based, multicenter study	Europe (The Republic of Poland)	D	GDS	78.0 7.7	Adult (65-104)	788	41.24
Polikandrioti *et al*[15]	-	-	Europe (Greece)	D and A	HADS	-	Adult (≥ 18 y)	170	Anxiety-low (38.25) (39.80/35.30); anxiety-moderate (26.47) (31.40/15.70); anxiety-high (34.71) (28.80/49.00); depression-low (63.53) (65.80/60.80); depression-moderate (15.29) (14.50/17.60); depression-high (20.00) (19.70/21.60)
Hagengaard *et al*[16]	2005-2014	Cohort study	Europe (Denmark)	D and A	ICD-10	-	-	146377	D (0.29); A (0.07)
Uchmanowicz *et al*[17]	2019	Cross-sectional study	Europe (The Republic of Poland)	D	HADS GDS	70.27 3.48	Adult (≥ 65y)	100	Anxiety (HADS 8-10) (22.00); anxiety (HADS 11-21) (20.00); depression (HADS 8-10) (26.00); depression (HADS 11-21) (28.00); depression (GDS 6-15) (51.00)
Krupenin *et al*[18]	2017-2018	-	Europe (Russia)	D and A	GDS	78[2]	Adult (≥ 65 y)	48	41.67
Wang *et al*[22]	-	SAGE-AF Study	North America (United States)	D and A	Anxiety-GAD Depression-PHQ-9	76.00 7.00	Adult (≥ 65 y)	1244	D (29.00); A (24.00)
Kim *et al*[23]	2009-2018	Cohort study	Asia (Korea)	D	ICD-10	46.99 14.06	Adult (≥ 20 y)	5031222	3.00 (1.04/1.92)

Jankowska-Polańska *et al*[24]	-	Cohort study	Europe (The Republic of Poland)	D and A	HADS	70 7	Adult (≥ 60 y)	158	Depression (8-10) (37.97); depression (11-21) (37.87); anxiety (8-10) (32.91); anxiety (11-21) (48.10)
Feng *et al*[25]	2006-2008	HUNT study	Europe (Germany)	D and A	HADS	53.4 15.2	Adult (≥ 20y)	37402	D (2.20); A (4.90)
Wändell *et al*[28]	1998-2012	Cohort study	Europe (Sweden)	D and A	ICD-10	-	Adult (≥ 45 y)	537513 (287959/249554)	D (3.91) (3.46/4.44); A (2.70) (2.23/3.25)
Piwoński *et al*[27]	-	Cross-sectional study	Europe (The Republic of Poland)	D	BDI	-	Adult (18-79 y)	124 (57/67)	47.58 (43.86/50.75)
Wu *et al*[33]	2020-2021	-	Asia (China)	D	PHQ-9	-	Adult (≥ 18 y)	329	35.56
Fenger-Grøn *et al* [34]	2005-2016	-	Europe (Denmark)	D	ICD-8/ICD-10	78.7 10.1	Adult (18-100 y)	147162	12.16
Rosman *et al*[36]	-	Cohort study	North America (USA)	D and A	ICD-9	30.29 9.19	Adult (18-60 y)	988090	9.04
Zhang *et al*[37]	2012-2013	Cross-sectional study	Asia (China)	D	PHQ-9	63.3 9.5	Adult (≥ 35 y)	134	63.00

[1]Ages in atrial fibrillation patients.

[2]Median age.

A: Anxiety; AF: Atrial fibrillation; BDI: Beck depression inventory; CES-D: Centre for epidemiological studies depression scale; D: Depression; GAD-7: 7-item generalized anxiety disorder-7 scale; GDS: Geriatric depression scale; HADS: Hospital anxiety and depression scale; HUNT study: The trøndelag health study; ICD: International classification of diseases; MDI: Major depression inventory; MH: Mental health; PHQ: Patient health questionnaire; SAFETY: Standard versus atrial fibrillation specific management study; SAGE-AF: Systematic assessment of geriatric elements in atrial fibrillation; STAI: Stait-trait anxiety inventory.

13.0% (95%CI: 0.117-0.142); 14.5% (95%CI: 0.132–0.158) in adults, 33.6% (95%CI: 0.246-0.425) in older adults ≥ 60 years old, 8.7% (95%CI: 0.063-0.111) in males, and 10.1% (95%CI: 0.069-0.133) in females (Table 2, Supplementary Figures 9-12).

Only three continents, Asia, Europe, and North America, reported a prevalence of anxiety in patients with AF. These were 1.10% (95%CI: 0.010-0.012), 13.9% (95%CI: 0.118-0.159), and 19.8% (95%CI: 0.149-0.248), respectively (Table 2, Supplementary Figure 13). Five studies reported the prevalence in five individual European countries, including Greece, 61.8% (95%CI: 0.540-0.691); Poland, 45.7% (95%CI: 0.396-0.518); United Kingdom, 33.3% (95%CI: 0.268-0.398); Norway, 4.9% (95%CI: 0.047-0.051); and Sweden, 2.7% (95%CI: 0.027-0.028). In Asia and North America, the prevalence of co-morbidity of anxiety with AF was reported only in China and the United States at 1.10% (95%CI: 0.010-0.012) and 19.8% (95%CI: 0.149-0.248), respectively (Table 2, Supplementary Figure 14). The worldwide prevalence of anxiety among patients with AF is shown in Figure 3.

A comparison of the occurrence of anxiety in patients with AF among different observational study types showed a prevalence of 42.0% (95%CI: 0.322-0.523), 8.1% (95%CI: 0.053-0.109), and 24.8% (95%CI: 0.218-0.277) in cross-sectional, cohort and other studies, respectively (Table 2, Supplementary Figure 15). Four criteria were used to diagnose anxiety. The prevalence rate using the state-trait anxiety inventory, HADS, ICD, and generalized anxiety disorder scale was 28.7% (95%CI: 0.201-0.386), 31.2% (95%CI: 0.174-0.449), 2.6% (95%CI: 0.013-0.039), 24.0% (95%CI: 0.217-0.265), respectively (Table 2, Supplementary Figure 16)

