ISSN 2220-3206 (online)

World Journal of *Psychiatry*

World J Psychiatry 2023 October 19; 13(10): 714-815

Published by Baishideng Publishing Group Inc

World Journal of Psychiatry

Contents

Monthly Volume 13 Number 10 October 19, 2023

ORIGINAL ARTICLE

Case Control Study

Retrospective Study

Observational Study

World Journal of Psychiatry

Monthly Volume 13 Number 10 October 19, 2023

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Psychiatry*, Ladislav Hosak, MD, PhD, Professor, Department of Psychiatry, University Hospital, Hradec Kralove 50005, Czech Republic. hosak@lfhk.cuni.cz

AIMS AND SCOPE

The primary aim of *World Journal of Psychiatry* (*WJP*, *World J Psychiatry*) is to provide scholars and readers from various fields of psychiatry with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJP mainly publishes articles reporting research results and findings obtained in the field of psychiatry and covering a wide range of topics including adolescent psychiatry, biological psychiatry, child psychiatry, community psychiatry, ethnopsychology, psychoanalysis, psychosomatic medicine, *etc.*

INDEXING/ABSTRACTING

The *WJP* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJP* as 3.1; IF without journal self cites: 2.9; 5-year IF: 4.2; Journal Citation Indicator: 0.52; Ranking: 91 among 155 journals in psychiatry; and Quartile category: Q3.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Rui-Rui Wu*; **Production Department Director:** *Xu Guo*; **Editorial Office Director:** *Jia-Ping Yan.*

NAME OF JOURNAL
World Journal of Psychiatry

ISSN
ISSN 2220-3206 (online)

LAUNCH DATE
December 31, 2011

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Rajesh R Tampi, Ting-Shao Zhu, Panteleimon Giannakopoulos

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3206/editorialboard.htm

PUBLICATION DATE
October 19, 2023

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatry 2023 October 19; 13(10): 714-723

DOI: 10.5498/wjp.v13.i10.714

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Case Control Study

Serum neuronal pentraxin 2 is related to cognitive dysfunction and electroencephalogram slow wave/fast wave frequency ratio in epilepsy

Xiao-Fen Huang, Ming-Xia Xu, Yue-Fan Chen, Yun-Qing Lin, Yuan-Xiang Lin, Feng Wang

Specialty type: Psychiatry

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Cicero N, Italy; Karakose T, Turkey

Received: August 16, 2023
Peer-review started: August 16, 2023
First decision: August 31, 2023
Revised: September 8, 2023
Accepted: September 22, 2023
Article in press: September 22, 2023
Published online: October 19, 2023

Xiao-Fen Huang, Ming-Xia Xu, Yue-Fan Chen, Yun-Qing Lin, Yuan-Xiang Lin, Department of Neurosurgery, The First Affiliated Hospital of Fujian Medical University, Fuzhou 350005, Fujian Province, China

Feng Wang, Department of Neurosurgery, National Regional Medical Center, Binhai Campus of the First Affiliated Hospital, Fujian Medical University, Fuzhou 350212, Fujian Province, China

Corresponding author: Feng Wang, MD, Doctor, Postdoc, Professor, Department of Neurosurgery, National Regional Medical Center, Binhai Campus of the First Affiliated Hospital, Fujian Medical University, No. 999 Huashan Road, Changle District, Fuzhou 350212, Fujian Province, China. fengwedu@163.com

Abstract

BACKGROUND

Cognitive dysfunction in epileptic patients is a high-incidence complication. Its mechanism is related to nervous system damage during seizures, but there is no effective diagnostic biomarker. Neuronal pentraxin 2 (NPTX2) is thought to play a vital role in neurotransmission and the maintenance of synaptic plasticity. This study explored how serum NPTX2 and electroencephalogram (EEG) slow wave/fast wave frequency ratio relate to cognitive dysfunction in patients with epilepsy.

AIM

To determine if serum NPTX2 could serve as a potential biomarker for diagnosing cognitive impairment in epilepsy patients.

METHODS

The participants of this study, conducted from January 2020 to December 2021, comprised 74 epilepsy patients with normal cognitive function (normal group), 37 epilepsy patients with cognitive dysfunction [epilepsy patients with cognitive dysfunction (ECD) group] and 30 healthy people (control group). The mini-mental state examination (MMSE) scale was used to evaluate cognitive function. We determined serum NPTX2 levels using an enzyme-linked immunosorbent kit and calculated the signal value of EEG regions according to the EEG recording. Pearson correlation coefficient was used to analyze the correlation between serum NPTX2 and the MMSE score.

RESULTS

The serum NPTX2 level in the control group, normal group and ECD group were 240.00 ± 35.06 pg/mL, 235.80 ± 38.01 pg/mL and 193.80 ± 42.72 pg/mL, respectively. The MMSE score was lowest in the ECD group among the three, while no significant difference was observed between the control and normal groups. In epilepsy patients with cognitive dysfunction, NPTX2 level had a positive correlation with the MMSE score (r = 0.367, P = 0.0253) and a negative correlation with epilepsy duration (r = −0.443, P = 0.0061) and the EEG slow wave/fast wave frequency ratio value in the temporal region (r = −0.339, P = 0.039).

CONCLUSION

Serum NPTX2 was found to be related to cognitive dysfunction and the EEG slow wave/fast wave frequency ratio in patients with epilepsy. It is thus a potential biomarker for the diagnosis of cognitive impairment in patients with epilepsy.

Key Words: Serum neuronal pentraxin 2; Cognitive dysfunction; Epilepsy; Electroencephalogram slow wave/fast wave frequency ratio; Biomarker

Core Tip: Here, we found serum neuronal pentraxin 2 (NPTX2) levels were found to be significantly higher in the normal group than in the cognitive dysfunction group. Additionally, NPTX2 levels showed a positive correlation with cognitive function scores and a negative correlation with epilepsy duration and electroencephalogram (EEG) slow wave/fast wave frequency ratio values in the temporal region. Serum NPTX2 level and the EEG slow wave/fast wave frequency ratio value had good sensitivity and specificity for evaluating cognitive dysfunction. These findings suggest that serum NPTX2 could be a valuable biomarker for diagnosing cognitive impairment in patients with epilepsy, providing important insights for clinical practice.

Citation: Huang XF, Xu MX, Chen YF, Lin YQ, Lin YX, Wang F. Serum neuronal pentraxin 2 is related to cognitive dysfunction and electroencephalogram slow wave/fast wave frequency ratio in epilepsy. *World J Psychiatry* 2023; 13(10): 714-723
URL: https://www.wjgnet.com/2220-3206/full/v13/i10/714.htm
DOI: https://dx.doi.org/10.5498/wjp.v13.i10.714

INTRODUCTION

Epilepsy is a common neurological disorder characterized by abnormal synchronous firing of neurons in the brain[1]. The causes of epilepsy are sometimes known and sometimes unknown (idiopathic epilepsy). Epidemiological studies have shown that approximately 70% of adults with epilepsy have cognitive dysfunction[2,3]. However, there are no effective cognitive assessment criteria for patients with epilepsy. Cognitive dysfunction in epilepsy patients occurs on multiple levels, including executive ability, attention, language, and memory ability. Various epilepsy-related factors are closely related to cognitive dysfunction, including epilepsy course, lesion location, underlying neuropathology, and antiepileptic seizure drugs[2]. Cognitive impairment is common in epileptic patients and is characterized by impairment in neurological function. Due to the lack of early diagnostic methods for cognitive impairment in epilepsy patients, unavoidable neurological damage is present in epilepsy patients[3,4].

Neuronal pentraxin 2 (NPTX2), also named "neuronal activity-regulated pentraxin", is first find in in 1995[5]. NPTX2 is being found to take part in neurotransmission, the maintenance of synaptic plasticity, and the formation of excitatory synapses at presynaptic and postsynaptic sites[6,7]. NPTX2 is also being found to take part in Parkinson's disease[8,9], ischemic diseases[10,11], and Alzheimer's disease[12,13]. A recent study reported that NPTX2 was a novel biomarker for Alzheimer's disease[14]. In addition, researchers have explored the role of NPTX2 in vascular dementia. A recent study reported significantly higher serum levels of NPTX2 in patients with vascular dementia than in healthy controls. Furthermore, NPTX2 serum levels were found to be significantly correlated with cognitive function scores in patients with vascular dementia[15]. However, we still known nothing about NPTX2 in epilepsy.

This study evaluated NPTX2 serum levels in epilepsy patients, and future study their relationship with the patients' cognitive function.

MATERIALS AND METHODS

Patients and ethical statement

This study enrolled 111 patients diagnosed with epilepsy at the First Affiliated Hospital of Fujian Medical University between January 2020 and December 2021. In addition, 30 healthy volunteers were recruited as a control group. The

inclusion criteria were as follows: (1) Clinically confirmed epilepsy [electroencephalogram (EEG) with or without epileptiform discharge]; (2) No seizures 24 h before enrollment; (3) Age between 18 and 60 years; (4) Clear consciousness and cooperative during the examinations; (5) Normal vision, hearing, and speech functions; (6) An education level of at least primary school and an ability to understand the scale content sufficiently to answer the questions; (7) Signed an informed consent form; and (8) Asymptomatic epilepsy (head computed tomography or magnetic resonance imaging does not show intracranial lesions). The exclusion criteria were as follows: (1) Liver dysfunction (alanine transaminase or aspartate aminotransferase > 50 U/L) or renal impairment (serum creatinine > 135 μmol/L); (2) In the acute stage of the disease course; (3) A long-term history of alcoholism or psychoactive substance abuse or recent use of drugs that could affect cognitive function such as antidepressants, antipsychotics, baclofen, and benzodiazepines; or (4) Uncooperative behavior. The study was conducted in accordance with the Declaration of Helsinki (revised in 2013) and was approved by the ethics board of the First Affiliated Hospital of Fujian Medical University (No. [2019]274). Informed consent was obtained from all participants.

Cognitive function assessment

The mini-mental state examination (MMSE) scale was used to evaluate cognitive function in all participants. The MMSE scale consists of 30 questions related to cognitive function; each correct answer receives one point. An MMSE scale score of less than 27 indicates cognitive dysfunction in persons with at least a junior high school education[16].

Serum NPTX2 assay

Fasting venous blood was drawn from all participants. The peripheral blood was centrifuged at room temperature to obtain serum, which was then frozen in liquid nitrogen, awaiting further tests. Serum NPTX2 was detected using a Human Neuronal pentraxin-2 (NPTX2) enzyme-linked immunosorbent assay kit (CSB-EL016030HU; CUSABIO, Houston, TX, United States).

EEG test

All patients with epilepsy were subjected to an EEG test. The test was conducted in a quiet room, and the patients were told to relax and stay awake with closed eyes. The patients were also subjected to induction tests such as opening their eyes and hyperventilation. The EEG detection parameter settings were as follows: Filter channel 0.5–30 Hz, time constant 0.3, paper feed speed 3 cm/s, gain 100 μV = 1 cm, and scalp resistance of each electrode not exceeding 5,000 Ω. After selecting monopolar lead tracing for 1 min and once the EEG signal was stable, the EEG signal sampling without artifacts and representing EEG background activity was selected. Each patient took 8 s for one sampling unit, with 10 sampling units selected intermittently. The EEG slow wave/fast wave frequency ratio (EEGs value) was calculated using the fast Fourier transform method: EEGs value = (δ+θ)/(α1+α2+β1+β2). δ (1.0–3.9 Hz), θ (4.0–7.9 Hz), α1 (8.0–10.0 Hz), α2 (10.1–13.9 Hz), β1 (14.0–19.9 Hz), and β2 (20.0–30.0 Hz).

Statistical analysis

Data were recorded in an Excel sheet and were analyzed using SPSS 25.0 (IBM, Corp., Armonk, NY, United States). Count data were expressed as percentages, while continuous data were expressed as mean ± SD. The Kolmogorov–Smirnov test was used to test whether the quantitative data were normally distributed. Normally distributed data were presented as (mean ± SD), and differences between groups were analyzed using unpaired Student's *t*-test. Non-normally distributed quantitative data were presented as the median (interquartile range), and differences between groups were analyzed using the Mann–Whitney U-test. The Pearson correlation coefficient was used to analyze the correlation between two variables of measurement data. Furthermore, the receiver operating characteristic curves were constructed, and the area under the curve (AUC) was calculated to assess the performance of NPTX2 serum levels and EEGs values in diagnosing cognitive dysfunction in patients with epilepsy. A P value < 0.05 was considered statistically significant.

RESULTS

Cognitive function and baseline data of patients with epilepsy

Cognitive function was assessed using the MMSE scale. The epilepsy patients with cognitive dysfunction (ECD) group recorded the lowest MMSE score among the three groups. Furthermore, no significant difference in MMSE scores was observed between the control and normal groups (P > 0.05, Figure 1). In addition, the age, gender, education and something related to epilepsy between normal group and ECD group are omparable (P > 0.05, Table 1).

Relationship between NPTX2 serum levels and clinical features

No statistically significant difference was observed in NPTX2 serum levels between the control and normal groups (P > 0.05). However, serum NPTX2 levels in normal group were significantly higher than that in the ECD group (P < 0.05, Figure 2). The serum level of NPTX2 was positively related to MMSE score (r = 0.367, P = 0.0253), not to age (r = 0.115, P = 0.497), and negatively related to epilepsy duration (r = -0.443, P = 0.0061, Figure 3) in the ECD group. In addition, no significant differences were found in gender, education level, epilepsy type, epilepsy drug types, or treatment protocol between the ECD and normal groups (Figure 4).

Table 1 Baseline data for epilepsy patients with different cognitive function and healthy volunteers

Variable	Control (*n* = 30)	Epilepsy		*P* value	
		Normal (*n* = 74)	ECD (*n* = 37)	*P*[1]	*P*[2]
Age (yr, mean ± SD)	33.93 ± 9.39	35.27 ± 9.73	34.68 ± 9.50	0.523	0.760
Gender, *n* (%)					
Male	17	48 (64.86)	20 (54.05)	0.434	0.270
Female	13	26 (35.14)	17 (45.95)		
Education level, *n* (%)					
Junior/senior high school	19	46 (62.16)	20 (54.05)	0.911	0.412
University or above	11	28 (27.84)	17 (45.95)		
Epilepsy onset age (yr, mean ± SD)	–	26.15 ± 7.41	25.62 ± 10.52	–	0.760
Epilepsy duration (yr, mean ± SD)	–	9.12 ± 5.60	9.05 ± 4.10		0.948
Epilepsy type, *n* (%)					
Focal	–	20 (27.03)	9 (24.32)	–	0.760
Overall	–	54 (72.97)	28 (75.68)		
Types of epilepsy drugs, *n* (%)					
0–1	–	57 (77.03)	26 (70.27)	–	0.440
2–3	–	17 (22.97)	11 (29.73)		
Epilepsy treatment protocol, *n* (%)					
VPN	–	39 (52.70)	19 (51.35)	–	0.890
No-VPN	–	35 (47.30)	18 (48.65)		

[1]Control group *vs*. epilepsy (normal) group.
[2]Epilepsy (normal) group *vs*. epilepsy patients with cognitive dysfunction group.
ECD: Epilepsy patients with cognitive dysfunction; VPN: Valproate.

Table 2 Comparison of electroencephalogram slow wave/fast wave frequency ratio for different brain regions of epilepsy patients with different cognitive function (mean ± SD)

Area of ECG	Epilepsy		*t*	*P*
	Normal (*n* = 74)	ECD (*n* = 37)		
Frontal region	0.54 ± 0.20	0.65 ± 0.20	2.781	0.006
Central region	0.45 ± 0.18	0.53 ± 0.16	2.441	0.016
Top region	0.39 ± 0.21	0.45 ± 0.16	1.461	0.147
Temporal region	0.39 ± 0.17	0.62 ± 0.13	7.127	< 0.001
Occipital region	0.28 ± 0.13	0.34 ± 0.19	1.827	0.070

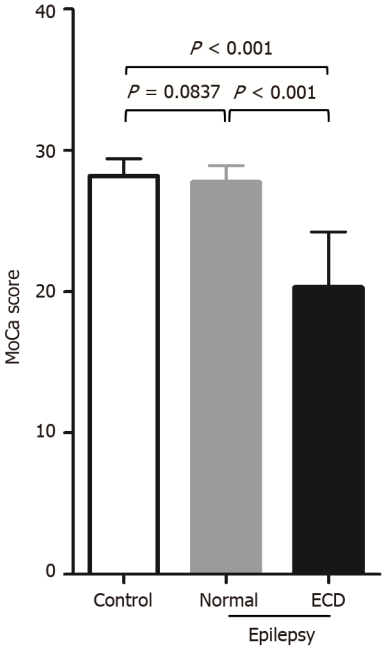
ECD: Epilepsy patients with cognitive dysfunction; ECG: Electrocardiogram.

Ratio of EEG slow wave/fast wave frequency in epilepsy patients

Patients in the normal and ECD groups showed different EEG slow wave/fast wave frequency ratios (EEG value). Patients in the normal group recorded lower EEGs values in the frontal, central, top, temporal, and occipital regions than patients in the ECD group. However, significant differences in EEG values were observed only in the frontal, central, and temporal regions ($P < 0.05$, Table 2).

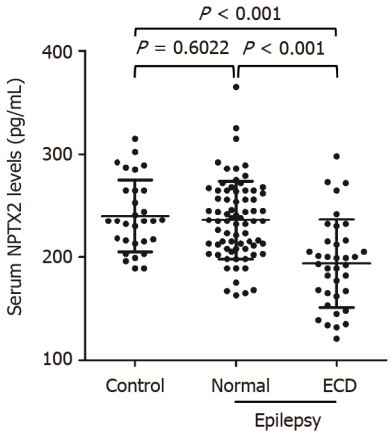
Relationship between NPTX2 serum levels and EEG values

The correlation analysis showed that NPTX2 serum levels in the group were not correlated with EEG values in the frontal or central region ($P > 0.05$). However, NPTX2 serum levels in the group were negatively correlated with the EEG values



DOI: 10.5498/wjp.v13.i10.714 **Copyright** ©The Author(s) 2023.

Figure 1 Mini-mental state examination score of cognitive function among the study participants. Control: Healthy volunteers (*n* = 30); Normal: Epilepsy patients with normal cognitive function (*n* = 74); epilepsy patients with cognitive dysfunction (*n* = 37). ECD: Epilepsy patients with cognitive dysfunction; MoCa: Montreal Cognitive Assessment; MMSE: Mini-mental state examination.



DOI: 10.5498/wjp.v13.i10.714 **Copyright** ©The Author(s) 2023.

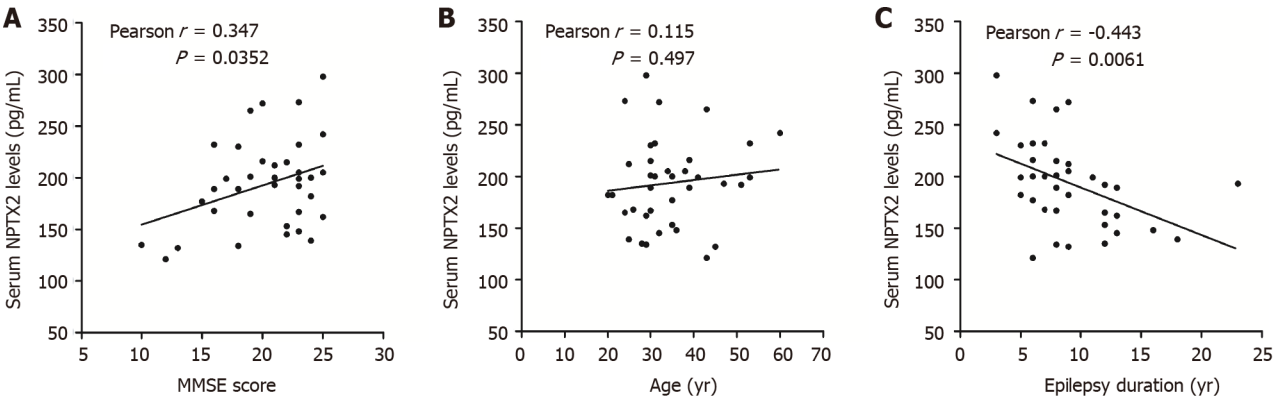
Figure 2 Serum levels of neuronal pentraxin 2 among study participants. Control: Healthy volunteers (*n* = 30); Normal: Epilepsy patients with normal cognitive function (*n* = 74); epilepsy patients with cognitive dysfunction (*n* = 37). ECD: Epilepsy patients with cognitive dysfunction; NPTX2: Neuronal pentraxin 2.

in the temporal region ($P < 0.05$, Figure 5).

Predictive analysis of NPTX2 serum levels and EEG values of the temporal region in cognitive dysfunction

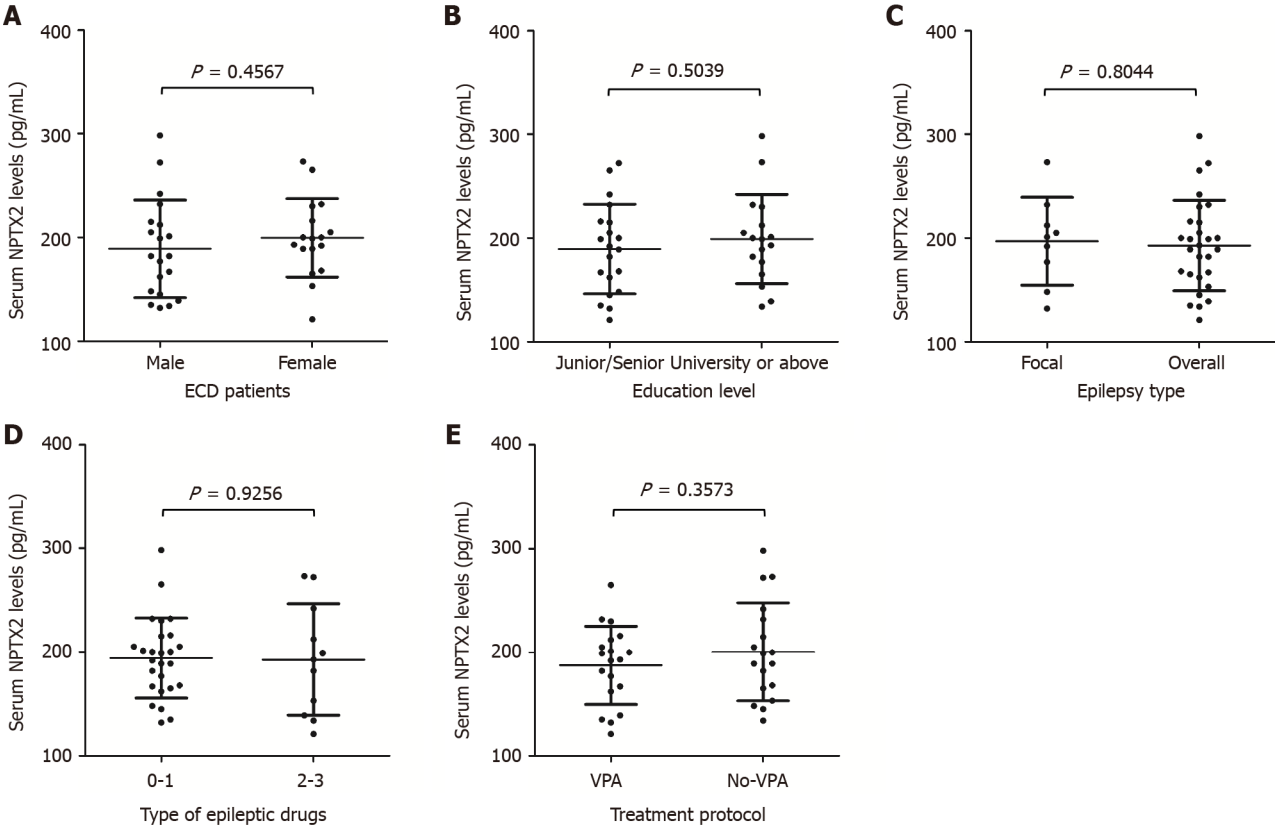
The AUC value of NPTX2 for diagnosing cognitive impairment in epilepsy patients is 0.777, and the 95%confidence interval (95%CI) is 0.679-0.876 (Figure 6). When the cutoff NPTX2 serum level for distinguishing cognitive function in patients with epilepsy was 206.50 pg/mL, the sensitivity and the specificity was 91.89% and 85.14%, respectively (Figure 6).

Moreover, the AUC value of electrocardiogram (ECG) for diagnosing cognitive impairment in epilepsy patients is 0.815, and the 95%CI is 0.739–0.892 (Figure 6). When the cutoff EEG value for distinguishing cognitive function in patients with epilepsy in the temporal region was set at 0.455, the sensitivity and the specificity was 91.89% and 68.92%, respectively (Figure 6).



DOI: 10.5498/wjp.v13.i10.714 **Copyright** ©The Author(s) 2023.

Figure 3 Correlation between Neuronal pentraxin 2 levels and Mini-mental state examination score, age and epilepsy duration. A to C: Correlation between serum levels of NPTX2 and MMSE score in (A), age (B), and epilepsy duration (C) in epilepsy patients with cognitive dysfunction. NPTX2: Neuronal pentraxin 2; MMSE: Mini-mental state examination.

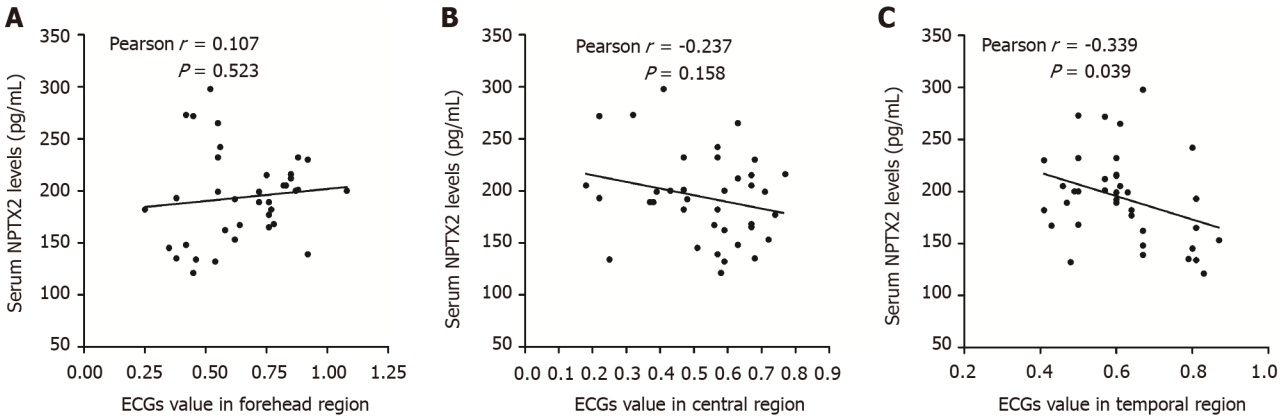


DOI: 10.5498/wjp.v13.i10.714 **Copyright** ©The Author(s) 2023.

Figure 4 Comparison between neuronal pentraxin 2 serum levels and different variables in patients with epilepsy and cognitive dysfunction. A to E: Gender(A), education level (B), epilepsy type (C), epilepsy drug types (D), and treatment protocol (E). ECD: Epilepsy patients with cognitive dysfunction; NPTX2: Neuronal pentraxin 2; VPA: Valproate.

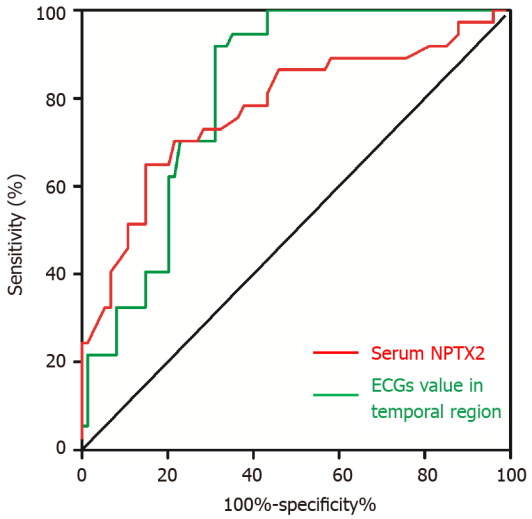
DISCUSSION

Epilepsy is a disease that damages the nervous system, causing damage to the patient's nervous system and subsequently leading to cognitive impairment[17,18]. Epilepsy patients with cognitive impairment are affected in various aspects of their lives. However, it can be confirmed that if diagnosed in the early stages of neu-rological damage, existing medicine has the ability to mitigate cognitive impairment caused by epilepsy. Due to the lack of biomarkers for diagnosing neurological damage in epilepsy patients, it is very difficult to diagnose early neurological damage in epilepsy patients, which also leads to varying degrees of cognitive impairment in epilepsy patients as adults. Therefore, there is a need to develop novel biomarkers for the early detection of cognitive impairment in epilepsy patients.



DOI: 10.5498/wjp.v13.i10.714 **Copyright** ©The Author(s) 2023.

Figure 5 Relationship between NPTX2 levels and ECG values in different regions. Correlation between NPTX2 serum levels and EEG values in the frontal (A), central (B), and temporal (C) regions of patients with epilepsy and cognitive dysfunction. ECG: Electrocardiogram; NPTX2: Neuronal pentraxin 2.



DOI: 10.5498/wjp.v13.i10.714 **Copyright** ©The Author(s) 2023.

Figure 6 Receiver operating characteristic curve for predicting serum level values and electroencephalogram values in temporal region in patients with epilepsy and cognitive dysfunction. ECG: Electrocardiogram; NPTX2: Neuronal pentraxin 2.

In this study, we first found that the serum NPTX2 in epilepsy were strongly higher than that in healthy people, and is related to the cognitive function score of epilepsy patients. However, previous studies have shown that NPTX2 is associated with neurological damage, such as significantly accelerating the onset time of Parkinson's mice by upregulating NPTX2 blood levels, and NPTX2 has been identified as associated with neurological damage in Parkinson's patients. In addition, previous studies have also found that the level of NPTX2 in the hippocampus of mice decreases due to cognitive decline caused by neuropathic pain, and it is related to cognitive function in mice after cerebral ischemia[19].

In 1995, NPTX2, a secreted protein, was first discovered[20]. Subsequently, research on NPTX2 was reported, and its main function was mainly studied in synapses, indicating that NPTX2 plays an important role in the nervous system[21, 22]. This function makes NPTX2 associated with the occurrence and development of many neurological diseases, such as stroke, Huntington's disease, and Amyotropic lateral sclerosis[23]. The development and damage of the nervous system are closely related to cognitive function, especially in the hippocampus, and has been reported to have significant expression levels in the cerebrospinal fluid of Alzheimer's disease patients, and it is related to the patient's cognitive function score[24]. In this study, we not only found that the levels of serum NPTX2 in ECD group were lowest, but also found that NPTX2 levels was strongly related to the the patient's cognitive function score. Therefore, these data indicate that NPTX2 is associated with nerve injury and cognitive impairment caused by nerve injury, making it a potential biomarker for diagnosing cognitive impairment in epilepsy patients.

EEG is widely used for diagnosis, identification, prognosis evaluation, and treatment efficacy assessment for neurological diseases, including epilepsy[25]. Quantitative EEG transforms the brain wave signals from the time domain in the ordinary EEG into the frequency domain[26]. Due to the inability to effectively control the onset time and pattern of epilepsy patients, it is very difficult for us to detect the EEG during the seizure period of epilepsy patients. Therefore, researchers usually study the EEG during the interval between seizures[27]. Therefore, we selected EEG in the

background of the interseizure period. This study found lower EEG values in the frontal, central, top, temporal, and occipital regions of patients with epilepsy and normal cognitive function than in those with epilepsy and cognitive dysfunction. Importantly, this study also found that NPTX2 serum levels were negatively correlated with EEG values in the temporal region of patients with epilepsy and cognitive dysfunction. These findings suggest that NPTX2 serum levels and temporal region's EEG values is related to cognitive impairment in epilepsy patients.

This study has several limitations. First, this study was conducted in a single center, and had a low sample size. Second, we did not monitor NPTX2 serum levels dynamically. Third, several factors that could affect NPTX2 serum levels—such as smoking, alcohol use, and drug use history—were not considered. Finally, our patient follow-up period was short.

CONCLUSION

In this study, we found that NPTX2 levels in epilepsy patients were lower than those in the healthy population and were associated with cognitive function scores, seizure duration, and ECG values in epilepsy patients. All in all, these results indicate that serum NPTX2 levels are potential biomarkers for diagnosing cognitive dysfunction in epilepsy patients.

ARTICLE HIGHLIGHTS

Research background

Cognitive dysfunction is a common complication in epileptic patients, but there is a lack of effective diagnostic biomarkers. This study investigated the relationship between serum levels of neuronal pentraxin 2 (NPTX2), an important molecule involved in neurotransmission and synaptic plasticity, and cognitive dysfunction in epilepsy patients. The study also explored the association between electroencephalogram (EEG) slow wave/fast wave frequency ratio and cognitive impairment. The aim was to determine if serum NPTX2 could serve as a potential biomarker for diagnosing cognitive impairment in epilepsy patients, addressing the need for reliable diagnostic tools in this population.

Research motivation

The high incidence of cognitive dysfunction in epileptic patients highlights the need for effective diagnostic biomarkers. Currently, there is a lack of reliable tools to identify cognitive impairment in this population. This study aimed to investigate the correlation between serum NPTX2 levels and EEG slow wave/fast wave frequency ratios with cognitive dysfunction in epilepsy patients. By exploring these potential biomarkers, the study aimed to contribute to the development of a diagnostic tool for identifying cognitive impairment in epilepsy patients, facilitating early intervention and improved patient care.

Research objectives

The main objectives of this study were to investigate the relationship between serum levels of NPTX2 and EEG with cognitive dysfunction in epilepsy patients. The study aimed to determine if serum NPTX2 could serve as a potential biomarker for diagnosing cognitive impairment in patients with epilepsy. Additionally, the study aimed to assess the correlation between serum NPTX2 levels, EEG patterns, and cognitive function using the mini-mental state examination (MMSE) scale. The ultimate goal was to contribute to the development of effective diagnostic tools for identifying cognitive impairment in epilepsy patients.

Research methods

The study enrolled three groups of participants: Normal group, 74 epilepsy patients without cognitive dysfunction; epilepsy patients with cognitive dysfunction group, 37 epilepsy patients with cognitive dysfunction; Control group, 30 healthy individuals. Cognitive function was evaluated using the MMSE scale. Serum levels of NPTX2 were measured using an enzyme-linked immunosorbent kit, and EEG recordings were used to calculate the slow wave/fast wave frequency ratio in different EEG regions. Statistical analyses were performed to compare variables among the groups and assess correlations between biomarkers and cognitive function. Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the diagnostic performance of serum NPTX2 and EEG patterns for cognitive dysfunction in epilepsy patients.

Research results

The study found no significant differences in age, gender, or education level among the three groups. There were also no significant differences in epilepsy-related factors between the normal group and the cognitive dysfunction group. Serum levels of NPTX2 were significantly higher in the normal group compared to the cognitive dysfunction group, while the control group showed no significant difference from the normal group. The cognitive dysfunction group had the lowest MMSE scores. The EEG slow wave/fast wave frequency ratio values were significantly higher in the cognitive dysfunction group compared to the normal group in various EEG regions. In epilepsy patients with cognitive dysfunction, NPTX2 levels correlated positively with the MMSE score and negatively with epilepsy duration and the EEG slow wave/fast wave frequency ratio value in the temporal region. ROC curve analysis demonstrated that serum NPTX2

level and EEG patterns had diagnostic potential for evaluating cognitive dysfunction in epilepsy patients.

Research conclusions

The study concluded that serum NPTX2 levels are associated with cognitive dysfunction and the EEG slow wave/fast wave frequency ratio in epilepsy patients. Serum NPTX2 shows potential as a diagnostic biomarker for cognitive impairment in epilepsy. The study found no significant differences in demographic and epilepsy-related factors between the normal and cognitive dysfunction groups. However, serum NPTX2 levels were significantly higher in the normal group compared to the cognitive dysfunction group. The EEG slow wave/fast wave frequency ratios were also higher in the cognitive dysfunction group. These findings suggest that serum NPTX2 and EEG patterns may serve as valuable indicators for diagnosing cognitive impairment in epilepsy patients.

Research perspectives

The findings of this study highlight the potential of serum NPTX2 as a diagnostic biomarker for cognitive impairment in epilepsy patients. Further research is needed to validate and expand upon these results. Future studies could explore the underlying mechanisms linking NPTX2 levels and cognitive dysfunction, investigating the role of NPTX2 in neurotransmission and synaptic plasticity. Additionally, larger sample sizes and longitudinal studies could provide more robust evidence regarding the relationship between serum NPTX2, EEG patterns, and cognitive dysfunction. Ultimately, establishing reliable biomarkers could aid in early detection and intervention for cognitive impairments in epilepsy, improving patient outcomes and quality of life.

FOOTNOTES

Author contributions: Huang X, Lin Y, and Wang F were responsible for the study's conception and design; Xu M and Chen Y provided administrative support; Huang X and Lin Y provided the study materials and patients; Xu M and Lin Y conducted data collection; Chen Y and Wang F conducted data analysis and interpretation; all authors contributed to the manuscript writing process and granted final approval for the manuscript.

Supported by 2022 Educational Research Program for Young and Middle-aged Teachers in Fujian Province (Science and Technology), No. JAT220107.

Institutional review board statement: The study was approved by the ethics board of First Affiliated Hospital of Fujian Medical University (No. [2019]274).

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

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

ORCID number: Xiao-Fen Huang 0009-0001-2609-0791; Feng Wang 0009-0003-3379-4580.

S-Editor: Lin C
L-Editor: A
P-Editor: Wu RR

REFERENCES

1 **Falco-Walter J**. Epilepsy-Definition, Classification, Pathophysiology, and Epidemiology. *Semin Neurol* 2020; **40**: 617-623 [PMID: 33155183 DOI: 10.1055/s-0040-1718719]
2 **Helmstaedter C**, Witt JA. Epilepsy and cognition - A bidirectional relationship? *Seizure* 2017; **49**: 83-89 [PMID: 28284559 DOI: 10.1016/j.seizure.2017.02.017]
3 **Kanner AM**, Helmstaedter C, Sadat-Hossieny Z, Meador K. Cognitive disorders in epilepsy I: Clinical experience, real-world evidence and recommendations. *Seizure* 2020; **83**: 216-222 [PMID: 33127274 DOI: 10.1016/j.seizure.2020.10.009]
4 **Li KY**, Huang LC, Chang YP, Yang YH. The effects of lacosamide on cognitive function and psychiatric profiles in patients with epilepsy. *Epilepsy Behav* 2020; **113**: 107580 [PMID: 33242771 DOI: 10.1016/j.yebeh.2020.107580]
5 **Hsu YC**, Perin MS. Human neuronal pentraxin II (NPTX2): conservation, genomic structure, and chromosomal localization. *Genomics* 1995;

28: 220-227 [PMID: 8530029 DOI: 10.1006/geno.1995.1134]

6 **Chang S**, Bok P, Tsai CY, Sun CP, Liu H, Deussing JM, Huang GJ. NPTX2 is a key component in the regulation of anxiety. *Neuropsychopharmacology* 2018; **43**: 1943-1953 [PMID: 29844474 DOI: 10.1038/s41386-018-0091-z]

7 **Wang Z**, Jin T, Le Q, Liu C, Wang X, Wang F, Ma L. Retrieval-Driven Hippocampal NPTX2 Plasticity Facilitates the Extinction of Cocaine-Associated Context Memory. *Biol Psychiatry* 2020; **87**: 979-991 [PMID: 31836174 DOI: 10.1016/j.biopsych.2019.10.009]

8 **Lang Y**, Li Y, Yu H, Lin L, Chen X, Wang S, Zhang H. HOTAIR drives autophagy in midbrain dopaminergic neurons in the substantia nigra compacta in a mouse model of Parkinson's disease by elevating NPTX2 *via* miR-221-3p binding. *Aging (Albany NY)* 2020; **12**: 7660-7678 [PMID: 32396526 DOI: 10.18632/aging.103028]

9 **Moran LB**, Hickey L, Michael GJ, Derkacs M, Christian LM, Kalaitzakis ME, Pearce RK, Graeber MB. Neuronal pentraxin II is highly upregulated in Parkinson's disease and a novel component of Lewy bodies. *Acta Neuropathol* 2008; **115**: 471-478 [PMID: 17987278 DOI: 10.1007/s00401-007-0309-3]

10 **Wang R**, Man Y, Zhou M, Zhu Y, Wang L, Yang J. Neuropathic pain-induced cognitive dysfunction and down-regulation of neuronal pentraxin 2 in the cortex and hippocampus. *Neuroreport* 2021; **32**: 274-283 [PMID: 33512875 DOI: 10.1097/WNR.0000000000001584]

11 **Cai M**, Zhu Y, Li Z, Josephs-Spaulding J, Zhou Y, Hu Y, Chen H, Liu Y, He W, Zhang J. Profiling the Gene Expression and DNA Methylation in the Mouse Brain after Ischemic Preconditioning. *Neuroscience* 2019; **406**: 249-261 [PMID: 30902679 DOI: 10.1016/j.neuroscience.2019.03.023]

12 **Xiao MF**, Xu D, Craig MT, Pelkey KA, Chien CC, Shi Y, Zhang J, Resnick S, Pletnikova O, Salmon D, Brewer J, Edland S, Wegiel J, Tycko B, Savonenko A, Reeves RH, Troncoso JC, McBain CJ, Galasko D, Worley PF. NPTX2 and cognitive dysfunction in Alzheimer's Disease. *Elife* 2017; **6** [PMID: 28440221 DOI: 10.7554/eLife.23798]

13 **Belbin O**, Xiao MF, Xu D, Carmona-Iragui M, Pegueroles J, Benejam B, Videla L, Fernández S, Barroeta I, Nuñez-Llaves R, Montal V, Vilaplana E, Altuna M, Clarimón J, Alcolea D, Blesa R, Lleó A, Worley PF, Fortea J. Cerebrospinal fluid profile of NPTX2 supports role of Alzheimer's disease-related inhibitory circuit dysfunction in adults with Down syndrome. *Mol Neurodegener* 2020; **15**: 46 [PMID: 32807227 DOI: 10.1186/s13024-020-00398-0]

14 **Libiger O**, Shaw LM, Watson MH, Nairn AC, Umaña KL, Biarnes MC, Canet-Avilés RM, Jack CR Jr, Breton YA, Cortes L, Chelsky D, Spellman DS, Baker SA, Raghavan N, Potter WZ; Alzheimer's Disease Neuroimaging Initiative (ADNI); Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium, Longitudinal CSF Proteomics Project Team. Longitudinal CSF proteomics identifies NPTX2 as a prognostic biomarker of Alzheimer's disease. *Alzheimers Dement* 2021; **17**: 1976-1987 [PMID: 33984181 DOI: 10.1002/alz.12353]

15 **Shao K**, Shan S, Ru W, Ma C. Association between serum NPTX2 and cognitive function in patients with vascular dementia. *Brain Behav* 2020; **10**: e01779 [PMID: 32748547 DOI: 10.1002/brb3.1779]

16 **Ahn SJ**, Kim TJ, Cha KS, Jun JS, Byun JI, Shin YW, Sunwoo JS, Lee S, Yu KS, Jang IJ, Chu K, Lee SK, Jung KY. Effects of perampanel on cognition and quantitative electroencephalography in patients with epilepsy. *Epilepsy Behav* 2021; **115**: 107514 [PMID: 33328106 DOI: 10.1016/j.yebeh.2020.107514]

17 **Zhu L**, Chen L, Xu P, Lu D, Dai S, Zhong L, Han Y, Zhang M, Xiao B, Chang L, Wu Q. Genetic and molecular basis of epilepsy-related cognitive dysfunction. *Epilepsy Behav* 2020; **104**: 106848 [PMID: 32028124 DOI: 10.1016/j.yebeh.2019.106848]

18 **Sen A**, Capelli V, Husain M. Cognition and dementia in older patients with epilepsy. *Brain* 2018; **141**: 1592-1608 [PMID: 29506031 DOI: 10.1093/brain/awy022]

19 **Lim B**, Tsolaki M, Soosaipillai A, Brown M, Zilakaki M, Tagaraki F, Fotiou D, Koutsouraki E, Grosi E, Prassas I, Diamandis EP. Liquid biopsy of cerebrospinal fluid identifies neuronal pentraxin receptor (NPTXR) as a biomarker of progression of Alzheimer's disease. *Clin Chem Lab Med* 2019; **57**: 1875-1881 [PMID: 31415236 DOI: 10.1515/cclm-2019-0428]

20 **Lim B**, Sando SB, Grøntvedt GR, Bråthen G, Diamandis EP. Cerebrospinal fluid neuronal pentraxin receptor as a biomarker of long-term progression of Alzheimer's disease: a 24-month follow-up study. *Neurobiol Aging* 2020; **93**: 97.e1-97.e7 [PMID: 32362369 DOI: 10.1016/j.neurobiolaging.2020.03.013]

21 **Xiao MF**, Roh SE, Zhou J, Chien CC, Lucey BP, Craig MT, Hayes LN, Coughlin JM, Leweke FM, Jia M, Xu D, Zhou W, Conover Talbot C Jr, Arnold DB, Staley M, Jiang C, Reti IM, Sawa A, Pelkey KA, McBain CJ, Savonenko A, Worley PF. A biomarker-authenticated model of schizophrenia implicating NPTX2 Loss of function. *Sci Adv* 2021; **7**: eabf6935 [PMID: 34818031 DOI: 10.1126/sciadv.abf6935]

22 **Swanson A**, Willette AA; Alzheimer's Disease Neuroimaging Initiative. Neuronal Pentraxin 2 predicts medial temporal atrophy and memory decline across the Alzheimer's disease spectrum. *Brain Behav Immun* 2016; **58**: 201-208 [PMID: 27444967 DOI: 10.1016/j.bbi.2016.07.148]

23 **Feyissa AM**, Tatum WO. Adult EEG. *Handb Clin Neurol* 2019; **160**: 103-124 [PMID: 31277842 DOI: 10.1016/B978-0-444-64032-1.00007-2]

24 **Benbadis SR**, Beniczky S, Bertram E, MacIver S, Moshé SL. The role of EEG in patients with suspected epilepsy. *Epileptic Disord* 2020; **22**: 143-155 [PMID: 32364504 DOI: 10.1684/epd.2020.1151]

25 **Sansevere AJ**, Hahn CD, Abend NS. Conventional and quantitative EEG in status epilepticus. *Seizure* 2019; **68**: 38-45 [PMID: 30528098 DOI: 10.1016/j.seizure.2018.09.011]

26 **Admiraal MM**, Ramos LA, Delgado Olabarriaga S, Marquering HA, Horn J, van Rootselaar AF. Quantitative analysis of EEG reactivity for neurological prognostication after cardiac arrest. *Clin Neurophysiol* 2021; **132**: 2240-2247 [PMID: 34315065 DOI: 10.1016/j.clinph.2021.07.004]

27 **Gao Y**, Tang X, Wen Y, Qian D, Pan X, Zhang L. Effects of the hospital-community-family ternary linkage continuous nursing model on compliance, cognitive function, resilience, and quality of life for children with epilepsy: a retrospective study. *Transl Pediatr* 2022; **11**: 239-248 [PMID: 35282024 DOI: 10.21037/tp-22-21]

World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatry 2023 October 19; 13(10): 724-731

DOI: 10.5498/wjp.v13.i10.724

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Retrospective Study

Correlation between cognitive impairment and metabolic imbalance of gut microbiota in patients with schizophrenia

Jing Ma, Xue-Qin Song

Specialty type: Psychiatry

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Cipriani A, United Kingdom; Dragano N, Germany

Received: June 6, 2023
Peer-review started: June 6, 2023
First decision: June 21, 2023
Revised: August 8, 2023
Accepted: August 15, 2023
Article in press: August 15, 2023
Published online: October 19, 2023

Jing Ma, First Department of Mood Disorders, The Second Affiliated Hospital of Xinxiang Medical College, Xinxiang 453000, Henan Province, China

Xue-Qin Song, Department of Psychiatry, The First Affiliated of Zhengzhou University, Zhengzhou 450052, Henan Province, China

Corresponding author: Xue-Qin Song, PhD, Chief Physician, Department of Psychiatry, The First Affiliated of Zhengzhou University, No. 1 Jian Dong Road, Zhengzhou 450052, Henan Province, China. sxq907907@163.com

Abstract

BACKGROUND

The gut microbiome interacts with the central nervous system through the gut-brain axis, and this interaction involves neuronal, endocrine, and immune mechanisms, among others, which allow the microbiota to influence and respond to a variety of behavioral and mental conditions.

AIM

To explore the correlation between cognitive impairment and gut microbiota imbalance in patients with schizophrenia.

METHODS

A total of 498 untreated patients with schizophrenia admitted to our hospital from July 2020 to July 2022 were selected as the case group, while 498 healthy volunteers who underwent physical examinations at our hospital during the same period were selected as a control group. Fluorescence *in situ* hybridization was employed to determine the total number of bacteria in the feces of the two groups. The cognitive function test package was used to assess the score of cognitive function in each dimension. Then, the relationship between gut microbiota and cognitive function was analyzed.

RESULTS

There were statistically significant differences in the relative abundance of gut microbiota at both phylum and class levels between the case group and the control group. In addition, the scores of cognitive function, such as attention/alertness and learning ability, were significantly lower in the case group than in the control group (all $P < 0.05$). The cognitive function was positively correlated with Actinomycetota, Bacteroidota, Euryarchaeota, Fusobacteria, Pseudo-

monadota, and Saccharibacteria, while negatively correlated with Bacillota, Tenericutes, and Verrucomicrobia at the phylum level. While at the class level, the cognitive function was positively correlated with Class Actinobacteria, Bacteroidia, Betaproteobacteria, Proteobacteria, Blastomycetes, and Gammaproteobacteria, while negatively correlated with Bacilli, Clostridia, Coriobacteriia, and Verrucomicrobiae.

CONCLUSION

There is a relationship between the metabolic results of gut microbiota and cognitive function in patients with schizophrenia. When imbalances occur in the gut microbiota of patients, it leads to more severe cognitive impairment.

Key Words: Schizophrenia; Cognitive function; Gut microbiota; Metabolic imbalance; Bacteria

Core Tip: The highlights of this study are as follows. First, individuals with schizophrenia have imbalanced intestinal microbiota compared to healthy individuals. Second, patients with schizophrenia exhibit cognitive impairments in various areas such as attention, memory, social cognition, and executive function. Additionally, specific microbial groups such as Actinomycetes, Bacteroides, and Proteobacteria have shown a positive correlation with cognitive function in patients with schizophrenia. Furthermore, there is a close relationship between metabolic imbalance of intestinal flora and cognitive impairment in individuals with schizophrenia. Lastly, further clinical trials are necessary to gather more data and insights for the development of effective treatments for schizophrenia.

Citation: Ma J, Song XQ. Correlation between cognitive impairment and metabolic imbalance of gut microbiota in patients with schizophrenia. *World J Psychiatry* 2023; 13(10): 724-731
URL: https://www.wjgnet.com/2220-3206/full/v13/i10/724.htm
DOI: https://dx.doi.org/10.5498/wjp.v13.i10.724

INTRODUCTION

Schizophrenia is a severe mental disorder with unknown etiology. Most of the patients are young and middle-aged. Frequently, the patients may encounter various obstacles in thinking, perception, emotion, and behavior, leading to a lack of coordination between mental activities and the surroundings[1]. Patients with schizophrenia exhibit characteristics such as a high disability rate, substantial burden, and an increased tendency of suicide. This disorder also causes hallucinations, delusions, language, and behavior abnormalities, with a long course and heterogeneous clinical manifestations. Schizophrenia has an impact on the physical and mental health, as well as social quality of life for patients, resulting in economic pressure and social burden. With the continuous advancement of biological technology, the understanding of schizophrenia is gradually deepening[2,3]. As one of the primary symptoms of schizophrenia, cognitive dysfunction includes two aspects, mental cognition and social cognition. Generally, it manifests before other psychotic symptoms of schizophrenia and persists throughout the course of the disease[4]. In recent years, there has been an increasing focus on the cognitive impairment of patients. Cognitive impairment can impede patients' social and occupational rehabilitation, and assessing cognitive function can predict the disease progression and treatment response[5]. Gut microbiota constitutes a complex and vast ecosystem. Scholars have proposed that gut microbiota can regulate the immune and inflammatory responses within the human body and influence neural development. However, the understanding of the relationship between gut microbiota and schizophrenia is still limited[6,7].

