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# **ABOUT COVER**

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REVIEW

# Risk factors, preventive interventions, overlapping symptoms, and clinical measures of delirium in elderly patients

Xi Mei, Yue-Hong Liu, Ya-Qing Han, Cheng-Ying Zheng

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# Abstract

Delirium is an acute reversible neuropsychiatric syndrome caused by multiple factors. It is associated with many adverse clinical outcomes including cognitive impairment, functional decline, prolonged hospitalization, and increased nursing service. The prevalence of delirium was high in department of cardiology, geriatric, and intensive care unit of hospital. With the increase in the aged population, further increases in delirium seem likely. However, it remains poorly recognized in the clinical practice. This article comprehensively discusses the latest research perspectives on the epidemiological data, risk factors, preventive interventions, overlapping symptoms, and clinical measures of delirium, including specific measures to manage delirium in clinical real-world situations. This article helps readers improve their knowledge and understanding of delirium and helps clinicians quickly identify and implement timely therapeutic measures to address various delirium subtypes that occur in the clinical settings to ensure patients are treated as aggressively as possible.

**Key Words:** Delirium; Risk factors; Preventive interventions; Research progress; Review; Clinical practice

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Core Tip: This paper reviews the whole delirium process and its latest research progress in risk factors, preventive interventions, identification of superimposed symptoms, and clinical measures to provide a comprehensive and systematic account of delirium and present the latest medical information. This article helps readers improve understanding of delirium and helps clinicians quickly identify and take timely therapeutic measures to address the various delirium subtypes that occur in the clinic setting. This is to ensure that patients can be treated as aggressively as possible.



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# INTRODUCTION

Delirium is a group of syndromes characterized by acute changes in attention, consciousness, and cognitive function that cannot usually be attributed to pre-existing neurocognitive disorders. According to ICD-11, delirium is an acute or subacute onset of attention deficit (i.e., diminished ability to direct, focus and maintain attention) and impaired consciousness (i.e., diminished orientation to the environment), with symptoms often fluctuating throughout the day with other cognitive deficits (e.g., memory, language, visuospatial function, or perceptual deficits) that can interfere with the sleep-wake cycle; the etiology is often nonpsychiatric behavioral disorders, substance or drug intoxication or withdrawal.

Regarding delirium incidence, epidemiological data vary across countries or regions, medical scenarios, and assessment methods[1]. In Table 1, the highest delirium incidence was found in post-surgical patients, intensive care unit (ICU) patients, and patients with dementia, with extremely high incidence in the elderly population with dementia (up to 56%), postcardiac surgery patients (range: 11%-46%), and patients in the ICU ward (range: 19%-82%).

Delirium leads to increased treatment needs, longer hospital stays, and increased burden of care for patients, with extremely high medical costs. However, 30%-40% of delirium cases can be prevented [1-3]. Therefore, a comprehensive and systematic understanding of the entire delirium process is important for preventing and responding to its occurrence. This study reviews the whole delirium process and its latest research progress in risk factors, preventive interventions, identification of superimposed symptoms, and clinical measures to provide a comprehensive and systematic account of delirium and to present the latest medical information.

# LITERATURE REVIEW METHODOLOGY

A search of PubMed and EMBASE databases was performed in July 2022. The search strategy focused on terms for "delirium AND risk factors AND epidemiology," "delirium AND preventive interventions," "delirium AND overlapping symptoms," "delirium AND clinical measures," and "delirium AND prevention and therapy" in 10 years. Although 8290 papers were initially evaluated, only those that fulfilled the following criteria were included in the study: (1) The article was published in English; (2) The trials included original data, as full articles in peer-reviewed journals were included; (3) The studies were representative of the general population or of specific patient populations; and (4) When two or more articles reported data from the same study sample, only the most relevant article was considered. Ultimately, 128 articles were retrieved, which were manually examined for relevance, and 89 articles were identified for further assessment.

# **RISK FACTORS**

Delirium is usually not triggered by a single factor. Patients are often exposed to multiple risk factors, broadly classified into inherent (or predisposing) and controllable risk factors (or precipitating)[4]. Identifying various factors, such as brain tissue hypoxia, inflammation, and drowsiness triggered by sedation, and controlling them can help prevent or improve delirium[5]. Patients with more inherent risk factors can trigger delirium with the action of a few controllable factors[6,7].

#### Predisposing factors

Advanced age: Delirium is very common among hospitalized older adults; however, its etiology remains unclear[6]. With increase in age, organs deteriorate, and brain and cerebrovascular functions decline even in a non-diseased individual[8]. Neurons use glucose provided by the cerebral microvascular system to produce ATP via glycolysis as an energy uptake pathway[9]. The accumulation of neuronal and cerebral microvascular damage throughout life disrupts the energy uptake pathway, leading to inadequate energy uptake and decreased energy metabolism in the brain or specific areas of the brain. This can result in dysfunction in various ways and lead to delirium development in older individuals[10].

**Cognitive decline or impairment:** Dementia and neurodevelopmental delay are risk factors for delirium. Patients with Alzheimer's disease have a relatively high risk of delirium. Delirium occurred at a significantly higher rate in patients with faster cognitive decline than in those with slower cognitive decline[11]. The same higher prevalence of delirium exists for neurodevelopmental delays in childhood[12]. This evidence confirms that a low cognitive level is a risk factor for delirium.

History of delirium: The duration of delusions varies greatly among individuals, with most cases lasting a few days and some lasting several months. Persistent delirium is not uncommon, with 20% of patients still having some symptoms 6 mo after delirium onset[13]. In such cases, the likelihood of delirium recurrence is extremely high. Patients who have experienced delirium once are more likely to experience delirium again. Moreover, delirium maybe a predictor of



Table 1 Incidence and prevalence of delirium							
Country or region/manuscript type	Medical scenario	Assessment method	Incidence (%)	Prevalence (%)			
United States[1]	Community	NR	NR	1-2			
Italy <sup>[79]</sup>	Community	DSM-5	NR	3.6			
Spain[80]	Community	DSM-4	NR	0.96			
Jordan[81]	Postcardiac surgery	CAM-ICU	9	NR			
Poland[82]	Postcardiac surgery	DSM-5 (age ≥ 65 yr)	21.4	NR			
		DSM-5 (age ≥ 80 yr)	33.5	NR			
Czech[83]	ICU	CAM-ICU	26.1	NR			
Systematic review[84]	ICU	Hyperactive	4	4			
		Hypoactive	11	17			
		Mixed	7	10			
Canada[85]	Dementia Ward	CAM (MMSE $\geq 10$ )	1.6	3.4			
		CAM (MMSE < 10)	6.9	33.3			
Italy[86]	Dementia Clinic	CAM	NR	13.3			
Australia[87]	Hospice care	DSM-5	40.2-45	42-88			
Systematic review[88]	Hospice care	NA	29	35			
Australia[89]	Post-stroke (3 d)	DSM-4	25	NR			
Portugal[90]	Post-stroke (1 d)	DRS	2	NR			
Systematic review[25]	Post-stroke	NA	NR	13-48			
Holland[91]	Psychiatric Outpatient Clinic	DRS-R98 (probable)	NR	19			
		DRS-R98	NR	2			

NR: Not reported; NA: Not available; ICU: Intensive care unit; DSM: Diagnostic and Statistical Manual of Mental Disorders; DRS: Delirium Rating Scale; CAM: Confusion Assessment Method.

cognitive decline and dementia<sup>[14]</sup>. History of delirium is common in patients with Alzheimer's disease dementia and dementia with Lewy bodies[15].

History of emotional disturbance: Severe depressive symptoms in preoperative patients were significantly associated with higher delirium incidence[16]. A cohort study showed that depression and post-traumatic stress disorder severity were positively associated with delirium duration during a 3-mo follow-up[17].

History of alcohol abuse: During alcohol withdrawal, norepinephrinergic hyperexcitability causes symptoms such as increased blood pressure, tremors, and anxiety, which can be controlled with adrenergic agonist drugs[18]. Such drugs are also used to prevent delirium in elderly patients undergoing cardiac surgery or other procedures, including clonidine or dexmedetomidine treatment[19]. Opioids increase norepinephrine release, thereby increasing the risk of delirium development[20,21]. The use of benzodiazepines in the clinical management of alcohol withdrawal syndrome has been associated with disrupted sleep patterns and delirium[22].

Malnutrition: Nutritional deficiency is a risk factor for delirium development<sup>[23]</sup>. Preoperative malnutrition is correlated with postoperative delirium. Moreover, elevated nutrition levels may reduce the risk of postoperative delirium[24].

Visual and auditory impairment: Visual and hearing impairment increases risk of delirium; in general medical patients, the risk of delirium is 2.1-3.5 times higher in patients with visual impairment than in those without. In contrast, in surgical patients, the risk of delirium is 1.1 and 1.3 times higher in patients with visual and hearing impairment, respectively[1].

Other factors: Other factors include frailty, cardiovascular disease, cerebral atrophy, white matter disease, low education level, male sex, and comorbidities[10].