Table 2 Prevalence of mental health in atrial fibrillation patients

Study or subgroup	Prevalence (95%CI)	I^2 (%)	*P* value
Depression			
Overall prevalence	22.0 (0.207, 0.233)	100	< 0.001
Prevalence in adults	24.3 (0.228, 0.257)	100	< 0.001
Gender			
Male	11.7 (0.088, 0.147)	97.3	< 0.001
Female	19.8 (0.144, 0.252)	98.7	< 0.001
Age group			
≥ 60 yr	40.3 (0.264, 0.541)	100	< 0.001
Other ages	20.4 (0.188, 0.221)	100.0	< 0.001
Study design			
Cross-sectional study	58.2 (0.468, 0.695)	91.7	< 0.001
Cohort study	15.3 (0.124, 0.182)	100	< 0.001
Others	24.4 (0.217, 0.271)	99.9	< 0.001
Region			
Asia	8.6 (0.072, 0.100)	100	< 0.001
Europe	30.2 (0.274, 0.330)	99.9	< 0.001
North America	28.8 (0.145, 0.431)	99.3	< 0.001
Oceania	29.0 (0.242, 0.341)	0	-
Diagnostic criteria			
BDI	43.4 (0.370, 0.499	0	-
HADS	32.3 (0.187, 0.459)	99.5	< 0.001
PHQ-9	34.4 (0.225, 0.463)	98.3	< 0.001
MDI	72.8 (0.693, 0.761)	0	-
CES-D	29.0 (0.242, 0.341)	0	-
ICD	6.3 (0.039, 0.087)	100	< 0.001
GDS	44.1 (0.380, 0.503)	41.2	0.183
Anxiety			
Overall prevalence	13.0 (0.117, 0.142)	99.9	< 0.001
Prevalence in adults	14.5 (0.132, 0.158)	99.7	< 0.001
Gender			
Male	8.7 (0.063, 0.111)	97.9	< 0.001
Female	10.1 (0.069, 0.133)	97.3	< 0.001
Age group			
≥ 60yr	33.6 (0.246, 0.425)	95.2	< 0.001
Other ages	7.6 (0.063, 0.088)	99.7	< 0.001
Region			
Asia	1.1 (0.010, 0.012)	-	-
Europe	13.9 (0.118, 0.159)	99.2	< 0.001
North America	19.8 (0.149, 0.248)	-	-
Study design			
Cross-sectional study	42.0 (0.322, 0.523)	0	-

Cohort study	8.1 (0.053, 0.109)	99.2	< 0.001
Other	24.8 (0.218, 0.277)	99.6	< 0.001
Diagnostic criteria			
STAI	28.7 (0.201, 0.386)	-	-
HADS	31.2 (0.174, 0.449)	99.4	< 0.001
ICD	2.6 (0.013, 0.039)	-	-
GAD	24.0 (0.217, 0.265)	-	-

BDI: Beck depression inventory; CES-D: Centre for Epidemiological Studies Depression Scale; GAD: Generalized anxiety disorder scale; GDS: Geriatric depression scale; HADS: Hospital anxiety and depression scale; ICD: International classification of diseases; MDI: Major depression inventory; PHQ-9: Patient health questionnaire; STAI: Stait-trait anxiety inventory.

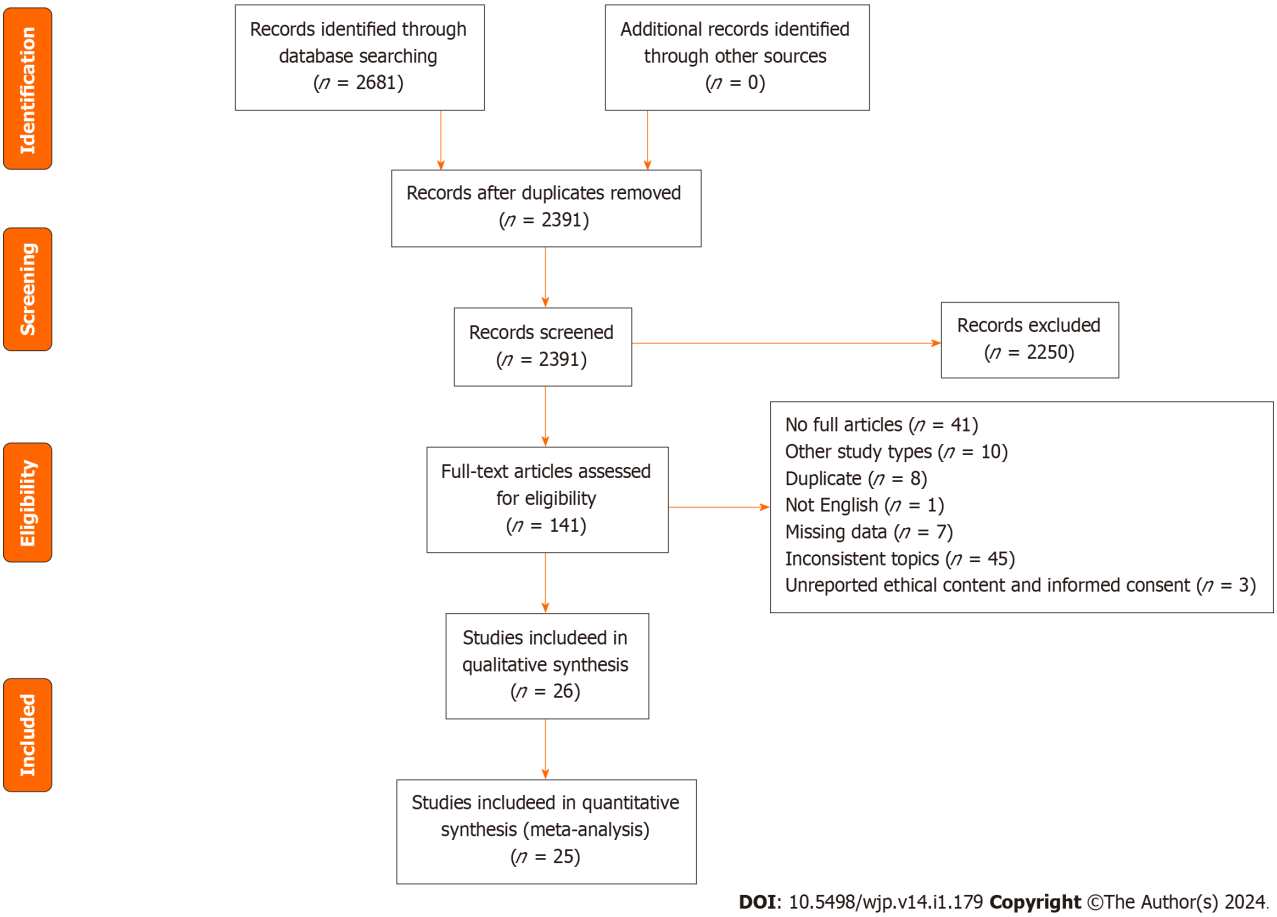

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Figure 1 Flow chart of search strategy according to PRISMA 2009 guidelines.

Meta-regression analysis

A meta-regression analysis was conducted to examine the sources of heterogeneity in the prevalence of anxiety and depression among patients with AF. We found that the diverse study types, diagnostic criteria, and age groups were sources of heterogeneity in the prevalence of AF comorbidity with anxiety (Table 3).

Sensitivity analyses

We performed a sensitivity analysis of the prevalence of depression and anxiety in patients with AF and found that the results were robust after applying the respective exclusions (Supplementary Figures 17 and 18).