In this study, cognitive function and gut microbiota were examined to explore the potential correlation between cognitive impairment and metabolic imbalance of gut microbiota in patients with schizophrenia.

MATERIALS AND METHODS

Materials

A total of 498 patients with schizophrenia admitted to The First Affiliated Hospital of Zhengzhou University from July 2020 to July 2021 were selected as the case group, and 498 healthy volunteers who underwent physical examination at the same hospital were randomly chosen as the control group.

Inclusion criteria were: patients who met the diagnostic criteria for schizophrenia in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition[8], patients with no abnormality in routine blood tests, and patients who were 18-years-old to 50-years-old.

Exclusion criteria were: patients with diabetes, thyroid disease, hypertension, heart disease, or other diseases that may affect the stability of gut microbiota; patients who suffered from diarrhea in the past 3 mo; or patients who were pregnant or lactating.

Determination of bacterial counts

The bacterial counts in patients were determined using fluorescence *in situ* hybridization. We utilized fluorescent tags as a substitute for isotope labeling. First, biotin labeling was carried out, followed by DNA probe hybridization. Next, fluorescein avidin was used to bind with the probe hybridization to the target DNA on the chromosomes to form a hybrid. Qualitative and quantitative analyses were then performed after detecting the fluorescence under a microscope.

Cognitive function scores

The first step was to determine whether the patient was conscious. Generally, the Glasgow scale was employed to assess the degree of consciousness disturbance. If the patient was conscious, the Short Form Mental State Examination was used to screen for cognitive dysfunction. Based on the results, the presence of cognitive impairment could be identified, and further assessment of cognitive function was conducted accordingly.

Statistical processing

SPSS21.0 software was used for the data analyses. The independent *t*-test was used for comparisons between the two groups. For multivariate regression analysis, the multiple linear regression model was employed when the dependent variable was continuous, whereas the logistic regression model was used when the dependent variable was dichotomous. $P < 0.05$ was considered statistically significant.

RESULTS

Distribution of gut microbiota at the phylum level in the two groups

As shown in Table 1, the case group exhibited a significantly higher relative abundance of Actinomycetota, Bacteroidota, Euryarchaeota, Fusobacteria, Pseudomonadota, and lower abundance of Bacillota, Tenericutes, and Verrucomicrobia when compared with the control group ($P < 0.05$).

Distribution of gut microbiota at the class level in the two groups

As shown in Table 2, compared with the control group, the case group exhibited a significantly higher relative abundance of Class Actinobacteria, Bacteroidia, Betaproteobacteria, Proteobacteria, Blastomycetes, and Gammaproteobacteria, and lower relative abundance of Bacilli, Clostridia, Coriobacteriia, and Verrucomicrobiae ($P < 0.05$).

Comparison of cognitive scores between the two groups

As shown in Table 3, the scores of attention or alertness, learning, memory, fine motors, social cognition, executive function, conversion, inhibition, planning, working memory, category fluency, information processing, and total cognitive score were all significantly lower in the case group than in the control group ($P < 0.05$).

Correlation analysis between cognitive function and gut microbiota at the phylum level

As shown in Table 4, cognitive function was positively correlated with Actinomycetota ($r = 6.591$, $P = 0.001$), Bacteroidota ($r = 5.625$, $P = 0.016$), Euryarchaeota ($r = 6.281$, $P = 0.183$), Fusobacteria ($r = 2.190$, $P = 0.026$), Pseudomonadota ($r = 6.364$, $P = 0.018$), and Saccharibacteria ($r = 5.196$, $P = 0.037$), while negatively correlated with Bacillota ($r = -0.976$, $P = 0.281$), Tenericutes ($r = -0.623$, $P = 0.001$), and Verrucomicrobia ($r = -0.191$, $P = 0.006$).

Correlation analysis of between cognitive function and gut microbiota at the class level

As shown in Table 5, cognitive function was positively correlated with Class Actinobacteria ($r = 3.257$, $P = 0.001$), Bacteroidia ($r = 6.294$, $P = 0.001$), Betaproteobacteria ($r = 6.281$, $P = 0.016$), Proteobacteria ($r = 6.270$, $P = 0.008$), Blastomycetes ($r = 5.671$, $P = 0.006$), and Gammaproteobacteria ($r = 4.195$, $P = 0.005$), while negatively correlated with Bacilli ($r = -0.981$, $P = 0.001$), Clostridia ($r = -0.124$, $P = 0.015$), Coriobacteriia ($r = -0.293$, $P = 0.019$), and Verrucomicrobiae ($r = -0.549$, $P = 0.010$).

DISCUSSION

Schizophrenia is a chronic and severe mental disorder characterized by disturbances in an individual's sensory, emotional, and behavioral functions[9]. Patients with schizophrenia have difficulties distinguishing between reality and the imaginary. They may exhibit slow reactions, and show a phenomenon of behavioral withdrawal, significantly affecting their ability to engage in normal social behavior. In medical terms, schizophrenia is classified as a disorder rather than a disease. This disorder often typically occurs during the young or prime stages of life. It encompasses disturbances in the body, mind, emotions, and behaviors, but the patients do not have a coma or mentally retarded imagination[10,11]. Some studies have found that genetic factors, brain structure, and environment factors contribute

Table 1 Relative abundance of gut microbiota at the phylum level in the two groups

Name of bacteria	Case group, *n* = 498	Control group, *n* = 498	*T* value	*P* value
Actinomycetota	2.95 ± 5.62	2.18 ± 3.60	2.575	0.01
Bacteroidota	34.27 ± 19.53	26.84 ± 16.07	6.556	0.001
Euryarchaeota	0.16 ± 0.57	0.00 ± 0.00	6.264	0.001
Bacillota	48.82 ± 17.96	61.37 ± 14.49	12.14	0.001
Fusobacteria	0.08 ± 0.57	0.02 ± 0.07	2.332	0.019
Pseudomonadota	15.82 ± 20.13	7.68 ± 11.59	7.82	0.001
Saccharibacteria	0.49 ± 0.27	0.01 ± 0.01	39.65	0.001
Tenericutes	0.23 ± 1.14	0.59 ± 1.92	3.598	0.001
Verrucomicrobia	0.57 ± 1.94	1.62 ± 5.19	4.229	0.001
Actinomycetota	2.95 ± 5.62	2.18 ± 3.60	2.575	0.01

Data are presented as mean ± SD.

Table 2 Relative abundance of gut microbiota at the class level in the two groups

Name of bacteria	Case group, *n* = 498	Control group, *n* = 498	*T* value	*P* value
Class Actinobacteria	2.81 ± 5.64	1.56 ± 2.81	4.427	0.001
Bacilli	2.01 ± 4.28	2.67 ± 5.60	2.090	0.036
Bacteroidia	31.28 ± 19.67	26.68 ± 16.18	4.030	0.001
Betaproteobacteria	1.50 ± 3.29	0.39 ± 0.52	7.437	0.001
Clostridia	45.92 ± 18.62	58.18 ± 13.92	11.770	0.001
Coriobacteriia	0.21 ± 0.49	0.58 ± 1.29	5.984	0.001
Proteobacteria	0.29 ± 0.39	0.15 ± 0.24	6.822	0.001
Blastomycetes	0.96 ± 1.19	0.67 ± 1.20	3.829	0.01
Gammaproteobacteria	13.84 ± 19.67	6.92 ± 11.37	6.797	0.001
Verrucomicrobiae	0.58 ± 1.69	1.82 ± 5.86	4.537	0.001

Data are presented as mean ± SD.

significantly to the development of this disorder. Therefore, comprehensive medical and psychological treatments are necessary to address the multifaceted nature of the condition.

Cognitive impairment is commonly observed in patients with schizophrenia, impacting various aspects such as information integration, memory, and attention. Symptoms of cognitive dysfunction are prominently manifested through memory decline in the general population[12,13]. In addition to memory decline, schizophrenia can result in impairments in executive function, visuospatial ability, comprehension, and numeracy. People's general cognition and social cognition are also closely associated with age. As the aging population continues to grow, the incidence of cognitive dysfunction is increasing[14,15]. A large number of clinical studies have demonstrated a certain correlation between schizophrenia and cognitive function. Effective interventions targeting overall cognition, emotions, and society aspects have shown promising results. In this study, patients with schizophrenia exhibited considerable declines in various cognitive aspects, including learning, memory, fine motor skills, social cognition, working memory, category fluency, information processing, and kinetic energy, when compared to healthy individuals. These results suggest association between cognitive function and schizophrenia, which is similar to the results of the above research.

Schizophrenia has profoundly impacted numerous families. Consequently, there is a paramount need to pursue effective treatment options and improve the patient prognosis[16]. Gut microbiota is a central regulator of metabolism in the human body and has been found to be associated with various mental diseases[17,18]. In modern society, there is a growing awareness of the diversity, complexity, and dynamics of gut microbiota. Differences in the structure and diversity of gut microbiota have been observed in patients with schizophrenia, with the control of the disorder having a great impact on the distribution of gut microbiota structure[19,20]. Some scholars have noted that alterations in the gut microbial community can affect the cytokine levels in the body, subsequently impacting the brain function and behaviors,

Table 3 Comparative analysis of cognitive scores between the two groups

Cognitive domain	Case group, *n* = 498	Control group, *n* = 498	*T* value	*P* value
Attention/alertness	40.27 ± 6.29	51.98 ± 9.92	22.250	0.001
Learning	36.27 ± 10.01	50.69 ± 10.08	22.650	0.001
Memory	40.31 ± 11.26	54.27 ± 7.19	23.320	0.001
Fine motors	37.29 ± 13.27	59.06 ± 7.91	31.450	0.001
Social cognition	41.09 ± 11.08	54.26 ± 10.87	18.930	0.001
Executive function	40.18 ± 7.04	52.37 ± 5.09	31.310	0.001
Conversion	41.06 ± 7.21	49.57 ± 7.61	18.120	0.001
Inhibition	38.62 ± 9.51	54.63 ± 9.67	26.340	0.001
Planning	42.14 ± 13.01	52.67 ± 10.17	14.230	0.001
Working memory	42.09 ± 13.02	53.19 ± 9.06	15.620	0.001
Category fluency	39.86 ± 10.05	53.18 ± 9.07	21.960	0.001
Information processing	33.43 ± 9.14	48.45 ± 7.39	28.520	0.001
Total score	40.64 ± 7.17	51.14 ± 5.29	26.300	0.001

Data are presented as mean ± SD of points.

Table 4 Correlation analysis between the total cognitive score and gut microbiota at the phylum level

Name of bacteria	Total cognitive score	
	R value	*P* value
Actinomycetota	6.591	0.001
Bacteroidota	5.625	0.016
Euryarchaeota	6.281	0.183
Bacillota	0.976	0.281
Fusobacteria	2.190	0.026
Pseudomonadota	6.364	0.018
Saccharibacteria	5.196	0.037
Tenericutes	0.623	0.001
Verrucomicrobia	0.191	0.006

and greatly affecting the prognosis of patients. In this study, we found that the relative abundance of gut microbiota in patients with schizophrenia differed significantly from that in healthy individuals, indicating an imbalance in the gut microbiota in patients with schizophrenia, which is consistent with the previous results. This article examined gut microbiota at a phylum level (Actinomycetota, Bacteroidota, Euryarchaeota, Fusobacteria, Pseudomonadota, *etc*) and a class level (Class Actinobacteria, Bacteroidia, Betaproteobacteria, Proteobacteria, Blastomycetes, and Gammaproteobacteria, *etc*). The results suggest that there is a certain correlation between gut microbiota and schizophrenia.

In this study, a correlation was identified between cognitive impairment and metabolic imbalance of gut microbiota. However, it is essential to acknowledge that the small sample size in this study may introduce some bias in the data. In the future, clinical trials with larger sample size should be conducted to provide more reliable data to guide the clinical treatment for patients with schizophrenia.

CONCLUSION

To summarize, this study revealed the presence of gut microbiota imbalance in schizophrenia patients and found the correlation between cognitive impairment and metabolic imbalance of gut microbiota in these patients. of intestinal flora, providing insights into the link between changes in gut microbiota and cognitive function, as well as the pathogenesis of schizophrenia. This research presents a novel approach that may pave the way for future treatments targeting schizo-

Table 5 Correlation analysis between the total cognitive score and gut microbiota at the class level

Name of bacteria	Total cognitive score	
	R value	*P* value
Actinobacteria	3.257	0.001
Bacilli	0.981	0.001
Bacteroidia	6.294	0.001
Betaproteobacteria	6.281	0.016
Clostridia	0.124	0.015
Coriobacteriia	0.293	0.019
Proteobacteria	6.270	0.008
Blastomycetes	5.671	0.006
Gammaproteobacteria	4.195	0.005
Verrucomicrobiae	0.549	0.010

phrenia.

ARTICLE HIGHLIGHTS

Research background

Schizophrenia is a severe mental disorder characterized by impaired thinking, perception, emotion, and behavior. It affects the physical and mental health of the patients, leading to a high disability rate, burden, and suicide tendency. Cognitive dysfunction is a primary symptom of schizophrenia and includes mental cognition and social cognition. It can significantly impact the overall functioning and quality of life of individuals with schizophrenia. In recent years, there has been increasing recognition of the importance of cognitive function in schizophrenia. Cognitive impairment can not only predict the progression of the disease but also affect the treatment response and functional outcomes. Therefore, understanding the factors that contribute to cognitive impairment in schizophrenia is crucial for improving patient outcomes. Gut microbiota, a complex ecosystem of microorganisms residing in the gastrointestinal tract, has been found to play a role in regulating immune and inflammatory responses, as well as influencing neural development. Emerging evidence has suggested a potential connection between gut microbiota and psychiatric disorders, including schizophrenia. However, the specific relationship between gut microbiota and cognitive impairment in schizophrenia patients remains limited and requires further exploration.

Research motivation

Recent research has suggested a potential link between gut microbiota and psychiatric disorders, including schizophrenia. However, the specific relationship between gut microbiota and cognitive impairment in schizophrenia remains poorly understood. This knowledge gap necessitates further investigation to explore the potential role of gut microbiota in the cognitive dysfunction observed in schizophrenia.

The motivation behind this study is to bridge this gap by investigating the correlation between cognitive impairment and gut microbiota imbalance in patients with schizophrenia. By examining the composition of gut microbiota and evaluating cognitive function in a large sample of untreated schizophrenia patients, we aimed to shed light on the potential mechanisms underlying cognitive dysfunction in this population.

The findings of this study provide significant clinical implications and contribute to the development of novel therapeutic strategies targeting the gut microbiota to improve cognitive outcomes of patients with schizophrenia. Ultimately, this research aims to enhance the understanding of the complex interplay between gut microbiota and cognitive impairment in schizophrenia, leading to improved diagnosis, treatment, and overall management of this mental disorder.

Research objectives

The objective of this research was to explore the correlation between cognitive impairment and gut microbiota imbalance in patients with schizophrenia. The study compared the composition and abundance of gut microbiota in untreated schizophrenia patients and healthy controls, evaluated cognitive function using a consensus version of the cognitive function test package, and examined the relationship between specific microbial groups and cognitive function.

Research methods

The research employed a case-control study design. A total of 498 untreated schizophrenia patients admitted to the

hospital from July 2020 to July 2022 were selected as the case group, while 498 healthy volunteers who underwent physical examinations at the same hospital during the same period served as the control group. The composition and abundance of gut microbiota were assessed using fluorescence *in situ* hybridization to determine the total number of bacteria in fecal samples from both groups. Cognitive function was evaluated using a cognitive function test package consensus version, which assesses various dimensions of cognitive function. Statistical analysis was performed to compare the relative abundance of actinomycetes and other microbial groups between the case and control groups, as well as to examine the relationship between specific gut microbiota and cognitive function. The statistical significance level was set at $P < 0.05$.

Research results

The research findings revealed the correlation between gut microbiota and cognitive function in patients with schizophrenia. There was a statistically significant difference in the relative abundance of Actinomycetota between the case group and the control group, indicating an imbalance in the gut microbiota of schizophrenia patients. Moreover, compared to the control group, the schizophrenia patients demonstrated statistically significant differences in scores related to attention/alertness, and learning ability, suggesting impaired cognitive function in these areas. Furthermore, specific microbial groups showed correlations with cognitive function: Actinomycetota, Bacteroidota, Fusobacteria, and Proteobacteria were found to be positively associated with cognitive function, while the Coriobacteriia showed a negative correlation. These findings provide evidence of the influence of gut microbiota on cognitive impairment in schizophrenia patients and underscore the importance of addressing gut microbiota imbalance as a potential therapeutic target for improving cognitive outcomes in this population.

Research conclusions

In conclusion, this research confirmed a relationship between gut microbiota metabolic imbalance and cognitive function in patients with schizophrenia. The study findings indicate that when there is an imbalance in the composition of gut microbiota, the cognitive function of schizophrenia patients is more severely affected. The relative abundance of Actinomycetota was found to significantly differ between the case group and the control group, suggesting an imbalance in gut microbiota in schizophrenia patients. Additionally, specific microbial groups, including Actinomycetota, Bacteroidota, Fusobacteria, and Proteobacteria, were positively correlated with cognitive function, while the Coriobacteriia showed a negative correlation. These results emphasize the importance of addressing gut microbiota imbalances as a potential target for improving cognitive impairment in schizophrenia patients. Further research and interventions focused on modulating gut microbial composition and promoting gut health may lead to improved cognitive outcomes in this population.

Research perspectives

In future research, it is recommended to conduct longitudinal studies to observe changes in gut microbiota and cognitive function over time in schizophrenia patients, as well as intervention studies to investigate the effects of modulating gut microbiota on cognitive outcomes. Mechanistic studies can provide insights into the underlying mechanisms of the gut-brain axis in schizophrenia. The identification of specific gut microbiota markers as diagnostic or prognostic biomarkers for cognitive impairment, exploring individual differences, and developing personalized therapeutic strategies are also important areas for further investigation. By pursuing these research perspectives, we can advance our understanding of the role of gut microbiota in schizophrenia-related cognitive impairment and potentially develop targeted interventions to improve cognitive outcomes in this population.

FOOTNOTES

Author contributions: Ma J and Song XQ designed the study; Ma J wrote the manuscript; Ma J and Song XQ collected and analyzed the data; Ma J and Song XQ revised and reviewed the manuscript; All authors have read and approved the final manuscript.

Institutional review board statement: The study was approved by the Ethics Committee of The First Affiliated of Zhengzhou University.

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

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

ORCID number: Xue-Qin Song 0009-0006-5013-3479.

S-Editor: Lin C
L-Editor: Filipodia
P-Editor: Chen YX

REFERENCES

1 **McCutcheon RA**, Reis Marques T, Howes OD. Schizophrenia-An Overview. *JAMA Psychiatry* 2020; **77**: 201-210 [PMID: 31664453 DOI: 10.1001/jamapsychiatry.2019.3360]
2 **Khavari B**, Cairns MJ. Epigenomic Dysregulation in Schizophrenia: In Search of Disease Etiology and Biomarkers. *Cells* 2020; **9** [PMID: 32764320 DOI: 10.3390/cells9081837]
3 **Jauhar S**, Johnstone M, McKenna PJ. Schizophrenia. *Lancet* 2022; **399**: 473-486 [PMID: 35093231 DOI: 10.1016/S0140-6736(21)01730-X]
4 **Xu C**, Tao X, Ma X, Zhao R, Cao Z. Cognitive Dysfunction after Heart Disease: A Manifestation of the Heart-Brain Axis. *Oxid Med Cell Longev* 2021; **2021**: 4899688 [PMID: 34457113 DOI: 10.1155/2021/4899688]
5 **Oset M**, Stasiolek M, Matysiak M. Cognitive Dysfunction in the Early Stages of Multiple Sclerosis-How Much and How Important? *Curr Neurol Neurosci Rep* 2020; **20**: 22 [PMID: 32444997 DOI: 10.1007/s11910-020-01045-3]
6 **Zhou B**, Yuan Y, Zhang S, Guo C, Li X, Li G, Xiong W, Zeng Z. Intestinal Flora and Disease Mutually Shape the Regional Immune System in the Intestinal Tract. *Front Immunol* 2020; **11**: 575 [PMID: 32318067 DOI: 10.3389/fimmu.2020.00575]
7 **Tang Q**, Cao L. [Intestinal flora and neurological disorders]. *Sheng Wu Gong Cheng Xue Bao* 2021; **37**: 3757-3780 [PMID: 34841782 DOI: 10.13345/j.cjb.210253]
8 **Somma A**, Adler LA, Gialdi G, Arteconi M, Cotilli E, Fossati A. The Validity of the World Health Organization Adult Attention-Deficit/Hyperactivity Disorder Self-Report Screening Scale for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition in Adolescence. *J Child Adolesc Psychopharmacol* 2021; **31**: 631-638 [PMID: 34166067 DOI: 10.1089/cap.2020.0158]
9 **Lu Y**, Yuan X, Wang M, He Z, Li H, Wang J, Li Q. Gut microbiota influence immunotherapy responses: mechanisms and therapeutic strategies. *J Hematol Oncol* 2022; **15**: 47 [PMID: 35488243 DOI: 10.1186/s13045-022-01273-9]
10 **Buckley PF**. Neuroinflammation and Schizophrenia. *Curr Psychiatry Rep* 2019; **21**: 72 [PMID: 31267432 DOI: 10.1007/s11920-019-1050-z]
11 **Zamanpoor M**. Schizophrenia in a genomic era: a review from the pathogenesis, genetic and environmental etiology to diagnosis and treatment insights. *Psychiatr Genet* 2020; **30**: 1-9 [PMID: 31764709 DOI: 10.1097/YPG.0000000000000245]
12 **Harvey PD**, Bosia M, Cavallaro R, Howes OD, Kahn RS, Leucht S, Müller DR, Penadés R, Vita A. Cognitive dysfunction in schizophrenia: An expert group paper on the current state of the art. *Schizophr Res Cogn* 2022; **29**: 100249 [PMID: 35345598 DOI: 10.1016/j.scog.2022.100249]
13 **Stogios N**, Gdanski A, Gerretsen P, Chintoh AF, Graff-Guerrero A, Rajji TK, Remington G, Hahn MK, Agarwal SM. Autonomic nervous system dysfunction in schizophrenia: impact on cognitive and metabolic health. *NPJ Schizophr* 2021; **7**: 22 [PMID: 33903594 DOI: 10.1038/s41537-021-00151-6]
14 **Roy DS**, Zhang Y, Aida T, Choi S, Chen Q, Hou Y, Lea NE, Skaggs KM, Quay JC, Liew M, Maisano H, Le V, Jones C, Xu J, Kong D, Sullivan HA, Saunders A, McCarroll SA, Wickersham IR, Feng G. Anterior thalamic dysfunction underlies cognitive deficits in a subset of neuropsychiatric disease models. *Neuron* 2021; **109**: 2590-2603.e13 [PMID: 34197733 DOI: 10.1016/j.neuron.2021.06.005]
15 **Wu Q**, Wang X, Wang Y, Long YJ, Zhao JP, Wu RR. Developments in Biological Mechanisms and Treatments for Negative Symptoms and Cognitive Dysfunction of Schizophrenia. *Neurosci Bull* 2021; **37**: 1609-1624 [PMID: 34227057 DOI: 10.1007/s12264-021-00740-6]
16 **Correll CU**. Using Patient-Centered Assessment in Schizophrenia Care: Defining Recovery and Discussing Concerns and Preferences. *J Clin Psychiatry* 2020; **81** [PMID: 32297720 DOI: 10.4088/JCP.MS19053BR2C]
17 **Stępnicki P**, Kondej M, Kaczor AA. Current Concepts and Treatments of Schizophrenia. *Molecules* 2018; **23** [PMID: 30127324 DOI: 10.3390/molecules23082087]
18 **Gomaa EZ**. Human gut microbiota/microbiome in health and diseases: a review. *Antonie Van Leeuwenhoek* 2020; **113**: 2019-2040 [PMID: 33136284 DOI: 10.1007/s10482-020-01474-7]
19 **Jia X**, Xu W, Zhang L, Li X, Wang R, Wu S. Impact of Gut Microbiota and Microbiota-Related Metabolites on Hyperlipidemia. *Front Cell Infect Microbiol* 2021; **11**: 634780 [PMID: 34490132 DOI: 10.3389/fcimb.2021.634780]
20 **Chen Y**, Zhou J, Wang L. Role and Mechanism of Gut Microbiota in Human Disease. *Front Cell Infect Microbiol* 2021; **11**: 625913 [PMID: 33816335 DOI: 10.3389/fcimb.2021.625913]

World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatry 2023 October 19; 13(10): 732-742

DOI: 10.5498/wjp.v13.i10.732

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Retrospective Study

Sleep disturbances are associated with anxiety, depression, and decreased quality of life in patients with coronary heart disease

Da Zheng, Rui-Juan Tan, Wei Liu, Peng-Cheng Song, Feng-De Li

Specialty type: Psychiatry

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Jaspal R, United Kingdom; Mistura M, Canada

Received: June 30, 2023
Peer-review started: June 30, 2023
First decision: July 18, 2023
Revised: August 8, 2023
Accepted: August 25, 2023
Article in press: August 25, 2023
Published online: October 19, 2023

Da Zheng, Feng-De Li, Department of Cardiovascular Medicine, Hengshui People's Hospital, Hengshui 053000, Hebei Province, China

Rui-Juan Tan, Department of Pharmacy, Hengshui People's Hospital, Hengshui 053000, Hebei Province, China

Wei Liu, Department of Psychiatry, Hengshui People's Hospital, Hengshui 053000, Hebei Province, China

Peng-Cheng Song, Department of Traditional Chinese Medicine, Hengshui People's Hospital, Hengshui 053000, Hebei Province, China

Corresponding author: Feng-De Li, Doctor, Department of Cardiovascular Medicine, Hengshui People's Hospital, No. 180 Renmin Road, Taocheng District, Hengshui 053000, Hebei Province, China. lifengdehssrmyy@163.com

Abstract

BACKGROUND

Studies have shown that sleep disorders are closely related to anxiety and depression, and the quality of life (QoL) of patients with sleep disorders is generally poor.

AIM

To examine the occurrence of sleep disorders in people with coronary heart disease (CHD) and their relationships with QoL, depression, and anxiety.

METHODS

As per the sleep condition, 240 CHD individuals were separated into two groups: non-sleep disorder group (n = 128) and sleep disorder group (n = 112). The self-rating anxiety scale (SAS), self-rating depression scale (SDS), and World Health Organization criteria for the Quality of Life Brief scale (WHOQOL-BREF) scores of the two groups were compared. Logistic regression method was used to analyze the independent risk factors of CHD patients with sleep disorders. Multivariate logistic regression analysis was employed to develop the risk prediction model. The association among the Pittsburgh Sleep Quality Index, SAS, and SDS was examined using Spearman's correlation analysis.

RESULTS

The incidence of sleep disorder was 46.67% in 240 patients. The scores of SAS and SDS in the sleep disorder group were higher than those in the non-sleep disorder group, and the WHOQOL-BREF scores were lower than those in the non-sleep disorder group ($P < 0.05$). The risk prediction model of sleep disturbances in CHD patients was constructed using the outcomes of multivariate logistic regression analysis, $P = 1/[1 + e (-2.160 + 0.989 \times (\text{female}) + 0.001 \times (\text{new rural cooperative medical insurance}) + 2.219 \times (\text{anxiety}) + 2.157 \times \text{depression})]$. The results of a Spearman's correlation study revealed that sleep quality was strongly adversely connected with the physiological field, psychological field, and social relation scores in QoL, and was considerably positively correlated with SAS and SDS ($P < 0.05$).

CONCLUSION

A multivariate logistic regression model can better predict the occurrence of sleep disorders in CHD patients. Sleep disorders in CHD patients are significantly correlated with QoL, depression, and anxiety.

Key Words: Coronary heart disease; Sleep disorder; Quality of life; Depression; Anxiety

Core Tip: Sleep disorder is a common clinical problem, and the correlation between sleep disorder and anxiety and depression has been widely discussed in clinical practice. This study explored the problem of sleep disorder in patients with coronary heart disease (CHD) and its correlation with anxiety, depression, and quality of life (QoL). The results showed that the incidence of sleep disorder is higher in patients with CHD, and is positively correlated with anxiety and depression, and negatively correlated with QoL.

Citation: Zheng D, Tan RJ, Liu W, Song PC, Li FD. Sleep disturbances are associated with anxiety, depression, and decreased quality of life in patients with coronary heart disease. *World J Psychiatry* 2023; 13(10): 732-742
URL: https://www.wjgnet.com/2220-3206/full/v13/i10/732.htm
DOI: https://dx.doi.org/10.5498/wjp.v13.i10.732

INTRODUCTION

Coronary heart disease (CHD) can damage people's health and lead to death. Sleep disorders are a prevalent aspect of CHD that can have a negative effect on a patient's quality of life (QoL), cause coronary events, increase disease progression, and influence patients' survival[1,2]. As a result, treating patients' sleep disorders will enable them to have a longer life expectancy. Exploring the influencing factors of sleep disorders is conducive to further research and evaluation of sleep disorders in CHD patients. Patients with CHD are more likely to experience negative feelings, depression, and anxiety as a result of the disease, which affects their QoL. The reason may be that CHD is critical and difficult to treat and may be accompanied by symptoms such as angina pectoris or arrhythmia, and excessive worry may lead to anxiety and depression[3,4]. There is currently little research on the influence of anxiety and depression on the sleep quality of CHD patients, and there are also few studies on the influence of demographic and clinical factors on sleep problems in CHD patients.

Our present research aimed to study and explore the current status of sleep disorders in CHD patients and its correlation with QoL, depression, and anxiety to establish a standard for therapeutic prevention and management of sleep disturbances in individuals with CHD.

MATERIALS AND METHODS

Data sources

Clinical data were gathered from 240 CHD patients (114 females and 126 males) with an age range of 48-79 years (average age = 61.58 ± 6.93) referred to our facility between January 2020 and September 2022. The study inclusion criteria: (1) All patients met the Diagnostic Criteria for Coronary atherosclerotic Heart Disease[5]; (2) the vital signs were stable after treatment; (3) no history of drug abuse; and (4) patients with normal communication ability. Exclusion criteria were: (1) Patients with depression, schizophrenia, or other mental diseases; (2) patients with cognitive impairment; (3) patients with cerebrovascular disease or central nervous system disease; (4) patients with malignant tumor disease; and (5) patients with heart failure. This study was approved by the ethics committee.

Data collection

General data such as sex, age, disease type, smoking, marital status, hypertension, diabetes, family history of CHD, dyslipidemia, education level, working status, and type of medical insurance of all patients were collected.

Observation indexes

(1) The Pittsburgh Sleep Quality Index (PSQI)[6] score of 240 CHD patients was collected. Each of the seven evaluation items on the scale received a score between 0 and 3, for a range of 0 to 21 points. A score > 7 points denotes poor sleep quality and a sleep disorder, whereas a score of 7 points shows good sleep quality and no sleep disorders. The lower the score, the poorer the sleep quality. Then 240 patients with CHD were divided into the sleep disorder group and non-sleep disorder group according to the PSQI score, and the incidence of sleep disorder in 240 patients with CHD was calculated; (2) The self-rating anxiety scale (SAS)[7] and self-rating depression scale (SDS)[7] scores of CHD patients with and without sleep disturbances were collected and compared. There are 20 items in SAS scale; ≥ 50 is classified as anxiety, and the higher the score, the more serious the anxiety. The SDS scale consists of 20 items; ≥ 53 points indicates depression, and the higher the score, the more serious the degree of depression; (3) The World Health Organization criteria for the Quality of Life Brief scale[8] score of CHD patients with and without sleep disturbances were collected and compared. The scale includes four dimensions, namely physiology, psychology, environment, and social relation, and each dimension scores 0-100 points; (4) A comparison of the general data for the sleep disorder group and the non-sleep disorder group was done; (5) To examine independent risk factors of sleep problems in CHD patients, components with statistically significant variations in basic information were considered in the multivariate logistic regression analysis; (6) The logistic regression analysis findings were used to develop the risk prediction model. The area under the curve (AUC), receiver operating characteristic (ROC), and Hosmer-Lemeshow analyses were employed to examine the model's degree of correlation, and the ROC curve was constructed to demonstrate how effectively the model predicts results. The closer the AUC is to 1.0, the higher the prediction efficiency; and (7) The association among PSQI, SAS, and SDS was investigated using Spearman's correlation analysis.

Statistical analyses

Two individuals working independently entered the study data into Excel tables, and SPSS 24.0 statistical software was employed to examine and interpret the data. The experimental data are expressed as the mean ± SD, and the *t*-test was used to compare homogeneous and normally distributed data. Numbers "*n*" and percentages "%" were employed to characterize the counting data, and the χ^2 test was performed to compare groups. For multivariate analyses, a logistic regression model was utilized, and Spearman's correlation analysis was performed for correlation analyses. The threshold for statistical significance was set at $P < 0.05$ for all bilateral tests.

RESULTS

Comparison of the incidence of sleep disorders in CHD patients

Among the 240 patients, 112 CHD patients had PSQI scores > 7 points and had a sleep disorder, with an incidence of 46.67%.

Comparison of QoL, depression, and anxiety scores of CHD individuals with sleep disorder and without sleep disorders

As can be seen in Table 1, the difference between the SDS and SAS scores in both groups was statistically significant ($P < 0.05$; Figure 1).

Comparison of QoL scores of CHD patients in both groups

The sleep disorder group scored lower on the social relation, psychological field, and physiological field compared to the non-sleep disorder group ($P < 0.05$). Environmental field scores between the two groups were not significantly different ($P > 0.05$) (Figure 2, Table 2).

Single-factor analysis of sleep disorders in CHD patients

No significant difference was observed in both groups in terms of disease type, smoking, marital status, hypertension, diabetes, family history of CHD, dyslipidemia, educational level, and working status. In the group of people with sleep disorders, there were more female patients ($P < 0.05$), patients under the age of 60, individuals in new rural cooperative medical systems, and patients with anxiety and depression (Table 3).

Multivariate logistic regression investigation of sleep disorders in individuals with CHD

The parameters with significant differences in the univariate study of sleep quality disorders in CHD patients were subjected to multivariate logistic regression analysis. The sleep disorder of patients was taken as dependent variables, and sex, age, medical insurance type, anxiety and depression were taken as independent variables (Table 4). Multivariate logistic regression analyses showed that females, new rural cooperative medical insurance, depression, and anxiety were independent risk factors for sleep disorders in individuals with CHD ($P < 0.05$; Table 5).

Establishment and calibration of the multivariate logistic regression model

The risk prediction model of sleep disturbances in CHD patients was established using the results of a multivariate logistic regression study, $P = 1/[1 + e (-2.160 + 0.989 \times (\text{female}) + 0.001 \times (\text{new rural cooperative medical insurance}) + 2.219 \times (\text{anxiety}) + 2.157 \times \text{depression})]$, and the Hosmer-Lemeshow test was used, $\chi^2 = 7.284$, $P = 0.506$, indicating a good

Table 1 Comparison of quality of life, depression, and anxiety scores of patients with coronary heart disease with and without sleep disorders

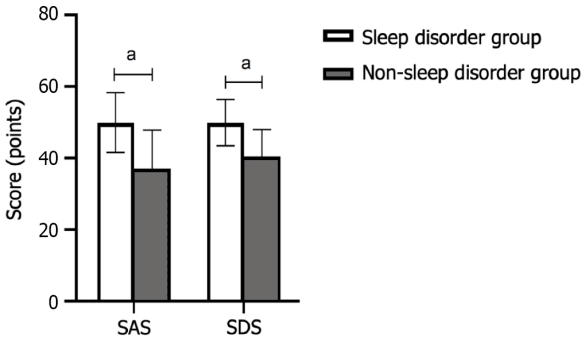
Group	SAS score	SDS score
Sleep disorder group, *n* = 112	49.93 ± 8.37[a]	49.89 ± 6.47[a]
Non-sleep disorder group, *n* = 128	37.02 ± 10.84	40.45 ± 7.53
t value	10.389	10.336
P value	< 0.001	< 0.001

[a]*P* < 0.05 *vs* non-sleep disorder group.
Data (points) are mean ± SD. SAS: Self-rating anxiety scale; SDS: Self-rating depression scale.

Table 2 Comparison of the quality of life scores of patients with coronary heart disease with and without sleep disorders

Group	Physiological field	Psychological field	Environmental field	Social relation
Sleep disorder group, *n* = 112	35.58 ± 5.75[a]	30.52 ± 4.72[a]	45.98 ± 5.40	42.93 ± 5.45[a]
Non-sleep disorder group, *n* = 128	38.88 ± 5.52	34.92 ± 3.82	46.63 ± 5.74	45.06 ± 4.30
t value	4.524	7.869	0.901	3.334
P value	< 0.001	< 0.001	0.369	0.001

[a]*P* < 0.05 *vs* non-sleep disorder group.
Data (points) are mean ± SD.



DOI: 10.5498/wjp.v13.i10.732

Figure 1 Comparison of both groups' self-rating depression scale and self-rating anxiety scale scores. [a]*P* < 0.05 *vs* non-sleep disorder group. SDS: Self-rating depression scale; SAS: Self-rating anxiety scale.

fit between the model and the observed values, as shown in Figure 3.

Prediction efficiency of the logistic regression model

Figure 4 illustrates the outcomes of ROC analysis, which revealed that the model had a good predictive effect ($P < 0.05$). Moreover, the AUC of the risk prediction model for sleep disorders in CHD patients was 0.851 with a 95% confidence interval (CI) of 0.803-0.900.

Correlation between sleep disorders and anxiety, depression, and QoL

As indicated in Table 6, Spearman's correlation analysis revealed that sleep quality exhibited a strong negative association with the physiological field, psychological field, and social relations of QoL, and was positively associated with SAS and SDS ($P < 0.05$; Figures 5 and 6).

DISCUSSION

Sleep disturbances have been linked to an increased risk of CHD and the development of CHD, according to several studies conducted both domestically and internationally[2,9,10]. Disease factors, psychological factors, and environ-

Table 3 Single factor analysis of sleep disorders in patients with coronary heart disease

Factor	Sleep disorder group, *n* = 112	Non-sleep disorder group, *n* = 128	χ^2/t value	*P* value
Sex				
Male	47 (41.69)[a]	79 (61.27)	9.347	0.002
Female	65 (58.04)[a]	49 (38.28)		
Age in yr	62.56 ± 7.18[a]	60.72 ± 6.61	2.070	0.040
≥ 60	56 (50.00)	30 (23.44)		
< 60	56 (50.00)	98 (76.56)		
Disease type				
Stable angina pectoris	57 (50.89)	67 (52.34)	0.050	0.822
Acute coronary syndrome	55 (49.11)	61 (47.66)		
Smoking				
Yes	44 (39.29)	46 (35.94)	0.286	0.593
No	68 (60.71)	82 (64.06)		
Marital status				
Single	6 (5.36)	9 (7.03)	0.286	0.593
Married	106 (94.64)	119 (92.97)		
Hypertension				
Yes	68 (60.71)	74 (57.81)	0.208	0.648
No	44 (47.89)	54 (42.19)		
Diabetes				
Yes	31 (27.68)	29 (22.66)	0.804	0.370
No	81 (72.32)	99 (77.34)		
Family history of CHD				
Yes	25 (22.32)	22 (17.19)	1.000	0.317
No	87 (77.68)	106 (82.81)		
History of dyslipidemia				
Yes	32 (28.57)	39 (30.47)	0.103	0.748
No	80 (71.43)	89 (69.53)		
Education level				
High school and below	54 (48.21)	62 (48.44)	0.001	0.972
College or above	58 (51.79)	66 (51.56)		
Working status				
On-the-job	26 (23.21)	42 (32.81)	3.023	0.221
Waiting for employment	6 (5.36)	8 (6.25)		
Retired	80 (71.43)	78 (60.94)		
Medical insurance type				
Medical insurance for urban workers	45 (40.18)[a]	85 (66.41)	16.551	< 0.001
New rural cooperative medical insurance	67 (59.82)[a]	43 (33.59)		
Anxiety, ≥ 50 points				
Yes	65 (58.04)[a]	14 (10.94)	60.006	< 0.001
No	47 (41.96)[a]	114 (89.06)		
Depression, ≥ 53 points				

Yes	41 (36.16)[a]	7 (5.47)	36.1987	< 0.001
No	71 (63.39)[a]	121 (94.53)		

[a]*P* < 0.05 *vs* non-sleep disorder group.
Data are mean ± SD or *n* (%). CHD: Coronary heart disease.

Table 4 Assignment

Factor	Assignment method
Age in yr	≥ 60 yr = 1, < 60 yr = 0
Sex	Male = 0, Female = 1
Medical insurance type	New rural cooperative medical insurance = 1
	Medical insurance for urban workers = 0
Anxiety	Yes = 1, No = 0
Depression	Yes = 1, No = 0

Table 5 Analysis of sleep disorders in patients with coronary heart disease using multiple logistic regression models

Variable	β value	SE	Wals χ^2	OR value	95%CI	*P* value
Sex	0.989	0.338	8.548	2.688	1.385-5.215	0.003
Age in yr	-0.108	0.342	0.099	0.898	0.459-1.755	0.753
Medical insurance type	1.176	0.338	12.098	0.001	1.671-6.291	0.001
Anxiety	2.219	0.380	34.020	9.200	4.365-19.394	< 0.001
Depression	2.157	0.493	19.143	8.647	3.290-22.726	< 0.001
Constant	-2.160	0.383	31.714	0.115		< 0.001

CI: Confidence interval; OR: Odds ratio; SE: Standard error.

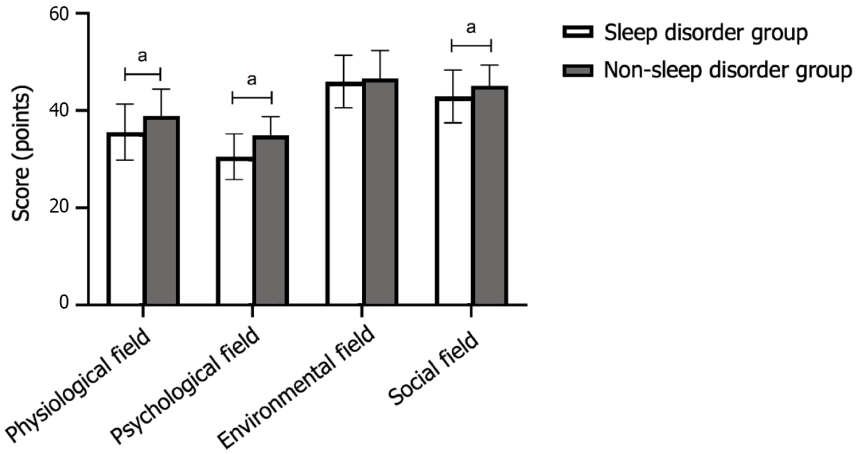
Table 6 Correlation between sleep disorders and quality of life, depression, and anxiety

Group	*r* value	*P* value
SAS	0.500	< 0.001
SDS	0.493	< 0.001
Physiological field	-0.215	< 0.001
Psychological field	-0.434	< 0.001
Environmental field	-0.080	0.217
Social relations	-0.198	0.002

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

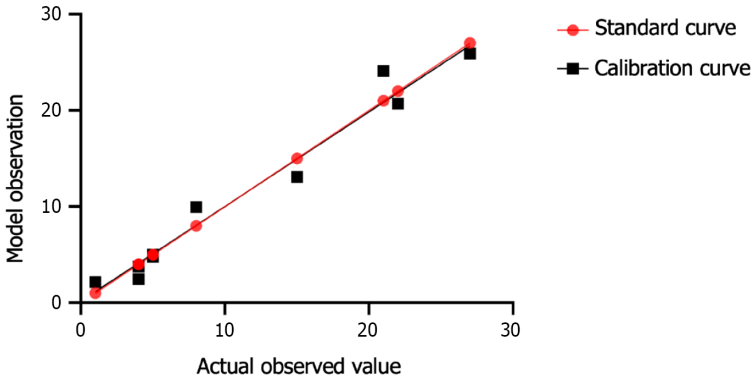
mental factors can affect the sleep quality of CHD patients. In this study, 46.67% of 240 CHD patients had sleep disorders, accounting for a relatively high proportion. Sleep disorders in CHD patients are very serious and should be paid attention to. In this study, CHD patients with sleep disorders had higher SAS and SDS scores than CHD patients without sleep disorders, and their QoL scores were substantially lower than those of patients without sleep disorders, showing that sleep disorders can have an impact on a patient's psychological health and QoL.

Multivariate logistic regression analyses showed that females, new rural cooperative medical insurance, depression, and anxiety were independent risk factors for sleep disorders in individuals with CHD ($P < 0.05$). According to research by Ulander *et al*[11], women are more prone than men to experience sleep disorders. According to Wang *et al*[12], female cancer patients have an increased incidence of sleep disorders. In line with the aforementioned study, these findings



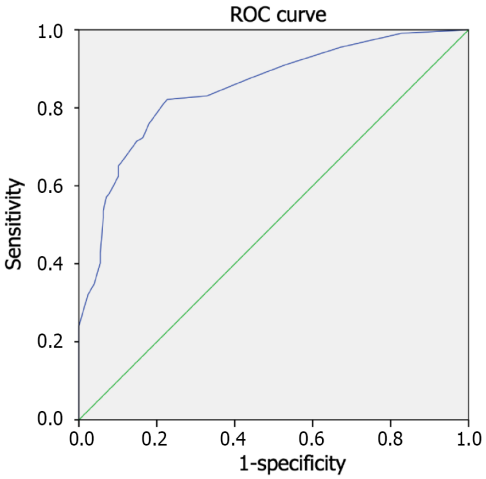
DOI: 10.5498/wjp.v13.i10.732 **Copyright** ©The Author(s) 2023.

Figure 2 Comparison of both groups' quality of life scores. [a]*P* < 0.05 *vs* non-sleep disorder group.



DOI: 10.5498/wjp.v13.i10.732 **Copyright** ©The Author(s) 2023.

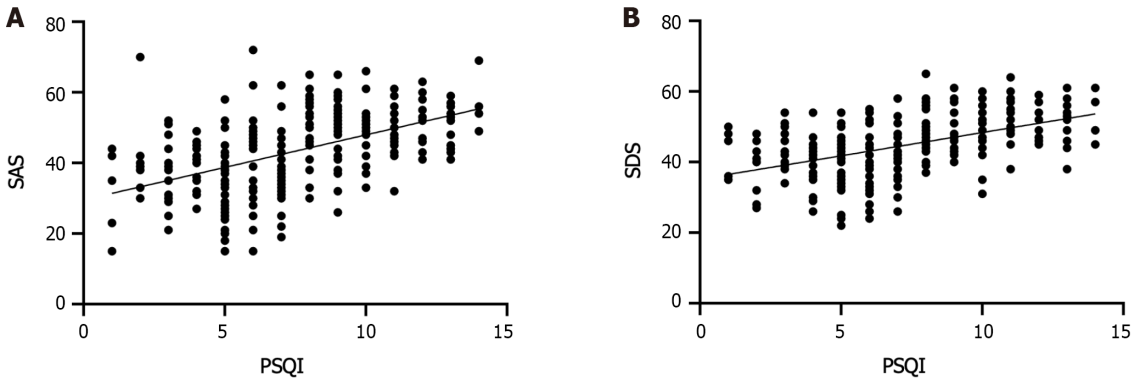
Figure 3 Calibration degree of the logistic regression model.



DOI: 10.5498/wjp.v13.i10.732 **Copyright** ©The Author(s) 2023.

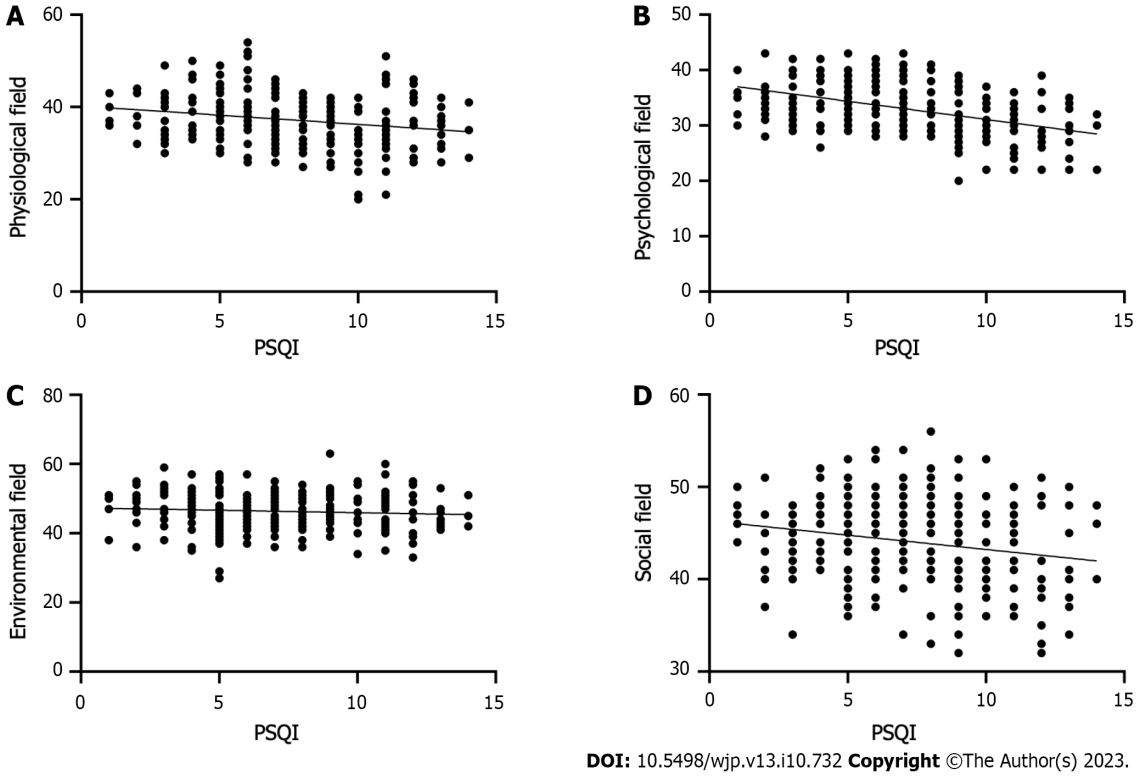
Figure 4 Prediction efficiency of the logistic regression model. ROC: Receiver operating characteristic.

support the previous study by showing that sex is a definite risk factor for anxiety problems in patients with CHD. It is speculated that the reason may be that female patients are more sensitive, their mood is easy to fluctuate, and their sleep quality is easy to be affected. The specific reason needs to be further explored. Most patients with the new rural cooperative medical insurance are rural patients. They are not as economically secure as patients in metropolitan areas, and there are disparities in the payment rates between the employee medical insurance and the new rural cooperative medical insurance, which adds to the financial strain on patients and their families and impairs patient sleep. The new



DOI: 10.5498/wjp.v13.i10.732 **Copyright** ©The Author(s) 2023.

Figure 5 Correlation between sleep disorders and anxiety and depression. A: Pittsburgh sleep quality index (PSQI) is correlated with physiological field; B: The correlation between PSQI and self-rating depression scale. SAS: Self-rating anxiety scale; SDS: Self-rating depression scale.



DOI: 10.5498/wjp.v13.i10.732 **Copyright** ©The Author(s) 2023.

Figure 6 Correlation between sleep disorders and quality of life. A: Pittsburgh sleep quality index (PSQI) is correlated with physiological field; B: PSQI is related to psychological field; C: Correlation between PSQI and environmental field; D: Correlation between PSQI and social field.

rural cooperative medical insurance is thus a significant risk factor for sleep problems in CHD patients in this study.