# Precipitating factors

Brain function impairment: Delirium is affected by various factors of brain function, including cerebrovascular injury [25], altered metabolic levels in the brain[26], neurotransmitter imbalance[27], and damage to brain network connections



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[28,29]. Excessive microglial activation, impaired endothelial barrier function, and blood-brain barrier dysfunction may be associated with delirium and severe cognitive impairment[30].

Acute somatic diseases: Acute somatic illnesses such as sepsis, hypoglycemia, and liver failure can increase the risk of delirium[31]. Septicaemia-related encephalopathy is a common neurological complication of sepsis that is poorly understood and is associated with increased morbidity and mortality. The clinical manifestations of the disease ranges from mild confusion and delusion to severe cognitive impairment and deep coma[30]. Recent popular theories such as the brain-gut axis, brain-kidney axis, and brain-spleen axis suggest that physical health can affect brain function to a certain extent[32,33].

Infection: Patients who develop delirium after infection show a significant increase in the presence of synaptic damage markers[34]. Patients with neocoronary pneumonia may also develop cerebral hypoxia and delirium[35].

Drug use: Drug use and withdrawal, including changes in medication use, are associated with delirium. Benzodiazepines, dihydropyridines, L-type calcium channel blockers commonly used to treat hypertension, antihistamines, and opioids may pose a high risk of delirium[36].

Sleep rhythm disorders: Sleep rhythm disturbance and sleep deprivation are important factors in delirium development in ICU patients[37]. Sleep disorders and delirium share many symptoms, and their similarity has led to the belief that they are highly correlated[38].

Electrolyte imbalance: Electrolyte imbalance is a risk factor for delirium. Studies have reported that in 53 patients with delirium with serum electrolyte imbalance, correction led to a significantly shorter delirium duration in 18 patients than in 35 patients without electrolyte correction[39].

Environment: The probability of delirium increases by being in a 24-h light environment in the ICU ward or by changes in the senses, including vision and hearing, due to environmental changes[40].

Pain and surgical anesthesia: Both pain and anesthetic drug use for pain relief may trigger delirium; however, the interaction between the two and the extent of their contribution to delirium remains unclear[36]. A multicenter randomized clinical trial, among patients over 65 years old with fragile hip fractures, reported no significant difference in the incidence of delirium between general anesthesia and regional anesthesia within 7 d after surgery [41].

Other factors: Other factors include poor feeding, drug combinations, lack of communication, and physical restraint (physical activity restriction).

# PREVENTIVE INTERVENTIONS

Prevention, targeting controllable factors, can effectively control delirium, including reducing its incidence by avoiding functional brain damage or preoperative precautions. Yale University School of Medicine conducted a randomized controlled trial for delirium prevention that demonstrated the feasibility of a multimodal non-pharmacologic protocol to reduce the delirium incidence from 15% to 9% [4]. In this study, the delirium prevention protocol focused on managing the following six risk factors: disorientation, inactivity, sleep deprivation, visual impairment, hearing impairment, and dehydration. This prevention program also applies to healthcare settings such as nursing homes[42]. The long-term care plan adaptation for elderly patients with high delirium risk factors in the geriatric ward care can effectively prevent delirium[43].

Non-pharmacological approaches to effective delirium prevention include occupational therapy. Tobar provides a detailed review of the role of occupational therapy in delirium prevention in critically ill patients and provides a vision for future research in this area[44]. Environmental improvements, including minimizing noise and light at night and promoting sleep consolidation, can also help prevent delirium onset[45]. Reducing physical activity limitations is also important to allow patients to move early; physical activity restriction triples the odds of delirium[46].

Pharmacological approaches to delirium prevention include the use of melatonin to preventing delirium. Melatonin improves sleep quality and increases sedation levels, preventing and reducing delirium incidence. However, melatonin does not reduce delirium duration in patients who already have delirium[47]. In response to sleep problems, it is also necessary to determine in the clinic whether the problem is organic or functional; organic diseases, such as heart and respiratory disease, can also include sleep problems. In functional sleep problems, adjusting the sleep rhythm can help prevent delirium occurrence. In addition, patients with sleep problems caused by fear of surgery and changes in the sleep environment are considered functional. The use of melatonin in such cases improves sleep rhythm and prevents delirium [48]. The use of other sleep-improving drugs, such as ramelteon, for delirium prevention has also been studied[49].

Antipsychotic use for delirium prevention remains highly controversial. A randomized placebo-controlled study showed that haloperidol had a preventive effect in elderly hip surgery patients at risk of delirium [50]. Numerous studies have been conducted on haloperidol for delirium prevention[51,52]. A risperidone trial for delirium prevention in postoperative cardiac patients found that postoperative delirium incidence was significantly lower in the 1 mg risperidone group than in the placebo group (11.1% vs 31.7%, P = 0.009)[53]. A review of studies concluded that antipsychotic medication use was not related to delirium duration, severity, or place of care and that there was high heterogeneity among studies[54]. Second-generation antipsychotics are more effective than placebo in preventing delirium onset; however, delirium severity was not reduced in patients receiving prophylactic antipsychotics[55].



# **IDENTIFICATION OF OVERLAPPING SYMPTOMS**

# **Clinical manifestations**

The clinical manifestations of delirium are complex and vary, and they are described by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, as altered attention, significantly different from the basal level and accompanied by changes in consciousness, cognitive decline, and sleep rhythm disturbances[56]. Delirium has a rapid onset and appearance of symptoms, duration of several hours or days, and a fluctuating nature. For ease of memory, the diagnostic criteria for delirium have been described more simply as A (attention and awareness), disturbances in attention and awareness; B (short period, hours or days), developing over a short period, usually hours or days; C (cognitive deficit), cognitive decline; D (disturbances in A and C), other cognitive deficits that interfere with A and C judgment, such as a complete coma state, are excluded; and E (exposure to medical conditions or drugs), exposure factors, such as surgery and medications.

The diagnostic process consisted of two basic steps. First, a bedside patient assessment was performed to determine the level of attention and arousal and the presence of other cognitive deficits, psychotic features, or mental status abnormalities. Second, the patient's baseline attention and consciousness status were determined by accompanying relatives or caregivers to obtain evidence of acute change.

#### Assessment methods

After the initial diagnosis, the patient must be further evaluated to obtain more details, including features such as delusions, hallucinations, and mood changes. These details are very important and affect the patient's subsequent treatment or management plan.

**Neuropsychological scales:** More than 50 assessment tool scales have been developed, with varying conditions of use, mainly including use when delirium first appears or is suspected, when monitoring delirium in hospitalized patients on a regular daily basis, during brief screening, during detailed symptom documentation and neuropsychological assessment, and when assessing delirium severity[57]. Table 2 shows the commonly used neuropsychological scale of delirium assessment.

Ancillary investigations: Delirium assessment should also consider its precipitating factors; therefore, detailed ancillary examinations such as blood, computed tomography (CT), magnetic resonance imaging (MRI), and electroencephalography (EEG) should be performed. In routine blood parameters, the mean red blood cell volume and aspartate aminotransferase can be delirium predictors in trauma patients[58]. Routine blood tests should corroborate the patient's medical history and clinical features. In addition, some cases of delirium are caused by primary central nervous system disease. Specific brain tests, such as CT or MRI, EEG, lumbar puncture, and antibody testing for autoimmune encephalitis, are selectively performed in such cases. However, it is not reasonable to perform CT in all patients with delirium. A study that included 1653 patients showed that only 11% of patients had positive CT findings, with cerebral hemorrhage being the most common cause of delirium[59]. MRI showed that reduced cerebral blood flow, oxygenation, and abnormal glucose uptake might be associated with delirium, including a high white matter signal in the brain[60].

# Differential diagnosis and superimposed symptoms

Although there are similarities in clinical manifestations between the delirium and dementia subtype, including fluctuating cognitive decline exhibited by dementia with Lewy body (DLB), visual hallucinations or delusions exhibited by DLB and Parkinson's disease dementia, and attention deficit in severe Alzheimer's disease (AD), all are similar to delirium presentation. However, there are also significant differences: in terms of the mode of onset, delirium is acute and dementia is slowly progressive; concerning duration, delirium usually lasts for a few hours or days, while dementia lasts for a long time; and there is decreased arousal in delirium and that in dementia remains relatively intact.

Previous studies have shown that symptoms such as dementia and depression sometimes appear in parallel with delirium, leading to poor prognosis and high in-hospital mortality and readmission rates. Identifying delirium superimposed dementia (DSD) is important for timely treatment. Patients with dementia who suddenly present with symptoms such as irritability, unexplained falls, resistance or reluctance to communicate with caregivers, drowsiness, and hallucinations need to be closely monitored for DSD and promptly treated symptomatically[61]. Delirium and depression are very common neuropsychiatric syndromes in the elderly, and accurate condition determination is necessary for providing the best treatment plan. However, the considerable clinical overlap of symptoms makes proper identification difficult, leading to adverse medical outcomes, such as clarifying whether the patient's mood disorder is a manifestation of delirium or depression or the comorbidity or primary stage before implementing therapeutic measures [62].