Publication bias

We analyzed the publication bias for the prevalence of depression and anxiety in adults with AF using Egger's and Begg's linear tests. We found the publication bias for these two disorders (Supplementary Figures 19-22). These parameters were then evaluated using the trim-and-fill method. We discovered an increase of 34 and 20 studies on depression and anxiety,

Table 3 Meta-regression analysis of prevalence of mental health in atrial fibrillation

Possible source of heterogeneity	Number of studies	Coef (95%CI)	*P* value
Depression			
Study design	24	0.40 (-0.18, 0.98)	0.18
Cross-sectional study	4	1.34 (0.21, 2.47)	0.02
Cohort study	6	-1.76 (-3.03, -0.49)	0.01
Others	14	-1.11 (-2.28, 0.05)	0.06
Region	24	0.46 (-0.12, 1.04)	0.11
Asia	5	-0.82 (-2.29, 0.64)	0.27
Europe	14	-0.12 (-1.33, 1.10)	0.85
North America	4	0.29 (-0.87, 1.44)	0.63
Oceania	1	0.16(-2.38, 2.70)	0.90
Age group	24	-0.67(-1.67, 0.33)	0.19
≥ 60	7	0.33 (-0.70, 1.36)	0.53
Other ages	17	-0.33 (-1.36, 0.70)	0.53
Diagnostic criteria	24	-0.22(0.45, 0.02)	0.07
BDI	2	0.28 (-2.22, 2.78)	0.83
HADS	6	-2.96 (-2.23, 1.64)	0.76
PHQ-9	6	0.02 (-1.86, 1.91)	0.98
MDI	1	0.93 (-1.56, 3.42)	0.47
CES-D	1	0.40 (-1.95, 2.76)	0.74
ICD	6	-1.73 (-3.64, 0.17)	0.07
GDS	2	0.44 (-1.60, 2.48)	0.67
Anxiety			
Region	13	-0.24 (-1.01, 0.52)	0.53
Asia	2	-1.03 (-2.87, 0.81)	0.27
Europe	8	1.00 (-0.98, 2.97)	0.32
North America	3	1.14 (-1.16,3.43)	0.32
Study design	13	-0.21 (-1.07, 0.65)	0.63
Cross-sectional study	1	1.95 (-0.59, 4.50)	0.13
Cohort study	4	-1.30 (-2.61, 0.01)	0.05
Others	8	1.22 (-0.15, 2.60)	0.08
Age group	13	-1.38 (-2.53, -0.24)	0.02
≥ 60	5	1.15 (-0.13, 2.43)	0.08
Other ages	8	-1.15 (-2.43, 0.13)	0.08
Diagnostic criteria	14	-0.84 (-1.63, -0.05)	0.04
STAI	1	0.15 (-2.01, 2.32)	0.89
HADS	9	0.07 (-1.54, 1.67)	0.94
ICD	3	-2.36 (-4.11, -0.61)	0.01
GAD	1	0.51 (-2.10, 3.13)	0.70

BDI: Beck depression inventory; CES-D: Centre for Epidemiological Studies Depression Scale; GAD: Generalized anxiety disorder scale; GDS: Geriatric depression scale; HADS: Hospital anxiety and depression scale; ICD: International classification of diseases; MDI: Major depression inventory; PHQ-9: Patient health questionnaire; STAI: Stait-trait anxiety inventory.

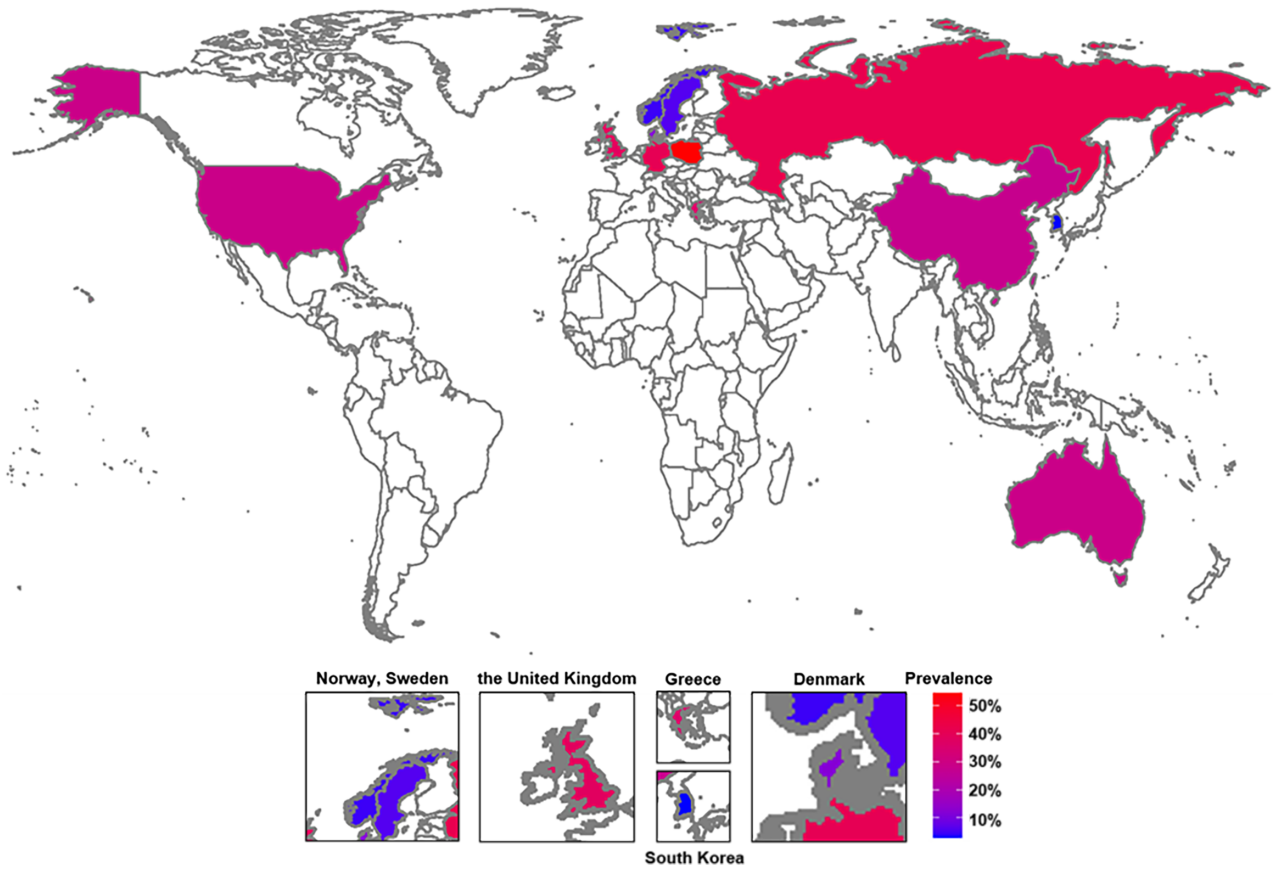

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Figure 2 Global prevalence of depression among adult patients with atrial fibrillation.

respectively, among patients with AF after five iterations. The prevalence of depression and anxiety in patients with AF decreased to 15.8% (95%CI: 0.14-0.17) and 7.9% (95%CI: 0.066-0.091), respectively.