Sejbuk *et al*[9] reported that anxiety is a negative factor affecting sleep quality. Bonanni *et al*[13] also believe that depression and anxiety are related to menopause insomnia. Anxiety and depression were found to be independently associated risk factors for sleep disorders in this investigation, which was similar to previous research findings. CHD patients have serious physical discomfort and reduced QoL, and their strong concern for prognosis is easy to affect sleep quality. Long-term sleep disorders can lead to increased blood pressure, cardiovascular system dysfunction and neurological dysfunction, and further, aggravate psychological stress[14,15]. By contrast, anxiety, depression, and other adverse emotions can seriously affect the endocrine of patients, causing body discomfort symptoms such as palpitation and chest tightness, further affecting sleep and leading to sleep disorders[16-18]. To increase the quality of their sleep, patients with depression and anxiety should receive psychological treatment, while female CHD patients and CHD patients with new rural cooperative medical insurance should receive clinical attention. A sleep disorder prediction model was developed using multivariate logistic regression, and its prediction performance was assessed using the ROC curve. This prediction model's AUC value was 0.851 (95%CI = 0.803-0.900), showing that it has a strong predictive value for sleep problems in CHD patients.

Sleep disorder is a process of dual physiological and psychological disorders[19], and some anxiety and depression patients tend to shift more attention to sleep problems, trying to improve physiological and psychological disorders by adjusting sleep, but they are more likely to be nervous, and further aggravate sleep disorders, forming a vicious cycle. Long-term anxiety, depression and sleep disorders cause and affect each other, seriously affecting patients' work and life, and in severe cases, it may lead to functional disorders and further reduce the QoL. In addition, sleep disorders are one of the main characteristics of depression, mainly manifested by early waking, difficulty in maintaining sleep, and waking dysthymic tendencies. Serious anxiety and depression can cause psychological stress and lead to autonomic nervous disorder, and the wake-up system of the brain related to sleep and the hypnotic system is in an unbalanced state, and the excitation of the wake-up system will further lead to sleep disorders[20-22].

Adverse emotions such as anxiety and depression before bedtime can promote the activity of the reticuloendothelial system, promote the release of norepinephrine, enhance the activity of the body, and cause sleep disorders. In this study, the Spearman's correlation study showed that sleep quality was inversely correlated with the physiological field, psychological field, and social relations in QoL and positively associated with SAS and SDS. This finding implies that patients with sleep disorders should focus on enhancing their poor mood and QoL to prevent an unnecessary vicious cycle that negatively affects their prognosis. The shortcoming of the present work is that it included too few influencing factors and could not identify the reason for the high incidence of sleep disorders. Besides, it only used SAS and SDS scales to conduct a simple psychological assessment of patients, and in-depth structured psychological interviews are not conducted, which may lead to bias in survey results. Therefore, it is necessary to increase the analysis of influencing factors for further and in-depth exploration.

CONCLUSION

In summary, risk variables for sleep disturbances in CHD patients include sex, new rural cooperative medical insurance, depression, and anxiety. The risk factor prediction model established by multivariate logistic regression has good predictive efficacy. The considerable inverse relationship between sleep disorders and QoL and the substantial positive relationship between sleep disorders and depression and anxiety suggests that individuals may be able to improve their depressive moods through psychological counselling and break the vicious cycle of mutual influence between a bad mood and sleep quality. In terms of economic pressure, cost-effective treatment programs can be selected for patients as far as possible to reduce the economic pressure on patients' families, which is conducive to improving their bad mood, improving their sleep quality and QoL, and improving their prognosis.

ARTICLE HIGHLIGHTS

Research background

Studies have shown that sleep disorders are closely related to anxiety and depression, and the quality of life (QoL) of patients with sleep disorders is generally poor. The significance of this study is to explore the status quo and risk factors of sleep disorders in patients with coronary heart disease (CHD) and their correlation with anxiety, depression and QoL. To provide reference for the prevention and treatment of sleep disorders in clinical CHD.

Research motivation

The current status of sleep disorders in patients with CHD is the main topic of this study. At present, it is clinically necessary to explore the current status of sleep disorders in patients with CHD and its correlation with anxiety, depression and QoL, so as to provide reference for the prevention and treatment of patients with CHD sleep disorders. The significance of this study is to explore the risk factors of patients with CHD sleep disorders and their correlation with anxiety, depression and QoL, encourage clinical teams to continue to explore CHD sleep disorders, and promote the continuous progress of sleep disorder prevention and treatment technology.

Research objectives

The incidence of sleep disorders in patients with CHD was 46.67%. Sex, female, new rural cooperative medical insurance, anxiety and depression were independent risk factors for CHD sleep disorders. It was confirmed that CHD sleep disorders were closely related to anxiety, depression and QoL, providing a new reference for clinical prevention and treatment of CHD sleep disorders in the future.

Research methods

The clinical data of patients were retrospectively analyzed, and the patients were divided into the sleep disorder group and the non-sleep disorder group according to their sleep conditions. The general data of the two groups were statistically analyzed by independent sample *t*-test and χ^2 test. The risk factors of sleep disorders in patients with CHD were analyzed by the logistic multivariate regression method and a risk prediction model was built. Receiver operating characteristic was used to analyze the effectiveness of the risk prediction model, and Spearman's correlation was used to analyze the correlation between sleep disorders and anxiety, depression, and QoL.

Research results

Patients with CHD sleep disorder are closely related to anxiety, depression and QoL, and sex, female, new rural medical insurance, anxiety and depression are risk factors for patients with CHD sleep disorder, providing a new reference for the prevention and treatment of patients with CHD sleep disorder. It is necessary to further expand the sample size to explore the influencing factors of patients with CHD sleep disorder.

Research conclusions

Patients with CHD sleep disorders can interact with anxiety and depression, forming a vicious circle, so clinical attention should be paid to psychological intervention for patients with CHD sleep disorders.

Research perspectives

Sleep disorders in patients with CHD are closely related to anxiety and depression, which can have a negative impact on QoL. Emotional intervention methods can be used to improve sleep disorders and QoL in patients with CHD.

FOOTNOTES

Author contributions: Zheng D initiated the project and designed the experiment; Tan RJ conducted the clinical data collection; Liu W performed postoperative follow-up and recorded the data; Song PC conducted a number of collation and statistical analyses; Li FD wrote the original manuscript and revised the paper; All authors read and approved the final manuscript.

Supported by Scientific Research Program on Chinese Medicine, No. 2023460.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of the Hengshui People's Hospital.

Informed consent statement: As the study used anonymous and pre-existing data, the requirement for the informed consent from patients was waived.

Conflict-of-interest statement: The authors have no financial relationships to disclose.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

ORCID number: Feng-De Li 0009-0008-8845-4088.

S-Editor: Qu XL
L-Editor: Filipodia
P-Editor: Zhang XD

REFERENCES

1 **Dey S**, Sun E, Frishman WH, Aronow WS. Sleep Disorders and Coronary Artery Disease. *Cardiol Rev* 2023; **31**: 219-224 [PMID: 36301202 DOI: 10.1097/CRD.0000000000000478]
2 **Huang BH**, Duncan MJ, Cistulli PA, Nassar N, Hamer M, Stamatakis E. Sleep and physical activity in relation to all-cause, cardiovascular disease and cancer mortality risk. *Br J Sports Med* 2022; **56**: 718-724 [PMID: 34187783 DOI: 10.1136/bjsports-2021-104046]
3 **Zhou Y**, Zhu XP, Shi JJ, Yuan GZ, Yao ZA, Chu YG, Shi S, Jia QL, Chen T, Hu YH. Coronary Heart Disease and Depression or Anxiety: A Bibliometric Analysis. *Front Psychol* 2021; **12**: 669000 [PMID: 34149564 DOI: 10.3389/fpsyg.2021.669000]
4 **Blumenthal JA**, Smith PJ, Jiang W, Hinderliter A, Watkins LL, Hoffman BM, Kraus WE, Liao L, Davidson J, Sherwood A. Effect of Exercise, Escitalopram, or Placebo on Anxiety in Patients With Coronary Heart Disease: The Understanding the Benefits of Exercise and Escitalopram in Anxious Patients With Coronary Heart Disease (UNWIND) Randomized Clinical Trial. *JAMA Psychiatry* 2021; **78**: 1270-1278 [PMID: 34406354 DOI: 10.1001/jamapsychiatry.2021.2236]
5 **Joseph J**, Velasco A, Hage FG, Reyes E. Guidelines in review: Comparison of ESC and ACC/AHA guidelines for the diagnosis and management of patients with stable coronary artery disease. *J Nucl Cardiol* 2018; **25**: 509-515 [PMID: 28884447 DOI: 10.1007/s12350-017-1055-0]
6 **Morris JL**, Rohay J, Chasens ER. Sex Differences in the Psychometric Properties of the Pittsburgh Sleep Quality Index. *J Womens Health (Larchmt)* 2018; **27**: 278-282 [PMID: 29154713 DOI: 10.1089/jwh.2017.6447]
7 **Dunstan DA**, Scott N, Todd AK. Screening for anxiety and depression: reassessing the utility of the Zung scales. *BMC Psychiatry* 2017; **17**: 329 [PMID: 28886698 DOI: 10.1186/s12888-017-1489-6]
8 **Young CA**, Mills R, Al-Chalabi A, Burke G, Chandran S, Dick DJ, Ealing J, Hanemann CO, Harrower T, Mcdermott CJ, Majeed T, Pinto A,

Talbot K, Walsh J, Williams TL, Tennant A; TONiC study group. Measuring quality of life in ALS/MND: validation of the WHOQOL-BREF. *Amyotroph Lateral Scler Frontotemporal Degener* 2020; 1-9 [PMID: 32597226 DOI: 10.1080/21678421.2020.1752244]

9 **Sejbuk M**, Mirończuk-Chodakowska I, Witkowska AM. Sleep Quality: A Narrative Review on Nutrition, Stimulants, and Physical Activity as Important Factors. *Nutrients* 2022; **14** [PMID: 35565879 DOI: 10.3390/nu14091912]

10 **Cheng M**, Lei X, Zhu C, Hou Y, Lu M, Wang X, Wu Q. The association between poor sleep quality and anxiety and depression symptoms in Chinese patients with coronary heart disease. *Psychol Health Med* 2022; **27**: 1347-1356 [PMID: 33506709 DOI: 10.1080/13548506.2021.1874440]

11 **Ulander M**, Rångtell F, Theorell-Haglöw J. Sleep Measurements in Women. *Sleep Med Clin* 2021; **16**: 635-648 [PMID: 34711387 DOI: 10.1016/j.jsmc.2021.07.004]

12 **Wang Z**, Du W, Jin S, Zhu Y, Quan C, Zhang X, Feng Y, Mo Y, Wang J. Analysis of preoperative sleep quality and related influencing factors in cancer patients. *Support Care Cancer* 2022; **31**: 4 [PMID: 36512163 DOI: 10.1007/s00520-022-07483-8]

13 **Bonanni E**, Schirru A, Di Perri MC, Bonuccelli U, Maestri M. Insomnia and hot flashes. *Maturitas* 2019; **126**: 51-54 [PMID: 31239118 DOI: 10.1016/j.maturitas.2019.05.001]

14 **Al Naamani Z**, Gormley K, Noble H, Santin O, Al Maqbali M. Fatigue, anxiety, depression and sleep quality in patients undergoing haemodialysis. *BMC Nephrol* 2021; **22**: 157 [PMID: 33910523 DOI: 10.1186/s12882-021-02349-3]

15 **Ghrouz AK**, Noohu MM, Dilshad Manzar M, Warren Spence D, BaHammam AS, Pandi-Perumal SR. Physical activity and sleep quality in relation to mental health among college students. *Sleep Breath* 2019; **23**: 627-634 [PMID: 30685851 DOI: 10.1007/s11325-019-01780-z]

16 **Al-Khani AM**, Sarhandi MI, Zaghloul MS, Ewid M, Saquib N. A cross-sectional survey on sleep quality, mental health, and academic performance among medical students in Saudi Arabia. *BMC Res Notes* 2019; **12**: 665 [PMID: 31639038 DOI: 10.1186/s13104-019-4713-2]

17 **Scott AJ**, Webb TL, Martyn-St James M, Rowse G, Weich S. Improving sleep quality leads to better mental health: A meta-analysis of randomised controlled trials. *Sleep Med Rev* 2021; **60**: 101556 [PMID: 34607184 DOI: 10.1016/j.smrv.2021.101556]

18 **Afonso P**, Fonseca M, Teodoro T. Evaluation of anxiety, depression and sleep quality in full-time teleworkers. *J Public Health (Oxf)* 2022; **44**: 797-804 [PMID: 34036369 DOI: 10.1093/pubmed/fdab164]

19 **He Y**, Sun LY, Peng KW, Luo MJ, Deng L, Tang T, You CX. Sleep quality, anxiety and depression in advanced lung cancer: patients and caregivers. *BMJ Support Palliat Care* 2022; **12**: e194-e200 [PMID: 32253349 DOI: 10.1136/bmjspcare-2018-001684]

20 **Korkmaz S**, Kazgan A, Çekiç S, Tartar AS, Balcı HN, Atmaca M. The anxiety levels, quality of sleep and life and problem-solving skills in healthcare workers employed in COVID-19 services. *J Clin Neurosci* 2020; **80**: 131-136 [PMID: 33099335 DOI: 10.1016/j.jocn.2020.07.073]

21 **Peixoto KO**, Resende CMBM, Almeida EO, Almeida-Leite CM, Conti PCR, Barbosa GAS, Barbosa JS. Association of sleep quality and psychological aspects with reports of bruxism and TMD in Brazilian dentists during the COVID-19 pandemic. *J Appl Oral Sci* 2021; **29**: e20201089 [PMID: 34320119 DOI: 10.1590/1678-7757-2020-1089]

22 **Rebora P**, Spedale V, Occhino G, Luciani M, Alvaro R, Vellone E, Riegel B, Ausili D. Effectiveness of motivational interviewing on anxiety, depression, sleep quality and quality of life in heart failure patients: secondary analysis of the MOTIVATE-HF randomized controlled trial. *Qual Life Res* 2021; **30**: 1939-1949 [PMID: 33616815 DOI: 10.1007/s11136-021-02788-3]

World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatry 2023 October 19; 13(10): 743-752

DOI: 10.5498/wjp.v13.i10.743

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Retrospective Study

Clinical value of ankle flexion and extension exercises combined with a psychological intervention in knee osteoarthritis

Yang Liu, Rong Chen, Yang Zhang, Qin Wang, Jiang-Li Ren, Chang-Xu Wang, Yuan-Kun Xu

Specialty type: Psychiatry

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Muller DJ, Canada; Reed JL, Canada

Received: August 1, 2023
Peer-review started: August 1, 2023
First decision: August 16, 2023
Revised: August 28, 2023
Accepted: September 5, 2023
Article in press: September 5, 2023
Published online: October 19, 2023

Yang Liu, Yuan-Kun Xu, Department of Orthopedics, The First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine, Guiyang 524000, Guizhou Province, China

Rong Chen, Yang Zhang, Department of Anesthesiology, The First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine, Guiyang 524000, Guizhou Province, China

Qin Wang, Department of Rheumatology and Immunology, The First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine, Guiyang 524000, Guizhou Province, China

Jiang-Li Ren, Department of Neurology, The First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine, Guiyang 524000, Guizhou Province, China

Chang-Xu Wang, Graduate School, Guizhou University of Traditional Chinese Medicine, Guiyang 550002, Guizhou Province, China

Corresponding author: Yuan-Kun Xu, PhD, Doctor, Department of Orthopedics, The First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine, No. 71 Baoshan North Road, Yunyan District, Guiyang 524000, Guizhou Province, China.
xuyuankun_21@163.com

Abstract

BACKGROUND

Considering the limited effectiveness of clinical interventions for knee osteoarthritis (KOA), it is necessary to continue to explore appropriate and effective treatment strategies to improve the condition of KOA patients.

AIM

To clarify the influence of ankle flexion and extension exercises combined with a psychological intervention on the psychological status and activities of daily living (ADLs) of patients with KOA.

METHODS

The research participants were 116 KOA patients admitted to The First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine between May 2019 and May 2022, including 54 patients receiving routine treatment, care and psychological intervention (control group) and 62 patients additionally treated

with ankle flexion and extension exercises (research group). The two groups were comparatively analyzed in terms of psychological status (Self-rating Anxiety/Depression Scale, SDS/SAS), ADLs, knee joint function (Lysholm Knee Scoring Scale), pain (Visual Analog Scale, VAS), fatigue (Multidimensional Fatigue Inventory, MFI), and quality of life (QoL; Short-Form 36 Item Health Survey, SF-36).

RESULTS

After evaluation, it was found that the postinterventional SDS, SAS, VAS, and MFI scores in the research group were significantly reduced compared with the baseline (before the intervention) values and those of the control group, while the postinterventional Lysholm, ADL and SF-36 scores were markedly elevated.

CONCLUSION

Therefore, ankle flexion and extension exercises are highly effective in easing negative psychological status, enhancing ADLs, daily living ability, knee joint function and QoL, and relieving pain and fatigue in KOA patients, thus warranting clinical promotion.

Key Words: Ankle flexion and extension exercises; Knee osteoarthritis; Psychology; Negative emotions; Activities of daily living; Quality of life

Core Tip: This study explores and verifies the clinical advantages of ankle flexion and extension exercises combined with a psychological intervention in knee osteoarthritis from the aspects of negative mood, activities of daily living, knee function, pain, fatigue, and quality of life.

Citation: Liu Y, Chen R, Zhang Y, Wang Q, Ren JL, Wang CX, Xu YK. Clinical value of ankle flexion and extension exercises combined with a psychological intervention in knee osteoarthritis. *World J Psychiatry* 2023; 13(10): 743-752
URL: https://www.wjgnet.com/2220-3206/full/v13/i10/743.htm
DOI: https://dx.doi.org/10.5498/wjp.v13.i10.743

INTRODUCTION

Knee osteoarthritis (KOA) is a chronic, inflammatory and degenerative joint disease that predominates in middle-aged and elderly women and is pathologically characterized by cartilage degeneration and bone overgrowth (osteophyte and subchondral thickening)[1-3]. KOA patients suffer from joint pain, swelling, stiffness, deformity, and dysfunction, which not only negatively affect patients' activities of daily living (ADLs) to varying degrees but also cause psychological distress to patients, affecting their quality of life (QoL); hence, it is also paramount to intervene in patients psychologically[4,5]. An in-depth analysis of the causes of KOA revealed that abnormal joint loads such as excessive exercise and past sprains, mechanical injuries, age, obesity, diet and genetic factors are factors that increase the risk of developing KOA[6]. According to epidemiological data, KOA is one of the important causes of lower-limb disability in the elderly population and may affect 40% of men and 47% of women, with an incidence of 60% among middle-aged and elderly individuals[7,8]. The pathogenesis of KOA is complicated. Although many attempts have been made to suppress the course of KOA, it is still necessary to continue to explore suitable and effective treatment strategies to improve the condition of KOA patients.

There are many clinical treatment options for KOA, including weight loss, exercise, painkillers, intra-articular hyaluronic acid, and joint replacement surgery[9]. Weight loss is mainly applicable to obese patients, while analgesics, intra-articular hyaluronic acid, and joint replacement surgery carry certain medication or surgical risks, especially for elderly patients with serious diseases[10]. Therefore, this study included an in-depth exploration of therapeutic strategies for KOA patients from the perspective of exercise. Exercise therapy, as a lifestyle intervention, mainly strengthens blood circulation by regulating venous reflux and congestion, thus increasing joint range of motion and muscle strength while positively influencing joint stability[11,12]. Ankle flexion and extension exercise is an exercise mode mainly based on ankle plantar flexion and ankle dorsiflexion, which has a positive effect on lower-limb blood circulation and muscle strength[13]. A report suggests that passive ankle flexion and extension exercises in elderly KOA patients can significantly resolve symptoms and pain with a certain degree of safety, suggesting the clinical application potential of this exercise program.

Considering that there are few studies on the clinical application of ankle flexion and extension exercises combined with a psychological intervention in KOA, this study evaluated the potential clinical value of these interventions from the aspects of psychology and ADLs.

MATERIALS AND METHODS

Patient source

The study population comprised 116 KOA patients admitted to The First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine between May 2019 and May 2022, including 54 patients receiving routine treatment and nursing (control group) and 62 patients additionally given ankle flexion and extension exercises (research group). The two patient groups did not differ much in baseline data and had clinical comparability ($P > 0.05$).

Criteria for patient enrollment and exclusion

Inclusion criteria were as follows: in accordance with the diagnostic criteria for KOA[14]; primary disease; intermittent joint narrowing, subchondral osteosclerosis, or cystic degeneration shown by radiographs; complete medical records; normal comprehension and expression ability; and high compliance.

The exclusion criteria were as follows: history of knee joint trauma or surgery; knee joint redness, swelling, heat pain, and obvious limitation of motion; complications with other serious chronic diseases that are not suitable for routine functional exercise; and cardio-cerebrovascular diseases, malignant tumors, or coagulation dysfunction.

Methods

The control group received routine therapy. A comfortable hospitalization environment was provided for patients. Meanwhile, nursing staff patiently addressed the doubts and concerns of patients and their families and provided vital sign monitoring, dietary guidance, psychological care, health education, nursing-patient interaction, and local massage. In addition, patients were informed of matters to be noted during the convalescence period to prevent and control the occurrence of complications and were assisted in relieving limb symptoms and reducing the pain of the primary lesion as much as possible. The psychological intervention is described below. First, relevant health education was carried out, and the etiology of KOA and the mechanism and purpose of the treatment were explained to patients in plain language to enhance their disease awareness and better understand the treatment methods, thus improving their cooperation as much as possible. Second, by enumerating patients who experienced positive outcomes (patients who experienced an ideal curative effect after following the doctor's advice) and patients who experienced negative outcomes (patients who experienced unsatisfactory curative effects due to noncompliance with the doctor's advice), the patients developed a greater realization of the importance and necessity of following the doctor's advice. Third, during the treatment, medical staff actively asked patients about their treatment feelings to optimize patients' treatment experience and find potential problems in time to give reasonable suggestions. Patients' psychological status was also considered, and psychological counseling was given in a timely manner. Moreover, the hospital provided a quiet and comfortable environment for patients so that they could take the initiative to receive diagnosis and treatment.

In addition to the measures implemented in the control group, the research group was also treated with cognitive education and ankle flexion and extension exercises. The cognitive education intervention is described below. Health and KOA-related cognitive education was conducted through multimedia lectures, mainly teaching the characteristics, functions, pathological mechanisms, risk factors and treatment methods of KOA, so that patients could understand the therapeutic value and mechanism of exercise therapy in KOA. Ankle flexion and extension exercise methods were as follows: (1) Supine ankle flexion and extension: The patient took the supine position with toes pointing to the ceiling as the starting position; the ankles were flexed and kept in that position for 10 s, followed by ankle dorsolateral extension that was maintained for 10 s before returning to the initial posture. The above exercises were performed for 20 repetitions per set with 5 sets per session and a 1-min break between sets; (2) Ankle flexion and extension in the seated position: The patient sat on the chair, with feet flat on the ground and toes pointing straight ahead; ankle plantar flexion of both feet was performed for 10 s, followed by ankle dorsiflexion for 10 s; finally, the patient returned to the initial posture. The above exercises were performed for 20 repetitions per set with 5 sets per session and a 1-minute rest between sets; and (3) Ankle flexion and extension in the standing position: The patient took a comfortable standing posture with one or both hands placed on the table or wall for support; foot plantar flexion followed by ankle dorsiflexion was performed; finally, the patient returned to the initial posture. The above exercises were performed for 10 repetitions per set with 5 sets per session and a 1-min break between sets. The ankle flexion and extension exercises in these three positions were performed in turn, that is, supine ankle flexion and extension on the first day, seated ankle flexion and extension on the second day, and standing ankle flexion and extension on the third day. Both groups were treated for three months.

Outcome measures

Psychological state. We used the Self-rating Depression/Anxiety Scale (SDS/SAS)[15] to evaluate patients' depression and anxiety before and after the intervention. Both scales have 20 items and a score range of 0-80 points, with the scores in direct proportion to the patient's depressive and anxious symptoms.

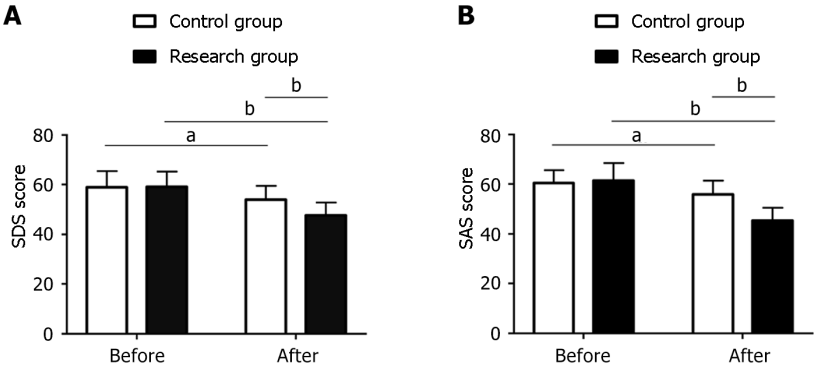
ADLs. Patients were evaluated before and after the intervention using the ADL Scale[16] for feeding, bathing, dressing, decorating, continence, and toileting domains, with a maximum score of 100. A higher score suggests a more significant improvement in patients' ADLs.

Knee joint function. Knee joint function assessment was made before and after treatment using the Lysholm Knee Scoring Scale[17], with the evaluation contents including pain, swelling, limping, blocking, instability, crouching, and climbing stairs. On a 100-point scale, higher scores are associated with better recovery of knee function.

Degree of pain. Before and after the intervention, patients were also assessed by the Visual Analog Scale (VAS; score range: 0-10)[18] to determine the degree of pain. The score is directly proportional to the degree of pain.

Table 1 Analysis of baseline data of knee osteoarthritis patients in the two groups

Factors	Control group (n = 54)	Research group (n = 62)	χ^2/t value	P value
Age (yr)	59.46 ± 6.95	58.55 ± 6.82	0.711	0.479
Sex (male/female)	25/29	27/35	0.894	0.466
Disease course (yr)	5.20 ± 2.55	5.37 ± 2.67	0.349	0.728
Single knee disease (yes/no)	38/16	41/21	0.813	0.269
Cause of illness (excessive exercise/sprain/others)	25/19/10	29/21/12	0.406	0.705
Education level (junior high school and below/senior high school and above)	34/20	38/24	0.404	0.725



DOI: 10.5498/wjp.v13.i10.743

Figure 1 Analysis of the influence of ankle flexion and extension exercises on knee osteoarthritis patients' psychological state. A: The research group had a postinterventional Self-Rating Depression Scale score that was lower than the preinterventional value and that of the control group; B: The research group had a postinterventional Self-Rating Anxiety Scale score that was lower than the preinterventional value and that of the control group. Note: $^aP < 0.05$; $^bP < 0.01$. SDS: Self-Rating Depression Scale; SAS: Self-Rating Anxiety Scale.

Fatigue. The fatigue of patients before and after the intervention was evaluated by the Multidimensional Fatigue Inventory (MFI)[19], a tool with a score ranging from 20 to 100 that is positively related to fatigue.

QoL. Finally, we assessed patients' QoL from eight dimensions [physical functioning (PF); role-physical (RP); bodily pain (BP); social functioning (SF); general health (GH); mental health (MH); role-emotional (RE), and vitality (VT) by referring to the Short-Form 36 Item Health Survey (SF-36)]. Each dimension has a score of 0-10 that is positively correlated with QoL.

Statistical methods

The mean ± SEM was used to describe the measurement data, and the independent-samples t-test was used to compare two sets of measurement data. The intergroup comparison of count data expressed by percentages (%) was made by the χ^2 test. Data analysis was performed using SPSS 19.0, and the significance threshold was $\alpha = 0.05$.

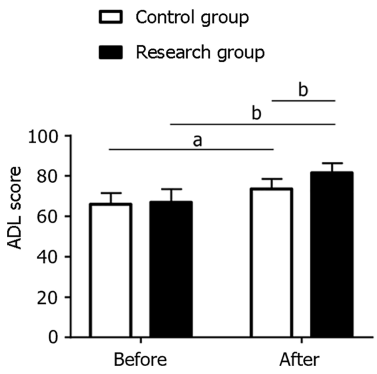
RESULTS

Analysis of baseline data of KOA patients in the two groups

Baseline data such as age, sex, course of disease, single knee disease, cause of disease and education level of KOA patients in the two groups were compared and analyzed, and no significant differences were found ($P > 0.05$). See Table 1.

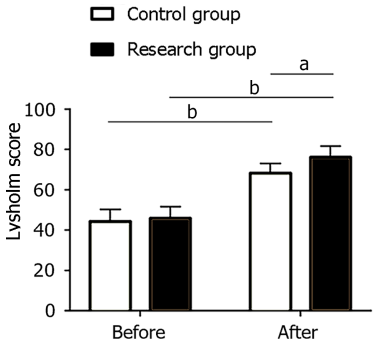
Analysis of the influence of ankle flexion and extension exercises on KOA patients' psychological state

We evaluated patients' negative psychological state by using the SDS and SAS. The results showed no significant difference in the two scale scores between the research and control groups prior to intervention [SDS: (59.15 ± 6.05) score *vs* (58.91 ± 6.44) score, SAS: (61.34 ± 7.13) score *vs* (60.37 ± 5.31) score, $P > 0.05$]. An obvious reduction in both scales was found in the two groups after the intervention [SDS: (47.60 ± 5.21) score *vs* (54.02 ± 5.51) score, SAS: (45.32 ± 5.16) score *vs* (55.83 ± 5.62) score, $P < 0.05$], especially in the research group ($P < 0.05$). See Figure 1.



DOI: 10.5498/wjp.v13.i10.743 **Copyright** ©The Author(s) 2023.

Figure 2 Analysis of the impact of ankle flexion and extension exercises on knee osteoarthritis patients' activities of daily living. The research group had a postinterventional activities of daily living score that was lower than the preinterventional value and that of the control group. [a]*P* < 0.05; [b]*P* < 0.01. ADL: Activities of daily living.



DOI: 10.5498/wjp.v13.i10.743 **Copyright** ©The Author(s) 2023.

Figure 3 Analysis of the influence of ankle flexion and extension exercises on knee osteoarthritis patients' knee joint function. The research group had a postinterventional Lysholm score that was higher than the preinterventional value and that of the control group. [a]*P* < 0.05; [b]*P* < 0.01.

Analysis of the impact of ankle flexion and extension exercises on KOA patients' ADLs

KOA patients' ADLs were assessed by the ADL scale. The ADL score did not differ markedly between the groups prior to intervention (66.97 ± 6.53) score *vs* (65.98 ± 5.65) score, $P > 0.05$), but it was elevated in both groups after the intervention (81.44 ± 4.95) score *vs* (73.50 ± 5.13) score, $P < 0.05$), with a higher postinterventional score in the research group ($P < 0.05$). See Figure 2.

Analysis of the influence of ankle flexion and extension exercises on KOA patients' knee joint function

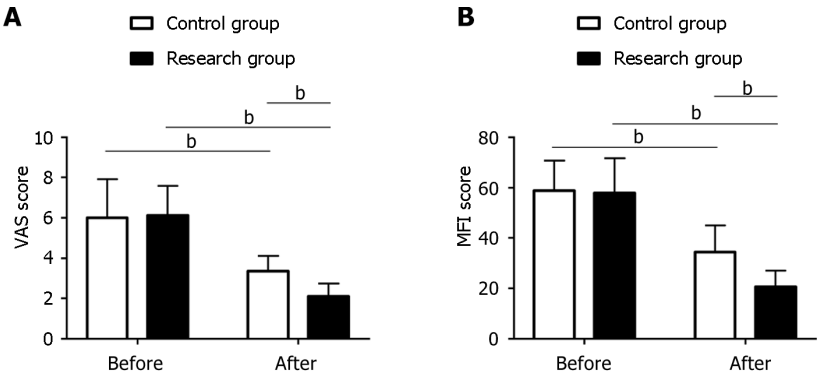
Knee function was assessed in both groups of KOA patients using the Lysholm Knee Scoring Scale. The two groups also showed similar Lysholm scores before the intervention (45.89 ± 5.69) score *vs* (44.43 ± 5.79) score, $P > 0.05$. An evident elevation in the Lysholm score was found in both arms after the intervention, with an even higher score in the research group (76.40 ± 5.25) score *vs* (68.39 ± 4.74) score, $P < 0.05$. See Figure 3.

Analysis of the impact of ankle flexion and extension exercises on pain and fatigue in KOA patients

By evaluating the VAS and MFI scores of both groups, the pain and fatigue status of KOA patients were determined. VAS and MFI scores were found to be similar in the two groups before the intervention [VAS: (6.11 ± 1.47) score *vs* (6.00 ± 1.91) score, MFI: (57.87 ± 13.85) score *vs* (58.81 ± 11.94) score, $P > 0.05$], but they were significantly reduced after the intervention, with even lower scores in the research group [VAS: (2.11 ± 0.63) score *vs* (3.35 ± 0.76) score, MFI: (20.55 ± 6.61) score *vs* (34.48 ± 10.50) score, $P < 0.05$]. See Figure 4.

Analysis of the impact of ankle flexion and extension exercises on KOA patients' QoL

The QoL of KOA patients in both groups was evaluated using the SF-36 scale. The data revealed no significant difference in SF-36 scores between the research and control groups before the intervention ($P > 0.05$). The SF-36 scores of both arms showed a significant upward trend after the intervention ($P < 0.05$), with a more significant increase in the research group ($P < 0.05$). See Figure 5.



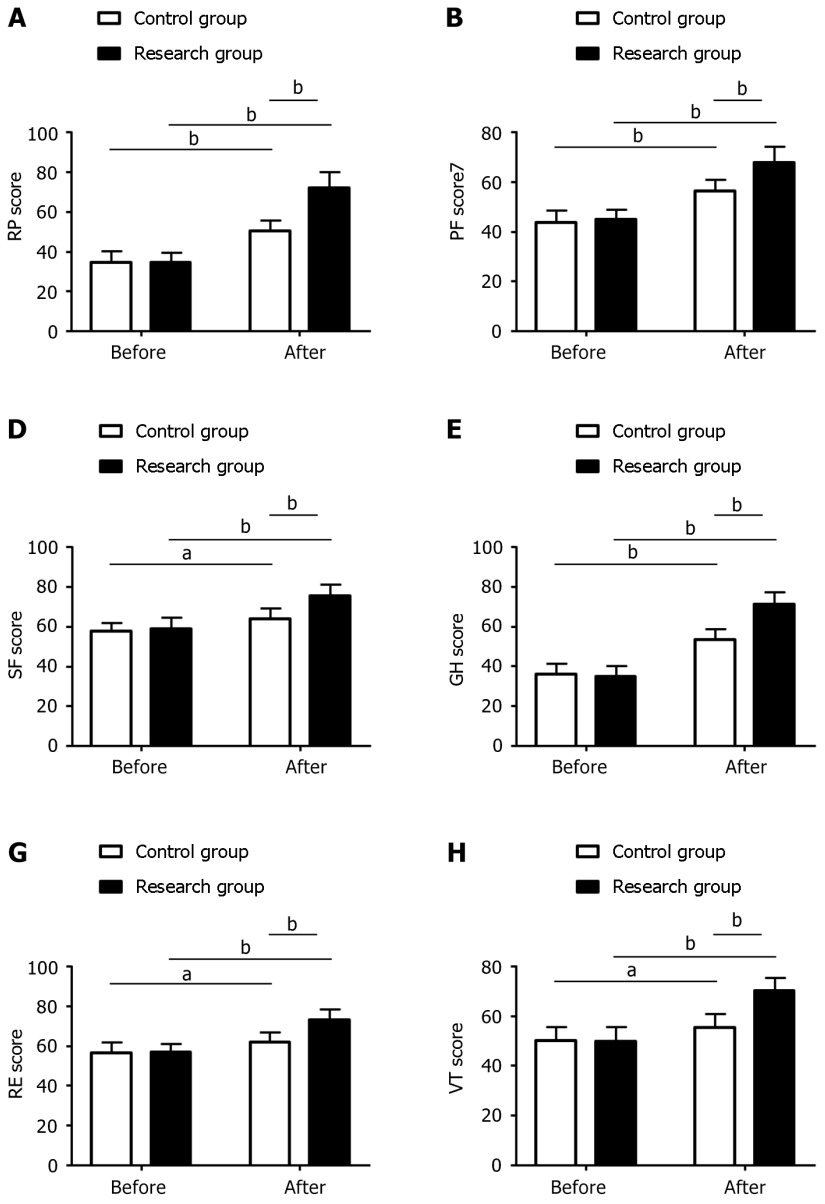
DOI: 10.5498/wjp.v13.i10.743

Figure 4 Analysis of the impact of ankle flexion and extension exercises on knee osteoarthritis patients' pain and fatigue. A: The research group had a postinterventional Visual Analog Scale score that was lower than the preinterventional value and that of the control group; B: The research group had a postinterventional MFI score that was lower than the preinterventional value and that of the control group. $^{a}P < 0.05$; $^{b}P < 0.01$. VAS: Visual Analog Scale; MFI: Multidimensional Fatigue Inventory.

DISCUSSION

KOA, with complex pathological mechanisms and triggers that are not fully understood, has no effective treatment at present[20]. Ankle flexion and extension exercises, as a type of exercise rehabilitation therapy, integrate and apply the knowledge of sports medicine, rehabilitation medicine, biomechanics and modern functional anatomy to provide KOA patients with an evidence-based exercise intervention[21]. In the research of Abbott *et al*[22], exercise therapy was proven to be beneficial to physical function recovery in KOA patients, suggesting the potential value of ankle flexion and extension exercises in KOA. In another study, exercise therapy was more effective in treating KOA than conventional therapy, contributing to more significant pain reduction and improved function and QoL[23]. Psychological intervention is a measure centered on patients' psychological state and emotional experience, which can improve patients' functional outcomes by eliminating or alleviating their psychological distress[24]. Previous studies have shown that psychological intervention can play a positive role in reducing the severity of KOA symptoms and improving life satisfaction by establishing a positive attitude toward illness[25].

According to the negative psychological state investigation in this study, the research group had markedly reduced SDS and SAS scores after the intervention, which were lower than those of the control group, suggesting that ankle flexion and extension exercises combined with a psychological intervention have a good regulatory effect on the negative psychological state of KOA patients. Song *et al*[26] reported that modified Tai Chi exercises, as a kind of kinesitherapy, can significantly relieve anxiety and depression in elderly female patients with KOA, similar to our findings. Negative emotions such as anxiety and depression in KOA patients have been shown to be related to factors such as high pain levels[27]. In this study, the research group who received ankle flexion and extension exercises experienced a significant reduction in pain levels after the intervention, which may help explain its relieving effect on negative emotions. Furthermore, in the investigation of ADLs, the research group showed a postinterventional ADL score that was evidently higher than the baseline and that of the control group, indicating that ankle flexion and extension exercises combined with a psychological intervention are beneficial to significantly improve the ADLs of KOA patients. This may be attributed to the improvement in muscle strength and range of motion in patients after ankle flexion and extension exercises, thus reducing activity limitations in such patients[28]. Subsequently, knee function analysis revealed markedly increased Lysholm scores in the research group that were higher than those in the control group after the intervention, which indicates that ankle flexion and extension exercises combined with a psychological intervention are conducive to enhancing the knee joint function of KOA patients. Exercise therapy, such as ankle flexion and extension exercises, has also been reported to alleviate KOA by enhancing muscle strength, restoring neuromotor control and improving the range of joint motion[29]. Later, the analysis of pain and fatigue showed marked reductions in VAS and MFI scores in the research group that were significantly lower than those in the control group, demonstrating that ankle flexion and extension exercises combined with a psychological intervention are significantly effective in mitigating pain and fatigue in KOA patients. Peeler *et al*[30] noted in their study that low-load exercise for KOA patients has significant advantages in improving ADLs and knee joint function, with a potent pain-relieving effect, which can support our research results. In addition, the fatigue of KOA patients is primarily associated with pathological pain and decreased physical function[31]. The alleviation of fatigue in KOA patients may be related to the reduction of pain and improvement of body function by ankle flexion and extension exercises, which agrees with the research results reported by Casilda-López *et al*[32]. Finally, the QoL assessment showed that the SF-36 scores of the research group increased significantly after the intervention and were markedly higher than those of the control group, indicating that ankle flexion and extension exercises combined with a psychological intervention can significantly boost QoL in KOA patients.



DOI: 10.5498/wjp.v13.i10.743

Figure 5 Analysis of the influence of ankle flexion and extension exercises on knee osteoarthritis patients' quality of life. A: The research group had a postinterventional Role-physical score that was higher than the preinterventional value and that of the control group; B: The research group had a postinterventional physical functioning score that was higher than the preinterventional value and that of the control group; C: The research group had a postinterventional bodily pain score that was higher than the preinterventional value and that of the control group; D: The research group had a postinterventional social functioning score that was higher than the preinterventional value and that of the control group; E: The research group had a postinterventional general health score that was higher than the preinterventional value and that of the control group; F: The research group had a postinterventional mental health score that was higher than the preinterventional value and that of the control group; G: The research group had a postinterventional role-emotional score that was higher than the preinterventional value and that of the control group; H: The research group had a postinterventional vitality score that was higher than the preinterventional value and that of the control group. $^{a}P < 0.05$; $^{b}P < 0.01$. PF: Physical functioning; RP: Role-physical; BP: Bodily pain; SF: Social functioning; GH: General health; MH: Mental health; RE: Role-emotional; VT: Vitality.

CONCLUSION

Taken together, while resulting in psychological relief and improvement of ADLs, ankle flexion and extension exercises combined with a psychological intervention can effectively restore knee joint function and mitigate pain and fatigue in KOA patients, thus playing a positive role in improving the quality of life of patients and warranting clinical promotion.

ARTICLE HIGHLIGHTS

Research background

Given the limited efficacy of clinical intervention in knee osteoarthritis (KOA), it is necessary to continue to explore appropriate and effective treatment strategies to improve the condition of KOA patients.

Research motivation

The pathogenesis of KOA is complex, and exploring effective treatment strategies is of great significance for the prevention and treatment of this disease.

Research objectives

The aim of this study is to clarify the influence of ankle flexion and extension exercises combined with psychological intervention on the psychology and activities of daily living (ADLs) of patients with KOA.

Research methods

The research participants were 116 KOA patients admitted between May 2019 and May 2022, including 54 cases receiving routine treatment, care and psychological intervention (control group) and 62 cases additionally treated with ankle flexion and extension exercises (research group) on the basis of the control group. The two groups were comparatively analyzed in terms of psychological status (Self-rating Anxiety/Depression Scale, SDS/SAS), ADLs (ADL scale), knee joint function (Lysholm Knee Scoring Scale), pain (Visual Analogue Scale, VAS), fatigue (Multidimensional Fatigue Inventory, MFI), and quality of life (QoL; Short-Form 36 Item Health Survey, SF-36).

Research results

After evaluation, it was found that the postinterventional SDS, SAS, VAS, and MFI scores in the research group were significantly reduced compared with the baseline (before the intervention) values and those of the control group, while the postinterventional Lysholm, ADL, and SF-36 scores were markedly elevated.

Research conclusions

Ankle flexion and extension exercises are highly effective in easing negative psychology, enhancing ADLs, knee joint function and QoL, and relieving pain and fatigue in KOA patients, which is worthy of clinical promotion.

Research perspectives

In addition to the positive effect on the negative psychological relief and improvement of ADLs of KOA patients, ankle flexion and extension exercises combined with a psychological intervention can also effectively restore knee joint function, alleviate pain and fatigue, and enhance patients' quality of life, providing an effective treatment option for KOA patients.

FOOTNOTES

Author contributions: Liu Y, Chen R, Zhang Y and Wang Q contributed equally to this work and are co-first authors; Liu Y, Chen R, Zhang Y and Wang Q concepted the study, supervised the study, contributed to the investigation, the visualization of the study, and originally drafted the manuscript; Xu YK collected the data; Wang CX contributed to the formal analysis; Liu Y, Chen R, Zhang Y, Wang Q and Ren JL contributed to the methodology; Xu YK validated the study; Liu Y, Chen R, Zhang Y, Wang Q and Ren JL reviewed and edited the manuscript.

Institutional review board statement: The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Medical Ethics Committee of The First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine.

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

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

ORCID number: Yang Liu 0009-0004-6453-2126; Rong Chen 0009-0000-3339-7233; Yang Zhang 0009-0009-7863-9879; Qin Wang 0009-0000-3802-9149; Jiang-Li Ren 0000-0002-0400-3159; Chang-Xu Wang 0009-0002-7087-7601; Yuan-Kun Xu 0000-0001-9192-1152.

S-Editor: Li L
L-Editor: A
P-Editor: Chen YX

REFERENCES

1 **Tang S**, Chen P, Zhang H, Weng H, Fang Z, Chen C, Peng G, Gao H, Hu K, Chen J, Chen L, Chen X. Comparison of Curative Effect of Human Umbilical Cord-Derived Mesenchymal Stem Cells and Their Small Extracellular Vesicles in Treating Osteoarthritis. *Int J Nanomedicine* 2021; **16**: 8185-8202 [PMID: 34938076 DOI: 10.2147/IJN.S336062]
2 **Katz JN**, Arant KR, Loeser RF. Diagnosis and Treatment of Hip and Knee Osteoarthritis: A Review. *JAMA* 2021; **325**: 568-578 [PMID: 33560326 DOI: 10.1001/jama.2020.22171]
3 **Coryell PR**, Diekman BO, Loeser RF. Mechanisms and therapeutic implications of cellular senescence in osteoarthritis. *Nat Rev Rheumatol* 2021; **17**: 47-57 [PMID: 33208917 DOI: 10.1038/s41584-020-00533-7]
4 **Lewinson RT**, Stefanyshyn DJ. Wedged Insoles and Gait in Patients with Knee Osteoarthritis: A Biomechanical Review. *Ann Biomed Eng* 2016; **44**: 3173-3185 [PMID: 27436294 DOI: 10.1007/s10439-016-1696-1]
5 **Axford J**, Butt A, Heron C, Hammond J, Morgan J, Alavi A, Bolton J, Bland M. Prevalence of anxiety and depression in osteoarthritis: use of the Hospital Anxiety and Depression Scale as a screening tool. *Clin Rheumatol* 2010; **29**: 1277-1283 [PMID: 20721594 DOI: 10.1007/s10067-010-1547-7]
6 **Strath LJ**, Jones CD, Philip George A, Lukens SL, Morrison SA, Soleymani T, Locher JL, Gower BA, Sorge RE. The Effect of Low-Carbohydrate and Low-Fat Diets on Pain in Individuals with Knee Osteoarthritis. *Pain Med* 2020; **21**: 150-160 [PMID: 30865775 DOI: 10.1093/pm/pnz022]
7 **Neogi T**. The epidemiology and impact of pain in osteoarthritis. *Osteoarthritis Cartilage* 2013; **21**: 1145-1153 [PMID: 23973124 DOI: 10.1016/j.joca.2013.03.018]
8 **Király M**, Kővári E, Hodosi K, Bálint PV, Bender T. The effects of Tiszasüly and Kolop mud pack therapy on knee osteoarthritis: a double-blind, randomised, non-inferiority controlled study. *Int J Biometeorol* 2020; **64**: 943-950 [PMID: 31377868 DOI: 10.1007/s00484-019-01764-4]
9 **Hong M**, Cheng C, Sun X, Yan Y, Zhang Q, Wang W, Guo W. Efficacy and Safety of Intra-Articular Platelet-Rich Plasma in Osteoarthritis Knee: A Systematic Review and Meta-Analysis. *Biomed Res Int* 2021; **2021**: 2191926 [PMID: 34337002 DOI: 10.1155/2021/2191926]
10 **Zhang D**, Song S, Bian Z, Huang Z. Clinical Effect of Catgut Embedding plus Warm Needle Moxibustion on Improving Inflammation and Quality of Life of Knee Osteoarthritis Patients. *Comput Math Methods Med* 2022; **2022**: 5315619 [PMID: 36245835 DOI: 10.1155/2022/5315619]
11 **Liu W**, Wang C, Yu G, Shi B, Wang J. Analysis of the Application Effect of Exercise Rehabilitation Therapy Based on Data Mining in the Prevention and Treatment of Knee Osteoarthritis. *Comput Math Methods Med* 2022; **2022**: 2109528 [PMID: 36105247 DOI: 10.1155/2022/2109528]
12 **Wang L**, Chen H, Lu H, Wang Y, Liu C, Dong X, Chen J, Liu N, Yu F, Wan Q, Shang S. The effect of transtheoretical model-lead intervention for knee osteoarthritis in older adults: a cluster randomized trial. *Arthritis Res Ther* 2020; **22**: 134 [PMID: 32513273 DOI: 10.1186/s13075-020-02222-y]
13 **Fung KWY**, Chow DHK, Shae WC. The clinical effects of mobilization with passive ankle dorsiflexion using a passive ankle dorsiflexion apparatus on older patients with knee osteoarthritis: A randomized trial. *J Back Musculoskelet Rehabil* 2021; **34**: 1007-1014 [PMID: 34057129 DOI: 10.3233/BMR-191799]
14 **Jang S**, Lee K, Ju JH. Recent Updates of Diagnosis, Pathophysiology, and Treatment on Osteoarthritis of the Knee. *Int J Mol Sci* 2021; **22** [PMID: 33807695 DOI: 10.3390/ijms22052619]
15 **Wang X**, Wu P, Luo Y, Tao SY, Li Y, Tang J, Jiang NN, Wang J, Zhao Y, Wang ZY. [Moxibustion for rheumatoid arthritis and its effect on related negative emotions]. *Zhongguo Zhen Jiu* 2022; **42**: 1221-1225 [PMID: 36397218 DOI: 10.13703/j.0255-2930.20211110-k0004]
16 **Ellegaard K**, von Bülow C, Røpke A, Bartholdy C, Hansen IS, Rifbjerg-Madsen S, Henriksen M, Wæhrens EE. Hand exercise for women with rheumatoid arthritis and decreased hand function: an exploratory randomized controlled trial. *Arthritis Res Ther* 2019; **21**: 158 [PMID: 31242937 DOI: 10.1186/s13075-019-1924-9]
17 **Collins NJ**, Misra D, Felson DT, Crossley KM, Roos EM. Measures of knee function: International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form (KOOS-PS), Knee Outcome Survey Activities of Daily Living Scale (KOS-ADL), Lysholm Knee Scoring Scale, Oxford Knee Score (OKS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Activity Rating Scale (ARS), and Tegner Activity Score (TAS). *Arthritis Care Res (Hoboken)* 2011; **63** Suppl 11: S208-S228 [PMID: 22588746 DOI: 10.1002/acr.20632]
18 **García-Coronado JM**, Martínez-Olvera L, Elizondo-Omaña RE, Acosta-Olivo CA, Vilchez-Cavazos F, Simental-Mendía LE, Simental-Mendía M. Effect of collagen supplementation on osteoarthritis symptoms: a meta-analysis of randomized placebo-controlled trials. *Int Orthop* 2019; **43**: 531-538 [PMID: 30368550 DOI: 10.1007/s00264-018-4211-5]
19 **Huang Z**, Pan X, Deng W, Huang Z, Huang Y, Huang X, Zhu Z, Han W, Zheng S, Guo X, Ding C, Li T. Implementation of telemedicine for knee osteoarthritis: study protocol for a randomized controlled trial. *Trials* 2018; **19**: 232 [PMID: 29665830 DOI: 10.1186/s13063-018-2625-4]
20 **Xiao CM**, Li JJ, Kang Y, Zhuang YC. Follow-up of a Wuqinxi exercise at home programme to reduce pain and improve function for knee osteoarthritis in older people: a randomised controlled trial. *Age Ageing* 2021; **50**: 570-575 [PMID: 32931545 DOI: 10.1093/ageing/afaa179]
21 **Holm PM**, Schrøder HM, Wernbom M, Skou ST. Low-dose strength training in addition to neuromuscular exercise and education in patients with knee osteoarthritis in secondary care - a randomized controlled trial. *Osteoarthritis Cartilage* 2020; **28**: 744-754 [PMID: 32179197 DOI: 10.1016/j.joca.2020.02.839]
22 **Abbott JH**, Robertson MC, Chapple C, Pinto D, Wright AA, Leon de la Barra S, Baxter GD, Theis JC, Campbell AJ; MOA Trial team. Manual therapy, exercise therapy, or both, in addition to usual care, for osteoarthritis of the hip or knee: a randomized controlled trial. 1: clinical effectiveness. *Osteoarthritis Cartilage* 2013; **21**: 525-534 [PMID: 23313532 DOI: 10.1016/j.joca.2012.12.014]
23 **Goh SL**, Persson MSM, Stocks J, Hou Y, Lin J, Hall MC, Doherty M, Zhang W. Efficacy and potential determinants of exercise therapy in

knee and hip osteoarthritis: A systematic review and meta-analysis. *Ann Phys Rehabil Med* 2019; **62**: 356-365 [PMID: 31121333 DOI: 10.1016/j.rehab.2019.04.006]

24 **das Nair R**, Mhizha-Murira JR, Anderson P, Carpenter H, Clarke S, Groves S, Leighton P, Scammell BE, Topcu G, Walsh DA, Lincoln NB. Home-based pre-surgical psychological intervention for knee osteoarthritis (HAPPiKNEES): a feasibility randomized controlled trial. *Clin Rehabil* 2018; **32**: 777-789 [PMID: 29424236 DOI: 10.1177/0269215518755426]

25 **Hausmann LRM**, Youk A, Kwoh CK, Ibrahim SA, Hannon MJ, Weiner DK, Gallagher RM, Parks A. Testing a Positive Psychological Intervention for Osteoarthritis. *Pain Med* 2017; **18**: 1908-1920 [PMID: 29044408 DOI: 10.1093/pm/pnx141]

26 **Song J**, Wei L, Cheng K, Lin Q, Xia P, Wang X, Yang T, Chen B, Ding A, Sun M, Chen A, Li X. The Effect of Modified Tai Chi Exercises on the Physical Function and Quality of Life in Elderly Women With Knee Osteoarthritis. *Front Aging Neurosci* 2022; **14**: 860762 [PMID: 35721018 DOI: 10.3389/fnagi.2022.860762]

27 **Klinger R**, Stuhlreyer J, Schmitz J, Zöllner C, Roder C, Krug F. [Psychological factors in the context of perioperative knee and joint pain: the role of treatment expectations in pain evolvement]. *Schmerz* 2019; **33**: 13-21 [PMID: 30569202 DOI: 10.1007/s00482-018-0350-2]

28 **Lempke L**, Wilkinson R, Murray C, Stanek J. The Effectiveness of PNF Versus Static Stretching on Increasing Hip-Flexion Range of Motion. *J Sport Rehabil* 2018; **27**: 289-294 [PMID: 28182516 DOI: 10.1123/jsr.2016-0098]

29 **Woo J**, Hong A, Lau E, Lynn H. A randomised controlled trial of Tai Chi and resistance exercise on bone health, muscle strength and balance in community-living elderly people. *Age Ageing* 2007; **36**: 262-268 [PMID: 17356003 DOI: 10.1093/ageing/afm005]

30 **Peeler J**, Ripat J. The effect of low-load exercise on joint pain, function, and activities of daily living in patients with knee osteoarthritis. *Knee* 2018; **25**: 135-145 [PMID: 29325839 DOI: 10.1016/j.knee.2017.12.003]

31 **Snijders GF**, van den Ende CH, Fransen J, van Riel PL, Stukstette MJ, Defoort KC, Arts-Sanders MA, van den Hoogen FH, den Broeder AA; Nijmegen OsteoArthritis Collaboration Study Group. Fatigue in knee and hip osteoarthritis: the role of pain and physical function. *Rheumatology (Oxford)* 2011; **50**: 1894-1900 [PMID: 21750001 DOI: 10.1093/rheumatology/ker201]

32 **Casilda-López J**, Valenza MC, Cabrera-Martos I, Díaz-Pelegrina A, Moreno-Ramírez MP, Valenza-Demet G. Effects of a dance-based aquatic exercise program in obese postmenopausal women with knee osteoarthritis: a randomized controlled trial. *Menopause* 2017; **24**: 768-773 [PMID: 28141662 DOI: 10.1097/GME.0000000000000841]

World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatry 2023 October 19; 13(10): 753-762

DOI: 10.5498/wjp.v13.i10.753

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Retrospective Study

Effects of different intervention methods on psychological flexibility, negative emotions and sleep quality in chronic hepatitis B

Ying Zheng, Xiao-Wei Wang, Chen-Xi Xia

Specialty type: Psychiatry

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Insel PS, Sweden; Shin H, South Korea

Received: August 7, 2023
Peer-review started: August 7, 2023
First decision: August 24, 2023
Revised: September 1, 2023
Accepted: September 11, 2023
Article in press: September 11, 2023
Published online: October 19, 2023

Ying Zheng, Xiao-Wei Wang, Chen-Xi Xia, Department of Infection, The First People's Hospital of Wenling, Wenling 317500, Zhejiang Province, China

Corresponding author: Chen-Xi Xia, MBBS, Associate Chief Nurse, Department of Infection, The First People's Hospital of Wenling, No. 333 Chuanan Road, Chenxi Street, Wenling 317500, Zhejiang Province, China. xiachx001@163.com

Abstract

BACKGROUND

Patients with chronic hepatitis B (CHB) experience various problems, including low psychological flexibility, negative emotions, and poor sleep quality. Therefore, effective nursing interventions are required to reduce adverse events. Acceptance and commitment therapy (ACT) combined with enabling cognitive-behavioral education (ECBE) can improve patients' psychological and sleep. Therefore, we speculate that this may also be effective in patients with CHB.