# **CLINICAL MEASURES AFTER DELIRIUM ONSET**

The best management strategy is a multifaceted intervention focused on treating precipitating illnesses, reviewing medication regimens, managing distress, mitigating comorbidities, and maintaining environmental comfort. Clinical measures are divided into non-pharmacologic, non-antipsychotic, and antipsychotic measures.

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Table 2 Common delirium assessment scales						
Name	Time (min)	Application	Sensitivity (%)	Specificity (%)	Rigorous training	Suitable for examining DSD
Confusion Assessment Method (CAM) [92,93]	3-10	No ICU	46-94	63-100	Yes	Yes
The 4A's test (4AT)[94]	< 2	No ICU	86-100	65-82	No	Yes
The 12-item Stanford Proxy Test for Delirium (S-PTD)[95]	5	No ICU	80	90	No	No
Richmond Agitation Screening Scale (RASS)[96,97]	1	Delirium has just started	65-75	82-90	No	Yes
The Recognizing Acute Delirium As part of your Routine (RADAR)[98]	<1	Delirium has just started	73	67	No	Yes
Confusion Assessment Method for ICU (CAM-ICU)[99]	< 5	ICU	28-100	53-99	Yes	Yes
Intensive Care Delirium Screening Checklist (ICDSC)[100]	7-10	ICU	73-97	69-97	Yes	No
Delirium Triage Screen (DTS)[101]	<1	Screening	82	96.1	No	No
Ultra Brief 2 Item Screener (UB-2)[102, 103]	<1	Screening	93	64	No	No
Simple Question for Easy Evaluation of Consciousness (SQEEC)[104]	<1	Screening	93	81	No	No
Delirium Rating Scale revised-98 (DRS- R98)[105]	20	Detailed neuropsychological assessment	57-93	82-98	Yes	Yes
Memorial Delirium Assessment Scale (MDAS)[106]	7-10	Detailed neuropsychological assessment	64-82	75-100	Yes	No
CAM Severity (CAM-S)[107]	5	Detailed neuropsychological assessment	NR	NR	No	No

NR: Not reported; ICU: Intensive care unit; DSD: Delirium superimposed dementia.

#### Non-pharmacologic measures

Non-pharmacological measures are recognized to be effective in dealing with delirium. The intervention protocols vary among studies and mainly include orientation, cognitive stimulation, early activity, non-pharmacological sleep improvement, sensory impairment correction, identification and intervention of potential controllable risk factors or postoperative complications, pain management, gastrointestinal function improvement, supplemental nutrition, and enhancing oxygen delivery.

The Hospital Elder Life Program (HELP) is a systematic non-pharmacological intervention program[63]. According to the British Institute for Health Care Excellence guidelines for preventing, diagnosing, and managing delirium, HELP added entries for coping with hypoxia, infection, pain, and constipation[64].

After delirium onset, non-pharmacological approaches are an indispensable way. Summarily, the main points are ABCDEF: A (assessing, preventing, and managing pain); B (both spontaneous awakening and spontaneous breathing trials), promoting spontaneous awakening and breathing; C (choice of analgesia and sedation), selection of a reasonable analgesic regimen; D (delirium assessment, management, and prevention), delirium pre-assessment, management, and prevention; E (early mobility), early activity; and F (family engagement), family involvement[65].

The primary treatment of delirium is still focused on identifying and managing potential triggers. In practice, the choice of clinical measures will vary according to patient-specific situations. It is crucial to summarize treatment strategies that minimize delirium severity and duration.

#### Non-antipsychotic measures

Antiepileptic drugs: Valproic acid is effective in both case reports and retrospective cohort studies for delirium treatment [66,67]. Valproic acid can be administered orally or intravenously and is effective in patients with delirium associated with alcohol withdrawal, a history of traumatic brain injury, or mood disorders. Valproic acid should be avoided in pregnant women and patients with significant hepatic or pancreatic dysfunction, active bleeding, or low platelet counts. Before starting valproic acid treatment, patients should have their blood counts and liver enzyme levels checked and monitored.

Alpha-2 agonists: Dexmedetomidine, an alpha-2 agonist, effectively reduces agitation associated with delirium, decreases CNS sympathetic activity, and indirectly reduces the risk of drug combinations by reducing the use of other delirium medications. A national study showed that dexmedetomidine effectively controlled delirium in postoperative patients



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other than those undergoing cardiac surgery[68].

**Melatonin:** The effects of melatonin on delirium have been described previously. Case and retrospective studies have shown that ramelteon helps treat delirium, especially active delirium[69,70]. Melatonin is well-tolerated and safe in the population. The role of melatonin and its receptor agonists in delirium treatment deserves to be studied in-depth. It can enhance sleep consolidation and maintain a good sleep-wake cycle in delirious patients.

**Vitamin B1:** Nutritional deficiencies, especially vitamin B deficiencies, are associated with delirium[71]. Vitamin B1 deficiency can lead to a range of changes in mental status, including Wernicke's encephalopathy (a triad of nystagmus, oculomotor paralysis, and altered mental status), Korsakoff's syndrome (irreversible memory impairment, usually the result of untreated Wernicke's encephalopathy), and delirium.

#### Antipsychotic measures

Although no medications have been approved by the United States Food and Drug Administration (FDA) specifically for treating delirium, antipsychotic medications are often used as first-line medications to respond to and manage patients when non-pharmacologic measures are insufficient to control or improve symptoms. However, antipsychotic use for delirium treatment remains controversial. Several studies have shown that the benefits of using antipsychotic medications outweigh the risks for patients, particularly in improving agitation and psychotic symptoms[72,73]. For the control of delirium incidence, duration, severity, length of hospital stay, and mortality, antipsychotic use does not achieve satisfactory results[54].

Obvious psychotic symptoms, such as hallucinations and delusions, can be controlled using antipsychotic drugs. Antipsychotic medications' sedative effect can effectively resolve agitation in patients with delirium. For the core delirium symptoms, including decreased attention and cognition, there is no evidence that antipsychotic medications are effective. More importantly, patients should be carefully monitored for adverse reactions and side effects after antipsychotic medication use.

The choice of medication should be based on the actual clinical situation of the patient to choose the option that maximizes the benefit[74]. For patients with severe circadian rhythm and perceptual disturbances, sedative antipsychotics, such as quetiapine, can be selected for nighttime use; for patients with overexcited delirium, haloperidol can be selected and administered intravenously or intramuscularly for those who cannot tolerate oral administration; for delirium in patients with PD or DLB, quetiapine is preferable because first-generation antipsychotics can aggravate motor symptoms in patients with PD; if these two groups of patients need parenteral medication, olanzapine or ziprasidone can be selected to be administered intramuscularly at minimal doses; olanzapine and risperidone can be selected for patients who cannot swallow; and olanzapine can be used to exert its antiemetic effect when delirium occurs in cancer patients.

Drug dosage was initially administered at the lowest dose and frequency, as assessed by symptom severity[74]. In addition, three major critical values need to be monitored: QTc prolongation (increased risk of sudden death from ventricular tachycardia), extrapyramidal symptoms, and all-cause death in patients with dementia. QTc prolongation is usually associated with antipsychotic use. An investigational study conducted by Pfizer for FDA comparing the QTc interval before and after the use of the maximum daily dose found QTc prolongation ranging from 4.7 ms (haloperidol) to 20.3 ms (ziprasidone)[75]. Patients with delirium should have an electrocardiogram before receiving antipsychotic medication and ensure no significant QTc prolongation interval during treatment. Patients with delirium receiving antipsychotics must also be monitored for extrapyramidal symptoms, such as inability to sit still, rigidity, and dystonia, which can exacerbate emotional disturbances and cause them to change their treatment plans.

# DISCUSSION

The complexity and variability delirium symptoms make determining treatment plans more difficult. Patients with delirium are usually admitted to the hospital from the emergency room. The key to treatment is to quickly identify the cause and promptly remove susceptibility factors and triggers, while supporting with symptomatic treatment, maintaining electrolyte balance, and supplementing nutrition. It is also important to prevent complications such as falls, aspiration (aspiration pneumonia), decubitus ulcers, and deep vein thrombosis. A thorough physical examination, detailed history taking, and necessary ancillary laboratory tests are important for detecting the primary cause. Common factors that cause delirium, including infection, cerebrovascular factors, pharmacological factors, surgical anesthesia, and major physical diseases of the heart, lungs, liver, and kidneys, were excluded. Symptomatic treatment of delirium caused by such factors effectively improves symptoms.

In addition, numerous somatic diseases can cause mild edema in the brain cells, leading to transient consciousness impairment. From this perspective, non-pharmacological measures, although not directly therapeutic, can facilitate and accelerate recovery. These include psychotherapy (suggestion), environmental measures (placement of familiar objects in the room), soft lighting (light therapy), and restraint (use during the attack period to avoid accidents). Subsequently, after correcting the primary physical illness, the brain function was restored and delirium symptoms disappeared.