DISCUSSION

To our knowledge, this is the first study to present the global prevalence of depression and anxiety in patients with AF. After a systematic and holistic evaluation, we identified a 22.0% and 13.0% prevalence of depression and anxiety, respectively, in patients with AF and 24.3% and 14.5% in adults. Furthermore, the prevalence of depression and anxiety in patients with AF was 11.7% and 8.7%, 19.8% and 10.1%, 40.3% and 33.6% in males, females and the elderly, respectively. This prevalence varied in regional distribution. A higher percentage of European (30.2%) and North American (19.8%) patients with AF experienced depression and anxiety, respectively, than those in other continents. Furthermore, the highest percentage of patients with AF and depression and anxiety were found in Poland (54.5%) and Greece (61.8%), respectively. Cardiovascular diseases remain the primary cause of morbidity worldwide, with the total disability-adjusted life years caused by AF and atrial flutter at 8.39 million in 2019[38]. Anxiety, inflammation, and left atrial dilation are significant predictors of the quality of life in patients with AF[39]. Another study indicated that as the severity of AF-specific symptoms increases, there is a positive correlation between the levels of anxiety and depression [19]. Furthermore, one-third of patients with AF were reported to have persistent levels of depression and anxiety at a 6-month follow-up[20]. These findings underscore the importance of identifying and increasing interventions for psychological factors in patients with AF. Our study demonstrated that depression and anxiety in patients with AF exhibit sex and regional differences. The prevalence of AF comorbidity with both depression and anxiety appears to be higher in females than males. This may be linked to sex differences, as studies have shown that women are more likely to develop AF than men[40]. The differences in biological factors between men and women, such as sex hormones, X and Y chromosomes, reactions to stimuli, and body fats, contribute to the sex differences[40]. Age is a crucial risk factor for AF, and its prevalence increases with age. We found that patients with AF aged > 60 years had a higher probability of comorbidity with depression and anxiety. Furthermore, the high prevalence of depression among patients with AF in Poland may be related to the inclusion of older populations in the reported studies. Additionally, the increasing disease burden due to the aging population in developed countries may contribute to the increasing prevalence of AF[41], the higher prevalence of depression and anxiety in Europe and North America in our study may be related to this aspect. Pathogenic links exist between AF and psychiatric disorders. Autonomic nerves innervate the heart, and AF can be

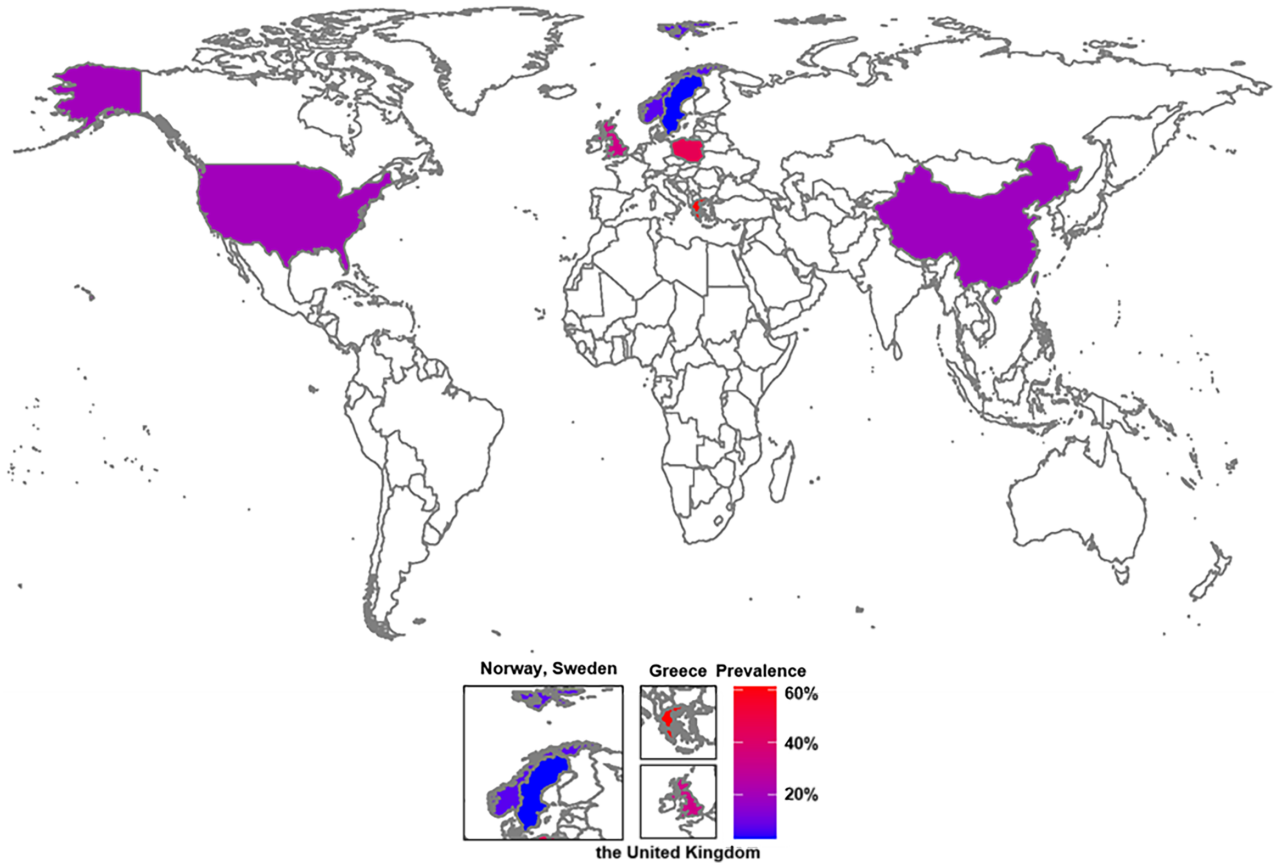

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Figure 3 Global prevalence of anxiety among adult patients with atrial fibrillation.

induced when the cardiac action potential receives a rapid discharge stimulus[42]. Previous studies have shown that in states of depression and anxiety, sympathetic nerves are overexcited, and catecholamine secretion increases. High concentrations of catecholamines can damage vascular endothelial cells and cause palpitations on the one hand, leading to the formation of arrhythmic substrates; on the other hand, they accelerate the heart rate, shorten the atrioventricular node's refractory period, depolarize the atrial ectopic pacing point, trigger the feedback mechanism, resulting in AF. In addition, catecholamines can overstimulate β-adrenergic receptors, affect calmodulin expression, impair calcium handling systems, and lead to atrial remodeling[43-45]. Inflammation is another important link between AF and depression or anxiety. Studies have shown that patients with AF have significantly higher serum levels of ultrasensitive C-reactive protein and interleukin 6, and anxiety and depression are strongly associated with these two inflammatory mediators[46,47]. The renin-angiotensin-aldosterone system (RAAS) is also implicated in AF and mental disorders. Anxiety and depression contribute to an active RAAS, which is accompanied by an increase in angiotensin secretion. Elevated levels of angiotensin II promote cardiac fibrosis, slow down cardiomyocyte signaling, and damage the myocardium, leading to myocardial remodeling and an increase in the number of folds, which provides a favorable environment for the development of AF[48-51]. Additionally, it has been demonstrated that chronic stimulation of a rat depression model with sigma-1 receptors with antidepressant effects attenuates atrial electrical remodeling, fibrosis, and AF susceptibility [52]. Furthermore, patients with significant depression share the *ZHX3* and *ADI1P1* genes with AF patients[53]. Overall, there are few studies on the co-morbidity mechanisms of AF and psychiatric disorders, which could be a direction for future research.