AIM

To investigate the effects of different intervention methods on psychological flexibility, negative emotions, and sleep quality in patients with CHB.

METHODS

This retrospective study examined clinical and evaluation data of 129 patients with CHB. Intervention methods were divided into a conventional group (routine nursing, $n = 69$) and a combination group (ACT combined with ECBE, $n = 60$). We observed changes in psychological flexibility, negative emotions, sleep quality, and self-care ability in both groups. Observation items were evaluated using the Acceptance and Action Questionnaire-2nd Edition (AAQ-II), Self-Rating Anxiety Scale (SAS), Self-Rating Depression Scale (SDS), Pittsburgh Sleep Quality Index (PSQI), and Exercise of Self-Care Agency Scale (ESCA).

RESULTS

Compared with the conventional group, the AAQ-II score of the combined group was lower ($F_{\text{between-group effect}} = 8.548$; $F_{\text{time effects}} = 25.020$; $F_{\text{interaction effects}} = 52.930$; all $P < 0.001$), the SAS score ($t = 5.445$) and SDS score ($t = 7.076$) were lower (all $P < 0.001$), as were the PSQI dimensions ($t_{\text{sleep quality}} = 4.581$, $t_{\text{fall sleep time}} = 2.826$, $t_{\text{sleep time}} = 2.436$, $t_{\text{sleep efficiency}} = 5.787$, $t_{\text{sleep disorder}} = 5.008$, $t_{\text{hypnotic drugs}} = 3.786$, $t_{\text{daytime dysfunction}} = 4.812$); all $P < 0.05$). The ESCA scores for all dimensions were higher ($t_{\text{health knowledge level}} = 6.994$, $t_{\text{self-concept}} = 5.902$, $t_{\text{self-responsibility}} = 19.820$, $t_{\text{self-care skills}} = 8.470$; all $P < 0.001$).

CONCLUSION
ACT combined with ECBE in patients with CHB can improve psychological flexibility and sleep quality, alleviate negative emotions, and improve self-care.

Key Words: Acceptance and commitment therapy; Empowerment cognitive-behavioral education; Chronic hepatitis B; Psychological flexibility; Negative emotion; Sleep quality

Core Tip: Chronic hepatitis B (CHB) is an infectious and progressive disease requiring basic treatment supplemented with effective nursing interventions. We analyzed the clinical data of 129 patients with CHB. Acceptance and commitment therapy combined with cognitive-behavioral education improved the psychological flexibility and sleep quality of patients with CHB, relieve negative emotions, and improve self-care ability, making a breakthrough in the problem of insufficient routine care.

Citation: Zheng Y, Wang XW, Xia CX. Effects of different intervention methods on psychological flexibility, negative emotions and sleep quality in chronic hepatitis B. *World J Psychiatry* 2023; 13(10): 753-762
URL: https://www.wjgnet.com/2220-3206/full/v13/i10/753.htm
DOI: https://dx.doi.org/10.5498/wjp.v13.i10.753

INTRODUCTION

Chronic hepatitis B (CHB) is a frequent chronic infectious disease. According to the World Health Organization in 2017 [1], the number of CHB infections worldwide reached 257 million. Approximately 900000 people worldwide die each year from hepatitis B virus (HBV) infection or its complications[1]. Due to the mutual influence of physiological, psychological, and social factors, patients with CHB often have various sleep disorders, thus reducing the therapeutic effect[2]. Drug therapies such as conventional antiviral therapy combined with effective nursing interventions can control disease progression[3].

Bedside delivery of health education to the patient improves understanding and self-management[4]. However, after receiving education, patients still have an insufficient sense of participation, low mastery of disease knowledge, and no change in incorrect understandings. Additionally, their psychological and behavioural adaptation to the disease is not obvious, and most patients have unresolved problems such as anxiety, depression, and poor sleep. This is related to the lack of conventional health education and targeted psychological counselling[5]. Moreover, the lack of routine CHB care is a clinical problem that needs to be resolved.

Acceptance and commitment therapy (ACT) is a new type of cognitive behavioral therapy based on functional contextualism and relational reference theory, which promotes individual acceptance of the present and self, and increases psychological flexibility[6]. Additionally, enabling cognitive-behavioral education (ECBE) is a psychological behavior therapy that aims to explore individual-centered problems; help individuals reconstruct cognitive processes; solve emotional, cognitive, and behavioral disorders; and promote the development of skills and positive beliefs that enable the individual to effectively deal with problems associated with their disease[7]. ACT and ECBE have been applied to the nursing care of patients with diabetes[8], cancer[9], and other diseases[10] and have achieved good results. However, the combination of these two therapies has not been previous investigated in the treatment of CHB. This study explored the effects ACT combined with ECBE on psychological flexibility, negative emotions, and sleep quality in patients with CHB.

MATERIALS AND METHODS

Research object

A total of 129 patients with CHB treated at The First People's Hospital of Wenling between January 2021 and June 2022 were retrospectively selected. Patients were divided into two groups, depending on whether they received routine care or ACT combined with ECBE intervention.

The inclusion criteria were as follows: (1) Diagnosis of CHB according to the criteria; (2) normal vision and hearing function; (3) a complete record of baseline data (sex, age, disease course, and liver function); and (4) assessment of psychological flexibility, negative emotions, and sleep quality.

The diagnostic criteria for CHB included a positive results for both serum surface antigen and HBV DNA[11]. Additionally, liver function index alanine aminotransferase continually increased and liver histological examination showed hepatitis lesions.

The following exclusion criteria was applied: (1) Severe sleep disorders or insomnia caused by other diseases; (2) Combined heart, liver, kidney, and other organ lesions; (3) Viral hepatitis other than CHB; and (4) Malignant tumors.

According to the different nursing intervention methods applied, the patients were classified into a conventional group (routine nursing care, n = 69) and a combination group (ACT combined with ECBE, n = 60). The research concepts used are presented in Figure 1.

Related research data collection

We collected baseline patient data from the electronic medical records, including sex, age, disease course, and evaluation data of psychological flexibility, negative emotions, sleep quality, and self-care agency.

Detailed intervention methods

Routine nursing: Based on principles of nursing practice, nursing staff provided nutritional interventions, medication guidance and safety nursing, early rehabilitation training, and relevant health education. Health education for patients with CHB was delivered through one-to-one communication or distribution of educational manuals to disseminate knowledge on the causes of CHB, treatment methods, risk factors, and other aspects of the disease. Relevant psychological counseling; daily personal self-care skills in a home setting and life guidance were discussed with patients on discharge from hospital.

ACT: Acceptance perception: Medical staff provided health education using graphic publicity pages or short videos to inform patients of the pathogenesis, routine treatment options, and precautions of CHB, to help increase understanding of CHB and the ramifications of the disease.

Cognitive disengagement: Family members were guided to encourage patients to actively cooperate with drug treatment or psychotherapy and strengthen family awareness of CHB to reduce the impact of adverse events or negative emotions. Under the guidance of nutritionists, dietary management and stress reduction training was also strengthened to adjust patients' negative emotions.

Experience life: Patients were encouraged to exchange experiences with their friends to can share the burden of disease and integrate into surrounding life and work. The encouragement and support of family and patient friends enabled patients to develop a good understanding of their disease and alleviate negative emotions such as fear, anxiety, and depression. Patients were also encouraged to share their experiences and empathize with life experiences, diverting patients' attention.

Self-awareness: Through patient communication and doctor-patient communication, patient awareness of the disease was strengthened, establishing confidence in treating the disease to establish correct cognition and attitude and understanding the disease.

Values: With the support of family members and medical staff, patients established social values, adjusted their mentality, returned to society and work, and developed positive attitudes towards life.

Positive coping: Through drug treatment, psychological intervention, and moderate exercise, patients strengthened their confidence, modified negative emotions, and actively cooperated with treatment.

ECBE: Clarify themes and processes: To understand the most harmful, extensive, and high-incidence problems and in CHB care, the nursing content included identifying problem(s), expressing feelings, setting goals, and making plans.

Clarify patient needs (problem establishment): Patient's thoughts and educational needs, such as changes during illness, daily mood and reasons, family support and care, disease knowledge, support, and help were identified.

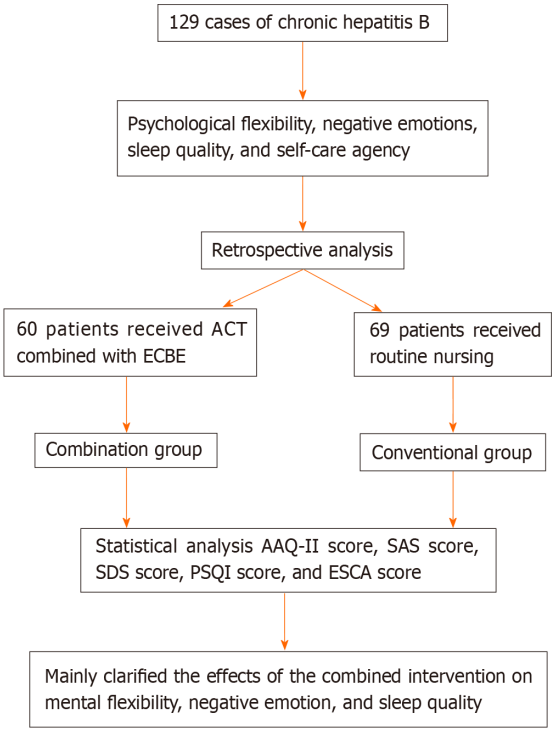
Scale assessments: Acceptance and Action Questionnaire-2nd Edition (AAQ-II), Self-Rating Anxiety Scale (SAS), Self-Rating Depression Scale (SDS), Pittsburgh Sleep Quality Index (PSQI), Exercise of Self-Care Agency Scale (ESCA), and Master of psychological flexibility, negative emotions, sleep quality, and self-care abilities scores were observed.

Goal setting Cognitive aspects: (1) CHB Education. By playing videos, issuing manuals or one-on-one communication, and conducting collective lectures, patients could fully understand the harm caused by CHB, importance of a good mentality, importance of drug treatment, and side effects; and (2) diet education. Based on the health belief model[12], a reasonable diet knowledge education plan was developed for patients to understand the importance of nutritional balance and related information. Specific information about nutritional balance for example, dietary calcium supplements (China's recommended amount of calcium is 800 mg per day), and increased fresh fruits and vegetable and protein-rich food (such as milk, poultry, fish) intake was provided. Education was delivered through videos, pictures, animations, and text.

Behavior: (1) Improved family support. Family members or spouses were included in the synchronous education program to develop basic knowledge of CHB nursing and psychological and physiological support. Family members were also instructed to create a good family atmosphere and environment, pay attention to the patients' psychological state, and provide timely counseling to reduce the negative emotions caused by loneliness and family apathy; and (2) Improve self-care. Help was provided to patients to understand the importance of self-care and prevention and treatment of common health problems in CHB. Nursing staff focused on the mental health of patients, teaching them physical and mental adjustment methods to prevent anxiety and depression.

Observation target

Psychological flexibility: Before the intervention, 3 mo after intervention, and 6 mo after, the psychological flexibility of the patients was evaluated using the AAQ-II scale[13]. The seven items were scored from 1 (never) to 7 (always) with a total score of 7-49 points. Higher scores indicated higher empirical avoidance and psychological flexibility. Cronbach's α coefficient of the scale was 0.880, indicating good reliability.



DOI: 10.5498/wjp.v13.i10.753

Figure 1 Research ideas. ACT: Acceptance and commitment therapy; ECBE: Enabling cognitive-behavioral education; AAQ-II: Action Questionnaire-2nd Edition; SAS: Self-Rating Anxiety Scale; SDS: Self-Rating Depression Scale; PSQI: Pittsburgh Sleep Quality Index; ESCA: Exercise of Self-Care Agency Scale.

Negative emotions: The SAS and SDS[14] were used to evaluate the degree of anxiety and depression before and 6 mo after the intervention. The two scales were composed of 20 items scored according to a four-level scoring method (score 1-4 points). Higher scores indicated more severe anxiety and depression.

Sleep quality: The PSQI[15] was used to evaluate sleep quality before and after the intervention. This scale included the following seven dimensions: sleep quality, sleep time, sleep time, sleep efficiency, sleep disorders, use of hypnotic drugs, and daytime dysfunction. Each dimension was scored on a scale of 0-3 points. Higher scores indicated worse sleep quality.

Self-care ability: Before and 6 mo after the intervention[16], self-care abilities, including health knowledge (14 items), self-concept (nine items), self-responsibility (eight items), self-care skills (12 items) and four other dimensions (health knowledge level, self-concept, self-responsibility, and self-care skills). The 43 items were scored using the five-level scoring method (0-4 points). Higher scores indicated better self-care ability. Cronbach's α coefficient was 0.76-0.87, indicating good internal consistency.

Statistical analysis

SPSS 20.0 [IBM SPSS Statistics software, IBM Corp (version 20.0), NY, United States] was used to analyze the data. The data are presented as mean ± SD. The *t*-test was used to compare the difference between two sets of data. One-way analysis of variance was used to compare the two groups. The Bonferroni *t*-test was used for multiple comparisons between multiple samples. Repeated-measures analysis of variance was used to compare data at different time points between groups. The number of cases and chi-square test were used to analyze the count data. A test value = 0.05 was used. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical characteristics

Baseline data such as sex, age, and course of disease were compared between the two groups. No significant differences were observed (all $P > 0.05$), indicating comparability (Table 1).

AAQ-II score

The AAQ-II score in the combination group was significantly lower than that in the conventional group. The AAQ-II scores of both groups decreased with time, with an interaction effect between group and time ($F_{\text{between-group effect}} = 8.548$; $F_{\text{time effects}} = 25.020$; $F_{\text{interaction effects}} = 52.930$; all $P < 0.001$) (Table 2).

Table 1 Basic data

Group	Gender (*n*, male/female)	Age (mean ± SD, yr)	Number of units(*n*, first visit/return visit)	Course of disease (mean ± SD, yr)		Educational level (*n*)			Child-Pugh grade	
				Course of CHB	Course of insomnia	Junior high school and below	High school	Bachelor's degree and above	Grade A	Grade B
Combination group (*n* = 60)	38/22	48.36 ± 10.25	19/41	12.25 ± 3.17	2.51 ± 0.86	15	28	17	39	21
Conventional group (*n* = 69)	41/28	49.21 ± 11.12	24/45	13.07 ± 3.58	2.22 ± 0.88	18	31	20	42	27
χ^2/t	0.207	0.449	0.140	1.368	1.887	0.041			0.234	
P	0.649	0.654	0.708	0.174	0.061	0.980			0.628	

CHB: Chronic hepatitis B.

Table 2 Action Questionnaire-2nd Edition scores

Time	Combination group (*n* = 60)	Conventional group (*n* = 69)	*t*	*P*
Before intervention	39.27 ± 6.22	38.72 ± 5.69	0.524	0.601
3 mo after intervention	31.26 ± 7.15	36.28 ± 6.67	4.123	< 0.001
6 mo after intervention	28.11 ± 6.32	33.51 ± 6.63	4.715	< 0.001
F	45.920	11.640	–	–
P	< 0.001	< 0.001	–	–

Multiple comparison results of PSQI scores at each time point between the conventional and combination groups showed significant differences in AAQ-II scores between the two time points in each group (all $P < 0.05$) (Table 3).

SAS and SDS score

The SAS scores of the combination group were 49.25 ± 5.35 and 37.56 ± 6.11, before and after intervention, respectively; $t = 11.150$, $P < 0.001$. The SDS scores were 53.58 ± 7.12 and 41.56 ± 5.38, before and after intervention, respectively; $t = 10.430$, $P < 0.001$.

The SAS scores of the conventional group were as follows: before intervention (48.68 ± 5.52), and after intervention (43.27 ± 5.79), $t = 5.618$, $P < 0.001$. The SDS scores were, before intervention (54.03 ± 6.69), after intervention (49.20 ± 6.69), $t = 4.241$, $P < 0.001$.

In comparison with the conventional group, the SAS ($t = 5.445$) and SDS ($t = 7.076$) scores of the combination group were lower after the intervention (both $P < 0.001$) (Figure 2).

PSQI score

The post-intervention scores for sleep quality, fall sleep time, sleep time, sleep efficiency, sleep disorders, use of hypnotic drugs, daytime dysfunction, and other dimensions in the combination group and the conventional group were lower than the corresponding pre-intervention scores (all $P < 0.001$). The scores for each dimension in the combination group were lower than those in the conventional group ($P < 0.05$) (Table 4).

ESCA score

The pre-intervention scores of health knowledge level, self-concept, self-responsibility, and self-care skills in the combination group were: 33.48 ± 5.36, 20.16 ± 3.25, 21.58 ± 4.39, and 31.25 ± 5.54 points. The same pre-intervention scores in the conventional group were: 34.02 ± 4.54, 20.67 ± 3.51, 21.24 ± 4.13, and 30.86 ± 6.62 points.

After the intervention, the scores of the above dimensions in the combination group were 51.27 ± 3.39, 31.25 ± 4.42, 29.17 ± 3.08, and 43.12 ± 4.24 points. The scores in the conventional group were 45.36 ± 5.73, 26.17 ± 5.24, 25.68 ± 4.42, and 35.56 ± 5.67 points.

Scores in both groups were higher after the interventions (all $P < 0.001$). The scores for each dimension in the combined group were higher than those in the conventional group (*t*: 6.994, 5.902, 5.128, and 8.470; all $P < 0.001$) (Figure 3).

Table 3 Multiple comparisons of Pittsburgh Sleep Quality Index scores at different time points (Bonferroni)

Group	(I) Time	(J) Time	Mean difference (I-J)	Standard error	*P*	95%CI	
						Lower limit	Upper limit
Combination group							
	Before intervention	3 mo after intervention	8.017	1.198	0.001	5.121	10.913
		6 mo after intervention	11.167	1.198	0.001	8.271	14.063
	3 mo after intervention	before intervention	-8.017	1.198	□0.001	-10.913	-5.121
		6 mo after intervention	3.150	1.198	0.028	0.254	6.046
	6 mo after intervention	Before intervention	-11.167	1.198	0.001	-14.063	-8.271
		3 mo after intervention	-3.150	1.198	0.028	-6.046	-0.254
Conventional group							
	Before intervention	3 mo after intervention	2.449	1.080	0.073	-0.157	5.056
		6 mo after intervention	5.217	1.080	0.001	2.611	7.824
	3 mo after intervention	Before intervention	-2.449	1.080	0.073	-5.056	0.157
		6 mo after intervention	2.768	1.080	0.033	0.162	5.375
	6 mo after intervention	Before intervention	-5.217	1.080	0.000	-7.824	-2.611
		3 mo after intervention	-2.768	1.080	0.033	-5.375	-0.162

95%CI: 95% confidence interval.

Table 4 Pittsburgh Sleep Quality Index score

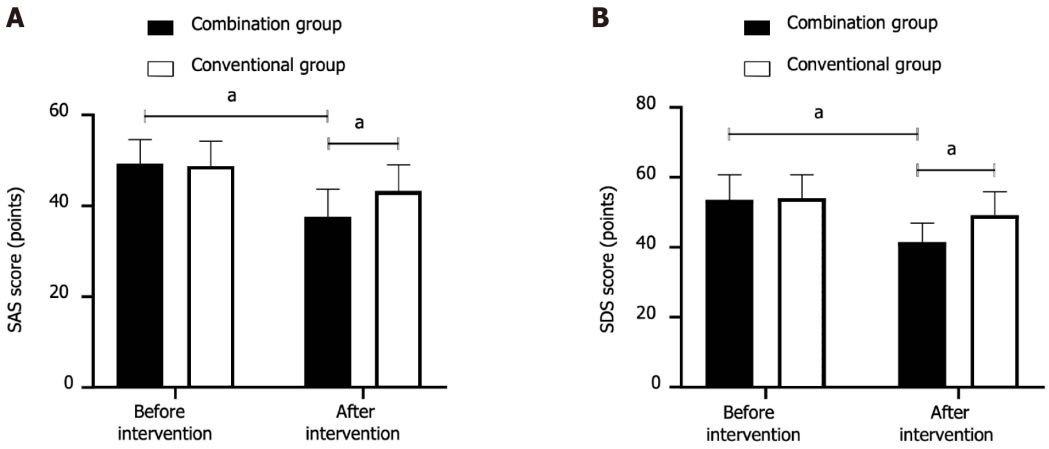
Group and time	Statistics	Sleep quality	Fall sleep time	Sleep time	Sleep efficiency	Sleep disorder	Hypnotic drugs	Daytime dysfunction
Combination group (*n* = 60)								
Before intervention		2.35 ± 0.65	2.43 ± 0.66	2.52 ± 0.61	2.33 ± 0.58	1.98 ± 0.52	2.05 ± 0.52	2.18 ± 0.54
After intervention		0.82 ± 0.42[1]	0.85 ± 0.44[1]	0.78 ± 0.48[1]	0.75 ± 0.46[1]	0.77 ± 0.52[1]	0.86 ± 0.36[1]	1.16 ± 0.31[1]
	t	15.310	15.430	17.360	16.530	12.750	14.570	12.690
	P	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Conventional group (*n* = 69)								
Before intervention		2.26 ± 0.57	2.35 ± 0.62	2.49 ± 0.64	2.29 ± 0.62	1.95 ± 0.47	2.01 ± 0.55	2.15 ± 0.56
After intervention		1.06 ± 0.35	1.06 ± 0.53	0.97 ± 0.58	1.05 ± 0.32	1.02 ± 0.37	1.02 ± 0.22	1.41 ± 0.58
	t	14.900	13.140	14.620	14.760	12.910	13.880	7.624
	P	0.001	0.001	0.001	0.001	0.001	0.001	0.001

[1]The index compared with normal group, $P < 0.05$.

DISCUSSION

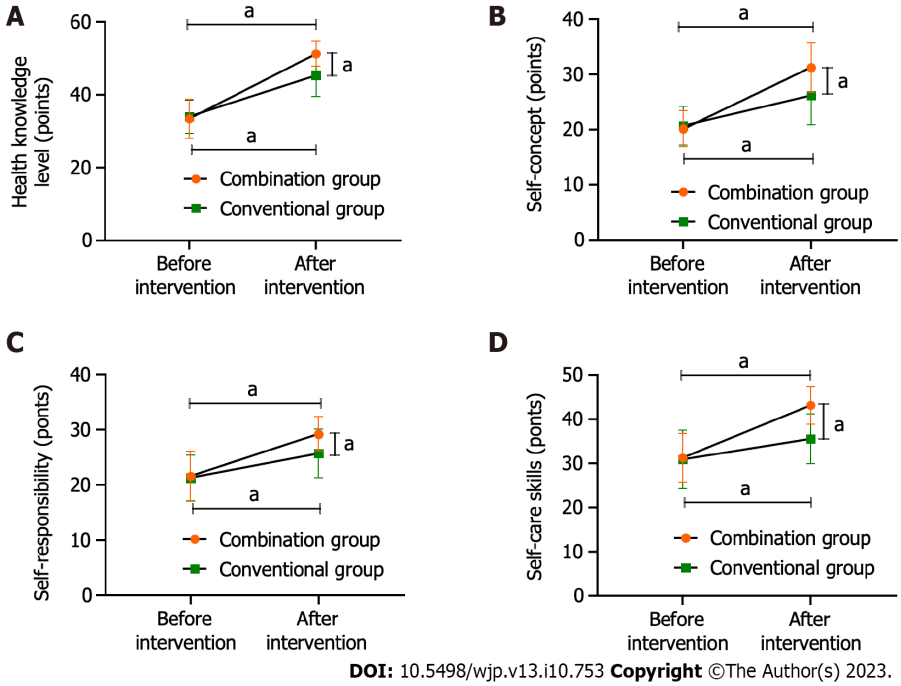
As CHB easily progresses to cirrhosis or liver cancer[17], there are considerable changes in the psychological, emotional, and living conditions of patients; effective nursing interventions are needed. Insomnia, a decline in sleep quality, is a common symptom in patients with CHB. primarily caused by an increase in endotoxin levels, unbalanced hormone secretion, and increased psychological burden which negatively impacts quality of life.

We found that the AAQ-II scores of both groups were lower after the intervention, and the combined group scores were lower, indicating that ACT combined with ECBE could reduce patient empirical avoidance behavior and enhance psychological flexibility. This is consistent with previous studies on adult patients with chronic pain [18]. Psychological



DOI: 10.5498/wjp.v13.i10.753 **Copyright** ©The Author(s) 2023.

Figure 2 Self-Rating Anxiety Scale score and Self-Rating Depression Scale score. A: The post-intervention Self-Rating Anxiety Scale score (t = 5.445); B: Self-Rating Depression Scale score (t = 7.076) in the combination group were lower than those in the conventional group (both P < 0.001). ^{a}P < 0.05. SAS: Self-Rating Anxiety Scale; SDS: Self-Rating Depression Scale.



DOI: 10.5498/wjp.v13.i10.753 **Copyright** ©The Author(s) 2023.

Figure 3 Exercise of Self-Care Agency Scale score. A: Health knowledge level; B: Self-concept; C: Self-responsibility; D: Self-care skills. The post-interventions scores of each dimension in the combined group were lower than those in the combination group. ^{a}P < 0.05.

flexibility refers to psychological and behavioral adaptations to changing situations during interactions between individuals and the environment[19], a protective factor for mental health[20].

CHB is characterized by progression to cirrhosis or liver cancer and a heavy economic burden, which can easily cause negative emotions and need for patients to escape and control their worries. ACT guides and encourages patients to accept all negative and positive experiences with an open and optimistic attitude. After ACT intervention, patients may no longer resist, control, or evade CHB but observe and accept it objectively. Additionally, patients with CHB can cope more effectively with the stimulation of surrounding environmental factors and take positive actions to reduce psychological pressure, anxiety and depression.

ECBE focuses on four aspects: Establishing problems, expressing emotions, setting goals, and formulating plans. It focuses on patients' psychological changes, unhealthy emotions, and sleep quality and adopts targeted interventions and supervision. ECBE also encourages patients to gradually reduce avoidance behaviours, anxiety, depression, insomnia, and other problems, improves psychological flexibility, and relieves negative emotions. Previous research[21] has demonstrated that psychological flexibility is closely related to anxiety and depression. According to the results of this study, the SAS and SDS scores of patients receiving ACT combined with ECBE nursing were significantly reduced, indicating that anxiety and depression were significantly alleviated, highlighting the effectiveness of the combined

intervention in relieving negative emotions in patients with CHB.

In this study, the scores of the PSQI were lower and ESCA scores were higher in the combination group, demonstrating that ACT combined with ECBE also played a significant role in regulating sleep quality and patient self-care ability. The sleep quality of patients with CHB is typically much lower[22]. For ACT combined with ECBE, nursing staff developed patient knowledge of CHB and helped to correct misunderstandings about the disease, reducing excessive worrying and negative emotions, and improving sleep quality.

Moreover, the low self-care ability of patients with CHB has been demonstrated[23]. Improving self-care ability is the final step in the implementation of ECBE. Nursing staff guide patients to understand the importance of self-care and the prevention and treatment of common health problems associated with CHB. They also promote patient self-care ability, an important component that is lacking in routine nursing. Furthermore, providing effective relief from negative emotions encourages patients to actively cooperate with treatment and related auxiliary interventions, accept guidance and transmission of nursing knowledge; it also enhances patient understanding of the disease and nursing measures, indirectly improving self-care abilities[24,25].

Some limitations should be noted. First, this was a single-center study; therefore, the application of these findings to those in different centers needs to be approached with caution and the results need to be corroborated in future studies. Second, this was a retrospective study, and the data may be subject to selection, information, and confounding biases. Therefore, prospective randomized controlled studies are required to obtain more accurate clinical data and generate more robust evidence.

CONCLUSION

The combination of ACT and ECBE in patients with CHB can improve psychological flexibility and sleep quality, alleviate negative emotions, and improve self-care abilities.

ARTICLE HIGHLIGHTS

Research background

Chronic hepatitis B (CHB) is an infectious, progressive disease. Patients experience a heavy psychological burden and severe insomnia symptoms.

Research motivation

Patients with CHB urgently require effective nursing interventions to alleviate mental flexibility, negative emotions, and sleep quality problems.

Research objectives

To analyze the effects of acceptance and commitment therapy (ACT) combined with enabling cognitive-behavioral education (ECBE) on mental flexibility, negative emotions, and sleep quality in CHB patients.

Research methods

We retrospectively analyzed the clinical data of 129 patients with CHB and observed changes and differences in Acceptance and Action Questionnaire-2nd edition (AAQ-II), Self-Rating Anxiety Scale (SAS), Self-Rating Depression Scale (SDS), Pittsburgh Sleep Quality Index (PSQI), and Exercise of Self-Case Agency Scale (ESCA) scores after routine nursing and ACT combined with ECBE intervention.

Research results

Compared to patients receiving conventional care, the AAQ-II, SAS, SDS, and PSQI scores in patients receiving ACT combined with ECBE were lower and ESCA scores were higher.

Research conclusions

ACT combined with ECBE is effective for CHB patients in China and overcomes the problem of nursing defects in CHB.

Research perspectives

We observed the mental flexibility, negative emotions, and sleep quality of patients with CHB according to two different nursing interventions: routine nursing and ACT combined with ECBE.

FOOTNOTES

Author contributions: Zheng Y designed and performed the study and wrote the paper; Xia CX designed the study and supervised the report; Wang XW designed the study and contributed to the analysis.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of The First People's Hospital of Wenling [Approval No. KY-2023-1032-01].

Informed consent statement: This was a retrospective study and the requirement for informed consent was waived.

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

Data sharing statement: Research data can be obtained from the corresponding author upon reasonable request.

Country/Territory of origin: China

ORCID number: Ying Zheng 0000-0003-0794-2351; Xiao-Wei Wang 0009-0001-1681-969X; Chen-Xi Xia 0009-0007-8098-6752.

S-Editor: Lin C
L-Editor: A
P-Editor: Zhang XD

REFERENCES

1 **GBD 2017 Cirrhosis Collaborators**. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol* 2020; **5**: 245-266 [PMID: 31981519 DOI: 10.1016/S2468-1253(19)30349-8]
2 **Yao Y**, Zhang HJ, Wang DH. Mediating effect of psychological distress on perceived stress on sleep quality in elderly patients with chronic viral hepatitis B. *Zhongguo Laonianxue Zazhi* 2019; **39**: 5627-5630 [DOI: 10.3969/j.issn.1005-9202.2019.22.074]
3 **Loureiro D**, Tout I, Narguet S, Bed CM, Roinard M, Sleiman A, Boyer N, Pons-Kerjean N, Castelnau C, Giuly N, Tonui D, Soumelis V, El Benna J, Soussan P, Moreau R, Paradis V, Mansouri A, Asselah T. Mitochondrial stress in advanced fibrosis and cirrhosis associated with chronic hepatitis B, chronic hepatitis C, or nonalcoholic steatohepatitis. *Hepatology* 2023; **77**: 1348-1365 [PMID: 35971873 DOI: 10.1002/hep.32731]
4 **Li JR**, Pan JM, Liang ML, Meng HX, Meng YX. Study on the Bedside Education Video Application during the Perioperative Period of Percutaneous Nephrolithotomy. *Shanghai Huli* 2019; **19**: 13-16 [DOI: 10.3969/j.issn.1009-8399.2019.10.004]
5 **Tomar A**, Bhardwaj A, Choudhary A, Bhattacharyya D. Association of Obstructive Sleep Apnea with Nocturnal Hypoxemia in Metabolic-Associated Fatty Liver Disease Patients: A Cross-sectional Analysis of Record-based Data. *J Family Med Prim Care* 2021; **10**: 3105-3110 [PMID: 34660454 DOI: 10.4103/jfmpc.jfmpc_412_21]
6 **Chapoutot M**, Peter-Derex L, Bastuji H, Leslie W, Schoendorff B, Heinzer R, Siclari F, Nicolas A, Lemoine P, Higgins S, Bourgeois A, Vallet GT, Anders R, Ounnoughene M, Spencer J, Meloni F, Putois B. Cognitive Behavioral Therapy and Acceptance and Commitment Therapy for the Discontinuation of Long-Term Benzodiazepine Use in Insomnia and Anxiety Disorders. *Int J Environ Res Public Health* 2021; **18** [PMID: 34639523 DOI: 10.3390/ijerph181910222]
7 **Nolan DR**, Gupta R, Huber CG, Schneeberger AR. An Effective Treatment for Tinnitus and Hyperacusis Based on Cognitive Behavioral Therapy in an Inpatient Setting: A 10-Year Retrospective Outcome Analysis. *Front Psychiatry* 2020; **11**: 25 [PMID: 32116842 DOI: 10.3389/fpsyt.2020.00025]
8 **Sakamoto R**, Ohtake Y, Kataoka Y, Matsuda Y, Hata T, Otonari J, Yamane A, Matsuoka H, Yoshiuchi K. Efficacy of acceptance and commitment therapy for people with type 2 diabetes: Systematic review and meta-analysis. *J Diabetes Investig* 2022; **13**: 262-270 [PMID: 34486816 DOI: 10.1111/jdi.13658]
9 **Zhang Z**, Leong Bin Abdullah MFI, Shari NI, Lu P. Acceptance and commitment therapy versus mindfulness-based stress reduction for newly diagnosed head and neck cancer patients: A randomized controlled trial assessing efficacy for positive psychology, depression, anxiety, and quality of life. *PLoS One* 2022; **17**: e0267887 [PMID: 35536828 DOI: 10.1371/journal.pone.0267887]
10 **Liu SM**, Ma YZ, Wang C, Yang QJ. Application of Acceptance Commitment Therapy in Patients after Amputation. *Qilu Huli Zazhi* 2022; **28**: 24-27
11 **Shi YW**, Yang RX, Fan JG. Chronic hepatitis B infection with concomitant hepatic steatosis: Current evidence and opinion. *World J Gastroenterol* 2021; **27**: 3971-3983 [PMID: 34326608 DOI: 10.3748/wjg.v27.i26.3971]
12 **Zhao YC**, Zhao M, Song S. Online Health Information Seeking Among Patients With Chronic Conditions: Integrating the Health Belief Model and Social Support Theory. *J Med Internet Res* 2022; **24**: e42447 [PMID: 36322124 DOI: 10.2196/42447]
13 **Zarvijani SAH**, Moghaddam LF, Parchebafieh S. Acceptance and commitment therapy on perceived stress and psychological flexibility of psychiatric nurses: a randomized control trial. *BMC Nurs* 2021; **20**: 239 [PMID: 34844575 DOI: 10.1186/s12912-021-00763-4]
14 **Zhang JW**, Wang Y, Shan HH, Duan JY, Yu J. The Application of Focused Care Model in the Management of Hepatitis B Patients in a Tertiary Care Hospital and the Impact on Patients' Quality of Life. *Comput Math Methods Med* 2022; **2022**: 7770955 [PMID: 36132545 DOI: 10.1155/2022/7770955]
15 **Yi CH**, Bair MJ, Wang JH, Wong MW, Liu TT, Lei WY, Liang SW, Lin L, Hung JS, Huang JF, Hsu YC, Chen CL. Improvement of patient-reported outcomes in patients achieving sustained virologic response with direct-acting antivirals for hepatitis C virus infection. *J Microbiol Immunol Infect* 2022; **55**: 643-650 [PMID: 35637143 DOI: 10.1016/j.jmii.2022.04.011]
16 **Cho H**, Park E. Canonical Correlation Between Self-Care Agency and Health-Related Self-Efficacy with Chronic Viral Hepatitis Patients.

Osong Public Health Res Perspect 2019; **10**: 281-288 [PMID: 31673489 DOI: 10.24171/j.phrp.2019.10.5.04]

17 **Ji D**, Chen Y, Bi J, Shang Q, Liu H, Wang JB, Tan L, Wang J, Li Q, Long Q, Song L, Jiang L, Xiao G, Yu Z, Chen L, Wang X, Chen D, Li Z, Dong Z, Yang Y. Entecavir plus Biejia-Ruangan compound reduces the risk of hepatocellular carcinoma in Chinese patients with chronic hepatitis B. *J Hepatol* 2022; **77**: 1515-1524 [PMID: 35985545 DOI: 10.1016/j.jhep.2022.07.018]

18 **Godfrey E**, Wileman V, Galea Holmes M, McCracken LM, Norton S, Moss-Morris R, Noonan S, Barcellona M, Critchley D. Physical Therapy Informed by Acceptance and Commitment Therapy (PACT) Versus Usual Care Physical Therapy for Adults With Chronic Low Back Pain: A Randomized Controlled Trial. *J Pain* 2020; **21**: 71-81 [PMID: 31173921 DOI: 10.1016/j.jpain.2019.05.012]

19 **Dai CH**, Wang X, Huang QH, Zeng XM, Xu PX. Effect of acceptance and commitment therapy on psychological flexibility and posttraumatic growth in patients with stroke. *Hushi Jinxiu Zazhi* 2020; **35**: 592-595 [DOI: 10.16821/j.cnki.hsjx.2020.07.004]

20 **Li J**, Zhao N, Zhang HY, Yang H, Yang J. Analysis of the mental health status and impact factors of middle-aged and elderly patients with chronic disea-ses in a rural area of Beijing. *Zhongguo Jiankang Jiaoyu* 2022; **38**: 322-327 [DOI: 10.16168/j.cnki.issn.1002-9982.2022.04.008]

21 **Davis AK**, Barrett FS, Griffiths RR. Psychological flexibility mediates the relations between acute psychedelic effects and subjective decreases in depression and anxiety. *J Contextual Behav Sci* 2020; **15**: 39-45 [PMID: 32864325 DOI: 10.1016/j.jcbs.2019.11.004]

22 **Huang X**, Zhang H, Qu C, Liu Y, Bian C, Xu Y. Depression and Insomnia Are Closely Associated with Thyroid Hormone Levels in Chronic Hepatitis B. *Med Sci Monit* 2019; **25**: 2672-2678 [PMID: 30973843 DOI: 10.12659/MSM.914444]

23 **Wu DX**, Wu Y, Li YH, Wang ZY, Li Y. Correlation analysis of self-care ability, self-efficacy and social support in outpatient patients with chronic hepatitis B. *Beijing Yixue* 2022; **44**: 188-190 [DOI: 10.15932/j.0253-9713.2022.02.023]

24 **Zhou DD**. Effect of empathic intervention on negative emotions and self-care ability in patients with decompensated hepatitis B cirrhosis. *Yixue Linchuang Yanjiu* 2019; **36**: 2484-2486 [DOI: 10.3969/j.issn.1671-7171.2019.12.071]

25 **Akbulut S**, Ozer A, Saritas H, Yilmaz S. Factors affecting anxiety, depression, and self-care ability in patients who have undergone liver transplantation. *World J Gastroenterol* 2021; **27**: 6967-6984 [PMID: 34790018 DOI: 10.3748/wjg.v27.i40.6967]

World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatry 2023 October 19; 13(10): 763-771

DOI: 10.5498/wjp.v13.i10.763

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Retrospective Study

Construction and validation of a personalized prediction model for postpartum anxiety in pregnant women with preeclampsia

Le-Jing Lin, Hai-Xian Zhou, Zhi-Yun Ye, Qi Zhang, Shu Chen

Specialty type: Psychiatry

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Kolla NJ, Canada; Leenen FH, Canada

Received: August 8, 2023
Peer-review started: August 8, 2023
First decision: August 24, 2023
Revised: September 1, 2023
Accepted: September 20, 2023
Article in press: September 20, 2023
Published online: October 19, 2023

Le-Jing Lin, Hai-Xian Zhou, Zhi-Yun Ye, Qi Zhang, Department of Obstetrics and Gynecology, Wenzhou Hospital of Integrated Traditional Chinese and Western Medicine, Wenzhou 325000, Zhejiang Province, China

Shu Chen, Department of Gynecology, Wenzhou Traditional Chinese Medicine Hospital, Wenzhou 325000, Zhejiang Province, China

Corresponding author: Shu Chen, MM, Attending Doctor, Department of Gynecology, Wenzhou Traditional Chinese Medicine Hospital, No. 9 Jiaowei Road, Lucheng District, Wenzhou 325000, Zhejiang Province, China. wzszyychenshu@126.com

Abstract

BACKGROUND

Preeclampsia is a pregnancy-specific multi-system disease with multi-factor and multi-mechanism characteristics. The cure for preeclampsia is to terminate the pregnancy and deliver the placenta. However, it will reduce the perinatal survival rate, prolong the pregnancy cycle, and increase the incidence of maternal complications. With relaxation of the birth policy, the number of elderly pregnant women has increased significantly, and the prevalence rate of preeclampsia has increased. Inappropriate treatment can seriously affect the normal postpartum life of pregnant women. Studies have shown that postpartum anxiety in women with preeclampsia can affect physical and mental health, as well as infant growth and development.

AIM

To analyze the factors influencing preeclampsia in pregnant women complicated with postpartum anxiety, and to construct a personalized predictive model.

METHODS

We retrospectively studied 528 pregnant women with preeclampsia who delivered in Wenzhou Hospital of Integrated Traditional Chinese and Western Medicine between January 2018 and December 2021. Their basic data were collected, and various physiological and biochemical indicators were obtained by laboratory examination. The self-rating anxiety scale was used to determine whether the women had postpartum anxiety 42 d after delivery. The independent factors influ-encing postpartum anxiety in early pregnant women with eclampsia were analyzed with multifactor logistic regression and a predictive model was constructed. The Hosmer-Lemeshow test and receiver operating characteristic (ROC) curve

were used to evaluate the calibration and discrimination of the predictive model. Eighty pregnant women with preeclampsia admitted to our hospital from January 2022 to May 2022 were retrospectively selected to verify the prediction model.

RESULTS

We excluded 46 of the 528 pregnant women with preeclampsia because of loss to follow-up and adverse outcomes. A total of 482 cases completed the assessment of postpartum anxiety 42 d after delivery, and 126 (26.14%) had postpartum anxiety. Bad marital relationship, gender discrimination in family members, hematocrit (Hct), estradiol (E2) hormone and interleukin (IL)-6 were independent risk factors for postpartum anxiety in pregnant women with preeclampsia ($P < 0.05$). Prediction model: Logit (P) = 0.880 × marital relationship + 0.870 × gender discrimination of family members + 0.130 × Hct - 0.044 × E2 + 0.286 × IL-6 - 21.420. The area under the ROC curve of the model was 0.943 (95% confidence interval: 0.919-0.966). The threshold of the model was -1.507 according to the maximum Youden index (0.757), the corresponding sensitivity was 84.90%, and the specificity was 90.70%. Hosmer-Lemeshow $\chi^2 = 5.900$, $P = 0.658$. The sensitivity, specificity and accuracy of the model were 81.82%, 84.48% and 83.75%, respectively.

CONCLUSION

Poor marital relationship, family gender discrimination, Hct, IL-6 and E2 are the influencing factors of postpartum anxiety in preeclampsia women. The constructed prediction model has high sensitivity and specificity.

Key Words: Preeclampsia; Postpartum anxiety; Risk factors; Predictive model

Core Tip: Preeclampsia is a progressive multisystem disease during pregnancy, characterized by new hypertension and proteinuria after 20 wk of pregnancy, and the condition develops continuously, which has a serious effect on the health of the mother and child. We analyzed the biochemical indicators of 528 pregnant women with preeclampsia and the independent factors influencing postpartum anxiety, and constructed a predictive model, with high clinical value.

Citation: Lin LJ, Zhou HX, Ye ZY, Zhang Q, Chen S. Construction and validation of a personalized prediction model for postpartum anxiety in pregnant women with preeclampsia. *World J Psychiatry* 2023; 13(10): 763-771
URL: https://www.wjgnet.com/2220-3206/full/v13/i10/763.htm
DOI: https://dx.doi.org/10.5498/wjp.v13.i10.763

INTRODUCTION

The incidence of preeclampsia can reach 8%[1], and studies have found that women with preeclampsia are more likely to suffer from postpartum anxiety[2-4], with an incidence of up to 20%[5]. Postpartum anxiety can aggravate maternal comorbidities, resulting in poor treatment compliance. Postpartum anxiety has short- or long-term adverse effects on maternal physical and mental health, as well as infant growth and development, and may lead to adverse events such as maternal drug abuse, suicide, and even infant injury[6,7]. Therefore, if we can predict the risk of postpartum anxiety in women with preeclampsia, targeted management and early intervention could avoid postpartum anxiety or improve postpartum psychological status. Current research focuses on the pregnancy outcome of women with preeclampsia, and few studies involve postpartum anxiety. In this study, we retrospectively studied 528 pregnant women with preeclampsia who delivered at our hospital between January 1, 2018 and December 31, 2021. The risk factors for preeclampsia in pregnant women complicated with postpartum anxiety were analyzed, and a predictive model was constructed to provide clinicians with an effective and practical risk assessment tool.

MATERIALS AND METHODS

General data

A total of 528 pregnant women with preeclampsia who delivered at Wenzhou Hospital of Integrated Traditional Chinese and Western Medicine Jianka between January 2018 and December 2021 were retrospectively selected. Inclusion criteria were: (1) Pre-eclampsia was diagnosed according to the relevant standards of obstetrics and gynecology[8]; (2) Conception occurred naturally, the fetus was normal, and the pregnancy was singleton; (3) No cognitive impairment or history of mental illness, and normal communication; and (4) Age > 18 years and living in the local area. Exclusion criteria were: (1) Prenatal anxiety; (2) Medical history of encephalopathy; (3) Severe heart, liver, kidney and other organ diseases; (4) Concurrent diseases of the immune system, nervous system, severe cardiovascular disease and malignant

tumors; (5) Adverse pregnancy outcomes (including arrhythmia, fetal growth restriction, intrauterine fetal death, neonatal death, severe neonatal asphyxia, neonatal defects and serious postpartum complications); and (6) Patients who had to withdraw from the study due to an emergency.

The predictive model was clinically verified by retrospectively selecting 80 pregnant women with preeclampsia who met the above criteria in Wenzhou Hospital of Integrated Traditional Chinese and Western Medicine between January and May 2022. Sample size calculation: (1) According to references, preeclampsia and the incidence of postpartum anxiety at about 20%, this study is expected to end in the multi-factor regression model analysis of 10 variables, according to the average number of events per predictor variable (EPV) sample size calculation, take EPV = 10, sample size = into variables × EPV/incidence rate = 10 × 10/20% = 500 cases, according to the inclusion and exclusion criteria and considering adverse outcomes, the sample size was 528; and (2) The sample size of the external validation was generally 1/4 to 1/2 of the modeling set, and the sample size = 1/4 of the modeling set, 120 cases (482/4) should be included. However, due to the influence of the external environment such as the epidemic situation and the actual situation of our hospital, 80 cases of preeclampsia pregnant women were finally included.

Data collection

General information: Age, educational level and occupation of pregnant women; occupation and educational level of spouse; family economic status; emotional status of husband and wife (self-rated as good or bad); whether pregnancy was planned; whether there was experience of raising children; whether there was gender discrimination on the part of oneself or family members (expecting to have male or female baby); whether there was regular maternity examination; and history of adverse pregnancy outcomes. Laboratory indicators included: Routine blood tests [including hematocrit (Hct), hemoglobin, and platelet count]; estrogen [including estradiol (E2)]; liver function (including alanine aminotransferase and aspartate aminotransferase); renal function (including creatinine and urea nitrogen); coagulation indicators (including fibrinogen and prothrombin time); and other biochemical indicators [including triglycerides and interleukin (IL)-6].