A primary method to prevent delirium is to simply shorten hospitalization, as much as possible [76,77]. Unfamiliar environment, and lack of separation between day and night and disorientation are frequent during admission are also major causes for delirium. Notably, early discharge is beneficial to patient recovery when their health condition is accurately assessed [78].

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The following aspects should be noted for the more controversial use of psychiatric drugs. First, psychiatric medications (first or second generation) usually inhibit a person's cognitive-behavioral activity. The principle is to use them as little as possible and for as short a time as possible. Second, psychiatric drugs were selected in the following cases: (1) The patient was agitated; (2) There were many hallucinatory delusions; (3) Behavioral disturbances; (4) Sleeplessness at night; and (5) Non-cooperation and poor compliance with general supportive therapy. Third, ECG should be checked regularly during treatment with psychiatric drugs, and QT interval changes should be closely monitored. When the following two factors are encountered: (1) Prolonged QT interval suggested by ECG on admission; and (2) electrolyte disturbance, psychiatric drugs should be used with caution. The safety of valium drugs is higher than that of psychiatric medications. When the two factors mentioned above improve after clinical treatment, psychiatric drugs or tranquilizer administration should be considered. When using valium, attention should be paid to whether the patient has obstructive respiratory diseases, myasthenia gravis, and other valium contraindications. Protective restraint is more appropriate when both psychotropic drugs and tranquilizers are at greater risk of use. Fourth, clinical readiness to assess the benefit of patients with psychotropic medications: (1) From the patient's perspective, the improvement of psychiatric-behavioral symptoms; and (2) from the caregiver's perspective, there is usually a significant psychosomatic burden of care for patients with delirium, and the severity of the caregiving burden directly affects the quality of patient care.

Patients usually recover within 7-10 d, with a few recovering in 2-4 wk, rarely developing into chronic delirium. Delirium has also been reported to have long-term effects on cognition[24]. The cognitive impairment that occurs after delirium onset in ICU patients is similar to that caused by moderate traumatic brain injury. Moreover, delirium can lead to more severe dementia in AD patients in addition to original dementia, and the risk of dementia development after delirium onset in older adults is eight times higher than that in normal older adults.

# CONCLUSION

#### Summary and outlook

This study comprehensively discussed the latest national and international research perspectives on delirium in terms of risk factors, preventive interventions, overlapping symptoms, and clinical and specific measures to clinically deal with delirium in real-world situations.

#### Key points

This paper reviews the whole delirium process and its latest research progress in risk factors, preventive interventions, identification of superimposed symptoms, and clinical measures to provide a comprehensive and systematic account of delirium and present the latest medical information. This article helps readers improve understanding of delirium and helps clinicians quickly identify and take timely therapeutic measures to address the various delirium subtypes that occur in the clinic setting. This is to ensure that patients can be treated as aggressively as possible.

# FOOTNOTES

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ORIGINAL ARTICLE

# **Case Control Study** Diagnostic and prognostic implications of non-high-density lipoprotein cholesterol and homocysteine levels for cognitive impairment in thalamic infarction

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# Abstract

# BACKGROUND

Patients with thalamic infarction experience abnormal blockages of multinucleated vessels, affecting the body and thereby the thalamus. Most patients with thalamic infarction have an adverse prognosis, which seriously affects their safety. Therefore, it is essential to analyze the independent risk factors that influence the prognosis of patients with thalamic infarction and develop corresponding preventive measures.

# AIM

To explore the effect of non-high-density lipoprotein cholesterol (non-HDL-C) and Homocysteine (Hcy) levels in cognitive impairment in thalamic infarction.

# **METHODS**

From March 2019 to March 2022, 80 patients with thalamic infarction were divided into a group with cognitive impairment [Montreal Cognitive Assessment (MoCA) score < 26; 35 patients] and a group with normal cognitive function (MoCA score of 26-30; 45 patients) according to the MoCA score. In addition, 50 healthy people in the same period were selected as the control group. A correlation between the non-HDL-C and Hcy levels and the MoCA score and receiver operating characteristic curve was observed, and the serum non-HDL-C and Hcy levels were analyzed for the diagnosis of cognitive impairment in patients with thalamic infarction. According to the Modified Rankin Scale (MRS) score, 80 patients with thalamic infarction were divided into a good prognosis group (MRS score  $\leq$  2) and a poor prognosis group (MRS score >2).

# RESULTS

The non-HDL-C and Hcy levels were significantly higher in the group with cognitive impairment than in the group with normal cognitive function (P < 0.05).



There was no significant difference in the non-HDL-C level between the control group and the group with normal cognitive function (P > 0.05). The MoCA scores of the group with cognitive impairment were significantly lower than those of the group with normal cognitive function and the control group (P < 0.05). There was a significant difference between the control group and the group with normal cognitive function (P < 0.05). The non-HDL-C and Hcy levels were correlated with the MoCA score (P < 0.05), cognitive impairment [areas under the curve (AUC) = 0.709, 95% confidence interval (95%CI): 0.599-0.816], the non-HDL-C level, and could predict cognitive impairment in patients with thalamic infarction (AUC = 0.738, 95%CI: 0.618-0.859). Hcy combined with non-HDL-C levels can predict cognitive impairment in patients with thalamic infarction (AUC = 0.769, 95%CI: 0.721-0.895).

# RESULTS

There were 50 patients in the good prognosis group and 30 patients in the poor prognosis group. Compared with the good prognosis group, in the poor prognosis group, the National Institutes of Health Stroke Scale (NIHSS) score, non-HDL-C level, Hcy level, large-area cerebral infarction, atrial fibrillation, and activated partial prothrombin time were statistically significant (P < 0.05). The non-HDL-C level, the Hcy level, the NIHSS score, extensive cerebral serum, and atrial fibrillation may all be independent risk factors for poor prognosis in patients with thalamic infarction (P < 0.05).

# CONCLUSION

Non-HDL-C and Hcy levels are positively correlated with cognitive impairment in patients with thalamic infarction. Non-HDL-C and Hcy levels can be used in the diagnosis of cognitive impairment in patients with thalamic infarction, and the combined detection effect is better. The main factors affecting the prognosis of patients with thalamic infarction are the non-HDL-C level, the Hcy level, the NIHSS score, large-area cerebral infarction, and atrial fibrillation. Clinically, corresponding preventive measures can be formulated based on the above factors to prevent poor prognosis and reduce mortality.

**Key Words:** Thalamic infarction; Cognitive impairment; Non-high-density lipoprotein cholesterol; High homocysteine level; Diagnostic value; Prognosis; Influencing factors; Correlation

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**Core Tip:** This study explored the diagnostic and prognostic implications of non-high-density lipoprotein cholesterol (non-HDL-C) and Homocysteine (Hcy) levels for cognitive impairment in patients with thalamic infarction. Both non-HDL-C and Hcy levels were found to be useful for the diagnosis of cognitive dysfunction in patients with thalamic infarction, with their combined detection being more effective. In addition, clinical precautions can be formulated based on their levels to prevent poor prognosis and reduce mortality.

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# INTRODUCTION

The organization and structure of the thalamus is extremely complex, such as the medial nuclear group and the former nuclear group. In patients with thalamic infarction, an abnormal blocking phenomenon occurs in the blood vessels of multiple nuclei, affecting the body and thereby the thalamus. The majority of patients are mainly characterized by dementia, aphasia and stubborn sexual behavior and insomnia, aggravating the degree of the thalamic infarction, which can lead to cognitive impairment[1]. One study reported that abnormal homocysteine (Hcy) levels led to changes in hippocampal signaling and neuroplasticity in mice[2]. Therefore, abnormal Hcy levels are believed to be related to cognitive impairment in patients with thalamic infarction. Non-high-density lipoprotein cholesterol (non-HDL-C), which mainly contains low density lipoprotein (LDL), intermediate density lipoprotein and chylomicron, is calculated by subtracting HDL from total cholesterol (TC). Other studies have also reported that there is a relationship between non-HDL-C levels and cognitive impairment[3]. For example, in the study of Weaver et al[4], non-HDL-C levels were positively correlated with cognitive impairment in patients with lacunar cerebral infarction. As the non-HDL-C level increased in patients with lacunar cerebral infarction, the degree of cognitive impairment increased. However, whether the same occurs in patients with thalamic infarction needs to be further explored. Hcy and non-HDL-C levels are related to cognitive impairment due to disease to a certain extent. Whether Hcy and non-HDL-C levels can be used in the diagnosis of cognitive dysfunction in patients with thalamic infarction is worth exploring. Most patients with thalamic infarction have a poor prognosis, and their safety is seriously affected. The analysis of independent risk factors, especially Hcy levels, for the prognosis of patients with thalamic infarction and the formulation of relevant prevention measures have important meaning for improving the prognosis of these patients, and whether non-HDL-C level changes can predict the prognosis of patients with thalamic infarction is worth studying. Therefore, this study mainly evaluated the use of Hcy and non-HDL-C levels in the diagnosis of cognitive impairment in patients with thalamic infarction, as well as the influencing factors of poor prognosis to provide a reference for the clinical development of preventive measures to improve the prognosis of these patients. At the same time, the efficient diagnosis of cognitive impairment in patients with thalamic infarction provides a reference for improving the prognosis of these patients, which is of great significance.