AF treatment involves using antiarrhythmic drugs, direct-current cardioversion, catheter ablation, or surgical ablation to restore and maintain sinus rhythm[54]. A recent randomized controlled trial showed that symptoms of depression and anxiety significantly improved in patients who underwent catheter ablation of AF[55]. In addition, there is evidence of significant improvement in depression and anxiety in patients with AF after treatment with newer anticoagulants, such as rivaroxaban and dabigatran, compared with oral warfarin[56,57]. Some antidepressants protect the body from cardiovascular damage. However, the use of antidepressants in the treatment of AF has been poorly studied[58]. Paroxetine is an antidepressant that reduces the number of episodes of paroxysmal AF and may exert its therapeutic effect by modulating the vagal tone in the brain and inhibiting vasovagal reflexes[59]. In addition, exercise therapy, such as yoga, is an effective option for managing depression and anxiety in patients with AF[60].

Few studies have reported the prevalence of depression and anxiety in patients with AF. Zhuo *et al*[61] elucidated the correlation between preoperative depression in patients with AF and recurrence after catheter ablation. Three studies analyzed the prevalence and risk index of depression and anxiety in patients with AF[10,11,62]. This study not only presents an analysis of the rate of depression and anxiety in patients with AF but also highlights regional discrepancies in

their prevalence by country, allowing for a more visual representation of the data.

Although we tried to be as rigorous as possible, this study had a few limitations. First, the studies we included were published in English or Chinese, which may have resulted in language bias. Second, the prevalence of anxiety in patients with AF was reduced after the trim-and-fill method. This might result from the inclusion of only observational studies in our analysis and our inability to find the "gray literature" in our study. However, after sensitivity analyses, the conclusions were robust. Third, although AF is divided into various types, such as paroxysmal and persistent AF, our study did not address this aspect because no previous study has analyzed the prevalence of diverse types of AF. Additionally, the scales and diagnostic criteria used to evaluate anxiety and depression differed in the included studies, leading to significant differences in prevalence. In the meta-regression, we also found that different scales were a source of heterogeneity and then divided them into subgroups for analysis. Further studies are needed to analyze the prevalence of depression and anxiety in patients with different types of AF and standardize the evaluation criteria for anxiety and depression as much as possible. The mechanism of AF comorbidity with depression and anxiety can be elucidated using molecular biology and cellular immunology, which is another direction for future research. Moreover, large-scale observational epidemiological studies are needed to analyze its prevalence and provide a basis for clinical diagnosis and treatment.

CONCLUSION

We integrated and systematically analyzed the prevalence of two psychiatric disorders, depression and anxiety, in patients with AF. We found that the prevalence of comorbid psychiatric disorders in patients with AF was associated with sex and region. These facts underscore the need for clinicians to actively engage in mental health interventions in managing patients with AF.

ARTICLE HIGHLIGHTS

Research background

Atrial fibrillation (AF), an irregular and rapid heart rate, is one of the most common types of cardiac arrhythmias. Research has shown that patients with AF are more prone to psychological problems than the general population. These problems increases the recurrence rate of AF while seriously affecting the quality of life, morbidity, and mortality rate of patients.

Research motivation

Anxiety and depression are the two most common mental health disorders worldwide. Studies have independently analyzed the risk of comorbidity with depression and anxiety in patients with AF. No study has systematically focused on the global epidemiology of these two mental disorders in patients with AF. A deeper understanding of the prevalence of comorbid depression and anxiety in these patients is essential in guiding clinical management.

Research objectives

To explore the prevalence of depression and anxiety in patients with AF.

Research methods

Five databases were searched from their establishment until January 2023. Observational studies reporting the co-morbidity of AF with depression and anxiety–were included. STATA SE 15.1 was applied to analyze the data. Subgroup, meta-regression, and sensitivity analyses were performed to estimate study heterogeneity.

Research results

The prevalence rates of depression and anxiety in adults with AF were 24.3% and 14.5%, respectively. Among adult males with AF, the prevalence of depression and anxiety were 11.7% and 8.7%, respectively. This prevalence varied with sex, age and region; in females, it was 19.8% and 10.1%, and 40.3% and 33.6% in the older adults, respectively. The highest prevalence rate of depression and anxiety was observed in European (30.2%) and North American (19.8%) patients with AF. Furthermore, the prevalence varied according to the different evaluation scales.

Research conclusions

We found that the prevalence of depression and anxiety among patients with AF was differentially distributed according to sex, region, and evaluation scales, suggesting the need for psychological interventions for patients with AF in clinical practice.

Research perspectives

To explore this association further, future studies should focus on assessing the prevalence of depression and anxiety in patients with different types of AF, delineating the mechanisms of AF comorbidity with depression and anxiety using molecular biology and cellular immunology, and carrying out a large-scale observational epidemiological study to

analyze its prevalence and provide a basis for clinical diagnosis and treatment.

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FOOTNOTES

Co-first authors: Shuai Zhang and Na Zhang.

Co-corresponding authors: Shuai Zhang and Lin Shen.

Author contributions: Zhang S and Shen L were co-corresponding authors who proposed the concept, designed the study and raised fundings; Zhang S and Zhang N were co-first authors for they contributed equally in this research. Additionally, Zhang S, Liu L and Zhang N were responsible for literature search, screening and writing drafts; Zheng W and Ma ZL extracted data; Zhang YL and Qiao SY assessed the quality of studies; Wei YH, Wu G, Yu QT and Deng B analyzed the data. All the authors read and approved the final manuscript. The reasons for designating Zhang S and Zhang N as co-first authors are twofold: Firstly, they made equal contributions to the writing and revision of the manuscript. Secondly, this study was conducted collaboratively, and appointing Zhang S and Zhang N as co-first authors facilitate effective communication in addressing issues related to research design, writing, and data analysis, thereby ensuring smooth progress in the research. The rationale behind selecting Zhang S and Shen L as co-corresponding authors lies in their equal contributions to formulating, conceptualizing, and executing the study, as well as providing funding support. In summary, the co-first and co-corresponding authors in this study not only ensured its seamless execution but also enhanced the rationality and depth of the research topic.