Postpartum anxiety criteria

The self-rating anxiety scale (SAS) was used to determine whether the parturients who completed the study had postpartum anxiety at 42 d postpartum. The SAS consisted of 20 items, with each item scoring 1 (none or few), 2 (sometimes yes), 3 (most of the time yes), and 4 (most of the time yes). In accordance with the Chinese standard, SAS score ≥ 50 indicated the presence of postpartum anxiety; a score of 50-59 indicated mild anxiety, 60-69 moderate anxiety, and ≥ 70 severe anxiety.

Statistical analysis

The data obtained were processed by SPSS 27.0. Measurement data and numerical data were expressed as mean ± SD and percentage, respectively, using t and χ^2 tests, respectively. The independent factors influencing postpartum anxiety in pregnant women with preeclampsia were analyzed using multifactor logistic regression and a predictive model was constructed. The Hosmer-Lemeshow test and receiver operating characteristic (ROC) curve were used to evaluate the calibration and discrimination of the predictive model. $P < 0.05$ indicated a significant difference.

RESULTS

Comparison of baseline data of pregnant women with preeclampsia

We excluded 46 of 528 pregnant women with preeclampsia because of loss to follow-up and adverse outcomes, and 482 women completed the anxiety assessment 42 d after delivery. Among them, 126 women (26.14%) experienced postpartum anxiety. The analysis of baseline data of 482 pregnant women with preeclampsia showed that marital relationship, gender discrimination of family members, Hct, E2 and serum IL-6 levels were factors potentially influencing postpartum anxiety in pregnant women with preeclampsia ($P < 0.05$) (Table 1).

Multifactor logistics regression analysis of pregnant women with preeclampsia complicated with postpartum anxiety

The significant factors above were used as covariates marital relationship (0 = good, 1 = bad), gender discrimination among family members (0 = none, 1 = yes). Concurrent postpartum anxiety was used as the dependent variable (0 = none, 1 = yes), and multifactor logistic regression analysis was performed. Bad marital relationship, gender discrimination among family members, Hct, E2 and IL-6 were independent risk factors for postpartum anxiety in pregnant women with preeclampsia ($P < 0.05$) (Table 2).

Construction and validation of predictive model for pregnant women with preeclampsia complicated with postpartum anxiety

According to the multivariate logistic regression model, a predictive model of postpartum anxiety in pregnant women with preeclampsia was constructed: Logit(P) = 0.880 × conjugal affection + 0.871 × gender discrimination in family members + 0.130 × Hct - 0.044 × E2 + 0.286 × IL-6 - 21.420. The ROC curve was drawn to evaluate the discrimination of the predictive model. The area under the ROC curve was 0.943 (95% confidence interval: 0.919-0.966). The threshold of the model was -1.507 according to the most approximate maximum Youden index (0.757), and the corresponding sensitivity and specificity were 0.849 and 0.907, respectively (Figure 1). The goodness-of-fit test was used to evaluate the

Table 1 Comparison of baseline data of pregnant women with preeclampsia, *n* (%)

Variable	Postpartum anxiety (*n* = 126)	No postpartum anxiety (*n* = 356)	t/χ^2	*P* value
Age (mean ± SD)	31.80 ± 3.99	32.04 ± 4.09	0.491	0.624
Degree of education			1.853	0.396
Junior high school and below	31 (24.60)	70 (19.66)		
Senior high school (technical secondary school)	61 (48.41)	172 (48.31)		
College (higher vocational) or above	34 (26.98)	114 (32.02)		
Occupation			5.433	0.143
Unemployed	25 (19.84)	50 (14.04)		
Workers and peasants	43 (34.13)	150 (42.13)		
Public official	19 (15.08)	37 (10.39)		
Other	39 (30.95)	119 (33.43)		
Per capita monthly household income			4.491	0.106
< 2500 RMB yuan	22 (17.46)	68 (19.10)		
2500-5000 RMB yuan	65 (51.59)	146 (41.01)		
> 5000 RMB yuan	39 (30.95)	142 (39.89)		
Spousal occupation			3.390	0.335
Unemployed	13 (10.32)	20 (5.62)		
Workers and peasants	59 (46.83)	181 (50.83)		
Public official	21 (16.67)	57 (16.01)		
Other	33 (26.19)	98 (27.53)		
Education level of spouse			3.994	0.136
Junior high school and below	19 (15.08)	40 (11.24)		
Senior high school (technical secondary school)	58 (46.03)	200 (56.18)		
College (higher vocational) or above	49 (38.89)	116 (32.58)		
Marital relationship			37.665	< 0.001
Good	39 (30.95)	223 (62.64)		
Bad	87 (69.05)	133 (37.36)		
Whether it was a planned pregnancy			1.338	0.247
Yes	80 (63.49)	246 (69.10)		
No	46 (36.51)	110 (30.90)		
Have any experience raising children			0.253	0.615
Yes	38 (30.16)	99 (27.81)		
No	88 (69.84)	257 (72.19)		
Whether the pregnant woman herself has gender discrimination			0.471	0.493
Yes	28 (22.22)	90 (25.28)		
No	98 (77.78)	266 (74.72)		
Gender discrimination among family members			24.318	< 0.001
Yes	86 (68.25)	152 (42.70)		
No	40 (31.75)	204 (57.30)		
Whether regular birth inspection			1.846	0.174

Yes	84 (66.67)	260 (73.03)		
No	42 (33.33)	96 (26.97)		
History of adverse pregnancy outcomes			0.256	0.613
Yes	30 (23.81)	77 (21.63)		
No	96 (76.19)	279 (78.37)		
Systolic blood pressure (mean ± SD, mmHg)	149.57 ± 7.3	149.50 ± 8.08	-0.087	0.930
Diastolic blood pressure (mean ± SD, mmHg)	100.37 ± 5.97	99.62 ± 6.70	-1.113	0.266
Hemoglobin (mean ± SD, g/L)	108.47 ± 25.25	112.90 ± 30.02	1.700	0.090
Hct (mean ± SD, %)	63.16 ± 8.49	47.23 ± 6.18	-22.421	< 0.001
Platelets (mean ± SD, × 10^9/L)	137.72 ± 33.06	141.53 ± 32.63	1.121	0.263
Fibrinogen (mean ± SD, g/L)	4.38 ± 1.03	4.59 ± 1.11	1.749	0.081
Prothrombin time (mean ± SD, s)	10.96 ± 3.04	11.27 ± 3.01	0.991	0.322
Creatinine (mean ± SD, mmol/L)	60.64 ± 18.51	58.91 ± 16.86	-0.963	0.336
Urea nitrogen (mean ± SD, mmol/L)	4.16 ± 1.09	3.99 ± 0.97	-1.597	0.111
Alanine transaminase (mean ± SD, U/L)	27.21 ± 7.12	26.70 ± 7.23	-0.685	0.494
Aspartate aminotransferase (mean ± SD, U/L)	29.85 ± 9.05	28.82 ± 9.31	-1.071	0.285
Triglyceride (mean ± SD, mmol/L)	4.67 ± 1.08	4.18 ± 1.09	-1.657	0.098
Estradiol (mean ± SD, pg/mL)	50.23 ± 15.00	57.97 ± 11.95	5.845	< 0.001
Interleukin-6 (mean ± SD, pg/mL)	56.39 ± 12.22	40.24 ± 10.12	-14.554	< 0.001

Hct: Hematocrit.

Table 2 Multifactor logistic regression analysis of postpartum anxiety in pregnant women with preeclampsia

Factor	*β*	Wald χ^2	*P* value	OR (95%CI)
bad marital relationship	0.880	4.594	0.032	2.412 (1.078-5.394)
Gender discrimination among family members	0.871	4.339	0.037	2.390 (1.053-5.425)
Hematocrit	0.130	35.391	< 0.001	1.139 (1.091-1.189)
Eastradiol	-0.044	8.039	0.005	0.957 (0.928-0.986)
Interleukin-6	0.286	64.504	< 0.001	1.331 (1.242-1.428)
Constant	-21.420	72.926	< 0.001	

OR: Odds ratio; CI: Confidence interval.

calibration of the predictive model, which showed Hosmer-Lemeshow χ^2 = 5.900, and P = 0.658 (Figure 2).

Clinical verification of predictive model for pregnant women with preeclampsia complicated with postpartum anxiety

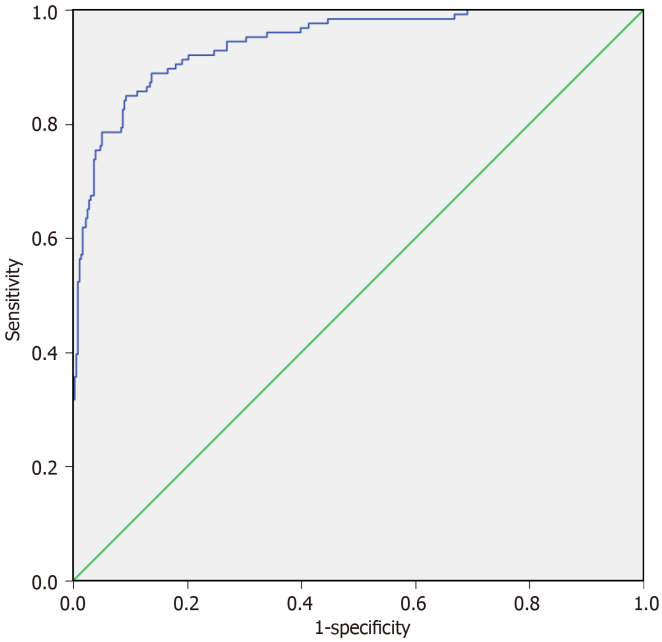
We retrospectively selected 80 pregnant women with preeclampsia in our hospital between January and May 2022 to clinically verify the predictive model. The sensitivity was 81.82%, specificity 84.48%, and accuracy 83.75% (Table 3).

DISCUSSION

The results of this study showed that serum transaminase levels, blood pressure, platelet levels, and coagulation indicators in pregnant women with preeclampsia with postpartum anxiety did not differ significantly from those in women without postpartum, which was consistent with previous studies[4]. We found that bad marital relationship, gender discrimination among family members, Hct, IL-6 and E2 were all independent factors influencing postpartum anxiety in pregnant women with preeclampsia. The care and support of husbands play a key role in improving the psychological status of pregnant women[9,10]. Therefore, strengthening the health education of the spouses of pregnant and lying-in

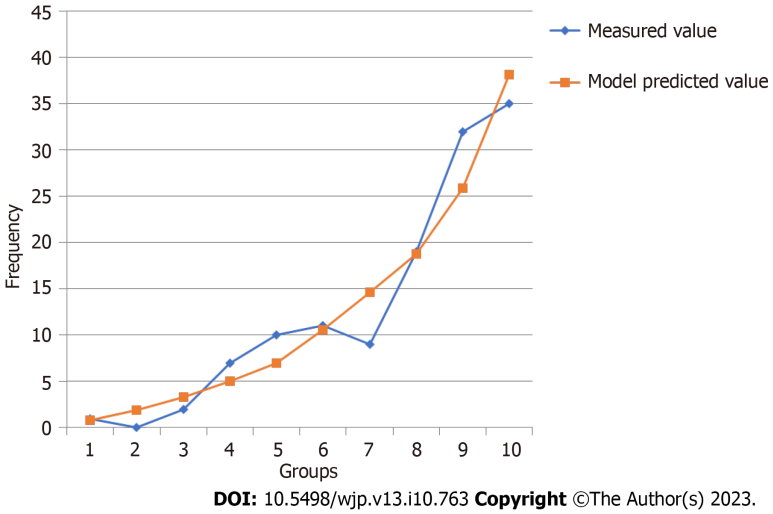
Table 3 Clinical validation of the predictive model

Postpartum anxiety	Models predict postpartum anxiety		Total
	Yes	No	
Yes	18	4	22
No	9	49	58
Total	27	53	80



DOI: 10.5498/wjp.v13.i10.763 **Copyright** ©The Author(s) 2023.

Figure 1 Receiver operating characteristic curve analysis of the predictive model for postpartum anxiety in preeclampsia.



DOI: 10.5498/wjp.v13.i10.763 **Copyright** ©The Author(s) 2023.

Figure 2 Goodness of fit test of a predictive model for postpartum anxiety in women with preeclampsia.

women and guiding them to attach importance to psychological care and support are important to reduce the risk of postpartum anxiety. The feudal thought of "son preference" is deeply rooted in China. Family members and even the pregnant women themselves care about the gender of the newborn[11]. When pregnant women with preeclampsia excessively consider the views of family members on the gender of their newborn, it can easily exert psychological pressure, leading to postpartum anxiety. Therefore, for pregnant women with preeclampsia, health education should be strengthened during prenatal examination, the idea of gender equality should be advocated, and possible gender discrim-

ination should be corrected in time to reduce the risk of postpartum anxiety of pregnant women.

There is a biological basis for postpartum anxiety in pregnant women with preeclampsia. Postpartum estrogen deficiency is an important reason for the significantly increased incidence of mental illness at 30 d postpartum[12], and E2 level is negatively correlated with the severity of female anxiety[13], which is similar to our study. The possible causes are that E2 can play an antianxiety role by improving the binding rate of serotonin reuptake transporter and the reuptake capacity of cells for serotonin. However, postpartum estrogen secretion from the uterus is stopped, the recovery of ovarian estrogen secretion function is slow, and the level of E2 is low, thus the antianxiety effect is weakened. If the level of E2 is low in pregnant women with preeclampsia, it may further decrease the level of postpartum estrogen, so anxiety is more likely to occur[14,15]. Ramiro-Cortijo *et al*[16] confirmed that the Hct in patients with preeclampsia was significantly higher than that of healthy people, and increased with aggravation of preeclampsia. Noori *et al*[17] showed that the prenatal Hct accurately predicted severity of depression and anxiety 6 wk after delivery. The results of this study showed that Hct was an independent factor influencing postpartum anxiety in pregnant women with preeclampsia, which was consistent with the above conclusions. Pregnant women with preeclampsia usually have overactivation of inflammation and immunity, and a large number of inflammatory factors are released into the blood, resulting in increased serum IL-6 level, which is positively correlated with the severity of preeclampsia[18]. Immune activation caused by inflammatory factors can lead to dysfunction of the neuroendocrine and immune systems[19,20]. Therefore, elevated serum IL-6 levels may cause postpartum anxiety in women with preeclampsia. Therefore, clinical attention should be paid to patients with abnormal indicators, and follow-up observation should be strengthened, or appropriate treatment should be given to adjust the level of related indicators.

In this study, a risk predictive model for pregnant women with preeclampsia complicated with postpartum anxiety was constructed based on the above independent influencing factors (bad marital relationship, gender discrimination of family members, Hct, IL-6 and E2). The ROC curve analysis results showed that the predictive model had good discrimination, and the goodness-of-fit test showed that the model had good calibration. The prospective clinical validation showed that the model had high sensitivity (81.82%), specificity (84.48%) and accuracy (83.75%), indicating that the predictive model had clinical practicability. The model was simple to use and had high accuracy. However, the number of cases in the time period selected for clinical verification is small, and the results may have certain errors. In the future will be incorporated into various validation.

CONCLUSION

Bad marital relationship, gender discrimination of family members, Hct, IL-6 and E2 are independent factors influencing postpartum anxiety in pregnant women with preeclampsia. The predictive model established based on these factors has high sensitivity, specificity and accuracy, strong operability, and high clinical value. However, this study was a single-center study, the clinical validation of the model was only conducted in our hospital, and the sample size was insufficient, so the results were inevitably biased. In the future, multi-center research and multi-center clinical verification will be carried out, and multi-factor, multi-sample and multi-time span will be adopted to explore, so as to enhance the reliability of the research results.

ARTICLE HIGHLIGHTS

Research background

Relaxation of the maternity policy has resulted in an increase in the number of elderly pregnant and lying-in women, and the prevalence of preeclampsia. Preeclampsia can lead to organ damage and system dysfunction.

Research motivation

To explore the factors influencing postpartum anxiety in pregnant women with preeclampsia and construct a predictive model, to provide an effective and practical risk assessment tool for clinical practice.

Research objectives

The object of this study is to explore the factors influencing postpartum anxiety in pregnant women with preeclampsia and construct a personalized model for predicting postpartum anxiety, to provide a reference for clinical trials.

Research methods

We retrospectively analyzed 528 pregnant women with preeclampsia who delivered in our hospital between 2018 and 2021. Various physiological and biochemical indicators were obtained through laboratory tests. Multivariate logistic regression, receiver operating characteristic curve, Hosmer-Lemeshow and other methods were used to analyze the factors influencing postpartum anxiety in pregnant women with preeclampsia and to construct a predictive model.

Research results

A total of 126 pregnant women with preeclampsia experienced postpartum anxiety. Bad marital relationship, gender discrimination among family members, hematocrit, estradiol hormone and interleukin-6 were independent risk factors

for postpartum anxiety in pregnant women with preeclampsia, and the predictive model constructed based on these factors had high accuracy.

Research conclusions

We analyzed the factors influencing postpartum anxiety in pregnant women with preeclampsia and constructed a predictive model with high sensitivity and accuracy, which provided a reference value for clinical practice.

Research perspectives

Firstly, multi-sample, multi-factor, multi-center and multi-time span clinical studies will be carried out in the future to enhance the reliability of the research results. In addition, different models were constructed for clinical application in pregnant women with preeclampsia and postpartum anxiety.

FOOTNOTES

Author contributions: Lin LJ and Chen S designed the study and wrote the paper; Zhou HX participated in the analysis; Ye ZY and Zhang Q provided clinical advice.

Institutional review board statement: The study was reviewed and approved by the Wenzhou Hospital of Integrated Traditional Chinese and Western Medicine, No. 20230424085200033546 5.

Informed consent statement: All patients have signed informed consent forms.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The dataset used for this study can be obtained from the corresponding author.

Country/Territory of origin: China

ORCID number: Le-Jing Lin 0009-0002-3931-7008; Hai-Xian Zhou 0009-0009-9107-0461; Zhi-Yun Ye 0009-0003-2858-2479; Qi Zhang 0009-0000-4539-1349; Shu Chen 0009-0002-4499-2868.

S-Editor: Wang JJ
L-Editor: A
P-Editor: Wang JJ

REFERENCES

1 ACOG Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. *Obstet Gynecol* 2019; **133**: 1 [PMID: 30575675 DOI: 10.1097/AOG.0000000000003018]
2 **Postma IR**, Bouma A, Ankersmit IF, Zeeman GG. Neurocognitive functioning following preeclampsia and eclampsia: a long-term follow-up study. *Am J Obstet Gynecol* 2014; **211**: 37.e1-37.e9 [PMID: 24495666 DOI: 10.1016/j.ajog.2014.01.042]
3 **Roberts L**, Davis GK, Homer CSE. Depression, Anxiety, and Post-traumatic Stress Disorder Following a Hypertensive Disorder of Pregnancy: A Narrative Literature Review. *Front Cardiovasc Med* 2019; **6**: 147 [PMID: 31649935 DOI: 10.3389/fcvm.2019.00147]
4 **Abedian Z**, Soltani N, Mokhber N, Esmaily H. Depression and anxiety in pregnancy and postpartum in women with mild and severe preeclampsia. *Iran J Nurs Midwifery Res* 2015; **20**: 454-459 [PMID: 26257800 DOI: 10.4103/1735-9066.161013]
5 **Nakić Radoš S**, Tadinac M, Herman R. Anxiety During Pregnancy and Postpartum: Course, Predictors and Comorbidity with Postpartum Depression. *Acta Clin Croat* 2018; **57**: 39-51 [PMID: 30256010 DOI: 10.20471/acc.2017.56.04.05]
6 **Kendig S**, Keats JP, Hoffman MC, Kay LB, Miller ES, Moore Simas TA, Frieder A, Hackley B, Indman P, Raines C, Semenuk K, Wisner KL, Lemieux LA. Consensus Bundle on Maternal Mental Health: Perinatal Depression and Anxiety. *Obstet Gynecol* 2017; **129**: 422-430 [PMID: 28178041 DOI: 10.1097/AOG.0000000000001902]
7 **Jordan V**, Minikel M. Postpartum anxiety: More common than you think. *J Fam Pract* 2019; **68**: 165;168;170;174 [PMID: 31039214]
8 **Tanaka ME**, Keefe N, Caridi T, Kohi M, Salazar G. Interventional Radiology in Obstetrics and Gynecology: Updates in Women's Health. *Radiographics* 2023; **43**: e220039 [PMID: 36729949 DOI: 10.1148/rg.220039]
9 **Pawluski JL**, Lonstein JS, Fleming AS. The Neurobiology of Postpartum Anxiety and Depression. *Trends Neurosci* 2017; **40**: 106-120 [PMID: 28129895 DOI: 10.1016/j.tins.2016.11.009]
10 **Jack SM**, Boyle M, McKee C, Ford-Gilboe M, Wathen CN, Scribano P, Davidov D, McNaughton D, O'Brien R, Johnston C, Gasbarro M, Tanaka M, Kimber M, Coben J, Olds DL, MacMillan HL. Effect of Addition of an Intimate Partner Violence Intervention to a Nurse Home Visitation Program on Maternal Quality of Life: A Randomized Clinical Trial. *JAMA* 2019; **321**: 1576-1585 [PMID: 31012933 DOI: 10.1001/jama.2019.3211]

11 **Huang C**, Fan Y, Hu S. The Prevalence and Influencing Factors of Postpartum Depression Between Primiparous and Secundiparous. *J Nerv Ment Dis* 2023; **211**: 190-194 [PMID: 36108287 DOI: 10.1097/NMD.0000000000001591]

12 **Fan F**, Zou Y, Tian H, Zhang Y, Zhang J, Ma X, Meng Y, Yue Y, Liu K, Dart AM. Effects of maternal anxiety and depression during pregnancy in Chinese women on children's heart rate and blood pressure response to stress. *J Hum Hypertens* 2016; **30**: 171-176 [PMID: 26084653 DOI: 10.1038/jhh.2015.64]

13 **Zhu W**, Chen Z, Shen Y, Wang H, Cai X, Zhu J, Tang Y, Wang X, Li S. Relationship between serum gonadal hormone levels and synkinesis in postmenopausal women and man with idiopathic facial paralysis. *Auris Nasus Larynx* 2022; **49**: 782-789 [PMID: 35227560 DOI: 10.1016/j.anl.2022.02.005]

14 **Bhatia NY**, Ved HS, Kale PP, Doshi GM. Importance of Exploring N-Methyl-D-Aspartate (NMDA) as a Future Perspective Target in Depression. *CNS Neurol Disord Drug Targets* 2022; **21**: 1004-1016 [PMID: 35352638 DOI: 10.2174/1871527321666220329141639]

15 **Edinoff AN**, Odisho AS, Lewis K, Kaskas A, Hunt G, Cornett EM, Kaye AD, Kaye A, Morgan J, Barrilleaux PS, Lewis D, Viswanath O, Urits I. Brexanolone, a GABA(A) Modulator, in the Treatment of Postpartum Depression in Adults: A Comprehensive Review. *Front Psychiatry* 2021; **12**: 699740 [PMID: 34594247 DOI: 10.3389/fpsyt.2021.699740]

16 **Ramiro-Cortijo D**, de la Calle M, Rodriguez-Rodriguez P, Phuthong S, López de Pablo ÁL, Martín-Cabrejas MA, Arribas SM. First trimester elevations of hematocrit, lipid peroxidation and nitrates in women with twin pregnancies who develop preeclampsia. *Pregnancy Hypertens* 2020; **22**: 132-135 [PMID: 32971355 DOI: 10.1016/j.preghy.2020.09.005]

17 **Noori M**, Donald AE, Angelakopoulou A, Hingorani AD, Williams DJ. Prospective study of placental angiogenic factors and maternal vascular function before and after preeclampsia and gestational hypertension. *Circulation* 2010; **122**: 478-487 [PMID: 20644016 DOI: 10.1161/CIRCULATIONAHA.109.895458]

18 **Demirer S**, Hocaoglu M, Turgut A, Karateke A, Komurcu-Bayrak E. Expression profiles of candidate microRNAs in the peripheral blood leukocytes of patients with early- and late-onset preeclampsia versus normal pregnancies. *Pregnancy Hypertens* 2020; **19**: 239-245 [PMID: 31899190 DOI: 10.1016/j.preghy.2019.11.003]

19 **Maes M**, Berk M, Goehler L, Song C, Anderson G, Gałecki P, Leonard B. Depression and sickness behavior are Janus-faced responses to shared inflammatory pathways. *BMC Med* 2012; **10**: 66 [PMID: 22747645 DOI: 10.1186/1741-7015-10-66]

20 **Jia Y**, Liu L, Sheng C, Cheng Z, Cui L, Li M, Zhao Y, Shi T, Yau TO, Li F, Chen L. Increased Serum Levels of Cortisol and Inflammatory Cytokines in People With Depression. *J Nerv Ment Dis* 2019; **207**: 271-276 [PMID: 30844940 DOI: 10.1097/NMD.0000000000000957]

World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatry 2023 October 19; 13(10): 772-783

DOI: 10.5498/wjp.v13.i10.772

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Observational Study

Depression among medical students in Tunisia: Prevalence and associated factors

Badii Amamou, Sondess Alouani, Amjed Ben Haouala, Saoussen Alouani, Mohamed Ayoub Tlili, Ahmed Mhalla, Ferid Zaafrane, Lotfi Gaha

Specialty type: Psychology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Laranjeira C, Portugal; Wang QX, China; Zhang YF, China

Received: December 5, 2022
Peer-review started: December 5, 2022
First decision: January 5, 2023
Revised: January 17, 2023
Accepted: March 22, 2023
Article in press: March 22, 2023
Published online: October 19, 2023

Badii Amamou, Sondess Alouani, Amjed Ben Haouala, Saoussen Alouani, Ahmed Mhalla, Ferid Zaafrane, Lotfi Gaha, Department of Psychiatry, Fattouma Bourguiba University Hospital of Monastir, Monastir 5000, Tunisia

Mohamed Ayoub Tlili, Department of Family and Community Medicine, Faculty of Medicine of Sousse, Sousse 4002, Tunisia

Corresponding author: Badii Amamou, MD, Associate Professor, Department of Psychiatry, Fattouma Bourguiba University Hospital of Monastir, Avenue Farhat Hached, Monastir 5000, Tunisia. amamoubadii@hotmail.fr

Abstract

BACKGROUND

Medical school is known for its lengthy process, which is both physically and emotionally draining. Students' mental balance would shrink as they progress in their medical training. A systematic review and meta-analysis reported that the prevalence of depressive symptoms among medical students remained relatively constant at 27.2%.

AIM

To assess the prevalence of depressive symptoms among Tunisian medical students and evaluate its associated factors.

METHODS

This is a descriptive cross-sectional study that was carried out in the second semester of the academic year 2017/2018, between April 2018 and July 2018 among 1138 medical students. Data were collected using a socio-demographic questionnaire and the Beck Depression Inventory-II (BDI-II).

RESULTS

Sixty-four percent (n = 728) of the participants had depressive symptoms, of which 266 (23.4%) met the criteria for mild, 271 (23.8%) for moderate, and 191 (16.8%) for severe depressive symptoms. Female gender, low socio-economic level, smoking habits and history of mental disorder, performing leisure and physical activities, satisfaction toward a career choice, and happiness perception were the main prognostic factors for depression among medical students. Although academic grades may not be considered a prognostic factor, final-year

students appeared to be less depressive than their colleagues.

CONCLUSION

These findings give insight into mental health issues and comorbidities among Tunisian medical students. It is a hopeful request for decision-makers and academic authorities to set serious measures and draw effective interventions to minimize the currency of psychological distress among this subpopulation.

Key Words: Depression; Psychiatry; Medical students; Mental health; Beck Depression Inventory; Tunisia

Core Tip: This study aimed to assess the prevalence of depressive symptoms among Tunisian medical students and evaluate its associated factors. This is a descriptive cross-sectional study that was carried out in the second semester of the academic year 2017/2018, between April 2018 and July 2018 among 1138 medical students. Sixty four percent (n = 728) of the participants had depressive symptoms, of which 266 (23.4%) met the criteria for mild, 271 (23.8%) for moderate, and 191 (16.8%) for severe depressive symptoms. Female gender, low socio-economic level, smoking habits and history of mental disorder, performing leisure and physical activities, satisfaction toward career choice, and happiness perception were the main prognostic factors for depression among medical students. Although academic grade may not be considered as a prognostic factor, final year students appeared to be less depressive than their colleagues.

Citation: Amamou B, Alouani S, Ben Haouala A, Alouani S, Tlili MA, Mhalla A, Zaafrane F, Gaha L. Depression among medical students in Tunisia: Prevalence and associated factors. *World J Psychiatry* 2023; 13(10): 772-783
URL: https://www.wjgnet.com/2220-3206/full/v13/i10/772.htm
DOI: https://dx.doi.org/10.5498/wjp.v13.i10.772

INTRODUCTION

The Global Burden of Diseases, Injuries, and Risk Factors Study 2017 (GBD 2017), conducted between 1990 and 2017 in 195 countries and territories, concluded that more than 264 million people of all ages were depressed[1].

Depression can be long-lasting or recurrent, and standing still impairs an individual's ability to function in his daily life[2].

Psychological distress among university students has witnessed a considerable rise, becoming a concern for public health authorities around the globe. And among university students, medical students are particularly more vulnerable to psychological distress and morbidity since medical education is reputed for its long process and it is physically and emotionally consuming[3,4].

Rotenstein *et al*[5] reported in a systematic review and meta-analysis conducted in 2016 that between 1982 and 2015, depressive symptom prevalence remained relatively constant at 27.2% for medical students with no significant difference between preclinical and clinical students.

Even though it is crucial for an educational institution to assess the mental status of its students, only a few Tunisian studies surveyed the currency of depression among medical students.

Within this framework, this study aimed to assess the prevalence of depressive symptoms among medical students in Tunisia and to evaluate its associated factors.

MATERIALS AND METHODS

Study design and participants

The present study is a descriptive cross-sectional study that was carried out in the second semester of the academic year 2017/2018, between April 2018 and July 2018 (away from exams). We recruited students from the four medical faculties in Tunisia [Faculty of Medicine of Monastir (FMM), Sousse, Tunis, and Sfax].

The minimal sample size required for the study was 322694. It was calculated using the formula: $n = \mu\alpha 2\ p\ (1\text{-}p)/\delta 2$, where "μα" is the one-sided magnitude of the confidence level (μα = 1.96) and "p" is the expected proportion of the outcome of interest with an assumption of 30% depression among medical students.

Only enrolled medical students from the first year to the fifth year were invited to complete an online survey as a main tool of the study.

To retrieve an adequate sample for the present study, all candidates were invited to complete an anonymous nationwide web-based questionnaire *via* their student delegate who published the questionnaire in their Facebook group, mentioning the purpose of the study and assuring the confidentiality and anonymity of each answer. The questionnaire was sent with a description of the study. Every person could only answer the questionnaire once.

As the response rate is the number of completed and sent survey responses divided by the number of people who viewed the survey, the present study response rate was measured to be 16.45%, considering students who reached the link and viewed the survey content (Figure 1).

Study instruments

The self-report questionnaire employed in the French language (the second language and official language for medical studies in Tunisia) took approximately 15 min to answer and collected data on.

Students' general characteristics: It consists of personal (age, gender, origin, personal medical history, tobacco use, alcoholism, marital status, self-assessment of their financial status, and current residence) and academic characteristics: Faculty, academic level, satisfaction toward career choice, and dropping out thoughts, leisure and sporting activities, participation in a stress management workshop, and a precedent visit to a psychiatrist/psychologist.

Beck Depression Inventory-II (BDI-II): It is a self-administrated tool, used to screen for the presence of depressive symptoms[6,7]. The BDI-II timeframe extends for 2 wk to correspond with the DSM-IV criteria for diagnosing depressive disorders and includes items measuring cognitive, affective, somatic, and vegetative symptoms of depression. With a sensitivity of 87% and specificity of 79%, the BDI-II was validated using adult and adolescent psychiatric outpatients.

Each participant is asked to answer 21 items rated on a 4-point Linkert scale indicating the degree of severity from 0 (not at all) to 3 (extreme form of each symptom). Cumulative score is calculated. The provisional diagnosis of depression is made if the BDI-II score is greater than 13 and the presence of severe depressive symptoms if the score is greater than or equal to 29. The severity of depression was classified into three categories: Mild, moderate, and severe depression[7,8].

Statistical analysis

The data collected were keyed into Excel for Windows and statistical analyses were carried out using the software package SPSS version 24 (SPSS Inc.). Descriptive analysis (frequencies, prevalence, mean, and standard deviation) was applied to evaluate the characteristics of the samples. The Chi-square (χ^2) test was carried out to compare the prevalence of depression between different groups, while the Student's *t*-test was used to analyze quantitative data (age) with the presence of depression. Variables whose *P* value was < 0.2 were entered as independent variables in regression analysis. The 95% confidence intervals (95%CI) were calculated for prevalence rates. Binary logistic regression models were used to show the predictive model of BDI based on the values of the independent variables (predictors). The level of significance was set at $P < 0.05$.

Ethical considerations

We explained the purpose of the study to all participants. The confidentiality and anonymity of each answer were guaranteed. A completed questionnaire was considered as consent to participate in the study. The present study was approved by the ethics committee of the FMM (No. 3067).

RESULTS

Description of general characteristics

The sample consisted of 1138 medical students, including 888 (78%) females and 250 (22%) males, with ages ranging from 18 to 37 years (mean, 22.0 years ± 2.3 years). There were 423 students (37.2%) who were enrolled in the Faculty of Medicine of Tunis (FMT), while 304 (26.7%), 248 (21.8%), and 163 (14.3%) were registered, respectively, in the FMM, Sousse (FMS) and Sfax (FMSF). Of the sample, there were 448 pre-clinical students (Year 1 and Year 2) (39.3%) and 690 clinical students (Year 3, Year 4, and Year 5) (60.6%).

Based on their financial status self-assessment, most of the students (921, 80.9%) were at a moderate socio-economic level while 146 (12.8%) were at a high level and 71 (6.2%) were at a low level. Fourteen percent of the participants were smokers and 16% revealed drinking habits. Almost 70% of the sample did not practice either leisure or physical activities. Only 158 (13.9%) had participated in a stress management workshop and 228 (20%) had sought psychiatric help.

Half of the sample were unsatisfied with their career choice and have thought, at least once, of dropping out of medical studies. Sixty-one percent of participants (699) admitted feeling unhappy. More personal and academically related details are illustrated in Table 1.

Depressive symptoms

The BDI-II total scores of participants ranged from 0 to 63 with a mean score of 18.73 ± 10.60 as shown in Table 2. Sixty-four percent (n = 728) of the participants had depressive symptoms, of which 266 (23.4%) met the criteria for mild, 271 (23.8%) for moderate, and 191 (16.8%) for severe depressive symptoms. Among 728 depressive students, only 177 (24.3%) had sought psychiatric help.

Students' general characteristics as determinants of depression

Personal characteristics: Female students were more depressed than males. Neither students' residency nor marital status showed a significant effect on depressive symptoms. Depression was more prevalent among smokers and students with low socio-economic levels.

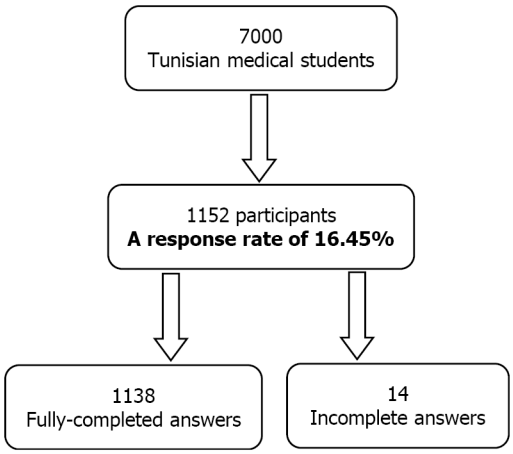
Table 1 Characteristics of study participants (*n* = 1138) (university year 2017/2018), *n* (%)

Characteristic		mean ± SD
Age, yr		22 (2.347) (min 18, max 37)
Gender	Female	888 (78)
	Male	250 (22)
Faculty	Monastir	304 (26.7)
	Sousse	248 (21.8)
	Sfax	163 (14.3)
	Tunis	423 (37.2)
Grade	Year 1	252 (22.1)
	Year 2	196 (17.2)
	Year 3	198 (17.4)
	Year 4	171 (15)
	Year 5	321 (28.2)
Marital status	Single	837 (73.6)
	Engaged	269 (23.6)
	Married	29 (2.5)
	Divorced	3 (0.3)
	Alone	193 (17)
	With friends/roommates	220 (19.3)
	Academic residency	127 (11.2)
	Family home	598 (52.5)
Socio-economic level	Low	71 (6.2)
	Moderate	921 (80.9)
	High	146 (12.8)
Children	Yes	23 (2)
	No	1115 (98)
History of medical illness	Yes	173 (15.2)
	No	965 (84.8)
History of mental illness	Yes	79 (6.9)
	No	1059 (93.1)
Leisure activities	Yes	349 (30.7)
	No	789 (69.3)
Physical activities	Yes	322 (28.3)
	No	816 (71.7)
Smoking habits	Yes	160 (14.1)
	No	978 (85.9)
Drinking habits	Yes	183 (16.1)
	No	955 (83.9)
Are you satisfied with your career choice?	Yes	619 (54.4)
	No	519 (45.6)
Have you ever thought of dropping out of medical studies?	Yes	664 (58.3)
	No	474 (41.7)

Stress management training	Yes	158 (13.9)
	No	980 (86.1)
Have you ever visited a psychiatrist?	Yes	228 (20)
	No	910 (80)
Why not?	No answer	261 (22.9)
	I feel fine. I don't need it	392 (34.4)
	I need it, but I am always busy	366 (23.2)
	I need it, but my circle of friends/family discouraged me	119 (10.5)
Are you happy?	Yes	439 (38.6)
	No	699 (61.4)

Table 2 Prevalence of depression among study participants (*n* = 1138)

BDI-II total score, mean ± SD		**Min 0, max 63, 18.730 (10.654)**
Depression level	Absence of depression	410 (36%)
	Low	266 (23.4%)
	Moderate	271 (23.8%)
	Severe	191 (16.8%)



DOI: 10.5498/wjp.v13.i10.772

Figure 1 Flowchart of the study.

Depressive symptoms were associated with age ($P = 0.048$; the age difference was not meaningful), gender ($P = 0.038$), socio-economic level ($P < 10^{-3}$), history of medical illness ($P = 0.034$), history of mental illness ($P < 10^{-3}$), and smoking habits ($P = 0.025$).

Academic characteristics: With 70% depressed students, Sousse Faculty of Medicine was ranked as the most depressed faculty. There was no difference between pre-clinical and clinical students. The lack of leisure and physical activities was significantly associated with the presence of depressive symptoms.

The presence of depression was associated with faculty ($P = 0.042$), leisure activities ($P < 10^{-3}$), physical activities ($P < 10^{-3}$), satisfaction toward career choices ($P < 10^{-3}$), dropping out thoughts ($P < 10^{-3}$), a precedent visit of a psychiatrist/psychologist ($P < 10^{-3}$), and happiness perception ($P < 10^{-3}$). Different correlations are illustrated in Table 3.

Association between depressive symptoms and sample characteristics: Regression analysis

Female gender, low socio-economic level, smoking habits, and history of mental disorders were identified to be the main prognostic factors for depression among medical students (Table 4).

Although academic grade and participation in a stress management workshop did not show a significant correlation in the univariate analysis, we added these two variables in the regression analysis as they were mentioned in the literature. Academic grade may not be considered a prognostic factor. However, as detailed in Table 4, final-year students seemed

Table 3 Association between characteristics of participants and symptoms of depression, *n* (%)

Characteristic		D-	D+	*P* value
Age, yr, mean ± SD		21.820 (2.059)	22.100 (2.492)	0.048
Gender	Female	306 (34.5)	582 (65.5)	0.038
	Male	104 (41.6)	146 (58.4)	
Faculty	Monastir	124 (40.8)	180 (59.2)	0.042
	Sousse	73 (29.4)	175 (70.6)	
	Sfax	63 (38.7)	100 (61.3)	
	Tunis	150 (35.5)	273 (64.5)	
Grade	Year 1	91 (36.1)	161 (63.9)	0.57
	Year 2	72 (36.7)	124 (63.3)	
	Year 3	74 (37.4)	124 (62.6)	
	Year 4	52 (30.4)	119 (69.6)	
	Year 5	121 (37.7)	200 (62.3)	
Accomodation	Alone	63 (32.6)	130 (67.4)	0.597
	With friends/roommates	79 (35.9)	141 (64.1)	
	Academic residency	43 (33.9)	84 (66.1)	
	Family home	225 (37.6)	373 (62.4)	
Marital status	Single	301 (36)	536 (64.0)	0.786
	Engaged	100 (37.2)	169 (62.8)	
	Married	8 (27.6)	21 (72.4)	
	Divorced	1 (33.3)	2 (66.7)	0.149
Children	Yes	5 (21.7)	18 (78.3)	
	No	405 (36.3)	710 (63.7)	
Socio-economic level	Low	9 (12.7)	62 (87.3)	$< 10^{-3}$
	Moderate	330 (35.8)	591 (64.2)	
	High	71 (48.6)	75 (51.4)	
History of medical illness	Yes	50 (28.9)	123 (71.1)	0.034
	No	360 (37.3)	605 (62.7)	
History of mental illness	Yes	14 (17.7)	65 (82.3)	$< 10^{-3}$
	No	396 (37.4)	663 (62.6)	
Leisure activities	Yes	172 (49.3)	177 (50.7)	$< 10^{-3}$
	No	238 (30.2)	551 (69.8)	
Physical activities	Yes	145 (45)	177 (55)	$< 10^{-3}$
	No	265 (32.5)	551 (67.5)	
Smoking habits	Yes	45 (28.1)	115 (71.9)	0.025
	No	365 (37.3)	613 (62.7)	
Drinking habits	Yes	63 (34.4)	120 (65.6)	0.622
	No	347 (36.3)	608 (63.7)	
Are you satisfied with your career choice?	Yes	305 (49.3)	314 (50.7)	$< 10^{-3}$
	No	105 (20.2)	414 (79.8)	
Have you ever thought of dropping out of medical studies?	Yes	167 (25.2)	497 (74.8)	$< 10^{-3}$
	No	243 (51.3)	231 (48.7)	

Stress management training	Yes	49 (31.0)	109 (69.0)	0.157
	No	361 (36.8)	619 (63.2)	
Have you ever visited a psychiatrist?	Yes	51 (22.4)	177 (77.6)	$< 10^{-3}$
	No	359 (39.5)	551 (60.5)	
	No			
Are you happy?	Yes	289 (65.8)	150 (34.2)	$< 10^{-3}$
	No	121 (17.3)	578 (82.7)	

Table 4 Binary logistic regression analysis of association between the sample and depression symptoms

Characteristic		Exp (B)	95%CI	*P* value
Gender		1.544	1.135-2.099	0.006
Socio-economic level	High	1		
	Moderate	1.83	1.276-2.633	0.001
	Low	6.589	3.000-14.469	$< 10^{-3}$
History of mental illness		2.693	1.470-4.932	0.001
Smoking habits		1.669	1.123-2.481	0.011
Grade	Year 1	1		
	Year 2	0.991	0.653-1.504	0.966
	Year 3	0.796	0.523-1.213	0.288
	Year 4	0.918	0.584-1.444	0.711
	Year 5	0.667	0.456-0.974	0.036
Leisure activities		0.459	0.344-0.613	$< 10^{-3}$
Physical activities		0.679	0.505-0.914	0.011
Satisfaction toward career choice		0.238	0.179-0.316	$< 10^{-3}$
Stress management training		1.609	1.085-2.385	0.018
Happiness perception		0.143	0.107-0.193	$< 10^{-3}$

to be less depressed than their colleagues.

Performing leisure and physical activities, satisfaction toward a career choice, happiness perception, and participation in a stress management workshop were considered prognostic factors for depression among participants.

DISCUSSION

Prevalence of depression among students

Sixty-four percent (n = 728) of the participants had depressive symptoms. These results seem to be higher than the aggregate prevalence of 27.2% (range, 9.3%-55.9%) reported by Rotenstein *et al*[5] in their systematic review and meta-analysis that covered 195 studies in 47 different countries, involving 129123 medical students. In a medical education journal, a meta-analysis that concerned a total of 62728 medical students pooled across 77 studies was published in March 2016[9], which reported similar results (28%).

The magnitude of depression found in our study closely resembled the findings from some neighboring countries: Egypt 60.2%[10], Bahrain 65.6%[11], *etc*. Lower prevalence were found in India[12] (18%), Thailand[13] (12.6%), Germany [14] (10.3%), *etc*.

Nationally, the proportion of depressed medical students was higher than what was reported in a previous Tunisian study[15] that was conducted at the University of Sfax and showed that out of 80 medical students, 31% were depressed. Similar results were found in another study that included Tunisian medical residents (30.5%)[16]. Both studies used the same screening tool (Hospital Anxiety and Depression scale)[15,16].

This variation worldwide can be explained to be due to sample size and data collection tools. Besides, diversity in cultural, religious, and spiritual peculiarities[17] in addition to dissimilarity in the healthcare system might also elucidate the disparity of findings between countries.

Association between characteristics of participants and symptoms of depression

Female gender: Globally, there were controverted issues given the impact of gender on depression symptoms. The significant correlation of poor mental health with female students found in the current study is supported by previous studies in Sweden[18], Nepal[19], Australia[20], *etc*. In contrast, no difference in depression between genders was disclosed in previous studies in Tunisia[16], Greece[21], Ethiopia[22], *etc*. Furthermore, regression analysis yielded mixed findings with some considering female gender as a risk factor for depression: South Africa[23], Turkey[24], South Korea [25], *etc*. Studies took a multitude of tracks to elucidate why female students were more prone to depression than their male peers, and they suggested social stigma, gender inequity, and cultural constraints as the main reasons[9,26,27].

Financial status: Based on their financial status self-assessment, students at a low socioeconomic level were more likely to get depressed than their peers. These outcomes are in harmony with those run in neighboring and foreign countries[3,10, 14,25,28]. The impact of financial status on the occurrence of depression was documented in numerous studies among general populations[29-32]. A large four-year study (The PATH Through Life Survey) was conducted by Butterworth and colleagues in the city of Canberra and the surrounding regions in south-east Australia, and it included 6715 participants from different cohorts (1975-1979; 1956-1960; and 1937-1941). The study proclaimed that the lack of financial resources was strongly associated with depression[33,34].

Mental problems: Out of 1138 participants, 79 (6.9%) reported having a history of mental illness. These results seem to be akin to those found in other studies[26,35]. Nineteen Saudi Arabian medical students (out of 398) reported having a psychological illness. Eighty-four percent of them met the BDI criteria for depression. The chi-square test detected a significant correlation ($P < 0.001$) and multiple linear regression inferred that the presence of psychological problems makes students 1.435 times more likely to get depressed [$P = 0.03$, exp(B) 4.200, 95%CI: 1.150-15.338][35]. These findings are congruous with those reported earlier by Asal *et al*[36], Pagnin *et al*[37], and Pillay *et al*[38], who found that depressive and anxiety features were related to students' history of poor mental health[36-38].

Smoking, drinking, and substance use: Out of 1138 participants, 160 (14.1%) had smoking habits while 183 (16.1%) had drinking habits. Smokers (115, 71.9%) and drinkers (120, 65.6%) met the BDI-II criteria for depression. The regression analysis considered smoking as a risk factor for depression. Many studies have looked for the link between substance use and the occurrence of depression[39]. On the other hand, Palestinian and Saudi Arabian studies that explored the impact of smoking only (but not drinking for cultural limitations) found no significant correlation with depression ($P = 0.08$)[26, 35]. Moreover, O. Coskun and colleagues[24] perceived no significant relationship between alcohol and the magnitude of depression. Correspondingly, studies among Ethiopian, Nepali, and Australian medical students found, also, no significant link between substance use and the development of depression[19,20,22]. Strikingly, a similar study was performed in the Netherlands. Authors noticed that first-year students who had drinking habits tended to be more balanced in their mental wellness than non-drinking students. Hence, drinking seems to be a coping tool wielded to ease the pressure but also to inflate social interactions and activities[40,41]. Even though drinking can be regarded as a relief from stress or a coping strategy, immoderate drinking may ruin liver and pancreas functioning, alter the cardiovascular system, and lead to tumoral issues as well as numerous psychiatric disorders[41-44].

Association between academic characteristics of participants and depression symptoms

Physical activities: Almost 70% of the sample did not practice any physical activity. Among them, 551 (67.5%) met the BDI-II criteria for depression. The regression analysis considered physical activity as a protective factor against depression[45].

A tiny number of studies had explored physical behavior among medical students. Abdelwahed and colleagues, for instance, observed that 210 out of 442 were performing physical activity at least three times a week. Yet, statistical analysis did not show any significant correlation between physical activity and depression ($P = 0.647$), anxiety ($P = 0.78$), or stress ($P = 0.76$)[10].

Worldwide, the impact of physical exercises was exemplified in numerous studies. A systematic review on the effects of physical activity on brain structure and function in youth related that physical activity can redesign white matter integrity and arousal of regions key to cognitive tasks[46]. Identically, Rebar and colleagues performed a meta-analysis of the impact of physical activity on depression and anxiety among the non-clinical population[47]. Authors concluded that physical activity was shown to decrease depression by a medium effect [standardized mean difference (SMD) = -0.50; 95%CI: -0.93 to -0.06] and anxiety by a small effect (SMD = -0.38; 95%CI: -0.66 to -0.11)[47].

Leisure activities and extracurricular involvement: More than half of the participants (69.3%) were not performing any leisure activity. Fifty hundred and fifty-one (69.8%) among them were found depressed. Statistical analysis proved a significant association between spare time ventures and the occurrence of depression: The odds of developing depression was reduced to half among socially active participants. These findings seem in line with a Nepalian study where 34% of students (221/651) were involved in extracurricular activities. While those who answered "Always" and "Often" as the frequency of their extra activities were 28.6% and 21.7% depressed, respectively, those who answered "Rarely" and "Never" were 42.4% and 41.7% depressed, respectively. Even though a strong correlation ($P < 10^{-3}$) was found in the chi-square test, having a spare schedule tends to be a protective factor against anxiety ($P = 0.012$, OR = 0.367, 95%CI: 0.165-0.799) but not depression[19]. The part taken by social life and social relationships turns out to be a key strand in the fight against depression and lessen stressful life pressures[22,40,48,49]. Dyrbye *et al*[28], who drove a longitudinal study among 3743 United States medical students from 2010 to 2014, noticed that students who avowed having low social support were more likely to manifest depressive features ($P < 10^{-3}$). Similarly, Turkish and Palestinian studies substantiated the strong correlation ($P < 10^{-3}$) that relates social interaction and social stand with the contingency of depression[24,35].

Satisfaction and dropping out ideas: Statistical analysis showed a strong correlation between students' dissatisfaction and depression ($P < 10^{-3}$). Unsatisfaction is, then, considered a risk factor for developing depression. These data closely resemble findings from other studies. Pokhrel *et al*[19] demonstrated that satisfied students in Nepal were less prone to depression (OR = 0.51, 95%CI: 0.33-0.80). Similarly, discontented KSA medical students tend to be more depressed than their peers ($P = 0.03$)[35]. Studies conducted in New Zealand[50] and Palestine[26] reported results in line with our study. The influence that satisfaction toward career choice has on students' mental health did not come out of anywhere. It arises from the reluctance to study medicine: Whether to please parents' desire to become a doctor or to go along with friends aiming to get higher social status. All of it ends by being hushed, knowing the reality of medicine[51].

Recommendations

As disclosed above, medical students are without a doubt prone to several mental afflictions. Therefore, preventing such distress among students should be a priority and a must.