# MATERIALS AND METHODS

#### General information

From March 2019 to March 2022, 80 patients diagnosed with thalamic infarction were selected and divided into a group with cognitive dysfunction [Montreal Cognitive Assessment (MoCA) score < 26, 35 patients] and a group with normal cognitive function (MoCA score of 26-30, 45 patients) according to the MoCA score. In addition, 50 healthy people in the same period were included as the control group. There was no significant difference in sex or age among the three groups (P > 0.05, see Table 1). After 2 years of follow-up, the prognosis of the 80 patients was evaluated. The selected patients with thalamic infarction were divided into a good prognosis group (Modified Rankin Scale (MRS) score  $\leq 2$  points) and a poor prognosis group (MRS score > 2 points) according to the MRS score. The inclusion criteria were as follows: patients who were diagnosed by computed tomography or magnetic resonance imaging; patients who met the Cerebrovascular Disease Conference criteria for the diagnosis of thalamic infarction<sup>[5]</sup>; patients who were admitted within 72 h of onset; and patients who had not taken diuretic drugs or antibiotics within 1 mo after admission. The exclusion criteria were as follows: Patients with dysfunction of the heart, lungs or other organs; patients with malignant tumors or other diseases; patients with immune system diseases; and patients with severe disorders of consciousness. Details are shown in Table 1.

# Research methods

Non-HDL-C and Hcy level detection: After fasting for 12 h, venous blood was drawn from the elbow at 6 am the next day, and the serum levels of TC and HDL-cholesterol were detected by an automatic biochemical analyzer. Non-HDL-C levels were calculated as follows: TC-HDL-C.

First, blank wells, standard wells and sample wells were set, corresponding to the addition of standard solution or the solution to be tested, and incubated. Then, biotinylated antibody and enzyme conjugate working solution was added. Next, the liquid in the wells was cleared, and the substrate solution was added.

MoCA score[6]: An MoCA score of less than 26 indicates cognitive impairment, and an MoCA score of 26-30 indicates normal cognition. The evaluation content mainly includes the following aspects: Visuospatial executive ability, naming, attention, language ability, abstraction, delayed recall and orientation. According to the MoCA score, patients with thalamic infarction were divided into a group with normal cognitive function and a group with cognitive dysfunction.

MRS score [7]: An MRS score ≤ 2 indicated a good prognosis, and an MRS score of 3-6 indicated a poor prognosis; a higher score indicated a worse prognosis. An MRS score of 0 indicated that no symptoms were present, and scores of 1 to 5 points indicated different degrees of disability; the higher the score was, the more severe the disability was. A score of 6 indicates patient death. For clinical symptoms, a score of 1 point indicated mild but not significant disability. Scores of two and three points indicated moderate disability, but with the ability to walk alone. A score of 4 points indicated a moderately severe disability, with the inability to walk independently, and a score of 5 points indicated a severe disability and the complete inability to take care of oneself. According to the MRS score, patients with thalamic infarction were divided into a good prognosis group and a poor prognosis group.

National Institutes of Health Stroke Scale score<sup>[8]</sup>: The Stroke Scale developed by the National Institutes of Health<sup>[9]</sup> includes level of consciousness, level of consciousness questioning, level of consciousness commands, and optimal gaze. The total score ranges from 0 to 42, with higher scores indicating more severe neurological damage.

Outcome measures: The diagnosis of cognitive impairment was determined and the prognosis of patients with thalamic infarction was predicted using non-HDL-C and Hcy levels. MoCA score, onset time, National Institutes of Health Stroke Scale (NIHSS) score, and activated partial prothrombin time (APTT) were also used as outcome measures.

#### Statistical methods

SPSS 26.0 and GraphPad Prism software were used to analyze the data. Data on the non-HDL-c level, Hcy level, MoCA score, onset time, NIHSS score, APTT, etc. were collected. The chi square test, LSD test (homogeneity of variance test P <0.05) and Tamheeni test (homogeneity of variance test P < 0.05) were performed in the three groups (group with cognitive impairment, control group and group with normal cognitive function), and  $\chi^2/t$  tests were performed in the two groups (good prognosis group and poor prognosis group) (all were in line with a normal distribution). The t test was used for quantitative data and the  $\chi^2$  test was used for qualitative data. The correlation between non-HDL-C and Hcy levels and the MoCA score was analyzed by Pearson correlation analysis. The diagnostic value of non-HDL-C and Hcy levels in patients with thalamic infarction was analyzed by receiver operating characteristic (ROC) curve analysis. The independent risk factors for poor prognosis in patients with thalamic infarction were analyzed by logistic regression analysis. Logistic regression analysis was used to analyze independent risk factors for a poor prognosis in patients with



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Table 1 Observed differences in basic data						
Group	The number of cases	Male/female	Age (yr)			
The control group	50	24/26	63.11 ± 6.45			
Cognitively normal group	45	25/15	$64.87 \pm 6.69$			
Cognitive impairment group	35	27/13	64.76 ± 6.45			
$\chi^2/F/P$ value	-	3.657/0.073	1.482/0.187			

thalamic infarction.

RESULTS

# Non-HDL-C and Hcy levels in the diagnosis of cognitive impairment in patients with thalamic infarction

**Differences in non-HDL-C and Hcy levels in each group:** The non-HDL-C and Hcy levels in the group with cognitive impairment were significantly higher than those in the group with normal cognitive function and the control group (P < 0.05), and there was no significant difference between the control group and the group with normal cognitive function (P > 0.05). Details are shown in Table 2.

Table 2 Differences in non-HDL-C and Hcy levels in each group (X $\pm$ S)						
Group	The number of cases	Non-HDL-C (tendency/L)	Hcy (mol/L)			
The control group	50	$3.11 \pm 0.52$	$11.66 \pm 0.71$			
Cognitively normal group	45	$3.24 \pm 0.54$	$23.22 \pm 3.68$			
Cognitive impairment group	35	$3.98 \pm 0.87^{1,2}$	$30.34 \pm 4.72^{1,2}$			
<i>F/P</i> value	-	6.393/0.000	25.417/0.000			

 $^1P \le 0.05$  compared with the control group.

 $^2P < 0.05$  compared with the group with normal cognitive function.

Non-HDL-C: Non-high-density lipoprotein cholesterol; Hcy: Homocysteine.

**Observation of differences in MoCA scores:** The MoCA score of the group with cognitive impairment was significantly lower than those of the group with normal cognitive function and the control group (P < 0.05), and there was no significant difference between the control group and the group with normal cognitive function (P>0.05). Details are shown in Table 3.

**Correlation analysis of non-HDL-C and Hcy levels with MoCA scores:** Non-HDL-C and Hcy levels were positively correlated with the MoCA score (P < 0.05). See Table 4 for details.

**ROC curve analysis of the use of serum non-HDL-C and Hcy levels in the diagnosis of cognitive impairment in patients with thalamic infarction:** The areas under the curve (AUC) of Hcy levels in predicting cognitive impairment in patients with thalamic infarction was 0.709 [95% confidence interval (95%CI): 0.599-0.816]. The AUC of non-HDL-C levels in predicting cognitive impairment in patients with thalamic infarction was 0.709 [95% confidence interval (95%CI): 0.599-0.816]. The AUC of non-HDL-C levels in predicting cognitive impairment in patients with thalamic infarction was 0.738 (95%CI: 0.618-0.859). The AUC of Hcy combined with non-HDL-C levels in predicting cognitive impairment in patients with thalamic infarction was 0.769 (95%CI: 0.721-0.895). See Table 5 and Figure 1 for details.

# The prognostic value of non-HDL-C and Hcy levels in patients with thalamic infarction

**Differences in the clinical characteristics of patients with thalamic infarction in the good and poor prognosis groups:** There were 50 patients in the good prognosis group and 30 patients in the poor prognosis group. There were significant differences in NIHSS scores, non-HDL-C levels, Hcy levels, and rates of massive cerebral infarction, atrial fibrillation, and APTT between the poor prognosis group and the good prognosis group (P < 0.05). Details are shown in Table 6.

Multivariate logistic regression analysis of the influencing factors of a poor prognosis in patients with thalamic infarction: Non-HDL-C levels, Hcy levels, NIHSS scores and atrial fibrillation may be independent risk factors for poor prognosis in patients with thalamic infarction (P < 0.05). Details are shown in Table 7.