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REFERENCES

1 **Baman JR**, Passman RS. Atrial Fibrillation. *JAMA* 2021; **325**: 2218 [PMID: 34061143 DOI: 10.1001/jama.2020.23700]
2 **Narayan SM**, Cain ME, Smith JM. Atrial fibrillation. *Lancet* 1997; **350**: 943-950 [PMID: 9314883 DOI: 10.1016/s0140-6736(97)06359-9]
3 **Elliott AD**, Middeldorp ME, Van Gelder IC, Albert CM, Sanders P. Epidemiology and modifiable risk factors for atrial fibrillation. *Nat Rev Cardiol* 2023; **20**: 404-417 [PMID: 36600003 DOI: 10.1038/s41569-022-00820-8]
4 **Kornej J**, Börschel CS, Benjamin EJ, Schnabel RB. Epidemiology of Atrial Fibrillation in the 21st Century: Novel Methods and New Insights. *Circ Res* 2020; **127**: 4-20 [PMID: 32716709 DOI: 10.1161/CIRCRESAHA.120.316340]
5 **Staerk L**, Sherer JA, Ko D, Benjamin EJ, Helm RH. Atrial Fibrillation: Epidemiology, Pathophysiology, and Clinical Outcomes. *Circ Res* 2017; **120**: 1501-1517 [PMID: 28450367 DOI: 10.1161/CIRCRESAHA.117.309732]
6 **Hindricks G**, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021; **42**: 373-498 [PMID: 32860505 DOI: 10.1093/eurheartj/ehaa612]
7 World Health Organization. Mental disorders. June 8, 2022. [cited 2 February 2023]. Available from: https://www.who.int/news-room/fact-sheets/detail/mental-disorders
8 **Goldfarb M**, De Hert M, Detraux J, Di Palo K, Munir H, Music S, Piña I, Ringen PA. Severe Mental Illness and Cardiovascular Disease:

JACC State-of-the-Art Review. *J Am Coll Cardiol* 2022; **80**: 918-933 [PMID: 36007991 DOI: 10.1016/j.jacc.2022.06.017]

9 **Bubien RS**, Knotts-Dolson SM, Plumb VJ, Kay GN. Effect of radiofrequency catheter ablation on health-related quality of life and activities of daily living in patients with recurrent arrhythmias. *Circulation* 1996; **94**: 1585-1591 [PMID: 8840848 DOI: 10.1161/01.cir.94.7.1585]

10 **Lomper K**, Ross C, Uchmanowicz I. Anxiety and Depressive Symptoms, Frailty and Quality of Life in Atrial Fibrillation. *Int J Environ Res Public Health* 2023; **20** [PMID: 36673821 DOI: 10.3390/ijerph20021066]

11 **Wu H**, Li C, Li B, Zheng T, Feng K, Wu Y. Psychological factors and risk of atrial fibrillation: A meta-analysis and systematic review. *Int J Cardiol* 2022; **362**: 85-92 [PMID: 35618103 DOI: 10.1016/j.ijcard.2022.05.048]

12 **Hu WS**, Lin CL. Suicide attempt in patients with atrial fibrillation - A nationwide cohort study. *Prog Neuropsychopharmacol Biol Psychiatry* 2019; **92**: 470-475 [PMID: 30707991 DOI: 10.1016/j.pnpbp.2019.01.013]

13 **Rewiuk K**, Wizner B, Klich-Rączka A, Więcek A, Mossakowska M, Chudek J, Szybalska A, Broczek K, Zdrojewski T, Grodzicki T. Atrial fibrillation independently linked with depression in community-dwelling older population. Results from the nationwide PolSenior project. *Exp Gerontol* 2018; **112**: 88-91 [PMID: 30219348 DOI: 10.1016/j.exger.2018.09.006]

14 **Rizzi SA**, Knight S, May HT, Woller SC, Stevens SM, Steinberg BA, Bair TL, Anderson JL, Muhlestein JB, Knowlton KU, Bunch TJ. Depression as a Driving Force for Low Time in Therapeutic Range and Dementia in Patients With and Without Atrial Fibrillation. *Am J Cardiol* 2021; **153**: 58-64 [PMID: 34176597 DOI: 10.1016/j.amjcard.2021.05.021]

15 **Polikandrioti M**, Koutelekos I, Vasilopoulos G, Gerogianni G, Gourni M, Zyga S, Panoutsopoulos G. Anxiety and Depression in Patients with Permanent Atrial Fibrillation: Prevalence and Associated Factors. *Cardiol Res Pract* 2018; **2018**: 7408129 [PMID: 29670767 DOI: 10.1155/2018/7408129]

16 **Hagengaard L**, Polcwiartek C, Andersen MP, Sessa M, Krogager ML, Gislason G, Schou M, Torp-Pedersen C, Søgaard P, Kragholm KH. Incident atrial fibrillation and risk of psychoactive drug redemptions and psychiatric hospital contacts: a Danish Nationwide Register-based Follow-up Study. *Eur Heart J Qual Care Clin Outcomes* 2021; **7**: 76-82 [PMID: 32502251 DOI: 10.1093/ehjqcco/qcaa048]

17 **Uchmanowicz I**, Lomper K, Gros M, Kałużna-Oleksy M, Jankowska EA, Rosińczuk J, Cyrkot T, Szczepanowski R. Assessment of Frailty and Occurrence of Anxiety and Depression in Elderly Patients with Atrial Fibrillation. *Clin Interv Aging* 2020; **15**: 1151-1161 [PMID: 32764902 DOI: 10.2147/CIA.S258634]

18 **Krupenin P**, Gabitova M, Bordovsky S, Kirichuk Y, Napalkov D, Preobrazhenskaya I, Sokolova A. Impact of atrial fibrillation on the rate of mild cognitive impairment in the elderly. *J Neurol Sci* 2018; **394**: 75-77 [PMID: 30219499 DOI: 10.1016/j.jns.2018.08.023]

19 **Thompson TS**, Barksdale DJ, Sears SF, Mounsey JP, Pursell I, Gehi AK. The effect of anxiety and depression on symptoms attributed to atrial fibrillation. *Pacing Clin Electrophysiol* 2014; **37**: 439-446 [PMID: 24215267 DOI: 10.1111/pace.12292]

20 **Thrall G**, Lip GY, Carroll D, Lane D. Depression, anxiety, and quality of life in patients with atrial fibrillation. *Chest* 2007; **132**: 1259-1264 [PMID: 17646231 DOI: 10.1378/chest.07-0036]

21 **von Eisenhart Rothe AF**, Goette A, Kirchhof P, Breithardt G, Limbourg T, Calvert M, Baumert J, Ladwig KH. Depression in paroxysmal and persistent atrial fibrillation patients: a cross-sectional comparison of patients enroled in two large clinical trials. *Europace* 2014; **16**: 812-819 [PMID: 24351885 DOI: 10.1093/europace/eut361]

22 **Wang W**, Saczynski J, Lessard D, Mailhot T, Barton B, Waring ME, Sogade F, Hayward R, Helm R, McManus DD. Physical, cognitive, and psychosocial conditions in relation to anticoagulation satisfaction among elderly adults with atrial fibrillation: The SAGE-AF study. *J Cardiovasc Electrophysiol* 2019; **30**: 2508-2515 [PMID: 31515920 DOI: 10.1111/jce.14176]

23 **Kim YG**, Lee KN, Han KD, Han KM, Min K, Choi HY, Choi YY, Shim J, Choi JI, Kim YH. Association of Depression With Atrial Fibrillation in South Korean Adults. *JAMA Netw Open* 2022; **5**: e2141772 [PMID: 34982161 DOI: 10.1001/jamanetworkopen.2021.41772]

24 **Jankowska-Polańska B**, Polański J, Dudek K, Sławuta A, Mazur G, Gajek J. The Role of Sleep Disturbance, Depression and Anxiety in Frail Patients with AF-Gender Differences. *J Clin Med* 2020; **10** [PMID: 33374533 DOI: 10.3390/jcm10010011]