Primary prevention is possible by supplying learners with seminars on time management, relaxation exercises, and mindfulness activities through counseling services such as the listening unit that has been established in our faculty. Finally, prioritizing students' welfare starts by providing space and needed materials to enhance students' physical exercises and group activities, delivering variable and healthy meals in university restaurants, and revising students' schedules to suit their academic, physical, and psychological needs.

Limitations

Overall, the authors acknowledge some limitations to this study. Being a descriptive cross-sectional study, causal links between the correlations could not be inaugurated. Preferably, further studies should be surveyed in longitudinal, prospective, and multicenter designs aiming to yield a greater overview of the circumstances. Even though the number of students who participated in this survey is much higher than those carried out in Tunisian and neighboring studies, a larger sample size would have risen the diligence and exactness of our study.

As our study was based on self-administrated questionnaires and all data employed were self-reported, it is possible that students could have understated or overstated their depressive symptoms. The choice, itself, of participating in the online survey may mirror some level of bias related to the personal traits and characteristics of the students. We have estimated the occurrence of depression among medical students using a self-reported inventory (BDI-II), there were no clinical assessments supervised by psychiatrists. Consequently, the diagnostic value may be restricted, and further psychiatric interviews are required to validate our results. Other students' characteristics that were correlated to the development of depressive symptoms were not explored among participants, such as emotional intelligence, coping skills, social support, religious beliefs, personality characteristics, and substance use disorders.

CONCLUSION

These findings give insight into Tunisian medical students' mental health issues and comorbidities. It is a hopeful request for decision-makers and academic authorities to take serious measures and offer effective interventions to minimize the currency of psychological distress among this subpopulation. To date, this is the largest study on depression among Tunisian and Maghrebian medical students. Yet, further research is recommended to explore other correlated factors and to evaluate the effectiveness of these measures on depression levels among medical students.

ARTICLE HIGHLIGHTS

Research background

Most medical schools in the world (including Tunisia) still recruit their students based solely on the university entrance exam score. Students' motivation, though being a crucial conjecture in their academic performance and well-being, has never been conventionally and structurally assessed in Tunisia. As a result, many students simply choose the medical field due to social codes, family influences, and cultural norms.

Research motivation

It is crucial for an educational institution to assess the mental status of students and its associated factors.

Research objectives

To assess the prevalence of depressive symptoms among Tunisian medical students and to evaluate its associated factors.

Research methods

This is an online survey of students from the four Tunisian medical faculties using Beck's depression questionnaire.

Research results

Sixty-four percent ($n = 728$) of the participants had depressive symptoms. Female gender, low socioeconomic level,

smoking habits and history of mental disorder, performing leisure and physical activities, satisfaction toward a career choice, and happiness perception were the main prognostic factors for depression among medical students.

Research conclusions

These findings give insight into mental health issues and comorbidity among Tunisian medical students. It is a hopeful request for decision-makers and academic authorities to take serious measures and offer effective interventions to minimize the currency of psychological distress among this subpopulation.

Research perspectives

Further studies are needed to explore other correlated factors (such as emotional intelligence, coping skills, social support, religious beliefs, and personality characteristics) and to evaluate the effectiveness of these measures on depression levels among Tunisian medical students.

FOOTNOTES

Author contributions: Amamou B, Alouani S, Ben Haouala A, Alouani S, Tlili MA, Mhalla A, Zaafrane F, and Gaha L contributed substantially to study conception and design, and data acquisition, analysis, and interpretation, and participated in drafting the manuscript or revising it critically for intellectual content; all authors approved the final version to be published.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of the Faculty of Medicine of Monastir (approval No. 3067).

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

Conflict-of-interest statement: The authors declare that they have no conflict of interest to disclose.

Data sharing statement: The data presented in this study are available on request from the corresponding author.

Country/Territory of origin: Tunisia

ORCID number: Badii Amamou 0000-0001-5079-6252; Amjed Ben Haouala 0000-0002-6058-244X; Ahmed Mhalla 0000-0002-9787-3478.

S-Editor: Chen YL
L-Editor: Wang TQ
P-Editor: Chen YL

REFERENCES

1 **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]

2 **Vilagut G**, Forero CG, Barbaglia G, Alonso J. Screening for Depression in the General Population with the Center for Epidemiologic Studies Depression (CES-D): A Systematic Review with Meta-Analysis. *PLoS One* 2016; **11**: e0155431 [PMID: 27182821 DOI: 10.1371/journal.pone.0155431]

3 **January J**, Madhombiro M, Chipamaunga S, Ray S, Chingono A, Abas M. Prevalence of depression and anxiety among undergraduate university students in low-and middle-income countries: a systematic review protocol. *Syst Rev* 2018; **7**: 57 [PMID: 29636088 DOI: 10.1186/s13643-018-0723-8]

4 **Mahroon ZA**, Borgan SM, Kamel C, Maddison W, Royston M, Donnellan C. Factors Associated with Depression and Anxiety Symptoms Among Medical Students in Bahrain. *Acad Psychiatry* 2018; **42**: 31-40 [PMID: 28664462 DOI: 10.1007/s40596-017-0733-1]

5 **Rotenstein LS**, Ramos MA, Torre M, Segal JB, Peluso MJ, Guille C, Sen S, Mata DA. Prevalence of Depression, Depressive Symptoms, and Suicidal Ideation Among Medical Students: A Systematic Review and Meta-Analysis. *JAMA* 2016; **316**: 2214-2236 [PMID: 27923088 DOI: 10.1001/jama.2016.17324]

6 **Survey Monkey**. Free online survey software and questionnaire tool. [cited 3 January 2021]. Available from: https://www.surveymonkey.com/welcome/sem/

7 **Smarr KL**, Keefer AL. Measures of depression and depressive symptoms: Beck Depression Inventory-II (BDI-II), Center for Epidemiologic Studies Depression Scale (CES-D), Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS), and Patient Health Questionnaire-9 (PHQ-9). *Arthritis Care Res (Hoboken)* 2011; **63** Suppl 11: S454-S466 [PMID: 22588766 DOI: 10.1002/acr.20556]

8 **Beck AT**, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. *J Pers Assess* 1996;

67: 588-597 [PMID: 8991972 DOI: 10.1207/s15327752jpa6703_13]
9 **Puthran R**, Zhang MW, Tam WW, Ho RC. Prevalence of depression amongst medical students: a meta-analysis. *Med Educ* 2016; **50**: 456-468 [PMID: 26995484 DOI: 10.1111/medu.12962]
10 **Abdel Wahed WY**, Hassan SK. Prevalence and associated factors of stress, anxiety and depression among medical Fayoum University students. *Alex J Med* 2017; **53**: 77-84 [DOI: 10.1016/j.ajme.2016.01.005]
11 **Abdelaziz AMY**, Alotaibi KT, Alhurayyis JH, Alqahtani TA, Alghamlas AM, Algahtani HM, Jahrami HA. The association between physical symptoms and depression among medical students in Bahrain. *Int J Med Educ* 2017; **8**: 423-427 [PMID: 29252203 DOI: 10.5116/ijme.5a2d.16a3]
12 **Vijayalakshmi P**, Thimmaiah R, Gandhi S, BadaMath S. Eating Attitudes, Weight Control Behaviors, Body Image Satisfaction and Depression Level Among Indian Medical and Nursing Undergraduate Students. *Community Ment Health J* 2018; **54**: 1266-1273 [PMID: 30159637 DOI: 10.1007/s10597-018-0333-x]
13 **Angkurawaranon C**, Jiraporncharoen W, Sachdev A, Wisetborisut A, Jangiam W, Uaphanthasath R. Predictors of quality of life of medical students and a comparison with quality of life of adult health care workers in Thailand. *Springerplus* 2016; **5**: 584 [PMID: 27247881 DOI: 10.1186/s40064-016-2267-5]
14 **Wege N**, Muth T, Li J, Angerer P. Mental health among currently enrolled medical students in Germany. *Public Health* 2016; **132**: 92-100 [PMID: 26880490 DOI: 10.1016/j.puhe.2015.12.014]
15 **Vaysse B**, Gignon M, Zerkly S, Ganry O. [Alcohol, tobacco, cannabis, anxiety and depression among second-year medical students. Identify in order to act]. *Sante Publique* 2014; **26**: 613-620 [PMID: 25490220 DOI: 10.1016/S0924-9338(15)30412-0]
16 **Marzouk M**, Ouanes-Besbes L, Ouanes I, Hammouda Z, Dachraoui F, Abroug F. Prevalence of anxiety and depressive symptoms among medical residents in Tunisia: a cross-sectional survey. *BMJ Open* 2018; **8**: e020655 [PMID: 30037867 DOI: 10.1136/bmjopen-2017-020655]
17 **Koenig HG**. Research on religion, spirituality, and mental health: a review. *Can J Psychiatry* 2009; **54**: 283-291 [PMID: 19497160 DOI: 10.1177/070674370905400502]
18 **Dahlin M**, Joneborg N, Runeson B. Stress and depression among medical students: a cross-sectional study. *Med Educ* 2005; **39**: 594-604 [PMID: 15910436 DOI: 10.1111/j.1365-2929.2005.02176.x]
19 **Pokhrel NB**, Khadayat R, Tulachan P. Depression, anxiety, and burnout among medical students and residents of a medical school in Nepal: a cross-sectional study. *BMC Psychiatry* 2020; **20**: 298 [PMID: 32539732 DOI: 10.1186/s12888-020-02645-6]
20 **Bore M**, Kelly B, Nair B. Potential predictors of psychological distress and well-being in medical students: a cross-sectional pilot study. *Adv Med Educ Pract* 2016; **7**: 125-135 [PMID: 27042156 DOI: 10.2147/AMEP.S96802]
21 **Nasioudis D**, Palaiodimos L, Dagiasis M, Katsarou A, Ntouros E. Depression in military medicine cadets: a cross-sectional study. *Mil Med Res* 2015; **2**: 28 [PMID: 26557991 DOI: 10.1186/s40779-015-0058-x]
22 **Kebede MA**, Anbessie B, Ayano G. Prevalence and predictors of depression and anxiety among medical students in Addis Ababa, Ethiopia. *Int J Ment Health Syst* 2019; **13**: 30 [PMID: 31080499 DOI: 10.1186/s13033-019-0287-6]
23 **Van der Walt S**, Mabaso WS, Davids EL, De Vries PJ. The burden of depression and anxiety among medical students in South Africa: A cross-sectional survey at the University of Cape Town. *S Afr Med J* 2019; **110**: 69-76 [PMID: 31865946 DOI: 10.7196/SAMJ.2019.v110i1.14151]
24 **Coskun O**, Ocalan AO, Ocbe CB, Semiz HO, Budakoglu I. Depression and hopelessness in pre-clinical medical students. *Clin Teach* 2019; **16**: 345-351 [PMID: 31397111 DOI: 10.1111/tct.13073]
25 **Roh MS**, Jeon HJ, Kim H, Han SK, Hahm BJ. The prevalence and impact of depression among medical students: a nationwide cross-sectional study in South Korea. *Acad Med* 2010; **85**: 1384-1390 [PMID: 20453812 DOI: 10.1097/ACM.0b013e3181df5e43]
26 **Shawahna R**, Hattab S, Al-Shafei R, Tab'ouni M. Prevalence and factors associated with depressive and anxiety symptoms among Palestinian medical students. *BMC Psychiatry* 2020; **20**: 244 [PMID: 32429889 DOI: 10.1186/s12888-020-02658-1]
27 **Azad N**, Shahid A, Abbas N, Shaheen A, Munir N. Anxiety And Depression In Medical Students Of A Private Medical College. *J Ayub Med Coll Abbottabad* 2017; **29**: 123-127 [PMID: 28712190]
28 **Dyrbye LN**, Wittlin NM, Hardeman RR, Yeazel M, Herrin J, Dovidio JF, Burke SE, Cunningham B, Phelan SM, Shanafelt TD, van Ryn M. A Prognostic Index to Identify the Risk of Developing Depression Symptoms Among U.S. Medical Students Derived From a National, Four-Year Longitudinal Study. *Acad Med* 2019; **94**: 217-226 [PMID: 30188367 DOI: 10.1097/ACM.0000000000002437]
29 **Fryers T**, Melzer D, Jenkins R. Social inequalities and the common mental disorders: a systematic review of the evidence. *Soc Psychiatry Psychiatr Epidemiol* 2003; **38**: 229-237 [PMID: 12719837 DOI: 10.1007/s00127-003-0627-2]
30 **Kessler RC**, Cleary PD. Social class and psychological distress. *Am Sociol Rev* 1980; **45**: 463-478 [PMID: 7406359]
31 **Muntaner C**, Eaton WW, Miech R, O'Campo P. Socioeconomic position and major mental disorders. *Epidemiol Rev* 2004; **26**: 53-62 [PMID: 15234947 DOI: 10.1093/epirev/mxh001]
32 **Skapinakis P**, Weich S, Lewis G, Singleton N, Araya R. Socio-economic position and common mental disorders. Longitudinal study in the general population in the UK. *Br J Psychiatry* 2006; **189**: 109-117 [PMID: 16880479 DOI: 10.1192/bjp.bp.105.014449]
33 **Butterworth P**, Rodgers B, Windsor TD. Financial hardship, socio-economic position and depression: results from the PATH Through Life Survey. *Soc Sci Med* 2009; **69**: 229-237 [PMID: 19501441 DOI: 10.1016/j.socscimed.2009.05.008]
34 **Butterworth P**, Cherbuin N, Sachdev P, Anstey KJ. The association between financial hardship and amygdala and hippocampal volumes: results from the PATH through life project. *Soc Cogn Affect Neurosci* 2012; **7**: 548-556 [PMID: 21551226 DOI: 10.1093/scan/nsr027]
35 **Hamasha AA**, Kareem YM, Alghamdi MS, Algarni MS, Alahedib KS, Alharbi FA. Risk indicators of depression among medical, dental, nursing, pharmacology, and other medical science students in Saudi Arabia. *Int Rev Psychiatry* 2019; **31**: 646-652 [PMID: 31117837 DOI: 10.1080/09540261.2019.1584095]
36 **Asal AR**, Abdel-Fattah MM. Prevalence, symptomatology, and risk factors for depression among high school students in Saudi Arabia. *Neurosciences (Riyadh)* 2007; **12**: 8-16 [PMID: 21857611 DOI: 10.5964/ejop.v2i3.335]
37 **Pagnin D**, de Queiroz V. Influence of burnout and sleep difficulties on the quality of life among medical students. *Springerplus* 2015; **4**: 676 [PMID: 26558179 DOI: 10.1186/s40064-015-1477-6]
38 **Pillay N**, Ramlall S, Burns JK. Spirituality, depression and quality of life in medical students in KwaZulu-Natal. *S Afr J Psychiatr* 2016; **22**: 731 [PMID: 30263152 DOI: 10.4102/sajpsychiatry.v22i1.731]
39 **Masri R**, Kadhum M, Farrell SM, Khamees A, Al-Taiar H, Molodynski A. Wellbeing and mental health amongst medical students in Jordan: a descriptive study. *Int Rev Psychiatry* 2019; **31**: 619-625 [PMID: 31578112 DOI: 10.1080/09540261.2019.1670402]

40 **Borst JM**, Frings-Dresen MH, Sluiter JK. Prevalence and incidence of mental health problems among Dutch medical students and the study-related and personal risk factors: a longitudinal study. *Int J Adolesc Med Health* 2016; **28**: 349-355 [PMID: 26234948 DOI: 10.1515/ijamh-2015-0021]

41 **Geisner IM**, Mallett K, Kilmer JR. An examination of depressive symptoms and drinking patterns in first year college students. *Issues Ment Health Nurs* 2012; **33**: 280-287 [PMID: 22545634 DOI: 10.3109/01612840.2011.653036]

42 **Archie S**, Zangeneh Kazemi A, Akhtar-Danesh N. Concurrent binge drinking and depression among Canadian youth: prevalence, patterns, and suicidality. *Alcohol* 2012; **46**: 165-172 [PMID: 21824740 DOI: 10.1016/j.alcohol.2011.07.001]

43 **Mason WA**, Kosterman R, Haggerty KP, Hawkins JD, Redmond C, Spoth RL, Shin C. Dimensions of adolescent alcohol involvement as predictors of young-adult major depression. *J Stud Alcohol Drugs* 2008; **69**: 275-285 [PMID: 18299769 DOI: 10.15288/jsad.2008.69.275]

44 **O'Hara RE**, Cooper ML. Bidirectional associations between alcohol use and sexual risk-taking behavior from adolescence into young adulthood. *Arch Sex Behav* 2015; **44**: 857-871 [PMID: 25808720 DOI: 10.1007/s10508-015-0510-8]

45 **Keating XD**, Guan J, Piñero JC, Bridges DM. A meta-analysis of college students' physical activity behaviors. *J Am Coll Health* 2005; **54**: 116-125 [PMID: 16255324 DOI: 10.3200/JACH.54.2.116-126]

46 **Valkenborghs SR**, Noetel M, Hillman CH, Nilsson M, Smith JJ, Ortega FB, Lubans DR. The Impact of Physical Activity on Brain Structure and Function in Youth: A Systematic Review. *Pediatrics* 2019; **144** [PMID: 31554668 DOI: 10.1542/peds.2018-4032]

47 **Rebar AL**, Stanton R, Geard D, Short C, Duncan MJ, Vandelanotte C. A meta-meta-analysis of the effect of physical activity on depression and anxiety in non-clinical adult populations. *Health Psychol Rev* 2015; **9**: 366-378 [PMID: 25739893 DOI: 10.1080/17437199.2015.1022901]

48 **Conijn M**, Boersma HJ, van Rhenen W. [Burnout in Dutch medical students: prevalence and causes]. *Ned Tijdschr Geneeskd* 2015; **159**: A8255 [PMID: 25923494]

49 **Moak ZB**, Agrawal A. The association between perceived interpersonal social support and physical and mental health: results from the National Epidemiological Survey on Alcohol and Related Conditions. *J Public Health (Oxf)* 2010; **32**: 191-201 [PMID: 19864495 DOI: 10.1093/pubmed/fdp093]

50 **Samaranayake CB**, Fernando AT. Satisfaction with life and depression among medical students in Auckland, New Zealand. *N Z Med J* 2011; **124**: 12-17 [PMID: 21959631]

51 **Karaoglu N**, Seker M. Anxiety and depression in medical students related to desire for and expectations from a medical career. *West Indian Med J* 2010; **59**: 196-202 [PMID: 21275126]

World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatry 2023 October 19; 13(10): 784-792

DOI: 10.5498/wjp.v13.i10.784

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Observational Study

Correlation and pathways of behavioral activation systems mediating physical activity level and depressive symptoms among college students

Jiang-Hua Zhu, Shu-Fan Li, Peng Wang, Xin Xin, Qun Zhao, Si-Cheng Chen, Xing Wang

Specialty type: Psychiatry

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Alkhatib AJ, Jordan; Girardi P, Italy; Shalaby MN, Egypt; Stogov MV, Russia

Received: June 5, 2023
Peer-review started: June 5, 2023
First decision: July 4, 2023
Revised: July 15, 2023
Accepted: August 7, 2023
Article in press: August 7, 2023
Published online: October 19, 2023

Jiang-Hua Zhu, Qun Zhao, Department of Physical Education, Donghua University, Shanghai 201620, China

Shu-Fan Li, Peng Wang, Xin Xin, Si-Cheng Chen, Xing Wang, School of Physical Education, Shanghai University of Sport, Shanghai 200438, China

Corresponding author: Xing Wang, PhD, Professor, School of Physical Education, Shanghai University of Sport, No. 399 Changhai Road, Yangpu District, Shanghai 200438, China. wangxing1933@sus.edu.cn

Abstract

BACKGROUND

Depression is a common mental disorder among college students. The main symptoms include being persistent low mood, sad emotional experiences, lack of pleasure, listlessness, and impaired cognitive function accompanied by tendencies of self-harm and suicide.

AIM

To clarify the pathways and effects of the behavioral activation system between physical activity and depressive symptoms in college students with depressive symptoms.

METHODS

This cross-sectional research screened 3047 college students. Of these, 472 had depressive symptoms, with a depression detection rate of 15.49%. Furthermore, 442 college students with depressive symptoms were analyzed. A one-way analysis of variance and Pearson's correlation, linear regression, and structural equation modeling analyses were used to explore the correlations and pathways of the interactions between the variables.

RESULTS

Depressive symptoms were significantly negatively correlated with physical activity (r = -0.175, $P < 0.001$), the behavioral activation system (r = -0.197, $P < 0.001$), and drive (r = -0.113, $P = 0.017$). Furthermore, it was negatively correlated with fun-seeking (FS) (r = -0.055, $P = 0.251$); however, it was not significant. Physical activity was significantly positively correlated with reward respons-

iveness (RR) (r = 0.141, *P* = 0.003) and drive (r = 0.124, *P* = 0.009) and not significantly positively correlated with FS (r = 0.090, *P* = 0.058). The mediating effect of RR between physical activity and depressive symptoms was significant [B = -0.025, 95% confidence interval (95%CI): -0.051 to -0.008, *P* = 0.001]. The direct and total effects of physical activity on depressive symptoms and were significant (B = -0.150, 95%CI: -0.233 to -0.073, *P* < 0.001; B = -0.175, 95%CI: -0.260 to -0.099, *P* < 0.001), respectively.

CONCLUSION

As physical activity levels increased, depression scores among college students decreased. The mediating effect of RR between physical activity and depressive symptoms was significant. Therefore, colleges and universities should encourage college students with depression to increase their physical activity and improve their behavioral activation system. Particular attention should be paid to RR, which may reduce the prevalence of depressive symptoms.

Key Words: College students; Physical activity; Depressive symptoms; Behavioral activation system; Mediating role

Core Tip: This study explored the specificity of the behavioral activation system for physical activity and reward motivation in college students with different depressive symptom scores. Furthermore, the inter-relationships among the three variables were examined *via* a cross-sectional research design. Pathways of the behavioral activation system that mediated the effect of physical activity level on depressive symptoms in college students with depressive symptoms were clarified.

Citation: Zhu JH, Li SF, Wang P, Xin X, Zhao Q, Chen SC, Wang X. Correlation and pathways of behavioral activation systems mediating physical activity level and depressive symptoms among college students. *World J Psychiatry* 2023; 13(10): 784-792
URL: https://www.wjgnet.com/2220-3206/full/v13/i10/784.htm
DOI: https://dx.doi.org/10.5498/wjp.v13.i10.784

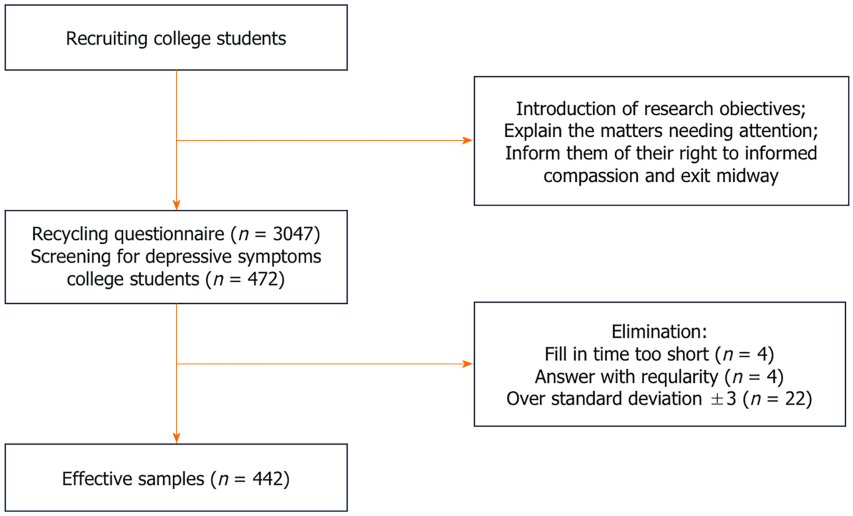
INTRODUCTION

Depression, a disabling mental disorder, seriously endangers the lives and health of people and ranks the 13th highest in the number of disability-adjusted life-years among all illnesses and injuries worldwide[1]. It is a common mental disorder among college students, with a detection rate of over 30%[2,3]. The main symptoms include persistent low mood, sad emotional experiences, lack of pleasure, listlessness, and impaired cognitive function, with tendencies of self-harm and suicide. The World Health Organization predicted that depression would rank first in the disease burden worldwide by 2030[4].

The behavioral activation system, also known as reward motivation, is located in the midbrain dopamine loop and refers to the convergent motivation for reward, promoting goal-directed behavior to obtain the reward, and producing positive emotions or hedonic pleasure experiences[5]. It is divided into three factors: Reward responsiveness (RR), drive, and fun-seeking (FS)[6]. Impaired reward function, or anhedonia, is a core symptom of depression, and deficits in the behavioral activation system can serve as functional deficits in depressive symptoms[7,8].

An inter-relationship between physical activity, depressive symptoms, and behavioral activation system exists. Appropriate physical activity significantly alleviates clinical symptoms in people with depressive symptoms[9-11] and reduces anxiety and depression levels in college students[12]. In addition, exercise is also strongly associated with behavioral activation system, such as enhancing the midbrain-striatal dopamine (DA) system and improving the brain reward function in adolescents[13]. Physical activity also positively affects the behavioral activation system, and thereby alleviates depressive symptoms.

Previous studies[7-11,13] examined the two-sided relationship between physical activity, behavioral activation system, and depressive symptoms. Physical activity enhanced the behavioral activation system and reduced depressive symptoms. Furthermore, the behavioral activation system acted as an influencing factor for depressive symptoms. However, whether the behavioral activation system intervened in the relationship between physical activity and depressive symptoms remains unclear. Furthermore, its pathways of actions, how it intervened through the three subdimensions of the behavioral activation system, and whether the effects were consistent also remain unclear. Therefore, this study conducted a cross-sectional research that aimed to provide a theoretical basis for a deeper understanding of the relationship between human behavior, emotion, and the nervous system. Furthermore, we aimed to provide a reference for researchers and college administrators. This study proposed the following research hypotheses: (1) Physical activity and the behavioral activation system would have specificity among college students with different depressive symptom scores; (2) Physical activity, the behavioral activation system, and depressive symptoms would be closely related; and (3) Behavioral activation system would mediate the relationship between physical activity and depressive symptoms with different effects of the sub-dimensions.



DOI: 10.5498/wjp.v13.i10.784

Figure 1 Flow chart of the participants recruitment.

MATERIALS AND METHODS

Participants

This study used a cross-sectional research design. In total, 3047 college students were recruited online based on voluntary participation to complete a questionnaire. College students with depressive symptoms were screened *via* the Beck Depression Inventory (BDI)-II, and 472 students had depressive symptoms, with a depression detection rate of 15.49% (Figure 1). Inclusion criteria were participants who were college students, aged 18-26 years, had a score of ≥ 14 on the BDI-II, with a scores of 14-19, 20-28, and 29-63 indicating mild, moderate, and severe depression, respectively, and had no other psychiatric disorders and no brain injury. The exclusion criteria were participants who took drugs, such as barbiturates, benzodiazepines, and chloral hydrate, majored in sports, and had contraindications for exercise. After 30 invalid questionnaires with regular responses, a short response time (< 3 min), or outliers that exceeded the standard deviation ± 3 were excluded, 442 valid questionnaires (93.64%) were obtained. This study was approved by the Ethics Committee of the Shanghai University of Sport (102772021RT007).

Measures

General information questionnaire: Participants' basic information, such as age, sex, height, weight, and family status were obtained.

International physical activity questionnaire short form: This 7-item questionnaire has been widely used to measure physical activity among Chinese university students. Of these, six questions enquired regarding individuals' physical activity, which included high-intensity and moderate-intensity physical activity, and walking, and the frequency of different intensity activities for one week and the cumulative time per day. The weekly physical activity levels were calculated and divided into high, medium, and low groups according to the relevant criteria. The higher the group level, the greater the intensity of daily physical activity. This scale's retest reliability coefficient was 0.718[14].

Behavioral inhibition/activation system scale: A revised Chinese version by Li *et al*[15] was adopted with 18 items, which included two dimensions: Behavioral inhibition and activation. The behavioral activation dimension, also known as the behavioral activation system, was selected and contained three subfactors: RR, drive, and FS. Each item was scored on a scale from 1 (fully agree) to 4 (fully disagree). Cronbach's alpha was 0.759[15].

BDI-II: This widely used 21-item self-assessment scale assessed depressive symptoms. Responses were rated on a 4-point Likert scale that ranged from 0 (no symptoms) to 3 (severe symptoms). Total scores of 0-13, 14-19, 20-28, and 29-63 indicated no, mild, moderate, and severe depression, respectively. The internal consistency coefficient was 0.948[16].

Statistical analysis

Measures were expressed as mean ± SD, and the results were retained to three decimal places. For questionnaire data that were not missing at random, interpolation of the means of the same category was performed to avoid biased estimated coefficients *via* the simple deletion method. One-way analysis of variance and least significant difference post-hoc multiple tests were applied to compare the specificity of physical activity and behavioral activation system among college students with different depressive symptom scores. Pearson's correlation and linear regression analyses were performed to explore the relationships among physical activity, depressive symptoms, and behavioral activation system. Two-tailed tests were adopted for statistical inference of all parameters, and the test level α was set at 0.05. $P < 0.05$, $P < 0.01$, and $P < 0.001$ all indicated statistical significance.

Table 1 Differences in physical activity and behavioral activation system in college students with different depressive symptom scores

Variables	Whole (442)	Levels of depressive symptoms			F-value	*P* value	Post hoc multiple comparisons		
		Severe (*n* = 58)	Moderate (*n* = 190)	Mild (*n* = 194)			Severe *vs* Moderate	Severe *vs* Mild	Moderate *vs* Mild
Physical activity (MET-min/week)	1308 ± 954	944 ± 617	1333 ± 1003	1392 ± 967	5.149	0.006	0.006	0.002	0.535
Reward responsiveness	11.88 ± 2.033	11.03 ± 2.232	11.81 ± 2.043	12.21 ± 1.885	7.865	< 0.001	< 0.001	0.010	0.053
Drive	11.22 ± 2.064	10.71 ± 2.656	11.15 ± 2.008	11.45 ± 1.888	3.129	0.045	0.154	0.016	0.152
Fun-seeking	14.17 ± 2.270	13.78 ± 2.968	14.10 ± 2.217	14.36 ± 2.067	1.654	0.192	0.341	0.085	0.260

Table 2 Regression analysis of each variable

Independent variables	B	95%CI		Beta	Coefficient significance test		SE	Collinearity diagnostics	
		Lower limit	Upper limit		*t*-value	*P* value		Tolerance	VIF
Reward responsiveness	-0.176	-0.268	-0.084	-0.176	-3.766	< 0.001[a]	0.047	0.980	1.020
Physical activity	-0.116	-0.242	-0.058	-0.116	-3.217	0.001	0.047	0.980	1.020

[a]*P* < 0.001.

Model summary: F = 14.259[a]; R = 0.247; R^2 = 0.061; Adjusted R^2 = 0.057. VIF: Variance inflation factor; 95%CI: 95% confidence interval.

Harman's single factor test was used to examine the effects of common method bias. Structural equation modeling was conducted to examine the role of behavioral activation system in mediating the relationship between physical activity and depressive symptoms. The non-parametric percentage bootstrap method was adopted for parameter estimation in the path analysis. Number of samples was set at 5000, with a bias-corrected 95% confidence interval (95%CI) for the product of the mediated paths, without 0 defining the mediating effect as statistically significant. Data calculations were performed using SPSS Statistics version 23.0, and Amos version 23.0.

RESULTS

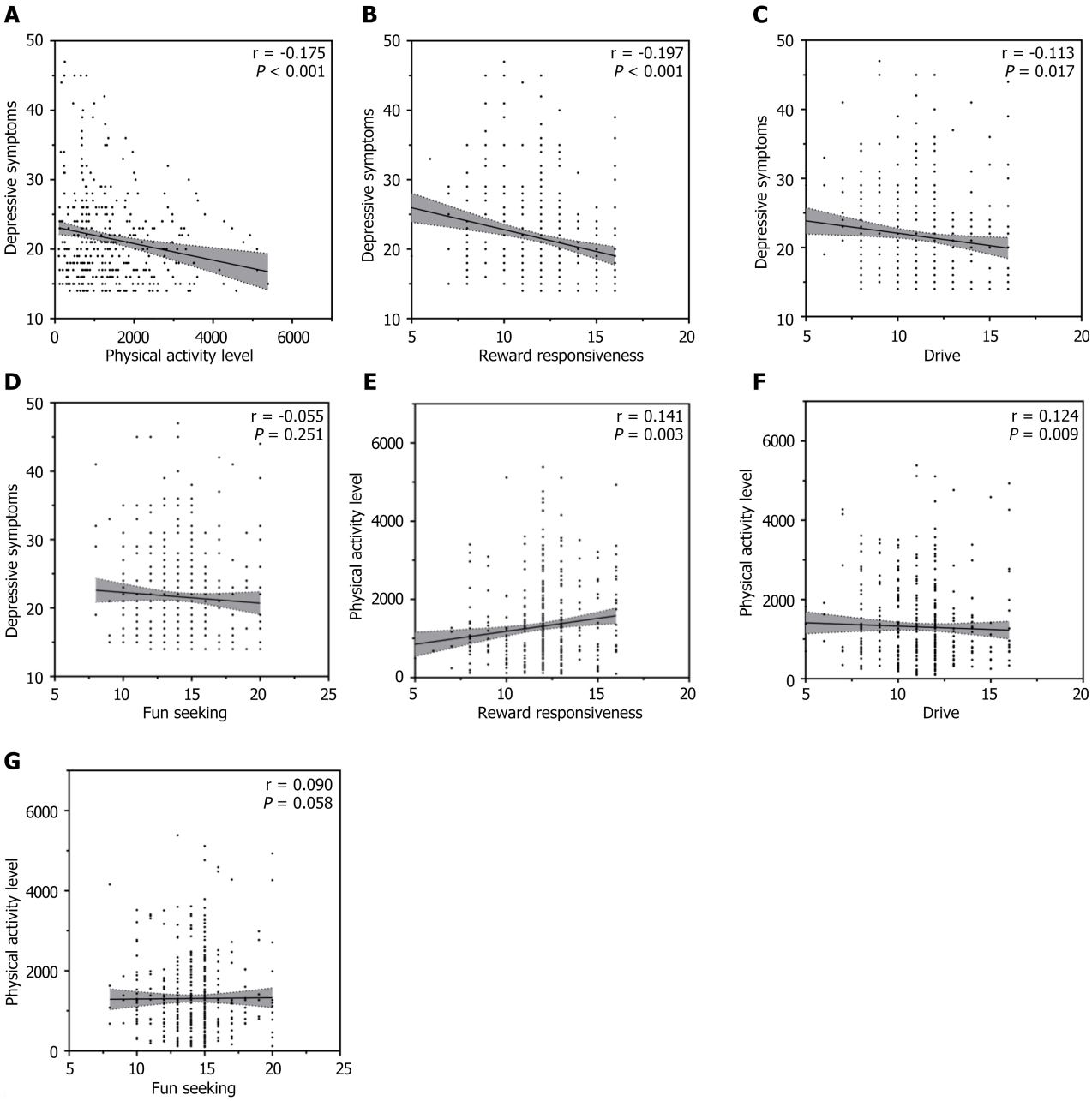
Specificity of physical activity and behavioral activation system in college students with different depressive symptom scores

There were no significant differences in FS behavior, physical activity, RR, and drive ($P < 0.05$) among college students with different depressive symptom scores. Post-hoc multiple comparisons indicated significant differences in physical activity and RR ($P < 0.05$) between college students with severe depressive symptoms and those with moderate depressive symptoms. In addition, there were also differences in physical activity, RR, and drive ($P < 0.01$) between those with severe depressive symptoms and those with mild depressive symptoms. Other indicators had no statistically significant differences. See Table 1 for further details.

Relationship between physical activity, depressive symptoms and behavioral activation system

Depressive symptoms were significantly negatively correlated with physical activity (r = -0.175, $P < 0.001$), RR (r = -0.197, $P < 0.001$), and drive (r = -0.113, $P = 0.017$). Furthermore, it was also negatively correlated with FS (r = -0.055, $P = 0.251$); however, it was not significant. Physical activity was significantly positively correlated with RR (r = 0.141, $P = 0.003$) and drive (r = 0.124, $P = 0.009$), and not significantly positively correlated with FS (r = 0.090, $P = 0.058$). Further details are shown in Figure 2.

To examine the extent of which physical activity and behavioral activation system explained depressive symptoms and explore the feasibility of the structural relationship model, depressive symptoms were considered as dependent variables, and physical activity, RR, drive, and FS as independent variables. Furthermore, a linear regression analysis was performed *via* stepwise regression. The goodness-of-fit of the prediction model was demonstrated (R = 0.247, R^2 = 0.061, adjusted R^2 = 0.057, and changed variable F = 10.349), which excluded drive and FS. As shown in Table 2, RR and physical activity were negative influencing factors, with 6.1% explanatory power for depressive symptom scores. The tolerance of each independent variable was > 0.1, and the variance inflation factor was < 5; thus, the effect of multicollinearity was excluded.



DOI: 10.5498/wjp.v13.i10.784

Figure 2 Correlations among the variables. A: Depressive symptoms were significantly negatively correlated with physical activity; B: Depressive symptoms were significantly negatively correlated with reward responsiveness; C: Depressive symptoms were significantly negatively correlated with drive; D: Depressive symptoms were negatively, but not significantly, associated with fun-seeking; E: Physical activity was significantly positively correlated with reward responsiveness; F: Physical activity was significantly positively correlated with drive; G: Physical activity were positively, but not significantly, associated with fun-seeking.

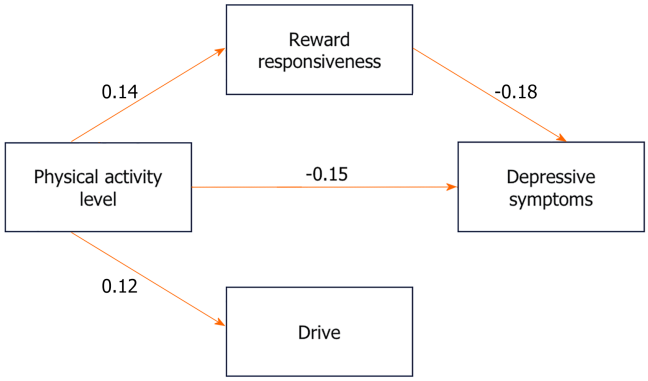
Construction and validation of a structural relationship model of indicators of physical activity, behavioral activation system, and depressive symptoms

To assess for common method bias, a validation factor analysis was conducted on the International Physical Activity Questionnaire, the Behavioral Activation System Scale, and the BDI *via* Harman's single factor test, nine factors with characteristic roots greater than 1 were obtained. The amount of variance explained by the first factor was 17.980%, which was less than the critical value of 40%. Therefore, the effect of common method bias was excluded. Based on the inter-relationships among physical activity, behavioral activation system, and depressive symptoms in college students, a model was established with physical activity, depressive symptoms, and behavioral activation system as the independent, dependent, and mediating variables, respectively. Mediated paths with insignificant coefficients were individually removed and recalculated until all mediated path coefficients passed the bootstrap significance test. Discrepancies divided by degrees of freedom (CMIN/df) = 0.286, root mean square residual (RMR) = 0.006, root mean square error of approximation (RMSEA) < 0.001, goodness-of-fit index (GFI) = 1.000, normed fit index (NFI) = 0.999, and comparative fit index (CFI) = 1.000 reached the reference standards of CMIN/df < 3, RMR < 0.05, RMSEA < 0.08, GFI, NFI, and CFI > 0.9[17], which indicated that the structural equation model fit well and was reasonable and reliable. The

Table 3 List of the intermediary effect coefficients

Types of effects	B	SE	Bias-corrected 95%CI		
			Lower limit	Upper limit	*P* value
Mediating effect of reward responsiveness	-0.025	0.011	-0.051	-0.008	0.001
Path coefficient of physical activity on drive	0.124	0.045	0.034	0.211	0.007
Direct effect	-0.150	0.041	-0.233	-0.073	< 0.001
Total effect	-0.175	0.040	-0.260	-0.099	< 0.001

95%CI: 95% confidence interval.



DOI: 10.5498/wjp.v13.i10.784

Figure 3 Schematic diagram of the structural relationship model between physical activity, behavioral activation system, and depressive symptom indicators in college students with depressive symptoms. There are direct pathways and reward responsiveness-mediated indirect pathways between physical activity and depressive symptoms.

path analysis is shown in Figure 3, and the results of the mediating effect test are presented in Table 3. The path coefficients of physical activity on FS were not significant. Furthermore, those of FS and driving on depressive symptom scores were not significant, and were excluded. There were significant path coefficient for physical activity on drive (B = 0.124, 95%CI: 0.034 to 0.211, P = 0.007), mediating effect mediated by RR (B = -0.025, 95%CI: -0.051 to -0.008, P = 0.001), direct effect of physical activity on depressive symptoms (B = -0.150, 95%CI: -0.233 to -0.073, P < 0.001), and total effect of physical activity on depressive symptoms (B = -0.175. 95%CI: -0.260 to -0.099, P < 0.001).

DISCUSSION

These results showed that the higher the level of physical activity among college students with depressive symptoms, the higher the behavioral activation system and lower their depressive symptom scores. Furthermore, the direct effect of physical activity on depressive symptoms was significant. The results supported those of previous studies on the relationship between behavioral activation system and depressive symptoms. Furthermore, our findings were generally consistent with previous results. Takagaki *et al*[18] found a negative association between the behavioral activation system and depressive symptoms among 18-19 years old college students with depressive symptoms in a Japanese University. Absence of pleasure was a core symptom of depression[19] which was related to the dysfunction of the brain's DA reward system[20]. Deficits in the reward system served as a susceptibility factor and predictor of depression, with state independence and heritability[21,22]. A cross-sectional study found that college students with higher levels of physical activity had lower detection rates of depressive symptoms and insufficient physical activity was a risk factor for depressive symptoms among college students. Experimental studies confirmed that increased physical activity was effective in improving depressive symptoms and stimulated the secretion of neurotransmitters, which increased the behavioral activation system and also alleviated depressive symptoms.

This study showed that only RR mediated the relationship between physical activity and depressive symptoms. Physical activity promoted the secretion of neurotransmitters, such as DA in the brain, enhanced the neuroplasticity of the DA system, and improved the reward function. This enhanced the RR and contributed to the maintenance and regulation of good emotions in individuals, promoted the generation of positive emotions, and suppressed negative emotions[23]. High reward responses acted as a protective factor against depression[24]. Furthermore RR purely reflected extroversion and convergent motivation[25], which maintained and regulated individual behavior. Hence, impulsive behaviors that met short-term interests were subordinated to needs more closely related to the individual's long-term

interests[26]. High RR prompted a positive response to rewards. It enhanced an individual's ability to obtain pleasurable experiences to avoid the exacerbation of their depressive symptoms[27,28]. Only the RR pathway mediated the relationship between physical activity and depressive symptoms. A possible reason was that RR, as the initial evaluation of reward, measured early "reward interest," "goal-drive", and "persistence." Furthermore, its effect on depressive symptoms may precede the other two dimensions. Reasons why drive and FS did not mediate the relationship between physical activity and depressive symptoms were drive referred to the degree of willingness to exert effort to obtain a reward and measured late "reward responsiveness" and "impulsivity;" FS was a continuous evaluation of the reward. Hence, drive and FS were more significant for major depression, and better predictors of treatment effect[29,30]. Our participants had different conditions, and relatively few individuals reported severe depression symptoms.

This study has some limitations. First, the data were from subjective reports, which may have some bias. Furthermore objective indicators are recommended for future measurements. This study was conducted as a cross-sectional study. Hence, longitudinal studies are required to further confirm the pathways of action.

CONCLUSION

The higher the level of physical activity, the higher the behavioral activation system and lower the depressive symptom score in college students with depression. Furthermore, there was only one pathway of action in the behavioral activation system, RR, which had a significant mediating effect between physical activity and depressive symptoms. Therefore, colleges and universities should encourage college students with depression to increase their physical activity and improve their behavioral activation system. Particular attention should be paid to RR, which may reduce the prevalence of depressive symptoms.

ARTICLE HIGHLIGHTS

Research background

Depression is a common mental disorder among college students. Key symptoms include persistent depressed mood, sad emotional experiences, lack of pleasure, listlessness, and impaired cognitive function, accompanied by self-harm and suicidal tendencies.

Research motivation

Reduce the prevalence of depressive symptoms in college students.

Research objectives

Elucidating pathways and effects of behavioral activation systems between physical activity and depressive symptoms in college students with depressive symptoms.

Research methods

One-way analysis of variance and Pearson correlation, linear regression, and structural equation modeling were used to explore the correlation and pathway of interactions between variables.

Research results

The mediating effect of reward responses between physical activity and depressive symptoms was significant [B = -0.025, 95% confidence interval (95%CI): -0.051 to -0.008, $P = 0.001$]. The direct and total effects of physical activity on depressive symptoms were significant ((B = -0.150, 95%CI: -0.233 to -0.073, $P < 0.001$; B = -0.175, 95%CI: -0.260 to -0.099, $P < 0.001$, respectively).

Research conclusions

Colleges and universities should encourage college students with depression to increase physical activity and improve behavioral activation systems. Particular attention should be paid to the ability to reward responses, which may reduce the prevalence of depressive symptoms.

Research perspectives

It is recommended to use objective measurement tools in future measurements; longitudinal studies are needed to further define the course of action.

FOOTNOTES

Author contributions: Zhu JH wrote the original manuscript and collected the data; Li SF collected and analyzed the data; Wang P wrote part of the manuscript; Xin X collected the data; Zhao Q curated the data; Chen SC curated the data; Wang X reviewed and edited.

Supported by Shanghai Key Lab of Human Performance (Shanghai University of sport), No. 11DZ2261100.

Institutional review board statement: This study was approved by the ethical committee of Shanghai University of Sport (102772021RT007), and all procedures were performed according to the relevant guidelines and regulations.

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 declare no conflicts of interest.

Data sharing statement: No additional data is available.

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.

Country/Territory of origin: China

ORCID number: Jiang-Hua Zhu 0000-0002-1100-2496; Shu-Fan Li 0000-0003-3389-1498; Peng Wang 0000-0001-6786-7387; Xin Xin 0000-0003-2876-8970; Qun Zhao 0009-0000-2184-3945; Si-Cheng Chen 0000-0002-6918-6988; Xing Wang 0000-0002-3230-3482.