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Table 3 Differences in Montreal Cognitive Assessment scores (X ± S)									
Group	The number of cases	Visuospatial executive ability	Named	Attention	Language ability	Abstract	Delayed recall	Directional	Total score
The control group	50	$3.12 \pm 1.04$	$2.80 \pm 0.45$	$5.84 \pm 0.37$	$2.88 \pm 0.33$	$1.78\pm0.51$	$3.10 \pm 1.23$	$5.86 \pm 0.35$	$25.46 \pm 2.41$
Cognitively normal group	45	$4.39\pm0.72$	$2.79\pm0.39$	$5.69\pm0.41$	$22.98 \pm 0.09$	$1.87\pm0.15$	$3.62\pm0.91$	$5.63\pm0.36$	$26.98 \pm 1.20$
Cognitive impairment group	35	1.73 ± 1.25	$1.62\pm0.98$	12.31 ± 1.09	$2.61\pm0.50$	$1.43\pm0.89$	$2.16\pm1.01$	$4.69 \pm 1.66$	$17.13 \pm 4.53^{1,2}$
<i>F/P</i> value	-	11.962/0.000	7.309/0.000	28.304/0.000	329.283/0.000	3.263/0.002	6.784/0.000	341.597/0.000	13.992/0.000

 $^{1}P < 0.05$  compared with the control group.

 $^{2}P$  < 0.05 compared with the group with normal cognitive function.

# DISCUSSION

This study first analyzed the use of non-HDL-C and Hcy levels in the diagnosis of cognitive impairment in patients with thalamic infarction; 80 patients with thalamic infarction were selected as the research object, and the MoCA score was used to evaluate the degree of cognitive impairment in the patients. Patients with thalamic infarction were divided into a group with cognitive impairment and a group with normal cognitive function, and medical healthy people were included as controls. The non-HDL-C and Hcy levels in the group with cognitive impairment were significantly higher than those in the group with normal cognitive function and the control group. At the same time, the MoCA scores of the group with cognitive impairment were higher than the scores of each subgroup. In addition, the scores of the group with normal cognitive function and the control group were higher. The higher the MoCA score was, the more normal a patient's cognitive function. The above results showed that there was a certain relationship between the non-HDL-C and Hcy levels and cognitive function in patients. The higher the non-HDL-C and Hcy levels were, the lower the cognitive function of patients. Pearson correlation analysis also showed that the non-HDL-C and Hcy levels were correlated with the MoCA score. The higher the non-HDL-C and Hcy levels were, the lower the MoCA score, indicating more severe cognitive impairment in patients. The results of this study have also been confirmed in a number of studies, such as the study by Fu *et al*[10]. The study found that the Hcy level was associated with cognitive dysfunction in patients with cerebral infarction. The relationship between non-HDL-C and Hcy levels and cognitive dysfunction was further analyzed. The increase in Hcy levels resulted in an abnormal decrease in the vasodilation response, and the activity of CO synthetase was affected; this increased the degree of endothelial injury, further leading to abnormal endothelial function, and promoting the shedding of a large number of endothelial cells. In turn, the formation of arteriosclerosis was affected, ultimately leading to cognitive dysfunction[11]. In addition, an abnormal increase in non-HDL-C levels in the body leads to cognitive dysfunction, which may be mainly related to atherosclerosis. The increased levels of non-HDL-C and LDL-C in the body may lead to the development of atherosclerosis, which may lead to arterial stenosis, increased plaque formation and changes in hemodynamics. An abnormal blood supply in the thalamus may lead to some structural dysfunction, such as in the hippocampus and adjacent tissues, eventually leading to cognitive dysfunction<sup>[12]</sup>.

The ROC curve was further used to analyze the diagnostic efficacy of non-HDL-C and Hcy levels for cognitive impairment in patients with thalamic infarction. The results showed that the combination of non-HDL-C and Hcy levels had higher diagnostic efficacy, which suggested that the combined measurement of non-HDL-C and Hcy levels could be considered to improve the diagnostic efficacy in the diagnosis of cognitive dysfunction in patients with thalamic

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# Table 4 Correlation analysis of non-high-density lipoprotein cholesterol and Homocysteine levels and the Montreal Cognitive Assessment score

Droinet	Нсу		non-HDL-C		
Project	<i>r</i> value	<i>P</i> value	<i>r</i> value	<i>P</i> value	
Viewspace/execution	0.292	0.003	0.233	0.000	
Named	0.478	0.000	0.487	0.004	
Attention	0.658	0.002	0.622	0.000	
Language ability	0.451	0.000	0.422	0.002	
Abstract	0.302	0.001	0.368	0.000	
Delay memories	0.367	0.000	0.308	0.002	
Directional	0.685	0.003	0.676	0.001	
MoCA scores	0.703	0.000	0.705	0.000	

Non-HDL-C: Non-high-density lipoprotein cholesterol; Hcy: Homocysteine; MoCA: Montreal Cognitive Assessment.

 Table 5 Receiver operating characteristic curve analysis of serum non-high-density lipoprotein cholesterol and Homocysteine levels

 for the diagnosis of cognitive impairment in patients with thalamic infarction

Variable	The critical value	AUC	Sensitivity	Specificity	95%CI	About an index
Hcy (µmol/L)	22.540	0.709	0.724	0.630	0.599-0.816	0.354
Non-HDL-C (tendency/L)	1.351	0.738	0.701	0.870	0.618-0.859	0.571
Hcy in combination with non- HDL-C	-	0.769	0.758	0.889	0.721-0.895	0.647

AUC: areas under the curve; Non-HDL-C: Non-high-density lipoprotein cholesterol; Hcy: Homocysteine.



Figure 1 Receiver operating characteristic curve analysis of serum non-high-density lipoprotein cholesterol and Homocysteine levels in the diagnosis of cognitive impairment in patients with thalamic infarction. Non-HDL-C: Non-high-density lipoprotein cholesterol; Hcy: Homocysteine.

infarction.

To analyze the independent risk factors for poor prognosis in patients with thalamic infarction, the patients were divided into groups according to their follow-up results, and the MRS score was used to evaluate the prognosis of the patients. The results showed that there were 50 patients with a good prognosis and 30 patients with a poor prognosis. There were statistically significant differences in the NIHSS score, non-HDL-C level, Hcy level, and rates of massive

Table 6 Differences in clinical characteristics between patients with thalamic infarction in the good and poor prognosis groups						
Project	Good prognosis group ( <i>n</i> = 50)	Poor prognosis group ( <i>n</i> = 30)	<b>χ</b> ²/t	P value		
Age (yr)	$65.12 \pm 6.74$	$64.13 \pm 10.07$	0.527	0.600		
Men	32 (64.00)	20 (66.67)	0.059	0.809		
Time of onset (h)	$20.39 \pm 3.21$	$20.42 \pm 3.19$	0.041	0.968		
Smoking history	26 (52.00)	16 (53.33)	0.013	0.908		
The history of drinking	24 (48.00)	13 (43.33)	0.164	0.685		
Hypertension	24 (48.00)	18 (60.00)	1.083	0.298		
Diabetes	14 (28.00)	9 (30.00)	0.037	0.848		
CHD	8 (16.00)	4 (13.33)	0.105	0.746		
NIHSS score	$14.52 \pm 5.43$	17.91 ± 5.78	2.639	0.010		
Non-HDL-C (tendency/L)	$3.08 \pm 0.46$	$3.79\pm0.57$	6.103	0.000		
Hcy (µmol/L)	$14.54\pm0.78$	$27.51 \pm 4.08$	21.909	0.000		
Massive cerebral infarction	13 (26.00)	15 (50.00)	4.747	0.029		
Atrial fibrillation	6 (12.00)	9 (30.00)	3.988	0.046		
APTT (1 S)	$31.55 \pm 3.45$	33.43 ± 4.32	2.144	0.035		

APTT: Activated partial prothrombin time; CHD: Coronary heart disease; Non-HDL-C: Non-high-density lipoprotein cholesterol; Hcy: Homocysteine; NIHSS: National Institutes of Health Stroke Scale.

Table 7 Multivariate logistic regression analysis of influencing factors of a poor prognosis in patients with thalamic infarction							
Variable	OR	95%CI	Wald	<i>P</i> value			
Atrial fibrillation	0.232	0.068-0.768	5.701	0.016			
Non-HDL-C	1.753	1.243-2.477	10.187	0.001			
Hcy	1.051	1.006-1.096	5.323	0.020			
APTT	1.127	1.003-1.186	4.116	0.077			
NIHSS score	1.091	1.004-1.268	4.134	0.012			

95% CI: 95% confidence interval; APTT: Activated partial prothrombin time; Non-HDL-C: Non-high-density lipoprotein cholesterol; Hcy: Homocysteine; NIHSS: National Institutes of Health Stroke Scale; OR: Odds ratio.

cerebral infarction, atrial fibrillation and APTT between the good prognosis group and the poor prognosis group. Logistic regression analysis showed that there were statistically significant differences in the NIHSS score, non-HDL-C level, Hcy level, and rates of atrial fibrillation and APTT between the groups. The non-HDL-C level, Hcy level, NIHSS score, massive cerebral infarction, and atrial fibrillation may be independent risk factors for poor prognosis in patients with thalamic infarction. Hcy levels can lead to an inflammatory response and abnormal endothelial cell function and promote thrombosis, which is one of the influencing factors for poor prognosis in patients with thalamic infarction[13]. Non-HDL-C levels can lead to the development of atherosclerosis in the body and increase the risk of cognitive dysfunction. The NIHSS score is a protective factor in patients with thalamic infarction. The NIHSS score can predict the recovery of patients' neurological function and be used to further judge patient prognosis[14]. Atrial fibrillation is a common arrhythmia and is also a risk factor in patients with thalamic infarction. Due to the generation of atrial fibrillation, cardiac structural abnormalities, hemodynamics, and the micro embolus synthetic quantity are increased, cerebral perfusion and cerebral hypoperfusion are reduced, differences in the ventricular rate occur and the heart rate, cerebral blood flow, and neuronal energy is affected. The nerve fiber and amyloid beta protein levels are reduced, which leads to disorders of speech speed and thinking expression and ultimately affects the prognosis of patients with thalamic infarction[15]. Clinically, for patients with thalamic infarction, relevant preventive measures can be formulated according to the above influencing factors, such as anticoagulant drug therapy to reduce the incidence of atrial fibrillation[16]. The NIHSS was used to evaluate neurological function in patients. Appropriate supplementation with folic acid or other antipsychotic drugs can reduce the Hcy level to a certain extent[17], and the prophylactic use of statins can reduce the non-HDL-C level [18].