25 **Feng T**, Malmo V, Laugsand LE, Strand LB, Gustad LT, Ellekjær H, Loennechen JP, Mukamal K, Janszky I. Symptoms of anxiety and depression and risk of atrial fibrillation-The HUNT study. *Int J Cardiol* 2020; **306**: 95-100 [PMID: 31759687 DOI: 10.1016/j.ijcard.2019.11.107]

26 **Wändell P**, Carlsson AC, Li X, Sundquist J, Sundquist K. Association Between Relevant Co-Morbidities and Dementia With Atrial Fibrillation-A National Study. *Arch Med Res* 2019; **50**: 29-35 [PMID: 31349951 DOI: 10.1016/j.arcmed.2019.05.007]

27 **Piwoński J**, Piwońska A, Jędrusik P, Stokwiszewski J, Rutkowski M, Bandosz P, Drygas W, Zdrojewski T. Depressive symptoms and cardiovascular diseases in the adult Polish population. Results of the NATPOL2011 study. *Kardiol Pol* 2019; **77**: 18-23 [PMID: 30406941 DOI: 10.5603/KP.a2018.0213]

28 **Wändell P**, Carlsson AC, Gasevic D, Wahlström L, Sundquist J, Sundquist K. Depression or anxiety and all-cause mortality in adults with atrial fibrillation--A cohort study in Swedish primary care. *Ann Med* 2016; **48**: 59-66 [PMID: 26758363 DOI: 10.3109/07853890.2015.1132842]

29 **Hsu NW**, Tsao HM, Chen HC, Lo SS, Chen SA, Chou P. Different Impacts of Atrial Fibrillation and Cardiac Premature Contractions on the Health-Related Quality of Life in Elderly People: The Yilan Study. *Tohoku J Exp Med* 2016; **238**: 75-83 [PMID: 26725845 DOI: 10.1620/tjem.238.75]

30 **Schnabel RB**, Michal M, Wilde S, Wiltink J, Wild PS, Sinning CR, Lubos E, Ojeda FM, Zeller T, Munzel T, Blankenberg S, Beutel ME. Depression in atrial fibrillation in the general population. *PLoS One* 2013; **8**: e79109 [PMID: 24324579 DOI: 10.1371/journal.pone.0079109]

31 **Ball J**, Carrington MJ, Wood KA, Stewart S; SAFETY Investigators. Women versus men with chronic atrial fibrillation: insights from the Standard versus Atrial Fibrillation spEcific managemenT studY (SAFETY). *PLoS One* 2013; **8**: e65795 [PMID: 23734260 DOI: 10.1371/journal.pone.0065795]

32 **Gehi AK**, Sears S, Goli N, Walker TJ, Chung E, Schwartz J, Wood KA, Guise K, Mounsey JP. Psychopathology and symptoms of atrial fibrillation: implications for therapy. *J Cardiovasc Electrophysiol* 2012; **23**: 473-478 [PMID: 22429764 DOI: 10.1111/j.1540-8167.2011.02264.x]

33 **Wu JH**, Li ST, Li QF, Jiang C, Li X, Ning M, Hu R, Du X, Dong JZ, Ma CS. The relationship between severity of atrial fibrillation symptoms and depression of patients and their caregivers. *Zhongguo Yiyao* 2021; **16**: 819-822

34 **Fenger-Grøn M**, Vestergaard CH, Frost L, Davydow DS, Parner ET, Christensen B, Ribe AR. Depression and Uptake of Oral Anticoagulation Therapy in Patients With Atrial Fibrillation: A Danish Nationwide Cohort Study. *Med Care* 2020; **58**: 216-224 [PMID: 31876644 DOI: 10.1097/MLR.0000000000001268]

35 **Ariansen I**, Dammen T, Abdelnoor M, Tveit A, Gjesdal K. Mental health and sleep in permanent atrial fibrillation patients from the general population. *Clin Cardiol* 2011; **34**: 327-331 [PMID: 21319172 DOI: 10.1002/clc.20883]

36 **Rosman L**, Lampert R, Ramsey CM, Dziura J, Chui PW, Brandt C, Haskell S, Burg MM. Posttraumatic Stress Disorder and Risk for Early Incident Atrial Fibrillation: A Prospective Cohort Study of 1.1 Million Young Adults. *J Am Heart Assoc* 2019; **8**: e013741 [PMID: 31564191 DOI: 10.1161/JAHA.119.013741]

37 **Zhang XY**. Association between depression and atrial fibrillation in rural populations of Liaoning Province. M.Sc. Thesis, China Medical University. 2017. Available from: https://d.wanfangdata.com.cn/thesis/ChJUaGVzaXNOZXdTMjAyMzA5MDESCFkzMjY4Mjk2Ggh2bG1raWN5aQ%3D%3D

38 **Roth GA**, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton AZ, Benjamin EJ, Benziger CP, Bonny A, Brauer M, Brodmann M, Cahill TJ, Carapetis J, Catapano AL, Chugh SS, Cooper LT, Coresh J, Criqui M, DeCleene N, Eagle KA, Emmons-Bell S, Feigin VL, Fernández-Solà J, Fowkes G, Gakidou E, Grundy SM, He FJ, Howard G, Hu F, Inker L, Karthikeyan G, Kassebaum N, Koroshetz W, Lavie C, Lloyd-Jones D, Lu HS, Mirijello A, Temesgen AM, Mokdad A, Moran AE, Muntner P, Narula J, Neal B, Ntsekhe M, Moraes de Oliveira G, Otto C, Owolabi M, Pratt M, Rajagopalan S, Reitsma M, Ribeiro ALP, Rigotti N, Rodgers A, Sable C, Shakil S, Sliwa-Hahnle K, Stark B, Sundström J, Timpel P, Tleyjeh IM, Valgimigli M, Vos T, Whelton PK, Yacoub M, Zuhlke L, Murray C, Fuster V; GBD-NHLBI-JACC Global Burden of Cardiovascular Diseases Writing Group. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. *J Am Coll Cardiol* 2020; **76**: 2982-3021 [PMID: 33309175 DOI: 10.1016/j.jacc.2020.11.010]

39 **Charitakis E**, Barmano N, Walfridsson U, Walfridsson H. Factors Predicting Arrhythmia-Related Symptoms and Health-Related Quality of Life in Patients Referred for Radiofrequency Ablation of Atrial Fibrillation: An Observational Study (the SMURF Study). *JACC Clin Electrophysiol* 2017; **3**: 494-502 [PMID: 29759606 DOI: 10.1016/j.jacep.2016.12.004]

40 **Suman S**, Pravalika J, Manjula P, Farooq U. Gender and CVD- Does It Really Matters? *Curr Probl Cardiol* 2023; **48**: 101604 [PMID: 36690310 DOI: 10.1016/j.cpcardiol.2023.101604]

41 **Chugh SS**, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH Jr, Zheng ZJ, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M, Murray CJ. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014; **129**: 837-847 [PMID: 24345399 DOI: 10.1161/CIRCULATIONAHA.113.005119]