S-Editor: Fan JR
L-Editor: A
P-Editor: Chen YX

REFERENCES

1 **GBD 2019 Mental Disorders Collaborators**. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Psychiatry* 2022; **9**: 137-150 [PMID: 35026139 DOI: 10.1016/S2215-0366(21)00395-3]

2 **Zhai WH**, Zhang Qi, Yan J. [Meta-analysis of the detection rate of depressive symptoms and related factors among Chinese university students before and after the new crown pneumonia epidemic]. *Zhongguo Xuexiao Weisheng* 2022; **43**: 1055-1060 [DOI: 10.16835/j.cnki.1000-9817.2022.07.023]

3 **Wang MY**, Han FF, Liu J, Huang KL, Peng HY, Huang MT, Zhao ZH. [A meta-analysis of the detection rate of depressive symptoms and related factors among college students]. *Zhongguo Xinliweisheng Zazhi* 2020; **34**: 1041-1047 [DOI: 10.3969/j.issn.1000-6729.2020.12.012]

4 **Ng M**, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, Mullany EC, Biryukov S, Abbafati C, Abera SF, Abraham JP, Abu-Rmeileh NM, Achoki T, AlBuhairan FS, Alemu ZA, Alfonso R, Ali MK, Ali R, Guzman NA, Ammar W, Anwari P, Banerjee A, Barquera S, Basu S, Bennett DA, Bhutta Z, Blore J, Cabral N, Nonato IC, Chang JC, Chowdhury R, Courville KJ, Criqui MH, Cundiff DK, Dabhadkar KC, Dandona L, Davis A, Dayama A, Dharmaratne SD, Ding EL, Durrani AM, Esteghamati A, Farzadfar F, Fay DF, Feigin VL, Flaxman A, Forouzanfar MH, Goto A, Green MA, Gupta R, Hafezi-Nejad N, Hankey GJ, Harewood HC, Havmoeller R, Hay S, Hernandez L, Husseini A, Idrisov BT, Ikeda N, Islami F, Jahangir E, Jassal SK, Jee SH, Jeffreys M, Jonas JB, Kabagambe EK, Khalifa SE, Kengne AP, Khader YS, Khang YH, Kim D, Kimokoti RW, Kinge JM, Kokubo Y, Kosen S, Kwan G, Lai T, Leinsalu M, Li Y, Liang X, Liu S, Logroscino G, Lotufo PA, Lu Y, Ma J, Mainoo NK, Mensah GA, Merriman TR, Mokdad AH, Moschandreas J, Naghavi M, Naheed A, Nand D, Narayan KM, Nelson EL, Neuhouser ML, Nisar MI, Ohkubo T, Oti SO, Pedroza A, Prabhakaran D, Roy N, Sampson U, Seo H, Sepanlou SG, Shibuya K, Shiri R, Shiue I, Singh GM, Singh JA, Skirbekk V, Stapelberg NJ, Sturua L, Sykes BL, Tobias M, Tran BX, Trasande L, Toyoshima H, van de Vijver S, Vasankari TJ, Veerman JL, Velasquez-Melendez G, Vlassov VV, Vollset SE, Vos T, Wang C, Wang X, Weiderpass E, Werdecker A, Wright JL, Yang YC, Yatsuya H, Yoon J, Yoon SJ, Zhao Y, Zhou M, Zhu S, Lopez AD, Murray CJ, Gakidou E. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014; **384**: 766-781 [PMID: 24880830 DOI: 10.1016/S0140-6736(14)60460-8]

5 **Pickering A**, Gray JA. Dopamine, appetitive reinforcement, and the neuropsychology of human learning: An individual differences approach. *PABST Science Publishers Lengerich, Germany* 2001; 113-149

6 **Carver CS**, White TL. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS Scales. *J Pers Soc Psychol* 1994; **67**: 319-333 [DOI: 10.1037/0022-3514.67.2.319]

7 **Wieman ST**, Arditte Hall KA, MacDonald HZ, Gallagher MW, Suvak MK, Rando AA, Liverant GI. Relationships Among Sleep Disturbance, Reward System Functioning, Anhedonia, and Depressive Symptoms. *Behav Ther* 2022; **53**: 105-118 [PMID: 35027152 DOI: 10.1016/j.beth.2021.06.006]

8 **McCarron RM**, Shapiro B, Rawles J, Luo J. Depression. *Ann Intern Med* 2021; **174**: ITC65-ITC80 [PMID: 33971098 DOI: 10.7326/AITC202105180]

9 **Cahuas A**, He Z, Zhang Z, Chen W. Relationship of physical activity and sleep with depression in college students. *J Am Coll Health* 2020; **68**: 557-564 [PMID: 30908132 DOI: 10.1080/07448481.2019.1583653]

10 **Kandola A**, Lewis G, Osborn DPJ, Stubbs B, Hayes JF. Depressive symptoms and objectively measured physical activity and sedentary behaviour throughout adolescence: a prospective cohort study. *Lancet Psychiatry* 2020; **7**: 262-271 [PMID: 32059797 DOI:

10.1016/S2215-0366(20)30034-1]
11 **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]
12 **Gu HB**, Wang XY, Ban MJ. [Association between physical activity and trajectories of change in anxiety and depression scores among college students]. *Zhongguo Xuexiao Weisheng* 2020; **41**: 1678-1681,1687 [DOI: 10.16835/j.cnki.1000-9817.2020.11.022]
13 **Li J**, Wang HJ, Chen W. [Advances in research on exercise to improve brain reward function to prevent obesity in children and adolescents]. *Zhongguo Ertong Baojian Zazhi* 2021; **29**: 165-168 [DOI: 10.11852/zgetbjzz2019-1285]
14 **Qu NN**, Li KJ. [Reliability and validity study of the Chinese version of the International Physical Activity Questionnaire]. *Zhonghua Liuxingbingxue Zazhi* 2004; **(03)**: 87-90 [DOI: 10.3760/j.issn:0254-6450.2004.03.021]
15 **Li YZ**, Zhang Y, Jiang Y, Li H, Mi S, Yi GJ, Gu HY. [Reliability analysis of the Chinese version of the Behavioral Inhibition/Activation System Scale]. *Zhongguo Xinliweisheng Zazhi* 2008; **(08)**: 613-616 [DOI: 10.3321/j.issn:1000-6729.2008.08.015]
16 **Wang Z**, Yuan CM, Huang J, Li ZX, Chen J, Zhang HY, Fang YR, Xiao ZP. [Reliability and validity of the Chinese version of the Beck Depression Inventory, Version 2, in patients with depression]. *Zhongguo Xinliweisheng Zazhi* 2011; **25**: 476-480 [DOI: 10.3969/j.issn.1000-6729.2011.06.014]
17 **Wen ZL**, Hou JT, Herbert M. Structural equation modeling tests:fit indices and chi-square criterion. *Acta Psychologica Sinica* 2004; **36** : 186-194
18 **Takagaki K**, Okamoto Y, Jinnin R, Mori A, Nishiyama Y, Yamamura T, Yokoyama S, Shiota S, Miyake Y, Ogata A, Shimoda H, Kawakami N, Furukawa TA, Yamawaki S. Mechanisms of behavioral activation for late adolescents: Positive reinforcement mediate the relationship between activation and depressive symptoms from pre-treatment to post-treatment. *J Affect Disord* 2016; **204**: 70-73 [PMID: 27341422 DOI: 10.1016/j.jad.2016.06.046]
19 **Kibitov AO**, Mazo GE. [Anhedonia in depression: neurobiological and genetic aspects]. *Zh Nevrol Psikhiatr Im S S Korsakova* 2021; **121**: 146-154 [PMID: 33834733 DOI: 10.17116/jnevro2021121031146]
20 **Rappaport BI**, Kandala S, Luby JL, Barch DM. Brain Reward System Dysfunction in Adolescence: Current, Cumulative, and Developmental Periods of Depression. *Am J Psychiatry* 2020; **177**: 754-763 [PMID: 32252540 DOI: 10.1176/appi.ajp.2019.19030281]
21 **Alloy LB**, Olino T, Freed RD, Nusslock R. Role of Reward Sensitivity and Processing in Major Depressive and Bipolar Spectrum Disorders. *Behav Ther* 2016; **47**: 600-621 [PMID: 27816074 DOI: 10.1016/j.beth.2016.02.014]
22 **Webb CA**, Dillon DG, Pechtel P, Goer FK, Murray L, Huys QJ, Fava M, McGrath PJ, Weissman M, Parsey R, Kurian BT, Adams P, Weyandt S, Trombello JM, Grannemann B, Cooper CM, Deldin P, Tenke C, Trivedi M, Bruder G, Pizzagalli DA. Neural Correlates of Three Promising Endophenotypes of Depression: Evidence from the EMBARC Study. *Neuropsychopharmacology* 2016; **41**: 454-463 [PMID: 26068725 DOI: 10.1038/npp.2015.165]
23 **Ma K**, Liu JM, Fu CY, Zhang H, Jia SH. [Research progress on the intervention effect and mechanism of exercise on depression]. *Zhongguo Tiyu Keji* 2020; **56**: 13-24 [DOI: 10.16470/j.csst.2020132]
24 **Markarian SA**, Pickett SM, Deveson DF, Kanona BB. A model of BIS/BAS sensitivity, emotion regulation difficulties, and depression, anxiety, and stress symptoms in relation to sleep quality. *Psychiatry Res* 2013; **210**: 281-286 [PMID: 23845417 DOI: 10.1016/j.psychres.2013.06.004]
25 **Smillie LD**, Jackson CJ, Dalgleish LI. Conceptual distinctions among Carver and White's (1994) BAS scales: A reward-reactivity versus trait impulsivity perspective. *Pers Individ Dif* 2006; **40**: 1039-1050 [DOI: 10.1016/j.paid.2005.10.012]
26 **Hamza CA**, Willoughby T, Heffer T. Impulsivity and nonsuicidal self-injury: A review and meta-analysis. *Clin Psychol Rev* 2015; **38**: 13-24 [PMID: 25779460 DOI: 10.1016/j.cpr.2015.02.010]
27 **Pinto-Meza A**, Caseras X, Soler J, Puigdemont D, Pérez V, Torrubia R. Behavioural Inhibition and Behavioural Activation Systems in current and recovered major depression participants. *Pers Individ Dif* 2006; **40**: 215-226 [DOI: 10.1016/j.paid.2005.06.021]
28 **Smillie LD**, Pickering AD, Jackson CJ. The new reinforcement sensitivity theory: implications for personality measurement. *Pers Soc Psychol Rev* 2006; **10**: 320-335 [PMID: 17201591 DOI: 10.1207/s15327957pspr1004_3]
29 **Kasch KL**, Rottenberg J, Arnow BA, Gotlib IH. Behavioral activation and inhibition systems and the severity and course of depression. *J Abnorm Psychol* 2002; **111**: 589-597 [PMID: 12428772 DOI: 10.1037//0021-843x.111.4.589]
30 **Wang XX**, Jiang CG, Zhang L, Feng ZZ. [Abnormalities in resting-state brain function in depression and their relationship to behavioral inhibition/activation]. *Disan Junyidaxue Xuebao* 2014; **36**: 1600-1603

World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatry 2023 October 19; 13(10): 793-802

DOI: 10.5498/wjp.v13.i10.793

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Observational Study

Analysis of mental health status and related factors in patients with acute cerebral infarction

Qing-Qin Chen, Fu-Mei Lin, Dan-Hong Chen, Yi-Min Ye, Guo-Mei Gong, Fen-Fei Chen, Su-Fen Huang, Shan-Ling Peng

Specialty type: Psychiatry

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Leff RA, United States; Pergolizzi S, Italy

Received: August 8, 2023
Peer-review started: August 8, 2023
First decision: August 24, 2023
Revised: September 2, 2023
Accepted: September 11, 2023
Article in press: September 11, 2023
Published online: October 19, 2023

Qing-Qin Chen, Yi-Min Ye, Guo-Mei Gong, Fen-Fei Chen, Su-Fen Huang, Quanzhou Medical College, Quanzhou 362000, Fujian Province, China

Fu-Mei Lin, Department of Emergency, Fuqing City Hospital Affiliated to Fujian Medical University, Fuqing 350300, Fujian Province, China

Dan-Hong Chen, Department of Neurology, Quanzhou First Hospital, Quanzhou 362000, Fujian Province, China

Shan-Ling Peng, Department of Nursing, The 900 Hospital of the Joint Service Support Force of the People's Liberation Army of China, Fuzhou 350025, Fujian Province, China

Corresponding author: Shan-Ling Peng, BSc, Associate Chief Nurse, Department of Nursing, The 900 Hospital of the Joint Service Support Force of the People's Liberation Army of China, No. 156 West Second Ring North Road, Gulou District, Fuzhou 350025, Fujian Province, China. psl3030@163.com

Abstract

BACKGROUND

Acute cerebral infarction (ACI) is characterized by a high incidence of morbidity, disability, recurrence, death and heavy economic burden, and has become a disease of concern in global researchers. As ACI has serious effects on patients' physical status, life and economy, often causing anxiety, depression and other psychological problems, these problems can lead to the aggravation of physical symptoms; thus, it is very important to understand the factors affecting the mental health of these patients.

AIM

To understand the elements that affect the mental health of patients who have suffered an ACI.

METHODS

A questionnaire survey was conducted among patients with ACI admitted to three tertiary hospitals (Quanzhou First Hospital, Fuqing City Hospital Affiliated to Fujian Medical University, and the 900 Hospital of the Joint Service Support Force of the People's Liberation Army of China) in Fujian Province from January 2022 to December 2022 using the convenience sampling method. ACI inpatients

who met the inclusion criteria were selected. Informed consent was obtained from the patients before the investigation, and a face-to-face questionnaire survey was conducted using a unified scale. The questionnaire included a general situation questionnaire, Zung's self-rating depression scale and Zung's self-rating anxiety scale. All questionnaires were checked by two researchers and then the data were input and sorted using Excel software. The general situation of patients with ACI was analyzed by descriptive statistics, the influence of variables on mental health by the independent sample *t* test and variance analysis, and the influencing factors on psychological distress were analyzed by multiple stepwise regression.

RESULTS

The average age of the 220 patients with ACI was 68.64 ± 10.74 years, including 142 males and 78 females. Most of the patients were between 60 and 74 years old, the majority had high school or technical secondary school education, most lived with their spouse, and most lived in cities. The majority of patients had a personal income of 3001 to 5000 RMB yuan per month. The new rural cooperative medical insurance system had the largest number of participants. Most stroke patients were cared for by their spouses and of these patients, 52.3% had previously smoked. Univariate analysis showed that gender, age, residence, course of disease, number of previous chronic diseases and smoking history were the main factors affecting the anxiety scores of patients with ACI. Age, living conditions, monthly income, course of disease and knowledge of disease were the primary variables influencing the depression score in patients with ACI. The findings of multivariate analysis revealed that the course of disease and gender were the most important factors influencing patients' anxiety scores, and the course of disease was also the most important factor influencing patients' depression scores.

CONCLUSION

Long disease course and female patients with ACI were more likely to have psychological problems such as a high incidence of emotional disorders. These groups require more attention and counseling.

Key Words: Acute cerebral infarction; Mental health; Self-rating depression scale; Self-rating anxiety scale; Influencing factor; Correlation analysis

Core Tip: In recent years, research on acute cerebral infarction has not only focused on the effects of the infarction on the body, but also the psychological effects. In this study, we found that long disease course may be the main factor leading to psychological problems in patients, and female patients with a high incidence of emotional disorders are more likely to have psychological problems. Such groups require more attention and psychological counseling.

Citation: Chen QQ, Lin FM, Chen DH, Ye YM, Gong GM, Chen FF, Huang SF, Peng SL. Analysis of mental health status and related factors in patients with acute cerebral infarction. *World J Psychiatry* 2023; 13(10): 793-802
URL: https://www.wjgnet.com/2220-3206/full/v13/i10/793.htm
DOI: https://dx.doi.org/10.5498/wjp.v13.i10.793

INTRODUCTION

Acute cerebral infarction (ACI) has become a disease of concern in global researchers due to its high incidence of morbidity, disability, recurrence, death and heavy economic burden[1,2]. Most patients have different degrees of limb function, cognitive function and other disorders following sudden ACI. Patients find it difficult to accept physical changes which have a greater impact on their psychological status. These cannot be resolved in a short period of time, and there are some emotional changes such as suspicion and anxiety. Long-term negative emotions are psychological burdens, which affect physical and mental health[3-5]. Early detection of psychological problems, exploring the source of these psychological problems, providing targeted solutions, reducing patients' psychological disorders while improving the recovery in limb function or cognition, and promoting rehabilitation are essential. Therefore, it is necessary to carry out a cross-sectional survey to understand the influencing factors on mental health status in patients with ACI, examine the key factors affecting mental health, improve the mental health status of patients with ACI, and pave the way for early clinical intervention.

MATERIALS AND METHODS

Study population and data collection

From January 2022 to December 2022, a questionnaire survey was conducted in patients with ACI admitted to three tertiary hospitals in Fujian Province (Quanzhou First Hospital, Fuqing City Hospital Affiliated to Fujian Medical University, and the 900 Hospital of the Joint Service Support Force of the People's Liberation Army of China).

Inclusion criteria were: (1) Diagnosis consistent with that in the Chinese acute stroke clinical research consensus; (2) High research compliance; (3) Basic listening and speaking ability; and (4) Patients with a temporary stable condition and clear consciousness.

Exclusion criteria were: (1) Patients with language communication, cognitive, hearing or mental disorders; (2) Those with severe respiratory failure, malignant tumor, liver, renal, and cardiac dysfunction; and (3) Incomplete clinical data or participation in other research.

All patients with ACI who met the inclusion requirements were included in the study. Before the investigation, consent was obtained from the subjects and the informed consent was signed. A unified scale was used to conduct a face-to-face questionnaire survey. Those with good reading and writing ability completed the questionnaire. If the patients had difficulty in completing the questionnaire, the researcher used a unified guidance language to describe the questions. When the patient understood the questions, the survey was completed according to the patient's opinions. The researcher collected and checked the questionnaires, and corrected any errors.

General information questionnaire

This questionnaire included demographic characteristics (gender, age, education level, marital status, medical insurance type, inpatient caregivers, smoking history, *etc*.) and disease-related data (course of disease, type of stroke, number of strokes, past chronic disease status, *etc*).

Assessment of anxiety and depression

To evaluate potential anxiety and depression, the Chinese versions of Zung's self-rating depression scale (SDS) and Zung's self-rating anxiety scale (SAS) were utilized. The commonly used SAS and SDS measures are quick and practical tools for assessing respondents' signs of anxiety and depression, and they have strong reliability and validity in the Chinese population. Each scale has 20 items that are rated on a scale of 1 to 4 to evaluate the assertions (rarely, occasionally, frequently, or always). The standard scale was created by multiplying the 20-80 point range of the overall score by 1.25. The higher the score, the more severe the anxiety or depression. According to the findings of the Chinese norm, the cut-off value of the SDS standard score was 53 points; mild depression was defined as 53-62 points, moderate depression as 63-72 points, and severe depression as more than 73 points. The SAS standard deviation cutoff was 50 points, with mild anxiety being between 50 and 59 points, moderate anxiety being between 60 and 69 points, and severe anxiety being more than 69 points.

Statistical analysis

All questionnaires were checked by two researchers, and then Excel software was used for data entry and collation. The SPSS26.0 program was utilized for data analysis. Descriptive statistical analysis was used for the general situation of patients with ACI. The independent sample *t* test and variance analysis were used to analyze the influence of each variable on mental health. Multiple stepwise regression analysis was used to analyze the influencing factors of psychological distress. $P < 0.05$ was considered statistically significant.

RESULTS

Demographic characteristics of patients with ACI

Demographic characteristics of the 220 patients with ACI (Table 1).

Disease-related information on patients with ACI

The disease course, frequency of onset, history of hypertension, history of diabetes, history of coronary heart disease, and history of chronic diseases patients with ACI was counted (Table 2).

Mental health status of patients with ACI

Among the 220 patients with ACI in this survey, 122 had depression, including 73 cases of mild depression, 39 cases of moderate depression, and 10 cases of severe depression. One hundred and sixty-three cases had anxiety, including 65 cases of mild anxiety, 61 cases of moderate anxiety, and 37 cases of severe anxiety (Table 3).

Effects of demographic sociological characteristics on mental health

The SAS score and SDS score of ACI patients were used as dependent variables, and gender, age, occupation, education level, marital status, living conditions, place of residence, personal monthly income, type of medical insurance, inpatient nursing staff, and smoking history were used as independent variables for univariate analysis. The results showed that gender, age, living conditions and smoking history were the main factors affecting the SAS score of ACI patients. Age, living conditions and personal monthly income were the main factors affecting the SDS score of ACI patients (Table 4).

Table 1 Demographic characteristics of acute cerebral infarction patients

Characteristics	Classification	*n*	Constituent ratio
Gender	Male	142	64.5%
	Female	78	35.5%
Age (yr)	≤ 59	49	22.3%
	60-74	94	42.7%
	≥ 74	77	35.0%
Degree of education	Primary school and below	39	17.7%
	Junior middle school	54	24.5%
	High school/technical secondary school	91	41.4%
	College degree or above	36	16.4%
Marital status	Married	134	60.9%
	Bereft of one's spouse	26	11.8%
	Divorce or other	60	27.3%
Living situation	Live with parents	10	4.5%
	Live with children	41	18.6%
	Live with partner	108	49.1%
	Living alone	61	27.7%
Domicile	City	114	51.8%
	Village	106	48.2%
Monthly profit (yuan)	≤ 1000	17	7.7%
	1001-3000	75	34.1%
	3001-5000	76	34.5%
	≥ 5001	52	23.6%
Medical insurance type	Medical insurance for urban employees	63	28.6%
	Medical insurance for urban residents	40	18.2%
	New rural cooperative	95	43.2%
	Self-paying	22	10.0%
Caregiver	Parents	11	5.0%
	Spouse	114	51.8%
	Children	76	34.5%
	Other	19	8.6%
History of smoking	No	105	47.7%
	Yes	115	52.3%

Effects of ACI on mental health

The SAS score and SDS score of stroke patients were used as dependent variables, and the duration of disease, number of strokes, history of hypertension, history of diabetes, history of coronary heart disease, number of previous chronic diseases, and knowledge were used as independent variables for univariate analysis. The results showed that the course of disease, chronic history and the number of previous chronic diseases were the main factors affecting the SAS score of ACI patients. The course of disease and the status of knowledge of the disease were the main factors affecting the SDS score of patients with ACI (Table 5).

Multivariate analysis of anxiety in patients with ACI

The data obtained from this survey were analyzed by stepwise regression analysis, the SAS score in patients with ACI was used as the dependent variable, and the variables that showed statistically significant SAS scores in the patient data (gender, age, location, disease course, number of chronic diseases, and smoking history) as independent variables. The

Table 2 Disease-related data of acute cerebral infarction patients

Factors	Classification	*n*	Constituent ratio
Course of disease	1-6 mo	96	43.64%
	7-12 mo	73	33.18%
	1-2 yr	36	16.36%
	More than 2 yr	15	6.82%
Number of ACIs	One	122	55.45%
	More than two	98	44.55%
History of hypertension	Yes	132	60.00%
	No	88	40.00%
History of diabetes	Yes	117	53.18%
	No	103	46.82%
History of coronary heart disease	Yes	109	49.55%
	No	111	50.45%
Number of previous chronic diseases	0	17	7.73%
	1	75	34.09%
	2	101	45.91%
	3	27	12.27%
Informed status of ACI	Fully informed	97	44.09%
	Partially informed	73	33.18%
	Completely uninformed	50	22.73%

ACI: Acute cerebral infarction.

Table 3 Mental health status of acute cerebral infarction patients

Factors	Classification	Number	Constituent ratio	mean ± SD
SDS	Without	93	42.27%	43.31 ± 7.49
	M	73	33.18%	57.29 ± 2.74
	M	39	17.73%	66.51 ± 2.68
	S	10	4.55%	76.30 ± 1.64
SAS	Without	57	25.91%	43.09 ± 8.86
	M	65	29.55%	52.85 ± 10.03
	M	61	27.73%	60.38 ± 8.28
	S	37	16.82%	75.92 ± 4.97

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

findings demonstrated that gender and progression of the illness were factors in the regression model (Table 6).

Multivariate analysis of depression in patients with ACI

The data obtained from this survey were analyzed by stepwise regression analysis, the SDS score in patients with ACI was used as the dependent variable, and the variables that showed statistically significant SAS scores in the patient data (age, place of residence, disease course, personal monthly income, and disease awareness) as independent variables. The findings demonstrated that the disease course was a factor in the regression equation (Table 7).

Table 4 Influence of sociological characteristics of the population on mental health

Factors	Classification	SAS (mean ± SD)	*F/t* value	*P* value	SDS (mean ± SD)	*F/t* value	*P* value
Gender	Male	54.74 ± 11.05	8.577[1]	0.004	52.36 ± 11.31	0.293[1]	0.589
	Female	62.5 ± 13.63			57.59 ± 11.78		
Age (yr)	≤ 59	51.33 ± 12.67	10.504	< 0.001	49.35 ± 11.18	8.878	< 0.001
	60-74	57.49 ± 11.42			53.67 ± 11.39		
	≥ 74	61.42 ± 12.38			57.97 ± 11.34		
Degree of education	Primary school and below	58.05 ± 12.82	0.494	0.687	55.38 ± 13.83	1.096	0.352
	Junior middle school	58.3 ± 11.05			53.15 ± 10.13		
	High school/technical secondary school	57.67 ± 13.43			55.33 ± 11.25		
	College degree or above	55.22 ± 12.36			51.72 ± 12.60		
Marital status	Married	57.51 ± 12.32	1.687	0.188	53.88 ± 11.88	1.559	0.213
	Bereft of one's spouse	61.23 ± 12.30			57.96 ± 9.28		
	Divorce or other	55.83 ± 13.04			53.33 ± 12.18		
Living situation	Live with parents	48.00 ± 10.71	3.849	0.01	44.40 ± 11.32	3.923	0.009
	Live with children	61.83 ± 10.76			57.88 ± 11.32	2.4	
	Live with partner	57.36 ± 12.82			53.61 ± 11.99	3.4	
	Living alone	56.36 ± 12.61			54.43 ± 10.72		
Domicile	City	55.97 ± 12.30	3.494[1]	0.063	54.18 ± 11.05	0.002[1]	0.96
	Village	59.12 ± 12.69			54.25 ± 12.46		
Monthly profit (yuan)	≤ 1000	56.35 ± 12.52	1.9	0.131	50.00 ± 15.36	2.845	0.039
	1001-3000	56.57 ± 11.94			54.13 ± 12.24		
	3001-5000	60.17 ± 12.45			56.88 ± 10.45		
	≥ 5001	55.27 ± 13.26			51.81 ± 10.76		
Medical insurance type	Medical insurance for urban employees	57.25 ± 13.46	1.245	0.294	55.60 ± 10.69	1.063	0.366
	Medical insurance for urban residents	54.3 ± 11.02			51.43 ± 11.08		
	New rural cooperative	58.78 ± 12.79			54.40 ± 12.64		
	Self-paying	58.41 ± 11.14			54.50 ± 11.53		
Caregiver	Parents	48.55 ± 5.09	2.189	0.09	51.36 ± 12.75	1.012	0.388
	Spouse	58.00 ± 13.10			53.80 ± 11.29		
	Children	58.41 ± 11.36			55.84 ± 12.41		
	Other	55.95 ± 15.26			51.84 ± 10.81		
History of smoking	No	55.63 ± 12.16	5.422[1]	0.021	53.39 ± 11.91	1.186[1]	0.277
	Yes	59.53 ± 12.77			55.11 ± 11.51		

[1]*t* value.
ACI: Acute cerebral infarction; SDS: Self-rating depression scale; SAS: Self-rating anxiety scale.

DISCUSSION

ACI is a sudden cerebrovascular disease. It is an acute attack when the patient's brain is blocked by blood vessels such as coronary arteries[6,7]. Due to the close connection between the cerebrovascular and central nervous system, patients with ACI often have a poor prognosis. Even after treatment, neurological dysfunction may persist. Some patients are prone to unpleasant feelings such as depression and anxiety during the onset of the disease, and then sleep disorders, neurasthenia and other symptoms, such psychological changes may be related to the occurrence of nerve defects[8-10]. In recent years, the study of ACI has not only focused on the effects on the body, but psychological effects have received more and more attention[11-13]. Patients with anxiety and depression often have a poor prognosis, longer recovery time and are

Table 5 Effects of acute cerebral infarction on mental health

Factors	Classification	SAS (mean ± SD)	*F/t/Welch* value	*P* value	SDS (mean ± SD)	*F/t/Welch* value	*P* value
Course of disease	1-6 mo	47.66 ± 9.80	72.127	< 0.001	46.36 ± 10.63	56.835[2]	< 0.001
	7-12 mo	62.97 ± 7.48			59.12 ± 7.83		
	1-2 yr	68.17 ± 9.99			58.81 ± 8.51		
	More than 2 yr	68.13 ± 6.55			69.53 ± 5.76		
Number of ACIs	One	56.63 ± 13.34	1.286[1]	0.258	53.10 ± 13.18	2.674[1]	0.103
	More than two	58.56 ± 11.48			55.60 ± 9.50		
History of hypertension	Yes	57.11 ± 12.28	0.309[1]	0.579	53.86 ± 11.60	0.293[1]	0.589
	No	58.07 ± 13.01			54.74 ± 11.96		
History of diabetes	Yes	57.14 ± 13.01	0.198[1]	0.657	54.09 ± 10.83	0.03[1]	0.863
	No	57.89 ± 12.07			54.36 ± 12.72		
History of coronary heart disease	Yes	57.02 ± 12.43	0.305[1]	0.581	54.36 ± 11.54	0.033[1]	0.857
	No	57.95 ± 12.72			54.07 ± 11.96		
Number of previous chronic diseases	0	64.94 ± 12.36	2.595	0.050	59.53 ± 10.33	2.277	0.081
	1	55.73 ± 12.07			52.09 ± 13.20		
	2	57.76 ± 12.34			55.13 ± 10.78		
	3	56.67 ± 13.67			53.33 ± 10.71		
Informed status of ACI	Fully informed	57.04 ± 12.63	2.444	0.089	55.14 ± 11.22	5.161	0.006
	Partially informed	55.84 ± 11.99			50.88 ± 12.02		
	Completely uninformed	60.78 ± 12.87			57.28 ± 11.31		

[1]*t* value.
[2]Welch value.
ACI: Acute cerebral infarction; SDS: Self-rating depression scale; SAS: Self-rating anxiety scale.

Table 6 Multivariate analysis of anxiety in patients with acute cerebral infarction

Variable	B	SE	Beta	*t* value	*P* value	95%CI
Constant	29.551	2.164		13.654	< 0.001	25.286-33.817
Course of disease	8.918	0.638	0.658	13.981	< 0.001	7.661-10.176
Sex	8.356	1.232	0.319	6.781	< 0.001	5.928-10.785

CI: Confidence interval.

Table 7 Multivariate analysis of depression in patients with acute cerebral infarction

Variable	B	SE	Beta	*t* value	*P* value	95%CI
Constant	41.149	1.457		28.252	< 0.001	38.279-44.02
Course of disease	8.769	0.7	0.647	12.524	< 0.001	7.389-10.149

CI: Confidence interval.

more likely to relapse[13,14]. Therefore, this study analyzed the influencing factors on mental health in patients with ACI, with the hope of identifying the key factors affecting mental health.

The SAS score and SDS score in the 220 patients with ACI included in this study were statistically significant. The total SAS score was 57.49 ± 12.56, which was significantly higher than the standard cut-off value. The total SDS score was 54.21 ± 11.73, which was significantly higher than the standard cut-off value, indicating that psychological problems are common in patients with ACI in China. The results of univariate analysis showed that gender, age, residence, course of disease, number of chronic diseases and smoking history were the primary elements influencing the anxiety score in patients with ACI. Age, living conditions, monthly income, course of disease and knowledge of ACI were primary elements influencing the depression score in patients with ACI. The analysis results showed that female patients had more severe anxiety than male patients. The levels of anxiety and depression increased with age. Similar to previous research results, a possible reason for this is that women and the elderly belong to a high-risk group with emotional disorders[15-17], and psychological problems are more likely to occur after ACI. The SAS and SDS scores of patients living with their children were higher, which matched the outcomes of earlier studies[18,19]. This may be because patients living with their children often need to take care of their families, and the lack of ability regarding family care after infarction leads to serious anxiety. The longer the disease course, the higher the SAS and SDS scores in patients, which matched the outcomes of earlier studies[20,21], and might be the result of an aggravation of psychological problems caused by long-term distress; the anxiety score in patients without a history of chronic disease was highest, which may be due to the increase in psychological pressure caused by the patient's abilities in their previous healthy state and their sudden need for care. The depression score in patients with ACI and higher monthly income was greatest, which may be due to the impact on work and income after illness, resulting in psychological problems. Patients who do not understand the disease have higher depression scores, which may be due to the fact that patients do not understand their disease status and do not know why they are more likely to worry about hospitalization, resulting in psychological problems. Furthermore, multivariate analysis showed that the course of disease and gender were the key factors affecting the anxiety score in patients, and the course of disease was also the key factor affecting the depression score in patients. According to these findings, psychological issues are more likely to occur in patients who have had their disorder for a longer period of time and in women.

The limitation of this study is that the sample size is too small to fully analyze more factors affecting the mental health status of ACI patients. In future studies, we will continue to collect data of ACI patients, and further evaluate the key factors affecting the mental health of ACI patients in a more comprehensive way, as well as the mediating and regulating effects of other influencing factors.

CONCLUSION

In summary, patients with ACI generally have psychological issues including despair and anxiety. A long disease course may be the main factor leading to psychological problems in patients, and female patients are more likely to have psychological problems such as a high incidence of emotional disorders. Such groups require more attention and psychological counseling.

ARTICLE HIGHLIGHTS

Research background

Acute cerebral infarction (ACI) is a sudden cerebrovascular disease. ACI occurs when the patient's brain is blocked by coronary arteries and other blood vessels, resulting in ischemia and hypoxia. Even after receiving treatment, there may be persistent neurological dysfunction. Patients with anxiety and depression tend to have a poor prognosis, take longer to recover and are more likely to relapse.

Research motivation

This study analyzed the factors affecting the mental health of patients with ACI, with the hope of identifying the key factors affecting mental health.

Research objectives

The object of this study is to improve the mental health status of patients with ACI, and pave the way for early clinical intervention.

Research methods

A questionnaire survey was conducted among patients with ACI admitted to three tertiary hospitals in Fujian Province from January 2022 to December 2022 using the convenience sampling method. Patients with ACI who were inpatients and met the inclusion criteria were selected. A face-to-face questionnaire survey was conducted using a unified scale. To evaluate potential signs of anxiety and depression, the Zung's self-rating depression scale and Zung's self-rating anxiety scale were used. All questionnaires were checked by two researchers and then the data were input and sorted using Excel software. The general situation of ACI patients was analyzed by descriptive statistics, the influence of variables on mental

health by the independent sample *t* test and variance analysis, and the influencing factors on psychological distress were analyzed by multiple stepwise regression.

Research results

Univariate analysis showed that gender, age, residence, course of disease, number of previous chronic diseases and smoking history were the main factors affecting anxiety scores in ACI patients. Age, living conditions, monthly income, course of disease and knowledge of ACI were the main factors affecting the depression score in ACI patients. According to the results of the multivariate analysis, the course of disease and gender were the key factors affecting the anxiety score, and the course of disease was also the key factor affecting the depression score.

Research conclusions

Patients with ACI generally have psychological issues including depression and anxiety. A long disease course may be the main factor leading to psychological problems in patients, and female patients are more likely to have psychological problems such as a high incidence of emotional disorders. Such groups require more attention and psychological counseling.

Research perspectives

More patient records should be collected to more comprehensively evaluate the key factors affecting the mental health of patients with ACI.

FOOTNOTES

Author contributions: Chen QQ and Lin FM contributed equally to this work and are co-first authors. Chen QQ and Lin FM contributed to the study design and manuscript preparation; Chen DH, Ye YM, and Chen FF involved in the data acquisition; Gong GM and Huang SF participated in the statistical analysis; Peng SL reviewed the manuscript.

Institutional review board statement: The study was approved by the Ethics Committee of Fuqing City Hospital Affiliated to Fujian Medical University.

Informed consent statement: All participants have signed an informed consent form.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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

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.

Country/Territory of origin: China

ORCID number: Qing-Qin Chen 0009-0000-7217-4366; Fu-Mei Lin 0009-0003-3763-5384; Dan-Hong Chen 0009-0009-9865-4961; Yi-Min Ye 0009-0005-4781-1200; Guo-Mei Gong 0009-0003-8303-2701; Fen-Fei Chen 0009-0009-7769-004X; Su-Fen Huang 0009-0009-9798-773X; Shan-Ling Peng 0009-0006-5426-330X.

S-Editor: Wang JJ
L-Editor: A
P-Editor: Wang JJ

REFERENCES

1 **Mo Z**, Tang C, Li H, Lei J, Zhu L, Kou L, Luo S, Li C, Chen W, Zhang L. Eicosapentaenoic acid prevents inflammation induced by acute cerebral infarction through inhibition of NLRP3 inflammasome activation. *Life Sci* 2020; **242**: 117133 [PMID: 31830477 DOI: 10.1016/j.lfs.2019.117133]

2 **Zhao Y**, Zhang X, Chen X, Wei Y. Neuronal injuries in cerebral infarction and ischemic stroke: From mechanisms to treatment (Review). *Int J Mol Med* 2022; **49** [PMID: 34878154 DOI: 10.3892/ijmm.2021.5070]

3 **Tu J**, Wang LX, Wen HF, Xu YC, Wang PF. The association of different types of cerebral infarction with post-stroke depression and cognitive impairment. *Medicine (Baltimore)* 2018; **97**: e10919 [PMID: 29879031 DOI: 10.1097/MD.0000000000010919]

4 **Zhao XJ**, Li QX, Liu TJ, Wang DL, An YC, Zhang J, Peng YB, Chen RY, Chang LS, Wang Y, Zhang L, Fan HY, Wang XJ, Zheng FX. Predictive values of CSS and NIHSS in the prognosis of patients with acute cerebral infarction: A comparative analysis. *Medicine (Baltimore)*

2018; **97**: e12419 [PMID: 30278519 DOI: 10.1097/MD.0000000000012419]

5 **Prussien KV**, Jordan LC, DeBaun MR, Compas BE. Cognitive Function in Sickle Cell Disease Across Domains, Cerebral Infarct Status, and the Lifespan: A Meta-Analysis. *J Pediatr Psychol* 2019; **44**: 948-958 [PMID: 31050352 DOI: 10.1093/jpepsy/jsz031]

6 **Kubota M**, Yoshida Y, Kobayashi E, Matsutani T, Li SY, Zhang BS, Mine S, Machida T, Takizawa H, Hiwasa T, Iwadate Y. Serum anti-SERPINE1 antibody as a potential biomarker of acute cerebral infarction. *Sci Rep* 2021; **11**: 21772 [PMID: 34741085 DOI: 10.1038/s41598-021-01176-8]

7 **Shao H**, He X, Zhang L, Du S, Yi X, Cui X, Liu X, Huang S, Tong R. Efficacy of Ligustrazine Injection as Adjunctive Therapy in Treating Acute Cerebral Infarction: A Systematic Review and Meta-Analysis. *Front Pharmacol* 2021; **12**: 761722 [PMID: 34880757 DOI: 10.3389/fphar.2021.761722]

8 **Deng M**, Zhong X, Gao Z, Jiang W, Peng L, Cao Y, Zhou Z, Huang L. Dynamic changes in Beclin-1, LC3B and p62 at various time points in mice with temporary middle cerebral artery occlusion and reperfusion (tMCAO). *Brain Res Bull* 2021; **173**: 124-131 [PMID: 33974897 DOI: 10.1016/j.brainresbull.2021.05.002]

9 **Sun Z**, Xu Q, Gao G, Zhao M, Sun C. Clinical observation in edaravone treatment for acute cerebral infarction. *Niger J Clin Pract* 2019; **22**: 1324-1327 [PMID: 31607719 DOI: 10.4103/njcp.njcp_367_18]

10 **Lyketsos CG**, Kozauer N, Rabins PV. Psychiatric manifestations of neurologic disease: where are we headed? *Dialogues Clin Neurosci* 2007; **9**: 111-124 [PMID: 17726911 DOI: 10.31887/DCNS.2007.9.2/clyketsos]

11 **Wang X**, Chen J, Liu YE, Wu Y. The Effect of Acceptance and Commitment Therapy on Psychological Nursing of Acute Cerebral Infarction with Insomnia, Anxiety, and Depression. *Comput Math Methods Med* 2022; **2022**: 8538656 [PMID: 35785139 DOI: 10.1155/2022/8538656]

12 **Xu T**, Tao F, Dong P, Wang H, Shi Z. A Psychological Intervention Program for Patients with Cerebral Infarction. *Dement Geriatr Cogn Disord* 2023; **52**: 83-90 [PMID: 37004504 DOI: 10.1159/000529601]

13 **Xie R**, Chen Y, Chen K, Chen Z. Intervention Effect of Rapid Rehabilitation Nursing Combined with Continuous Nursing after Discharge on Patients with Cerebral Infarction in Recovery Period and the Changes in Motor Function, Mental State, and Quality of Life. *Evid Based Complement Alternat Med* 2021; **2021**: 8065868 [PMID: 34691226 DOI: 10.1155/2021/8065868]

14 **Otte C**. Incomplete remission in depression: role of psychiatric and somatic comorbidity. *Dialogues Clin Neurosci* 2008; **10**: 453-460 [PMID: 19170402 DOI: 10.31887/DCNS.2008.10.4/cotte]

15 **Rapee RM**, Oar EL, Johnco CJ, Forbes MK, Fardouly J, Magson NR, Richardson CE. Adolescent development and risk for the onset of social-emotional disorders: A review and conceptual model. *Behav Res Ther* 2019; **123**: 103501 [PMID: 31733812 DOI: 10.1016/j.brat.2019.103501]

16 **Bixo M**, Johansson M, Timby E, Michalski L, Bäckström T. Effects of GABA active steroids in the female brain with a focus on the premenstrual dysphoric disorder. *J Neuroendocrinol* 2018; **30** [PMID: 29072794 DOI: 10.1111/jne.12553]

17 **Ciasca EC**, Ferreira RC, Santana CLA, Forlenza OV, Dos Santos GD, Brum PS, Nunes PV. Art therapy as an adjuvant treatment for depression in elderly women: a randomized controlled trial. *Braz J Psychiatry* 2018; **40**: 256-263 [PMID: 29412335 DOI: 10.1590/1516-4446-2017-2250]

18 **Cheng LS**, Tu WJ, Shen Y, Zhang LJ, Ji K. Combination of High-Sensitivity C-Reactive Protein and Homocysteine Predicts the Post-Stroke Depression in Patients with Ischemic Stroke. *Mol Neurobiol* 2018; **55**: 2952-2958 [PMID: 28456936 DOI: 10.1007/s12035-017-0549-8]

19 **Jiménez I**, Sobrino T, Rodríguez-Yáñez M, Pouso M, Cristobo I, Sabucedo M, Blanco M, Castellanos M, Leira R, Castillo J. High serum levels of leptin are associated with post-stroke depression. *Psychol Med* 2009; **39**: 1201-1209 [PMID: 19356259 DOI: 10.1017/S0033291709005637]

20 **Geraets AF**, Köhler S, Jansen JF, Eussen SJ, Stehouwer CD, Schaper NC, Wesselius A, Verhey FR, Schram MT. The association of markers of cerebral small vessel disease and brain atrophy with incidence and course of depressive symptoms - the maastricht study. *J Affect Disord* 2021; **292**: 439-447 [PMID: 34144369 DOI: 10.1016/j.jad.2021.05.096]

21 **Hung CY**, Wu XY, Chung VC, Tang EC, Wu JC, Lau AY. Overview of systematic reviews with meta-analyses on acupuncture in post-stroke cognitive impairment and depression management. *Integr Med Res* 2019; **8**: 145-159 [PMID: 31304087 DOI: 10.1016/j.imr.2019.05.001]

World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatry 2023 October 19; 13(10): 803-815

DOI: 10.5498/wjp.v13.i10.803

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Observational Study

International study of the Complex Stress Reaction Syndrome: Implications for transdiagnostic clinical practice

Sari Goldstein Ferber, Aron Weller, Adele M Hayes, Tracy D Vannorsdall, Yaroup Ajlouni, Mo'nes Qudah, Gil Zalsman, Gal Shoval, Tommaso Benedetto Jannini, Racquel Fiedler, Lily X Chen, Danielle R Shayani, Elin Kachuki Dory, Dana Stolowicz-Melman, Connor Evans, Megan Trow, Giorgio Di Lorenzo, Rodolfo Rossi

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Eseadi C, Nigeria; Stoyanov D, Bulgaria

Received: July 11, 2023
Peer-review started: July 11, 2023
First decision: August 16, 2023
Revised: August 25, 2023
Accepted: September 11, 2023
Article in press: September 11, 2023
Published online: October 19, 2023

Sari Goldstein Ferber, Adele M Hayes, Danielle R Shayani, Department of Psychological and Brain Sciences, University of Delaware, Newark, DE 19716, United States

Sari Goldstein Ferber, Department of Psychology, Bar Ilan University, Ramat Gan 5290002, Israel

Aron Weller, Racquel Fiedler, Elin Kachuki Dory, Dana Stolowicz-Melman, Department of Psychology and The Gonda Brain Research Center, Bar Ilan University, Ramat Gan 5290002, Israel

Tracy D Vannorsdall, Department of Psychiatry and Behavioral Sciences, Department of Neurology, The Johns Hopkins University School of Medicine, Baltimore, MD 21287, United States

Yaroup Ajlouni, Mo'nes Qudah, Jordan Health Aid-International, Amman 1234, Jordan

Gil Zalsman, Gal Shoval, Geha Mental Health Center, Petah Tiqva, Israel and Faculty of Medicine, Tel Aviv University, Ramat Aviv 6997801, Israel

Gil Zalsman, Division of Molecular Imaging and Neuropathology, Department of Psychiatry, Columbia University, New York, NY 10032, United States

Gal Shoval, Department of Neuroscience, Princeton University, Princeton, NJ 08544, United States

Tommaso Benedetto Jannini, Rodolfo Rossi, Department of Systems Medicine, Tor Vergata University of Rome, Rome 00133, Italy

Lily X Chen, UNSW School of Psychology, UNSW Sydney, Sydney 2052, Australia

Connor Evans, Department of Biology, Pacific University, Forest Grove, OR 97116, United States

Megan Trow, Oregon Chapter of Fulbright Association, Oregon, OR 97045, United States

Giorgio Di Lorenzo, Department of Systems Medicine, Tor Vergata University of Rome, Rome 00179, Italy

Giorgio Di Lorenzo, IRCCS, Fondazione Santa Lucia, Rome 00179, Italy

Corresponding author: Sari Goldstein Ferber, PhD, Affiliate Associate Professor, Department of Psychological and Brain Sciences, University of Delaware, 108 Wolf Hall, Newark, DE 19716, United States. sgf@udel.edu

Abstract

BACKGROUND

The debate regarding diagnostic classification systems in psychiatry (categorial *vs* dimensional systems) has essential implications for the diagnosis, prevention and treatment of stress reactions. We previously found a unique pattern of stress reaction in a study executed during the coronavirus disease 2019 pandemic using large representative samples in two countries, and termed it the Complex Stress Reaction Syndrome (CSRS).

AIM

To investigate CSRS, Type A (psychiatric symptoms, spanning anxiety, depression, stress symptoms, and post-traumatic stress disorder (PTSD)), with or without long-coronavirus disease (COVID) residuals (CSRS, Type B, neuropsychiatric symptoms spanning cognitive deficits and fatigue, excluding systemic symptoms). Our two-tailed hypothesis was that CSRS is a condition related to an unrecognized type of stress reaction in daily life in the general population (Type A) or that it is related to the severe acute respiratory syndrome coronavirus 2 infection and its long-COVID residuals (Type B).

METHODS

977 individuals in four continents (North America, Europe, Australia and the Middle East) completed the online study questionnaire in six languages using the Qualtrics platform. The study was managed by six teams in six countries that promoted the study on social media. The questionnaire assessed anxiety, depression, stress symptoms and PTSD (CSRS, Type A), cognitive deficits and fatigue (CSRS, Type B). The data were analyzed using Proportion Analyses, Multivariate Analysis of Co-Variance (MANCOVA), linear regression analyses and validated clinical cutoff points.

RESULTS

The results of the Proportion Analyses showed that the prevalence of 4 symptoms spanning anxiety, depression, stress symptoms, and PTSD was significantly higher than the most prevalent combinations of fewer symptoms across 4 continents, age groups, and gender. This supports the transdiagnostic argument embedded in the CSRS (Type A). The same pattern of results was found in infected/recovered individuals. The prevalence of the 4 psychiatric symptoms combination was significantly greater than that of 5 and 6 symptoms, when adding cognitive deficits and fatigue, respectively. MANCOVA showed a significant three-way interaction (age × gender × continent). Further analyses showed that the sources of this three-way interaction were threefold relating to two sub-populations at-risk: (1) Individuals that self-identified as non-binary gender scored significantly higher on all 4 psychiatric symptoms of the CSRS, Type A at young age groups (< 50 years old) in North America compared to (self-identified) women and men located in the 4 continents studied, and to other ages across the adult life span; and (2) This pattern of results (CSRS, Type A) was found also in women at young ages (< 40 years old) in North America who scored higher compared to men and women in other continents and other ages. Linear regression analyses confirmed the MANCOVA results.

CONCLUSION

These results show a combined mental health risk factor related to stress reactivity, suggesting that the CSRS is sensitive to populations at risk and may be applied to future identification of other vulnerable sub-populations. It also supports the transdiagnostic approach for more accurate prevention and treatment. Time will tell if such transdiagnostic syndromes will be part of the discussions on the next revisions of the traditional classification systems or whether the crisis in psychiatry further evolves.

Key Words: Transdiagnostic; Complex Stress Reaction Syndrome; Stress reactivity; Affective disorders; Debate in psychiatry

Core Tip: The debate regarding diagnostic classification systems in psychiatry (categorial *vs* dimensional systems) has essential implications for the diagnosis, prevention and treatment of stress reactions and affective disorders. The results of this international study show a combined mental health risk factor related to stress reactivity and reduced positive affectivity, suggesting that the Complex Stress Reaction Syndrome (Type A) is sensitive to populations at risk and may be applied to future identification of other vulnerable sub-populations. It also supports the transdiagnostic approach for more accurate prevention and treatment. Time will tell if such transdiagnostic syndromes will be part of the discussions on the next revisions of the traditional classification systems or whether the crisis in psychiatry further evolves.

Citation: Goldstein Ferber S, Weller A, Hayes AM, Vannorsdall TD, Ajlouni Y, Qudah M, Zalsman G, Shoval G, Jannini TB, Fiedler R, Chen LX, Shayani DR, Kachuki Dory E, Stolowicz-Melman D, Evans C, Trow M, Di Lorenzo G, Rossi R. International study of the Complex Stress Reaction Syndrome: Implications for transdiagnostic clinical practice. *World J Psychiatry* 2023; 13(10): 803-815
URL: https://www.wjgnet.com/2220-3206/full/v13/i10/803.htm
DOI: https://dx.doi.org/10.5498/wjp.v13.i10.803

INTRODUCTION

The debate on diagnostic classification systems and the resulting crisis in psychiatry is evolving[1]. Many professionals doubt the validity of the categorical model, Diagnostic and Statistical Manual of mental disorders (DSM) and International Classification of Diseases (ICD), as clinical practice, supported by scientific evidence, shows that mixed symptomology is often presented by many patients without meeting the full criteria of any traditional diagnostic category[2]. Updated search in *Reference Citation Analysis* (https://www.referencecitationanalysis.com/), Google Scholar and PubMed, shows that the transdiagnostic approach is evolving and that cutting edge studies are published in very high-ranked journals[3-7].

There are at least four transdiagnostic new classification systems: Hierarchical Taxonomy to Psychopathology[8], Research Domain Criteria[9], Bipolar-Schizophrenia Network on intermediate phenotypes[10], and Neuroscience-Based Nomenclature[11]. These dimensional transdiagnostic approaches showed biological evidence of specific underlying mechanisms for several mental disorders[12-15]. However, others claim that the findings on underlying biological mechanisms relate to a too wide range of disorders, ruling out the option of differential diagnosis and more accurate derived prevention and treatment[15,16]. The option of including dimensional categories in the traditional classifications has yet to be discussed.

The debate in psychiatry has crucial implications for the diagnosis of stress reactions. Optimal stress reactions are prerequisites of adaptive coping from evolutionary perspectives[17-19]. However, stress reactions are patient-specific, environment-specific, and timing-specific. Therefore, they include a wide range of behaviors and emotional conditions, which cross traditional classification categories and are addressed only partially by these systems[12-14,20,21]. Of special interest is the condition of exposure to multiple stressors, investigated mostly in disaster situations such as flooding, pandemics, hurricanes, earthquakes, and wars[22-25]. In the etiological explanations of the traditional nosology, the interactions of individual differences in coping capacities with the number and extent of environmental stressors have not been evidence-based to date.

Specifically, we previously found a unique transdiagnostic pattern of stress reaction in a binational study using large representative samples in two countries, Italy and Israel, executed during the coronavirus disease 2019 (COVID-19) pandemic[26]. The results showed a transdiagnostic combination of four stress-related symptoms [anxiety, depression, stress symptoms, and post-traumatic stress disorder (PTSD)] that was significantly more prevalent than combinations of fewer symptoms. We termed this combination of four symptoms the Complex Stress Reaction Syndrome (CSRS). We found this pattern of results in the two countries despite cultural and language differences between the two countries and between the methodologies used, suggesting convergent validity of the CSRS.

The pattern of multiple associated symptoms has been widely reported by others regarding the COVID-19 pandemic's impacts on mental health[27-29]. According to WHO reports, 22% of the population develops mental health problems in a dimensional pattern, reactive to emergencies[30]. Accordingly, we related the CSRS to the COVID-19 situation and included CSRS, Type A (psychiatric symptoms) and Type B (psychiatric and neuropsychiatric symptoms in COVID-infected and recovered individuals, excluding systemic symptoms of long-COVID)[26,31]. However, the possibility that CSRS is relevant in the post-COVID era, to capture the mixed clinical picture resulting from concomitant daily stressors in the general population, has only recently been proposed[16].

In a recent paper, we outlined the detailed description of the conceptual development of the CSRS, including its origins in clinical practice and its uniqueness as one transdiagnostic category[16], rather than a total transdiagnostic denial of the traditional psychiatric classifications as suggested by others. The framework underpinning the current study presents an elaboration of the first validation of the CSRS in our published binational study[26], by the inclusion of participants located in four continents in this current study, beyond the validation of the CSRS in only two countries.

In the current multi-lingual international study, conducted across four continents, we aimed to investigate our two-tailed hypothesis that the CSRS is a condition related to the unrecognized type of stress reaction in daily life in the general population (Type A) or related to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral infection and its long-COVID neuropsychiatric residuals (Type B).

MATERIALS AND METHODS

Institutional review board

Institutional review board approvals for this international study were provided by The Johns Hopkins University, Baltimore, Maryland, United States, and by Bar Ilan University, Ramat-Gan, Israel. The study survey used the Qualtrics platform (Qualtrics, Provo, Utah, United States) for data collection.

Sample

From a sample of 2024 individuals who approached the study questionnaire and partially completed it, 977 completed the entire study questionnaire, and this sample was used for the statistical analyses.

Inclusion criteria: Age > 18 years old.

Recruitment regions: Middle East, North America, Australia, Europe.

Activating recruitment teams: A team of research assistants executed the study on media platforms in each of the six active countries located in four continents. These teams were located in Israel, Jordan, Italy, Sweden, United States and Australia. Each team was led by at least one psychiatrist or psychologist.

Languages: The survey (*i.e.* the clinical research tools) was translated from English to 5 languages (Arabic, Hebrew, Italian, Swedish and German) using back translations to English for validation. All posts on the social media platforms were published in all 6 languages of the study to enhance recruitment.

Qualtrics: We uploaded the study survey in 6 languages on the Qualtrics platform. The data were saved on this platform and analyzed periodically for the recruitment rate. The final statistical analyses were executed using the data saved on this platform.

Study period: February 1, 2022-March 1, 2023.

Clinical research tools: We used the following clinical screening tools to identify mental health status (CSRS, Type A): Generalized anxiety disorder-7 (anxiety measure[32]; Cronbach's alpha = 0.931), patient health questionnaire-8[33] (depression measure; Cronbach's alpha = 0.903), perceived stress scale[34] (stress measure; Cronbach's alpha = 0.901), international trauma questionnaire[35] (a PTSD measure; Cronbach's alpha = 0.921). We also used neuropsychiatric measures for infected or recovered individuals (CSRS, Type B): (1) The Perceived Deficits Questionnaire-5, (a cognitive impairment measure[36]; Cronbach's alpha = 0.88); and (2) Fatigue[37], (Cronbach's alpha = 0.654). Participants were asked whether they were SARS-CoV-2 infected/recovered or not. These data were analyzed using validated clinical cutoff points to identify symptomatic conditions above the normative scores on each tool. Anonymity of participants was maintained throughout the study.

Participation time: Surveys took approximately 15 min to complete as measured in a pilot study before the onset of this research.

Recruitment

Instagram: We opened an account with promoting videos and photos related to the study and periodically added more related materials. The materials were translated and posted in all six languages of the study. The account displayed a link to the survey's international Qualtrics platform. Each post was user friendly.

Facebook: We used Facebook online groups to post a link to the survey. In the case of private Facebook groups, the research assistants in each active participating country contacted the group managers for permission.

Reddit: We promoted the study using this social media platform which is friendly and popular in the United States and Australia.

Online meetings: The international study teams in the six active countries conducted periodical, online meetings with the leading author and professional leads across each recruitment site to track the recruitment process and rate. To manage recruitment goals in each region, the leading author shared figures of the participants' rate per region, extracted from the data already gathered at those points.