# CONCLUSION

In conclusion, non-HDL-C and Hcy levels are positively correlated with cognitive impairment in patients with thalamic infarction. Non-HDL-C and Hcy levels can be used for the diagnosis of cognitive impairment in patients with thalamic infarction, and the combined detection effect is better. The prognostic factors of patients with thalamic infarction mainly include the non-HDL-C level, Hcy level, NIHSS score, and rates of large area cerebral infarction and atrial fibrillation. Clinically, corresponding preventive measures can be formulated according to the above factors to prevent poor prognosis and reduce mortality. However, there are some shortcomings in this study. The sample source is biased, the sample size is small, and thalamic infarction is not a common disease because non-HDL-C and Hcy levels may also be affected by other factors. Only the combination of non-HDL-C and Hcy levels in the diagnosis of cognitive dysfunction in patients indicates great deficiencies. This only indicates that non-HDL-C and Hcy levels can be detected simultaneously in the auxiliary diagnosis of cognitive dysfunction in patients with thalamic infarction to improve the diagnostic efficiency.

# ARTICLE HIGHLIGHTS

# Research background

In patients with thalamic infarction, the blood vessels of multiple nuclei are abnormally blocked, affecting the body and thus the thalamus. Abnormal Homocysteine (Hcy) levels are believed to be related to cognitive impairment in patients with thalamic infarction. Meanwhile, there is a positive correlation between non-high-density lipoprotein cholesterol (non-HDL-C) levels and cognitive impairment in lacunar cerebral infarction.

# Research motivation

The analysis of the impact of independent risk factors, especially Hcy levels, on the prognosis of patients with thalamic infarction and the formulation of relevant prevention measures carries great clinical implications for improving patient outcomes. In addition, the value of changes in non-HDL-C levels in predicting the prognosis of patients with thalamic infarction deserves investigation.

#### Research objectives

To provide a reference for the clinical development of preventive measures to improve the prognosis of patients with thalamic infarction and to efficiently diagnose cognitive impairment in such patients.

# Research methods

Eighty patients with thalamic infarction were included and divided into a group with cognitive impairment [Montreal Cognitive Assessment (MoCA) score: < 26] and a group without (MoCA score: 26-30), depending on their MoCA scores. In addition, 50 concurrent healthy controls were selected as a control group. Correlations of the non-HDL-C and Hcy levels with the MoCA score and receiver operating characteristic curve were observed. Serum non-HDL-C and Hcy levels were further analyzed. Furthermore, patients were grouped as a good prognosis group [Modified Rankin Scale (MRS) score: ≤ 2] and a poor prognosis group (MRS score: > 2) according to the MRS score, and the clinical characteristics were comparatively analyzed.

# Research results

There was a certain relationship between non-HDL-C and Hcy levels and cognitive function in patients, with higher non-HDL-C and Hcy levels indicating worse cognitive function of patients. Pearson correlation analysis also identified an association between non-HDL-C and Hcy levels and MoCA scores. Specifically, the higher the levels of non-HDL-C and Hcy, the lower the MoCA score, indicating more severe cognitive impairment in patients.

# Research conclusions

Non-HDL-C and Hcy levels are positively correlated with cognitive impairment in patients with thalamic infarction, indicating their potential to diagnose cognitive impairment in such patients. In addition, their combined detection contributes to higher diagnostic efficacy.

# Research perspectives

Simultaneous detection of non-HDL-C and Hcy levels can assist in the diagnosis of cognitive dysfunction in patients with thalamic infarction, which is of great clinical significance for improving the prognosis of these patients.

# FOOTNOTES

Author contributions: Zhu SY and Zhang H conceived and designed the study; Zhu SY and Ge W guided the study; Zhu SY and Zhang H collected the clinical date; Zhu SY and Zhang H analyzed the data; All authors drafted and revised the manuscript.



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**Case Control Study** 

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ORIGINAL ARTICLE

# Brain-derived neurotrophic factor, sex hormones and cognitive decline in male patients with schizophrenia receiving continuous antipsychotic therapy

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# Abstract

# BACKGROUND

There are systematic differences in clinical features between women and men with schizophrenia (SCZ). The regulation of sex hormones may play a potential role in abnormal neurodevelopment in SCZ. Brain-derived neurotrophic factor (BDNF) and sex hormones have complex interacting actions that contribute to the etiology of SCZ.

# AIM

To investigate the influence of BDNF and sex hormones on cognition and clinical symptomatology in chronic antipsychotic-treated male SCZ patients.

# **METHODS**

The serum levels of follicle-stimulating hormone, luteinizing hormone (LH), estradiol (E2), progesterone, testosterone (T), prolactin (PRL) and BDNF were compared between chronic antipsychotic-treated male (CATM) patients with SCZ (n = 120) and healthy controls (n = 120). The Positive and Negative Syndrome Scale was used to quantify SCZ symptoms, while neuropsychological tests were used to assess cognition. Neuropsychological tests, such as the Digit Cancellation Test (DCT), Semantic Verbal Fluency (SVF), Spatial Span Test (SS), Paced Auditory Serial Addition Test (PASAT), Trail Making Task (TMT-A), and Block Design Test (BDT), were used to assess executive functions (BDT), attention (DCT, TMT-A), memory (SS, PASAT), and verbal proficiency (SVF).

# RESULTS

Although E2 levels were significantly lower in the patient group compared to the



healthy controls, T, PRL, and LH levels were all significantly higher. Additionally, the analysis revealed that across the entire sample, there were positive correlations between E2 Levels and BDNF levels as well as BDNF levels and the digital cancellation time. In CATM patients with SCZ, a significant correlation between the negative symptoms score and PRL levels was observed.

#### **CONCLUSION**

Sex hormones and BDNF levels may also be linked to cognitive function in patients with chronic SCZ.

Key Words: Brain-derived neurotrophic factor; Clinical symptoms; Cognitive function; Schizophrenia; Sex hormones

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Core Tip: Brain-derived neurotrophic factor (BDNF) and sex hormones are known to be involved to the psychopathology of schizophrenia (SCZ). However, the influence of BDNF and sex hormones on cognition and symptoms in chronic antipsychotic-treated male (CATM) SCZ patients have yet to be investigated. Testosterone, prolactin (PRL) and luteinizing hormone were significantly higher in the patient group than in the healthy controls while estradiol (E2) levels were significantly lower. Analysis also identified positive correlations between E2 levels and BDNF levels, and BDNF levels and the digital cancellation time, in the whole sample. we found significant correlations between PRL levels and negative symptoms score in CATM patients with SCZ.

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# INTRODUCTION

It has been proved that there are differences in schizophrenia (SCZ) clinical side effects between females and males[1]. In SCZ, gender differences may play a significant role in the factors that mediate schizophrenic expression[2]. The current study hypothesizes that sex hormones alter the manifestation of symptoms, either directly or indirectly, and account for many of the observed gender differences[3]. The organizational and activational effects of sex hormones on SCZ have received a lot of critical attention[4]. During a crucial period in the fetus's life, organizational effects have a permanent impact on the developing brain. Evidence recommends that adjustments to sex hormones might be related to the neurodevelopmental etiology of SCZ[5]. The actuating impacts are the immediate impact of circulating chemicals. When hormone levels rise, the impact will appear, and when hormone levels fall, the impact will become weaker. Both luteinizing hormone (LH) and testosterone (T) play a role in puberty by promoting the expansion of white matter in the frontal and temporal connections[6]. It is important to note that the regions of the brain that are most affected by adolescent gonadal hormones are also the regions of the brain that are most relevant to the pathophysiology of SCZ[7]. Recent research indicates that T and masculinity predict hippocampus or cerebellum volumes that are typically larger in men[8], whereas estradiol (E2) levels were associated with bilateral insula resting-state functional connectivity in girls[9]. Adolescent hormonal changes may activate genes that regulate normal neurodevelopment, leading to an increase in connectivity and a decrease in gray matter[10].