42 **Khan AA**, Lip GYH, Shantsila A. Heart rate variability in atrial fibrillation: The balance between sympathetic and parasympathetic nervous system. *Eur J Clin Invest* 2019; **49**: e13174 [PMID: 31560809 DOI: 10.1111/eci.13174]

43 **Severino P**, Mariani MV, Maraone A, Piro A, Ceccacci A, Tarsitani L, Maestrini V, Mancone M, Lavalle C, Pasquini M, Fedele F. Triggers for Atrial Fibrillation: The Role of Anxiety. *Cardiol Res Pract* 2019; **2019**: 1208505 [PMID: 30906592 DOI: 10.1155/2019/1208505]

44 **Ran Q**, Zhang C, Wan W, Ye T, Zou Y, Liu Z, Yu Y, Zhang J, Shen B, Yang B. Pinocembrin ameliorates atrial fibrillation susceptibility in rats with anxiety disorder induced by empty bottle stimulation. *Front Pharmacol* 2022; **13**: 1004888 [PMID: 36339600 DOI: 10.3389/fphar.2022.1004888]

45 **Varró A**, Tomek J, Nagy N, Virág L, Passini E, Rodriguez B, Baczkó I. Cardiac transmembrane ion channels and action potentials: cellular physiology and arrhythmogenic behavior. *Physiol Rev* 2021; **101**: 1083-1176 [PMID: 33118864 DOI: 10.1152/physrev.00024.2019]

46 **Hazarapetyan L**, Zelveian PH, Grigoryan S. Inflammation and Coagulation are Two Interconnected Pathophysiological Pathways in Atrial Fibrillation Pathogenesis. *J Inflamm Res* 2023; **16**: 4967-4975 [PMID: 37927962 DOI: 10.2147/JIR.S429892]

47 **Milaneschi Y**, Kappelmann N, Ye Z, Lamers F, Moser S, Jones PB, Burgess S, Penninx BWJH, Khandaker GM. Association of inflammation with depression and anxiety: evidence for symptom-specificity and potential causality from UK Biobank and NESDA cohorts. *Mol Psychiatry* 2021; **26**: 7393-7402 [PMID: 34135474 DOI: 10.1038/s41380-021-01188-w]

48 **Vian J**, Pereira C, Chavarria V, Köhler C, Stubbs B, Quevedo J, Kim SW, Carvalho AF, Berk M, Fernandes BS. The renin-angiotensin system: a possible new target for depression. *BMC Med* 2017; **15**: 144 [PMID: 28760142 DOI: 10.1186/s12916-017-0916-3]

49 **Murck H**, Held K, Ziegenbein M, Künzel H, Koch K, Steiger A. The renin-angiotensin-aldosterone system in patients with depression compared to controls--a sleep endocrine study. *BMC Psychiatry* 2003; **3**: 15 [PMID: 14585110 DOI: 10.1186/1471-244x-3-15]

50 **Chrissobolis S**, Luu AN, Waldschmidt RA, Yoakum ME, D'Souza MS. Targeting the renin angiotensin system for the treatment of anxiety and depression. *Pharmacol Biochem Behav* 2020; **199**: 173063 [PMID: 33115635 DOI: 10.1016/j.pbb.2020.173063]

51 **Healey JS**, Morillo CA, Connolly SJ. Role of the renin-angiotensin-aldosterone system in atrial fibrillation and cardiac remodeling. *Curr Opin Cardiol* 2005; **20**: 31-37 [PMID: 15596957]

52 **Liu X**, Qu C, Yang H, Shi S, Zhang C, Zhang Y, Liang J, Yang B. Chronic stimulation of the sigma-1 receptor ameliorates autonomic nerve dysfunction and atrial fibrillation susceptibility in a rat model of depression. *Am J Physiol Heart Circ Physiol* 2018; **315**: H1521-H1531 [PMID: 30216117 DOI: 10.1152/ajpheart.00607.2017]

53 **Zhang F**, Cao H, Baranova A. Shared Genetic Liability and Causal Associations Between Major Depressive Disorder and Cardiovascular Diseases. *Front Cardiovasc Med* 2021; **8**: 735136 [PMID: 34859065 DOI: 10.3389/fcvm.2021.735136]

54 **January CT**, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, Heidenreich PA, Murray KT, Shea JB, Tracy CM, Yancy CW. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation* 2019; **140**: e125-e151 [PMID: 30686041 DOI: 10.1161/CIR.0000000000000665]

55 **Al-Kaisey AM**, Parameswaran R, Bryant C, Anderson RD, Hawson J, Chieng D, Segan L, Voskoboinik A, Sugumar H, Wong GR, Finch S, Joseph SA, McLellan A, Ling LH, Morton J, Sparks P, Sanders P, Lee G, Kistler PM, Kalman JM. Atrial Fibrillation Catheter Ablation vs Medical Therapy and Psychological Distress: A Randomized Clinical Trial. *JAMA* 2023; **330**: 925-933 [PMID: 37698564 DOI: 10.1001/jama.2023.14685]

56 **Cosansu K**, Ureyen CM, Yılmaz S. Effect of novel oral anticoagulants on Hospital Anxiety and Depression Scale scores. *Herz* 2019; **44**: 743-749 [PMID: 31236605 DOI: 10.1007/s00059-019-4828-1]

57 **Turker Y**, Ekinozu I, Aytekin S, Turker Y, Basar C, Baltaci D, Kaya E. Comparison of Changes in Anxiety and Depression Level Between Dabigatran and Warfarin Use in Patients With Atrial Fibrillation. *Clin Appl Thromb Hemost* 2017; **23**: 164-167 [PMID: 26276685 DOI: 10.1177/1076029615600792]

58 **Chang L**, Liu N. The Safety, Efficacy, and Tolerability of Pharmacological Treatment of Depression in Patients with cardiovascular disease: A look at antidepressants and integrative approaches. *Heart and Mind* 2017; **1**: 8-16 [DOI: 10.4103/hm.hm_6_16]

59 **Shirayama T**, Sakamoto T, Sakatani T, Mani H, Yamamoto T, Matsubara H. Usefulness of paroxetine in depressed men with paroxysmal atrial fibrillation. *Am J Cardiol* 2006; **97**: 1749-1751 [PMID: 16765127 DOI: 10.1016/j.amjcard.2006.01.038]

60 . Yoga and atrial fibrillation. *Eur Heart J* 2016; **37**: 2855 [PMID: 27923819 DOI: 10.1093/eurheartj/ehw372]

61 **Zhuo C**, Ji F, Lin X, Jiang D, Wang L, Tian H, Xu Y, Liu S, Chen C. Depression and recurrence of atrial fibrillation after catheter ablation: a meta-analysis of cohort studies. *J Affect Disord* 2020; **271**: 27-32 [PMID: 32312694 DOI: 10.1016/j.jad.2020.03.118]

62 **Fu Y**, He W, Ma J, Wei B. Relationship between psychological factors and atrial fibrillation: A meta-analysis and systematic review. *Medicine (Baltimore)* 2020; **99**: e19615 [PMID: 32311930 DOI: 10.1097/MD.0000000000019615]

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