Statistical analyses

The statistical approach included three steps: (1) We analyzed the frequency of all combinations of symptoms, to determine the most frequent combinations of two, three, four (CSRS, Type A), five and six (CSRS, Type B) symptoms. We then compared between the most prevalent combinations of each number of symptoms using Proportion Analyses; (2) Multivariate Analysis of Co-Variance (MANCOVA) to identify subpopulations at risk; and (3) We confirmed the identification of the subpopulations at risk by linear regression analyses.

RESULTS

This sample included 655 women, 296 men, and 26 individuals who self-identified as non-binary gender. Of those, 253 aged 18-29, 294 aged 30-39, 204 aged 40-49, 151 aged 50-59, and 75 aged above 60 years old.

All symptoms were significantly correlated (Table 1). Proportion Analyses showed that in the general population, the prevalence of the four-symptom combination (CSRS, Type A) Anxiety, Depression, Stress and PTSD (30.98%, 95%CI: 28-33.8) was greater than that of the most prevalent combination of three symptoms (Anxiety, Stress, and PTSD; 12.78%, 95%CI: 10.7-14.9, $P < 0.001$) and the most prevalent combination of two symptoms (Anxiety and Stress; 6.24%, 95%CI: 4.8-7.8, $P < 0.001$), as well as more prevalent than the one most prevalent symptom (Stress; 18.81%, 95%CI: 16.6-21.6, $P < 0.001$) (Table 2).

In the infected population we found the same pattern of results. As shown for the general population, in infected individuals the prevalence of the combination of four symptoms, Anxiety, Depression, Stress and PTSD (27%, 95%CI: 24.1-31.8) was greater than that of the most prevalent combination of three symptoms (Anxiety, Stress, and PTSD; 12.2%, 95%CI: 9.7-15.3, $P < 0.001$), greater than that of the most prevalent combination of two symptoms (Anxiety and Stress; 5.9%, 95%CI: 4.2-8.3, $P < 0.001$), and that of the one most prevalent symptom (Stress; 21%, 95%CI: 18-25, $P < 0.01$).

However, when we added long-COVID neuropsychiatric symptoms (Cognitive deficits and Fatigue, CSRS, Type B) to the four psychiatric symptoms (CSRS, Type A), the prevalence of four psychiatric symptoms (CSRS, Type A) was still significantly greater than the most prevalent combinations of five symptoms (when adding Cognitive deficits, 8%, 95%CI: 6.3-11.1) or six symptoms (when adding Cognitive Deficits and Fatigue, 4%, 95%CI: 2.8-6.3) at $P = 0.003$, $P < 0.001$, respectively), showing that the prevalence of CSRS, Type A is significantly greater than all combinations of symptoms studied. Thus, these results endorse our two-tailed hypothesis, confirming that one tail of the two (CSRS, Type A) is significant. These findings suggest that the CSRS, Type A is applicable for the general population without direct association with the neuropsychiatric part of long-Covid (CSRS, Type B), and that it is not necessarily related to the viral infection and its suspected residuals. Bonferroni correction for multiple comparisons was conducted and the results were significant at $P < 0.01$.

As shown in Table 2, more people reported the combination of all 4 psychiatric symptoms (CSRS, Type A) than the combinations of fewer symptoms.

In further analyses to detect subpopulations at risk, a MANCOVA was conducted with four continents, five age groups and three types of gender as independent variables, while keeping the 4 psychiatric components of the CSRS, Type A as dependent variables, controlling for COVID-infected/recovered *vs* non infected/recovered individuals as a covariate. A three-way interaction was found: Continent × age × gender [$F(14,925) = 1.747$, $P < 0.05$ with observed power of 0.903] (Figures 1 and 2). The covariate did not significantly add to the explained variance. Follow up analyses showed that the sources of the three-way interaction were threefold, consistently over the 4 dependent variables (Anxiety, Depression, Stress and PTSD, CSRS, Type A): (1) In North America, participants aged < 50 years old, self-identifying as non-binary, reported significantly higher scores than both women and men ($P < 0.05$); (2) Women at young ages (< 40 years old) in North America scored higher compared to men and women in other continents and other ages; and (3) In North America, women at young ages (< 40 years old) and participants self-identifying as non-binary gender, aged < 50, scored above the clinical cutoff points, although women's scores were significantly lower ($P < 0.05$) than the scores of the non-binary gender at these young ages.

The sources of the three-way interaction, which in turn correspond to identified populations at risk, were confirmed by linear regression analyses, which do not require an assumption of variables' normal distributions.

Specifically, Anxiety score was negatively associated with being a man [b = -1.42 (-2.22, -0.62)] and positively associated with non-binary gender [b = 3.81 (1.53, 6.10)], negatively associated with age groups 50-60 [b = -1.36 (-2.56, -0.15)] and > 60 [b = -3.06 (-4.59, -1.53)] and living in Australia [b = -2.96 (-3.85, -2.07)] or the Middle-East [b=-2.06 (-3.84, -1.36)] compared to North America.

Depression score was negatively associated with being a man [b = -1.57 (-2.42, -0.72)] and positively associated with non-binary gender [b = 5.08 (2.65, 7.51)] while negatively associated with age group > 60 [b = -2.89 (4.52, 1.26)] and living in Australia [b = -2.01 (-2.96, -1.06)] or the Middle-East [b = -2.97 (-4.28, -1.64)] compared to North America.

Stress symptoms score was negatively associated with being a man [b = -2.02 (-3.15, -0.88)] and positively associated with non-binary gender [b = 4.65 (1.40, 7.90)], negatively associated with age groups 50-60 [b = -2.12 (-3.84, -0.40)] and > 60 [b = -5.33 (-7.51, -3.16)] and living in Australia [b = -3.24 (-4.51, -3.98)] or the Middle East [b = -4.49 (-6.25, -2.72)] compared to North America.

PTSD score was negatively associated with being a man [b = -2.89 (-4.09, -1.70)] and positively associated with non-binary gender [b = 6.34 (2.92, 9.75)], negatively associated with older age group > 60 [b = -4.86 (-7.15, -2.57)] and living in Australia [b = -3.53 (-4.86, -2.20)], Europe [b = -3.43 (-6.02, -0.85)] or the Middle East [b = -4.44 (-6.29, -2.59)] compared to North America.

DISCUSSION

The results of this study show that the prevalence of 4 symptoms, combining anxiety, depression, stress symptoms and PTSD, was significantly higher than the most prevalent combinations of fewer symptoms across 4 continents, age groups (> 18 years old), and gender. This supports the transdiagnostic hypothesis embedded in the CSRS (Type A) and shows its clinical value as a future potential diagnosis spanning 4 conventional diagnostic categories.

Table 1 Correlation coefficients between all six dependent variables

Correlation table	PHQ	PSS	ITQ	GAD	Cognitive	Fatigue
PHQ	1	0.79[a]	0.74[a]	0.80[a]	0.4[a]	0.24[a]
PSS	0.79[a]	1	0.74[a]	0.79[a]	0.3[a]	0.25[a]
ITQ	0.74[a]	0.74	1	0.71[a]	0.34[a]	0.31[a]
GAD	0.80[a]	0.79[a]	0.71	1	0.311	0.25[a]
Cognitive	0.4[a]	0.3[a]	0.34[a]	0.311[a]	1	0.30[a]
Fatigue	0.24[a]	0.25[a]	0.31[a]	0.25[a]	0.30[a]	1

[a]$P < 0.001$.

As shown in Table 1, all components of the CSRS type A and type B are significantly correlated. PHQ: Patient Health Questionnaire; PSS: Perceived Stress Scale; ITQ: International Trauma Questionnaire; GAD: Generalized Anxiety Disorder.

Table 2 All combinations of symptoms reported

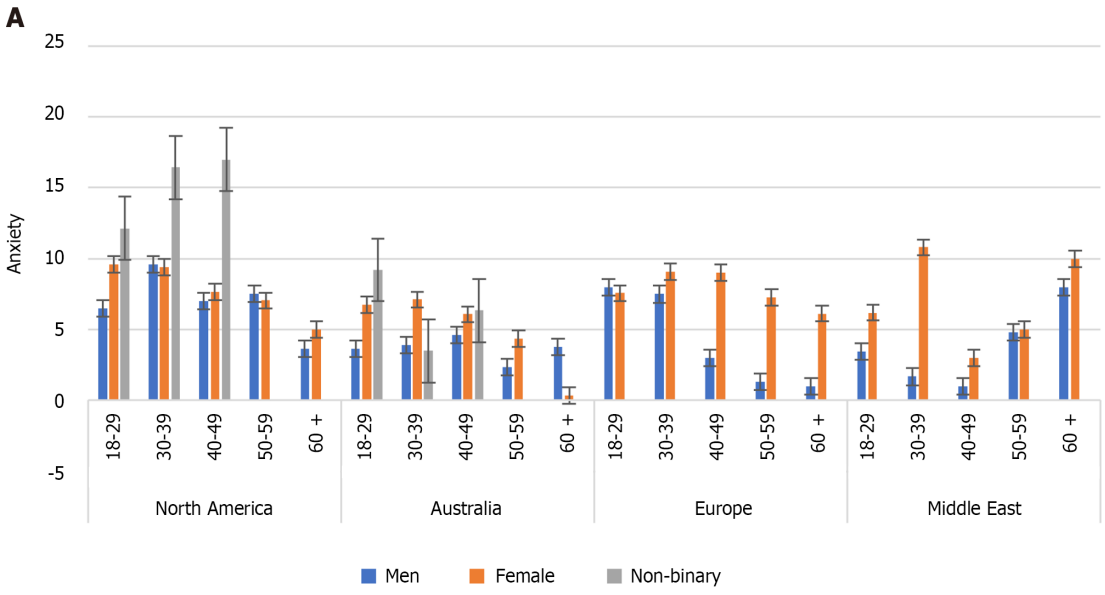
General population	Percentage
Combination	
None	10
Stress	20
Depression	0
Anxiety	3
PTSD	2
Stress + depression	0
Anxiety + depression	0
PTSD + depression	0
Stress + anxiety	6
Stress + PTSD	4
Anxiety + PTSD	1
Stress + depression + anxiety	3
Stress+ depression + PTSD	1
Stress + anxiety + PTSD	13
Depression+ anxiety + PTSD	0
All	31

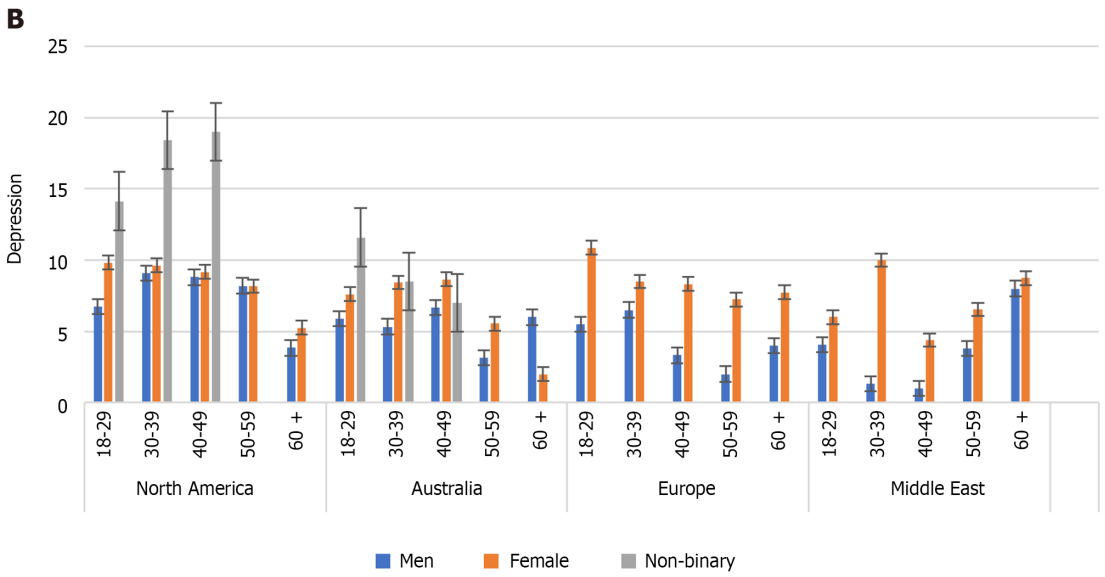
PTSD: Post-traumatic stress disorder.

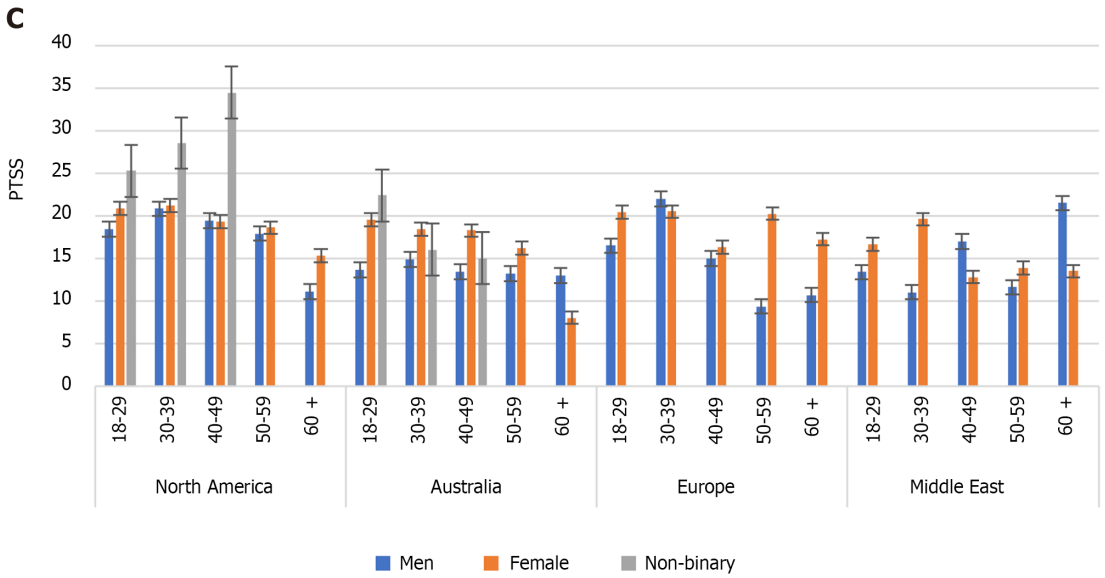
The results show that the CSRS is sensitive to demographic variability and especially to the differences between cultures, locations and gender types. The overall analyses confirm the transdiagnostic hypothesis by showing that over 4 continents and gender types more symptoms were significantly more prevalent than fewer symptoms.

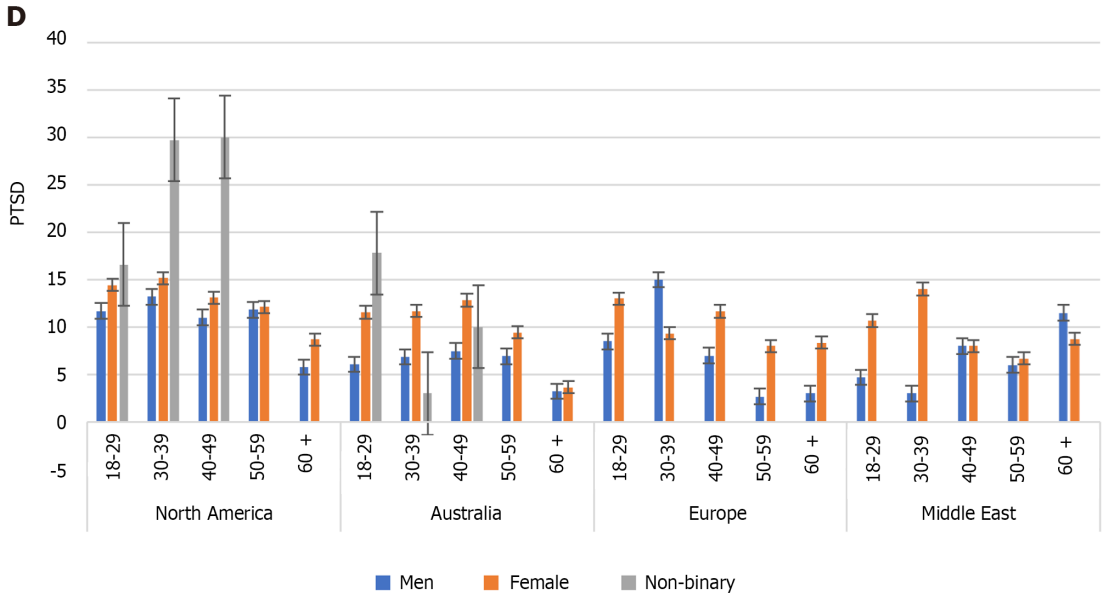
One identified source for the significant three-way interaction found in this study (age × gender × continent), and confirmed by regression analyses showed, that the group that self-identified as non-binary gender scored significantly higher on all four psychiatric symptoms of the CSRS at young ages (< 40 years old) in North America compared to (self-identified) women and (self-identified) men located in the 4 continents studied, and to other ages across the adult life span. These results show a combined mental health risk factor, suggesting that the CSRS, Type A is sensitive to populations at risk and may be applied to future identification of other vulnerable sub-populations.

In the scientific literature, identifying as non-binary at a young age has been recognized as a risk factor for increased mental health problems compared to other age groups and to other gender identities including other types on the gender identity spectrum such as the transgender identity[38,39]. The reduced affective wellbeing of those who identify as non-binary gender have been documented in research and theoretical conceptualizations[38,40,41]. To describe the unique type of distress that non-binary gender individuals might experience the term "gender minorities stress" was suggested


A
Anxiety
25
20
15
10
5
0
-5
18-29
30-39
40-49
50-59
60 +
North America
Australia
Europe
Middle East
Men
Female
Non-binary


B
Depression
25
20
15
10
5
0
18-29
30-39
40-49
50-59
60 +
North America
Australia
Europe
Middle East
Men
Female
Non-binary


C
PTSS
40
35
30
25
20
15
10
5
0
18-29
30-39
40-49
50-59
60 +
North America
Australia
Europe
Middle East
Men
Female
Non-binary



DOI: 10.5498/wjp.v13.i10.803

Figure 1 The measures assessing the four psychiatric features of the Complex Stress Reaction Syndrome (CSRS, Type A, mean ± SD). A: The Generalized Anxiety Disorder (anxiety measure); B: The Patient Health Questionnaire-8 (depression measure); C: The Perceived Stress Scale (perceived stress measure); D: The International Trauma Questionnaire (post-traumatic stress disorder measure).

[42]. We note that more conservative social views in continents other than North America may have inhibited people from identifying as non-binary and prevented an even larger magnitude of the non-binary gender stress reactivity in our findings. The emotional burden of this minority and its dramatic impact on this study's results attests to the extreme distress experienced by this sub-population.

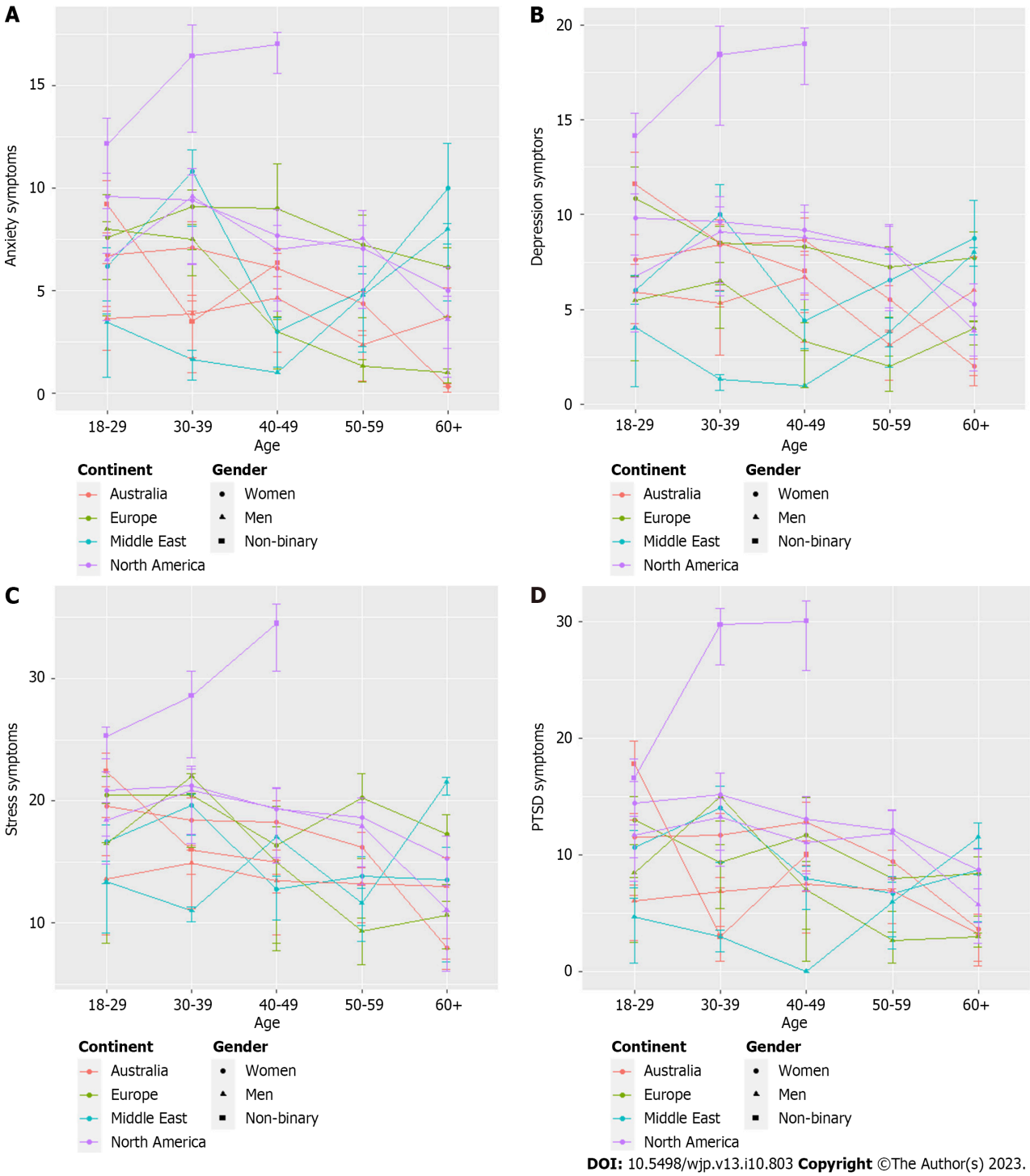
An additional source for the three-way interaction is related to another sub-population at risk which scored above the clinical cutoffs of all the four types of symptomatology included in the CSRS, Type A, young age groups identifying as a woman in North America. Being a woman at young age has been reported as a risk factor long before the COVID-19 outbreak[43,44], during the COVID-19 pandemic[45] and in the post-COVID era[46] in very large, epidemiological studies. Thus, our results show the sensitivity of the CSRS, Type A in measuring a specific stress reactivity spanning several conventional categories in both minoritized and majority subpopulations.

In this study, the psychiatric pattern of symptoms (CSRS, Type A) was similar in infected/recovered SARS-CoV-2 patients and in the non-infected population, suggesting that the CSRS, Type A is sensitive to a clinical picture in daily life, beyond its relevance to catastrophes, including the COVID-19 pandemic[16]. The neuropsychiatric part of the CSRS relating to neuropsychiatric components of the long-COVID syndrome (CSRS, Type B), did not add to the explained variance and the same pattern of results was found in infected/recovered individuals. These results show that the psychiatric part of the CSRS (Type A), when controlling for infected-non infected conditions, is the type of CSRS which is sensitive to at-risk sub-populations. In accordance with a current debate, this study also suggests that the long-COVID syndrome is a too broad diagnostic category in neuropsychiatry, resulting in recent contradictory results[47,48]. Thus, the CSRS shows relevance for daily life stressors, beyond the pandemic situation and not as a mandatory result of the viral infection.

Thus, the CSRS, Type A represents a unique transdiagnostic clinical picture combining symptomatology of affective disorders with stress reactivity[16,26,31]. The prevalence of affective disorders spans a wide range of symptomatology, with dramatic cross-cultural differences[49]. Reports on prevalence of stress reactions are also present across a wide range mental disorders[50]. Furthermore, earlier studies reported that at-risk populations do not necessarily meet the full criteria of affective disorders and stress reactivity categories[40,44]. As it arises from the current findings, and according to our previous arguments[26], the CSRS, Type A identifies, and is sensitive to individual differences in stress reactivity and reduced positive affectivity, within a transdiagnostic spectrum.

The correlative design of this study is the most appropriate for the current stage of CSRS development as only after assuring the face validity of the hypothesized syndrome by empirical data, including its highly associated symptoms, a follow up design on etiological questions related to more causal assumptions may be investigated. In fact, to show that any transdiagnostic hypothesis is related to associations between symptoms spanning several traditional categories, a correlative design should be employed.

As the aim of this research is primarily transdiagnostic, its correlative design affords testing the relationship and extent of association between a given number of variables (symptoms) spanning traditional classifications without meeting them in full. This type of design also allows testing whether a correlative combination of more symptoms is more prevalent than a combination of fewer symptoms from a given number of hypothesized variables, in a given hypothesized combination.



DOI: 10.5498/wjp.v13.i10.803

Figure 2 Three-way interactions between continents, age groups and gender identifying the sub-populations at risk by the four psychiatric features of the Complex Stress Reaction Syndrome (CSRS, Type A). A: Three-way-interaction for the Generalized Anxiety Disorder (anxiety measure); B: Three-way-interaction for the Patient Health Questionnaire-8 (depression measure); C: Three-way-interaction for the Perceived Stress Scale (perceived stress measure); D: Three-way-interaction for the International Trauma Questionnaire (post-traumatic stress disorder measure).

The correlative design used in this study aimed also to show the sensitivity of CSRS to populations at risk who score beyond the clinical cutoff of the measures used. As such, the study also aimed to investigate the generalizability of the CSRS across continents, gender types and age-groups. This required comparisons between continents, gender types and age-groups. Thus, a correlative design and its aligned conclusion on associations between symptoms as related to demographic factors, may be derived even when employing statistical comparisons between independent (demographic, in this case) variables, and their assumed related "causal" impact on the dependent (CSRS, Type A) variables. The advantage of this approach and conclusions regarding association between independent (demographic) and dependent (CSRS, Type A) variables is threefold from both scientific and clinical perspectives: (1) It shows the generalizability of the CSRS; (2) It shows the CSRS, Type A as clinically essential for the identification of populations at risk, suggesting that the CSRS, Type A is sensitive to a unique transdiagnostic mental health condition; and (3) It includes a suspected indication

to treat. Furthermore, the results of the analysis of variance were confirmed by significant associations between the same demographic variables and the most prevalent combination of symptoms (CSRS, Type A) in linear regression analyses. Thus, the same populations at risk, as well as the sensitivity of the CSRS to these populations, are apparent in the results of this study.

The limitations of this study lie in the sampling methods utilized, which used convenience sampling[51]. This type of convenience online sampling became very popular and legitimate during the pandemic, although very large samples have been criticized before and after the pandemic[52,53]. Additional limitations include the use of self-report measures (symptoms) and not diagnostic interviews (signs), and the possible bias towards samples who are computer literate. However, in our binational research[26], we combined the methodology of representative sampling (Israel) with convenience sampling (Italy) and found similar results, although employing two different sampling methodologies, supporting the validity of the online convenience sampling. Yet to come, international studies with representative sampling, are warranted for further support of the CSRS, Type A validity and its clinical value.

This current international study emphasizes the importance of transdiagnostic approaches for clinical identification of individual differences and sub-populations at risk that do not meet the full criteria of any traditional category. This will afford the development of more accurate prevention and treatment for those with emotional needs who remain without a clear diagnosis and proper clinical care.

CONCLUSION

This study shows a global new picture of the indication to treat derived from (1) The different populations included from around the globe; and (2) Allowing a transdiagnostic perspective. Although the categorical model of diseases remains largely used worldwide[26], the future will tell if transdiagnostic categories will be part of the next revisions of the DSM and ICD conventional systems to facilitate a resolution of the crisis in the field of psychiatry[1]. Indeed, a transdiagnostic approach recognizes the inherent complexity and heterogeneity of mental disorders by focusing on shared underlying dimensions rather than rigid diagnostic categories. This allows for a more nuanced understanding of psychopathology and better captures the overlapping symptomatology often observed across different disorders. Hence, future international transdiagnostic clinical research is warranted. To support psychiatrists in their clinical practice, future research may utilize transdiagnostic approaches to classify patients who show a mixed clinical picture when applied in face-to-face clinical meetings (signs) compared to remote self-scoring (symptoms) by the same patients.

ARTICLE HIGHLIGHTS

Research background

The debate regarding diagnostic classification systems in psychiatry (categorial *vs* dimensional systems) has essential implications for the diagnosis, prevention and treatment of stress reactions.

Research motivation

We previously found a unique pattern of stress reaction in a study executed during the coronavirus disease 2019 pandemic using large representative samples in two countries, and termed it the Complex Stress Reaction Syndrome (CSRS). In the current international study, in four continents, using six languages we aimed to investigate the generalization of the CSRS and its sensitivity to populations at risk.

Research objectives

We aimed to investigate CSRS, Type A [psychiatric symptoms, spanning anxiety, depression, stress symptoms, and post-traumatic stress disorder (PTSD)], with or without long-COVID residuals (CSRS, Type B, neuropsychiatric symptoms spanning cognitive deficits and fatigue, excluding systemic symptoms). Our two-tailed hypothesis was that CSRS is a condition related to an unrecognized type of stress reaction in daily life in the general population (Type A) or that it is related to the severe acute respiratory syndrome coronavirus 2 infection and its long-COVID residuals (Type B).

Research methods

Media-supported study using the Qualtrics platform.

Research results

The results of the Proportion Analyses showed that the prevalence of 4 symptoms spanning anxiety, depression, stress symptoms, and PTSD was significantly higher than the most prevalent combinations of fewer symptoms across 4 continents, age groups, and gender (CSRS, Type A). Further analyses identified two populations at risk: (1) Individuals that self-identified as non-binary gender; and (2) Women at young ages (< 40 years old) in North America.

Research conclusions

These results show a combined mental health risk factor related to stress reactivity, suggesting that the CSRS is sensitive to populations at risk and may be applied to future identification of other vulnerable sub-populations. It also supports the

transdiagnostic approach for more accurate prevention and treatment. Time will tell if such transdiagnostic syndromes will be part of the discussions on the next revisions of the traditional classification systems or whether the crisis in psychiatry further evolves.

Research perspectives

A follow-up international study to investigate whether the condition of multiplicity of stressors is the etiological source for developing the CSRS, Type A clinical status, is warranted.

ACKNOWLEDGEMENTS

The authors thank Daniel Mandelbaum for his assistance in statistical analyses. We also thank Adi Ramot for graphical contributions to the media posts.

FOOTNOTES

Author contributions: Goldstein Ferber S developed the CSRS conceptualization and was the leading author; Rossi R supervised the statistical analyses and data collection; All the other authors contributed to the study and the last version of this paper.

Institutional review board statement: IRB approvals for this international study were provided by The Johns Hopkins University, Baltimore, Maryland, USA, and by Bar Ilan University, Ramat-Gan, Israel. The study survey used the Qualtrics platform (Qualtrics, Provo, Utah, USA) for data collection.

Informed consent statement: All study participants provided online informed consent prior to study enrollment.

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

Data sharing statement: The study data are available upon request.

Country/Territory of origin: United States

ORCID number: Sari Goldstein Ferber 0000-0001-6843-3695; Tommaso Benedetto Jannini 0000-0003-2936-4150.

Corresponding Author's Membership in Professional Societies: Sigma Xi Honor Society Nomination.

S-Editor: Fan JR
L-Editor: A
P-Editor: Zhang XD

REFERENCES

1 **Di Nicola V**, Stoyanov D. Psychiatry in crisis: At the crossroads of social sciences, the humanities, and neuroscience. *Psychiatr Cri* 2021; 1-174 [DOI: 10.1007/978-3-030-55140-7]

2 **Di Nicola V**, Stoyanov D. Psychiatric Nosology Revisited: At the Crossroads of Psychology and Medicine. *Psychiatry Cri* 2021; 31-41 [DOI: 10.1007/978-3-030-55140-7_3]

3 **Waszczuk MA**, Jonas KG, Bornovalova M, Breen G, Bulik CM, Docherty AR, Eley TC, Hettema JM, Kotov R, Krueger RF, Lencz T, Li JJ, Vassos E, Waldman ID. Dimensional and transdiagnostic phenotypes in psychiatric genome-wide association studies. *Mol Psychiatry* 2023 [PMID: 37402851 DOI: 10.1038/s41380-023-02142-8]

4 **Solmi M**, Soardo L, Kaur S, Azis M, Cabras A, Censori M, Fausti L, Besana F, Salazar de Pablo G, Fusar-Poli P. Meta-analytic prevalence of comorbid mental disorders in individuals at clinical high risk of psychosis: the case for transdiagnostic assessment. *Mol Psychiatry* 2023 [PMID: 37296309 DOI: 10.1038/s41380-023-02029-8]

5 **Lee JJ**, Piras E, Tamburini S, Bu K, Wallach DS, Remsen B, Cantor A, Kong J, Goetz D, Hoffman KW, Bonner M, Joe P, Mueller BR, Robinson-Papp J, Lotan E, Gonen O, Malaspina D, Clemente JC. Gut and oral microbiome modulate molecular and clinical markers of schizophrenia-related symptoms: A transdiagnostic, multilevel pilot study. *Psychiatry Res* 2023; **326**: 115279 [PMID: 37331068 DOI: 10.1016/j.psychres.2023.115279]

6 **Endrass T**, Weiss F. Performance Monitoring: A Transdiagnostic Biomarker of Adaptive Behavior in Mental Disorders. *Biol Psychiatry* 2023; **93**: 962-963 [PMID: 37197835 DOI: 10.1016/j.biopsych.2023.03.007]

7 **Taquet M**, Griffiths K, Palmer EOC, Ker S, Liman C, Wee SN, Kollins SH, Patel R. Early trajectory of clinical global impression as a transdiagnostic predictor of psychiatric hospitalisation: a retrospective cohort study. *Lancet Psychiatry* 2023; **10**: 334-341 [PMID: 36966787

DOI: 10.1016/S2215-0366(23)00066-4]

8 **Kotov R**, Krueger RF, Watson D, Achenbach TM, Althoff RR, Bagby RM, Brown TA, Carpenter WT, Caspi A, Clark LA, Eaton NR, Forbes MK, Forbush KT, Goldberg D, Hasin D, Hyman SE, Ivanova MY, Lynam DR, Markon K, Miller JD, Moffitt TE, Morey LC, Mullins-Sweatt SN, Ormel J, Patrick CJ, Regier DA, Rescorla L, Ruggero CJ, Samuel DB, Sellbom M, Simms LJ, Skodol AE, Slade T, South SC, Tackett JL, Waldman ID, Waszczuk MA, Widiger TA, Wright AGC, Zimmerman M. The Hierarchical Taxonomy of Psychopathology (HiTOP): A dimensional alternative to traditional nosologies. *J Abnorm Psychol* 2017; **126**: 454-477 [PMID: 28333488 DOI: 10.1037/abn0000258]

9 **Casey BJ**, Craddock N, Cuthbert BN, Hyman SE, Lee FS, Ressler KJ. DSM-5 and RDoC: progress in psychiatry research? *Nat Rev Neurosci* 2013; **14**: 810-814 [PMID: 24135697 DOI: 10.1038/nrn3621]

10 **Reininghaus U**, Böhnke JR, Chavez-Baldini U, Gibbons R, Ivleva E, Clementz BA, Pearlson GD, Keshavan MS, Sweeney JA, Tamminga CA. Transdiagnostic dimensions of psychosis in the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP). *World Psychiatry* 2019; **18**: 67-76 [PMID: 30600629 DOI: 10.1002/wps.20607]

11 **Caraci F**, Enna SJ, Zohar J, Racagni G, Zalsman G, van den Brink W, Kasper S, Koob GF, Pariante CM, Piazza PV, Yamada K, Spedding M, Drago F. A new nomenclature for classifying psychotropic drugs. *Br J Clin Pharmacol* 2017; **83**: 1614-1616 [PMID: 28401576 DOI: 10.1111/bcp.13302]

12 **Sambuco N**, Bradley MM, Lang PJ. Hippocampal and amygdala volumes vary with transdiagnostic psychopathological dimensions of distress, anxious arousal, and trauma. *Biol Psychol* 2023; **177**: 108501 [PMID: 36646300 DOI: 10.1016/j.biopsycho.2023.108501]

13 **Gudmundsson OO**, Walters GB, Ingason A, Johansson S, Zayats T, Athanasiu L, Sonderby IE, Gustafsson O, Nawaz MS, Jonsson GF, Jonsson L, Knappskog PM, Ingvarsdottir E, Davidsdottir K, Djurovic S, Knudsen GPS, Askeland RB, Haraldsdottir GS, Baldursson G, Magnusson P, Sigurdsson E, Gudbjartsson DF, Stefansson H, Andreassen OA, Haavik J, Reichborn-Kjennerud T, Stefansson K. Attention-deficit hyperactivity disorder shares copy number variant risk with schizophrenia and autism spectrum disorder. *Transl Psychiatry* 2019; **9**: 258 [PMID: 31624239 DOI: 10.1038/s41398-019-0599-y]

14 **Gong Q**, Scarpazza C, Dai J, He M, Xu X, Shi Y, Zhou B, Vieira S, McCrory E, Ai Y, Yang C, Zhang F, Lui S, Mechelli A. A transdiagnostic neuroanatomical signature of psychiatric illness. *Neuropsychopharmacology* 2019; **44**: 869-875 [PMID: 30127342 DOI: 10.1038/s41386-018-0175-9]

15 **Parkes L**, Satterthwaite TD, Bassett DS. Towards precise resting-state fMRI biomarkers in psychiatry: synthesizing developments in transdiagnostic research, dimensional models of psychopathology, and normative neurodevelopment. *Curr Opin Neurobiol* 2020; **65**: 120-128 [PMID: 33242721 DOI: 10.1016/j.conb.2020.10.016]

16 **Goldstein Ferber S**, Shoval G, Weller A, Zalsman G. Not one thing at a time: When concomitant multiple stressors produce a transdiagnostic clinical picture. *World J Psychiatry* 2023; **13**: 402-408 [PMID: 37547732 DOI: 10.5498/wjp.v13.i7.402]

17 **Darwin C**. On the Origin of Species. New York: PF Collier & Son, 2007: 1809-1822 [DOI: 10.5962/bhl.title.959]

18 **Lazarus RS**, Folkman S. Stress, Appraisal, and Coping. New York: Springer, 2009: 444 [DOI: 10.1017/s0141347300015019]

19 **Ferber SG**, Weller A, Maor R, Feldman Y, Harel-Fisch Y, Mikulincer M. Perceived social support in the social distancing era: the association between circles of potential support and COVID-19 reactive psychopathology. *Anxiety Stress Coping* 2022; **35**: 58-71 [PMID: 34652983 DOI: 10.1080/10615806.2021.1987418]

20 **Nasrallah HA**. Re-inventing the DSM as a transdiagnostic model: Psychiatric disorders are extensively interconnected. *Ann Clin Psychiatry* 2021; **33**: 148-150 [PMID: 34398730 DOI: 10.12788/acp.0037]

21 **Castellini G**, Castellani W, Lelli L, Sauro CL, Dini C, Lazzeretti L, Bencini L, Mannucci E, Ricca V. Association between resting energy expenditure, psychopathology and HPA-axis in eating disorders. *World J Clin Cases* 2014; **2**: 257-264 [PMID: 25032200 DOI: 10.12998/wjcc.v2.i7.257]

22 **Cherry KE**, De Vito AN, Calamia MR, Elliott EM, Yu S, Sampson L, Galea S, Mansoor M, McKneely KJ, Nguyen QP. Disaster stressors and psychological well-being in older adults after a flood. *Psychol Aging* 2021; **36**: 660-666 [PMID: 33856820 DOI: 10.1037/pag0000602]

23 **Corley SS**, Ornstein KA, Rasul R, Lieberman-Cribbin W, Maisel H, Taioli E, Schwartz RM. Mental Health Effects of Hurricane Sandy on Older Adults. *J Appl Gerontol* 2022; **41**: 1131-1142 [PMID: 34752154 DOI: 10.1177/07334648211052992]

24 **Fernández-de-Las-Peñas C**, Martín-Guerrero JD, Florencio LL, Navarro-Pardo E, Rodríguez-Jiménez J, Torres-Macho J, Pellicer-Valero OJ. Clustering analysis reveals different profiles associating long-term post-COVID symptoms, COVID-19 symptoms at hospital admission and previous medical co-morbidities in previously hospitalized COVID-19 survivors. *Infection* 2023; **51**: 61-69 [PMID: 35451721 DOI: 10.1007/s15010-022-01822-x]

25 **Waddell SL**, Jayaweera DT, Mirsaeidi M, Beier JC, Kumar N. Perspectives on the Health Effects of Hurricanes: A Review and Challenges. *Int J Environ Res Public Health* 2021; **18** [PMID: 33803162 DOI: 10.3390/ijerph18052756]

26 **Goldstein Ferber S**, Shoval G, Rossi R, Trezza V, Di Lorenzo G, Zalsman G, Weller A, Mann JJ. Transdiagnostic considerations of mental health for the post-COVID era: Lessons from the first surge of the pandemic. *World J Clin Cases* 2023; **11**: 809-820 [PMID: 36818632 DOI: 10.12998/wjcc.v11.i4.809]

27 **Xiong J**, Lipsitz O, Nasri F, Lui LMW, Gill H, Phan L, Chen-Li D, Iacobucci M, Ho R, Majeed A, McIntyre RS. Impact of COVID-19 pandemic on mental health in the general population: A systematic review. *J Affect Disord* 2020; **277**: 55-64 [PMID: 32799105 DOI: 10.1016/j.jad.2020.08.001]

28 **Pierce M**, Hope H, Ford T, Hatch S, Hotopf M, John A, Kontopantelis E, Webb R, Wessely S, McManus S, Abel KM. Mental health before and during the COVID-19 pandemic: a longitudinal probability sample survey of the UK population. *Lancet Psychiatry* 2020; **7**: 883-892 [PMID: 32707037 DOI: 10.1016/S2215-0366(20)30308-4]

29 **Rossi R**, Socci V, Pacitti F, Di Lorenzo G, Di Marco A, Siracusano A, Rossi A. Mental Health Outcomes Among Frontline and Second-Line Health Care Workers During the Coronavirus Disease 2019 (COVID-19) Pandemic in Italy. *JAMA Netw Open* 2020; **3**: e2010185 [PMID: 32463467 DOI: 10.1001/jamanetworkopen.2020.10185]

30 **World Health Organization**. Mental health in emergencies 2022. [cited 31 July 2023]. Available from: https://www.who.int/news-room/fact-sheets/detail/mental-health-in-emergencies

31 **Goldstein Ferber S**, Shoval G, Zalsman G, Weller A. Does COVID-19 related symptomatology indicate a transdiagnostic neuropsychiatric disorder? - Multidisciplinary implications. *World J Psychiatry* 2022; **12**: 1004-1015 [PMID: 36158308 DOI: 10.5498/wjp.v12.i8.1004]

32 **Spitzer RL**, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med* 2006; **166**: 1092-1097 [PMID: 16717171 DOI: 10.1001/archinte.166.10.1092]

33 **Kroenke K**, Strine TW, Spitzer RL, Williams JB, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. *J Affect Disord* 2009; **114**: 163-173 [PMID: 18752852 DOI: 10.1016/j.jad.2008.06.026]

34 **Cohen S**, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav* 1983; **24**: 385-396 [PMID: 6668417]

35 **Cloitre M**, Hyland P, Prins A, Shevlin M. The international trauma questionnaire (ITQ) measures reliable and clinically significant treatment-related change in PTSD and complex PTSD. *Eur J Psychotraumatol* 2021; **12**: 1930961 [PMID: 34211640 DOI: 10.1080/20008198.2021.1930961]

36 **Strober LB**, Binder A, Nikelshpur OM, Chiaravalloti N, DeLuca J. The Perceived Deficits Questionnaire: Perception, Deficit, or Distress? *Int J MS Care* 2016; **18**: 183-190 [PMID: 27551243 DOI: 10.7224/1537-2073.2015-028]

37 **Linnhoff S**, Haghikia A, Zaehle T. Cognitive fatigue-related sensory gating deficits in people with multiple sclerosis. *Neurobiol Dis* 2023; **176**: 105950 [PMID: 36493977 DOI: 10.1016/j.nbd.2022.105950]

38 **Newcomb ME**, Hill R, Buehler K, Ryan DT, Whitton SW, Mustanski B. High Burden of Mental Health Problems, Substance Use, Violence, and Related Psychosocial Factors in Transgender, Non-Binary, and Gender Diverse Youth and Young Adults. *Arch Sex Behav* 2020; **49**: 645-659 [PMID: 31485801 DOI: 10.1007/s10508-019-01533-9]

39 **Matsuno E**, Budge S. Non-binary/Genderqueer Identities: a Critical Review of the Literature. *Curr Sex Health Rep* 2017; **9**: 116-120 [DOI: 10.1007/s11930-017-0111-8]

40 **de Graaf NM**, Huisman B, Cohen-Kettenis PT, Twist J, Hage K, Carmichael P, Kreukels BPC, Steensma TD. Psychological Functioning in Non-binary Identifying Adolescents and Adults. *J Sex Marital Ther* 2021; **47**: 773-784 [PMID: 34344272 DOI: 10.1080/0092623X.2021.1950087]

41 **Coyne CA**, Poquiz JL, Janssen A, Chen D. Evidence-Based Psychological Practice for Transgender and Non-Binary Youth: Defining the Need, Framework for Treatment Adaptation, and Future Directions. *Evid Based Pract Child Adolesc Ment Health* 2020; **5**: 340-353 [DOI: 10.1080/23794925.2020.1765433]

42 **Kung KTF**. Autistic Traits, Gender Minority Stress, and Mental Health in Transgender and Non-Binary Adults. *J Autism Dev Disord* 2023 [PMID: 36652125 DOI: 10.1007/s10803-022-05875-7]

43 **Hirschfeld RM**, Cross CK. Epidemiology of affective disorders. *Arch Gen Psychiatry* 1982; **39**: 35-46 [PMID: 7055407 DOI: 10.1001/archpsyc.1982.04290010013003]

44 **de Graaf R**, Bijl RV, Smit F, Vollebergh WA, Spijker J. Risk factors for 12-month comorbidity of mood, anxiety, and substance use disorders: findings from the Netherlands Mental Health Survey and Incidence Study. *Am J Psychiatry* 2002; **159**: 620-629 [PMID: 11925301 DOI: 10.1176/appi.ajp.159.4.620]

45 **Rossi R**, Socci V, Pacitti F, Mensi S, Di Marco A, Siracusano A, Di Lorenzo G. Mental Health Outcomes Among Healthcare Workers and the General Population During the COVID-19 in Italy. *Front Psychol* 2020; **11**: 608986 [PMID: 33363500 DOI: 10.3389/fpsyg.2020.608986]

46 **Alibudbud R**. Gender in mental health: Comparison of the rate and social factors of depression, anxiety, and stress among young adult Filipino heterosexual cisgender men and women and LGBT+ individuals. *Int J Soc Psychiatry* 2023; **69**: 430-437 [PMID: 35734786 DOI: 10.1177/00207640221106874]

47 **Ferrara F**, Zovi A, Masi M, Langella R, Trama U, Boccellino M, Vitiello A. Long COVID could become a widespread post-pandemic disease? A debate on the organs most affected. *Naunyn Schmiedebergs Arch Pharmacol* 2023; **396**: 1583-1589 [PMID: 36773054 DOI: 10.1007/s00210-023-02417-5]

48 **Thaweethai T**, Jolley SE, Karlson EW, Levitan EB, Levy B, McComsey GA, McCorkell L, Nadkarni GN, Parthasarathy S, Singh U, Walker TA, Selvaggi CA, Shinnick DJ, Schulte CCM, Atchley-Challenner R, Alba GA, Alicic R, Altman N, Anglin K, Argueta U, Ashktorab H, Baslet G, Bassett IV, Bateman L, Bedi B, Bhattacharyya S, Bind MA, Blomkalns AL, Bonilla H, Bush PA, Castro M, Chan J, Charney AW, Chen P, Chibnik LB, Chu HY, Clifton RG, Costantine MM, Cribbs SK, Davila Nieves SI, Deeks SG, Duven A, Emery IF, Erdmann N, Erlandson KM, Ernst KC, Farah-Abraham R, Farner CE, Feuerriegel EM, Fleurimont J, Fonseca V, Franko N, Gainer V, Gander JC, Gardner EM, Geng LN, Gibson KS, Go M, Goldman JD, Grebe H, Greenway FL, Habli M, Hafner J, Han JE, Hanson KA, Heath J, Hernandez C, Hess R, Hodder SL, Hoffman MK, Hoover SE, Huang B, Hughes BL, Jagannathan P, John J, Jordan MR, Katz SD, Kaufman ES, Kelly JD, Kelly SW, Kemp MM, Kirwan JP, Klein JD, Knox KS, Krishnan JA, Kumar A, Laiyemo AO, Lambert AA, Lanca M, Lee-Iannotti JK, Logarbo BP, Longo MT, Luciano CA, Lutrick K, Maley JH, Marathe JG, Marconi V, Marshall GD, Martin CF, Matusov Y, Mehari A, Mendez-Figueroa H, Mermelstein R, Metz TD, Morse R, Mosier J, Mouchati C, Mullington J, Murphy SN, Neuman RB, Nikolich JZ, Ofotokun I, Ojemakinde E, Palatnik A, Palomares K, Parimon T, Parry S, Patterson JE, Patterson TF, Patzer RE, Peluso MJ, Pemu P, Pettker CM, Plunkett BA, Pogreba-Brown K, Poppas A, Quigley JG, Reddy U, Reece R, Reeder H, Reeves WB, Reiman EM, Rischard F, Rosand J, Rouse DJ, Ruff A, Saade G, Sandoval GJ, Schlater SM, Shepherd F, Sherif ZA, Simhan H, Singer NG, Skupski DW, Sowles A, Sparks JA, Sukhera FI, Taylor BS, Teunis L, Thomas RJ, Thorp JM, Thuluvath P, Ticotsky A, Tita AT, Tuttle KR, Urdaneta AE, Valdivieso D, VanWagoner TM, Vasey A, Verduzco-Gutierrez M, Wallace ZS, Ward HD, Warren DE, Weiner SJ, Welch S, Whiteheart SW, Wiley Z, Wisnivesky JP, Yee LM, Zisis S, Horwitz LI, Foulkes AS; RECOVER Consortium. Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection. *JAMA* 2023; **329**: 1934-1946 [PMID: 37278994 DOI: 10.1001/jama.2023.8823]

49 **De Vaus J**, Hornsey MJ, Kuppens P, Bastian B. Exploring the East-West Divide in Prevalence of Affective Disorder: A Case for Cultural Differences in Coping With Negative Emotion. *Pers Soc Psychol Rev* 2018; **22**: 285-304 [PMID: 29034806 DOI: 10.1177/1088868317736222]

50 **Gradus JL**. Prevalence and prognosis of stress disorders: a review of the epidemiologic literature. *Clin Epidemiol* 2017; **9**: 251-260 [PMID: 28496365 DOI: 10.2147/CLEP.S106250]

51 **Simkus J**. Convenience Sampling: Definition, Method and Examples. Psychology 2023. [cited 31 July 2023]. Available from: https://www.simplypsychology.org/convenience-sampling.html

52 **Pierce M**, McManus S, Jessop C, John A, Hotopf M, Ford T, Hatch S, Wessely S, Abel KM. Says who? The significance of sampling in mental health surveys during COVID-19. *Lancet Psychiatry* 2020; **7**: 567-568 [PMID: 32502467 DOI: 10.1016/S2215-0366(20)30237-6]

53 **Kaplan RM**, Chambers DA, Glasgow RE. Big data and large sample size: a cautionary note on the potential for bias. *Clin Transl Sci* 2014; **7**: 342-346 [PMID: 25043853 DOI: 10.1111/cts.12178]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com