T has genomic and non-genomic impacts on the cerebrum through androgen receptors, and is involved in hippocampal CA1 neuron morphology[11]. It has been established that estrogen plays a role in cognitive processes such as memory, learning, and mood regulation[12]. Studies in rats have shown that progesterone (P), a neurosteroid, has numerous impacts on cognition, for example, upgrading learning and memory, advancing nerve development and mvelination<sup>[13]</sup>.

Sex hormones and brain-derived neurotrophic factor (BDNF) have been linked to cognitive function in an increasing number of studies. For example, a new investigation on ovariectomized rodents showed that E2 essentially expanded spatial learning and memory by increasing 17  $\beta$ -E2 and BDNF levels in the hippocampus[14]. The BDNF pathway plays a role in the protective effects of estrogen. Additionally, P interferes with estrogen's protective effect under certain conditions[15]. In grown-up male rodents, treatment with T and BDNF intuitively affected androgen receptor articulation [16] as well as dendritic length[17]. According to our previous research, patients with chronic SCZ who suffer from attention and spatial memory impairments have elevated serum T levels<sup>[18]</sup>. However, there are currently insufficient systematic studies on the interplay between BDNF and follicle-stimulating hormone (FSH), LH, E2, P, T, and prolactin (PRL) in chronic antipsychotic-treated male (CATM) patients.

We hypothesize that neurotrophic factors mediate cognitive decline in male patients with chronic SCZ via hormones. This article focuses on the following issues: (1) Whether patients with chronic SCZ have altered levels of BDNF and sex hormones (including FSH, LH, E2, P, T, and PRL); (2) Whether there is a connection between BDNF and sex hormone levels; and (3) Whether the communication between BDNF and sex hormones is involved in the clinical symptoms and



# MATERIALS AND METHODS

#### Participants

This was a case-control study, and the sample size calculation method was as follows: = 0.05,  $\beta$  = 0.20, Meant = 0.25, and Meanc = 0.21; the sample size calculation was input into the Biostatistics website (www.cnstat.org/samplesize/12/), and the difference between the two sets of means was compared, *n* = 200 (cases). If the maximum number of lost cases was considered to be 20%, then the total number of cases in both groups should be: 200 + 200 0.2  $\approx$  240 (cases), nt = 120 (cases), nc = 120 (cases) and power = 0.8036.

A total of 120 CATM patients with SCZ from the Affiliated WuTaiShan Hospital of the Medical College of Yangzhou University (Yangzhou, China) were recruited between February 2018 and July 2019. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, these patients fulfilled the criteria for SCZ. In addition, 120 healthy males were included as control subjects. The controls were matched by age and education with the SCZ group. All the controls were in good physical health and had no mental illness. Table 1 depicts the demographic characteristics of the patient group and the healthy control group. Participants in this study must have taken antipsychotic medication for at least a year. Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS). Subjects were excluded if they had a history of substance abuse or dependence, neurological diseases, or serious psychiatric comorbidities.

The WuTaiShan Hospital Ethics Committee approved the study (approval No. 2018-011), and written informed consent was provided by each participant.

#### Hormone assay

Serum samples were centrifuged (3000 rpm for 10 min) and then stored at -80°C. Sex hormone levels (FSH, LH, E2, P, T, PRL) were estimated using an Entrance immunoassay analyzer and the manufacturer's reagents (Beckman Coulter Inc., Brea, CA, United States). After that, an enzyme-linked immunosorbent assay (Emax Immunoassay System kit) was used to measure the concentration of BDNF (Promega, Madison, WI, United States) according to the instructions of the manufacturer.

#### Neurocognitive assessments

A neuropsychological battery of cognitive tests, such as the Digit Cancellation Test (DCT), Semantic Verbal Fluency (SVF), Spatial Span Test (SS), Paced Auditory Serial Addition Test (PASAT), Trail Making Task (TMT-A), and Block Design Test (BDT), were used to assess cognitive performance.

The followings were evaluated by the neurocognitive battery: Executive functions: Executive functions were evaluated using the BDT. Maintaining focus and attention: Attention was evaluated using the DCT and TMT-A. Memory: The SS and PASAT were used to measure memory. Verbal proficiency: Verbal fluency was assessed by the SVF test.

#### Statistical analysis

SPSS 17.0 was used for the statistical analysis (SPSS Inc., Chicago, IL, United States). We first compared the qualities and mental execution between the controls and patients, and then compared the BDNF and sex hormone levels of patients and controls using the independent samples *t*-test. The next step was to investigate the connections between BDNF levels and cognitive function in the entire sample (n = 240) and between sex hormone levels and BDNF levels. Pearson's product moment correlation was used to investigate the connections between the patient group's PANSS scores and sex hormone levels. After taking into account any potential confounders, the relationship between sex hormone levels and PANSS scores, BDNF levels, and cognitive function was modeled using multiple linear regression. The Bonferroni correction was used to adjust for multiple comparisons. The significance level was set at P < 0.05.

#### RESULTS

#### Demographic data, sex hormones, BDNF, and cognitive performances in patients and healthy controls

The characteristics and clinical data of 120 CATM patients with SCZ and 120 controls are presented in Table 1. There were significant differences in body mass index (BMI) between patients and controls (P < 0.001). The patient group had significantly higher levels of LH (P < 0.05), T (P < 0.05), and PRL (P < 0.001) than the controls (both P < 0.001), and significantly lower levels of BDNF and E2 than the controls (both P < 0.001). The patients performed worse in all mental subscales (all P < 0.001). These data are shown in Table 2.

#### Interrelationships of sex hormones and BDNF in all subjects

In all subjects (n = 240), LH, E2, T, and PRL (P < 0.05) were all fundamentally connected to BDNF levels before adjustment of confounding factors (age, schooling, smoking, BMI). Only the relationships between BDNF levels and LH, E2, and PRL remained significant (P < 0.05) after confounding factors were removed. The relationship between E2 and BDNF remained statistically significant after Bonferroni correction (P < 0.01). These data are shown in Table 3.

treated male patients with schizophrenia and healthy controls (mean ± SD)							
Variable	CATM patients ( <i>n</i> = 120)	Healthy controls ( <i>n</i> = 120)	F or χ² ( <i>P</i> value)				
Age (yr)	51.0 ± 10.3	$52.2 \pm 6.4$	27.4 (0.28)				
Education (years)	9.2 ± 3.0	9.1 ± 2.8	0.8 (0.62)				
Smokers (%)	60.8	65.9	0.6 (0.4)				
BMI (kg/m <sup>2</sup> )	$25.7 \pm 3.4$	$24.0 \pm 2.2$	33.5 (< 0.001)				
BDNF (ng/mL)	$2.5 \pm 1.6$	9.7 ± 3.2	35.5 (0.00)				
FSH (ng/mL)	$8.6 \pm 6.7$	9.0 ± 6.6	0.1 (0.67)				
LH (ng/mL)	6.7 ± 3.3	$4.9 \pm 2.6$	1.6 (0.00)				
E2 (ng/mL)	$40.5 \pm 17.1$	56.2 ± 24.3	4.5 (0.00)				
P (ng/mL)	$0.8 \pm 0.3$	$0.8 \pm 0.4$	0.2 (0.84)				
T (ng/mL)	$4.8 \pm 1.8$	$4.0 \pm 1.2$	2.4 (0.01)				
PRL (ng/mL)	$25.4 \pm 22.4$	$10.6 \pm 5.5$	24.1 (0.00)				
Age of onset (yr)	$22.9 \pm 5.8$						
Duration of illness (yr)	28.0 ± 9.3						
PANSS score							
Positive symptoms	$11.3 \pm 4.9$						
Negative symptoms	$20.1 \pm 10.0$						
General psychopathology	31.2 ± 9.0						
Total score	$62.6 \pm 20.2$						

BDNF: Brain-derived neurotrophic factor; CATM: Chronic antipsychotic-treated male; BMI: Body mass index; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; E2: Estradiol; P: Progesterone; T: Testosterone; PRL: Prolactin; PANSS: Positive and Negative Syndrome Scale.

Table 2 Comparison of cognitive scores between chronic antipsychotic-treated male schizophrenia patients and healthy controls							
Cognitive index	CATM patients	Controls	F ( <i>P</i> value)	MD (95%CI)			
DCT	304.1 ± 215.0	$130.8 \pm 43.3$	50.8 (< 0.001)	173.2 (124.0 to 222.4)			
SVF	$16.0 \pm 7.8$	27.6 ± 7.9	0.0 (< 0.001)	-11.6 (-8.7 to -14.5)			
SS	11.6 ± 4.2	$16.4 \pm 4.2$	0.1 (< 0.001)	-4.7 (-3.4 to -6.1)			
TMT-A	101.3 ± 57.9	$50.0 \pm 21.7$	26.5 (< 0.001)	51.3 (35.6 to 67.0)			
BDT	$17.1 \pm 9.0$	$31.8 \pm 8.8$	0.2 (< 0.001)	-14.7 (-11.6 to -17.8)			
PASAT correct	$19.8 \pm 10.5$	$34.0 \pm 10.2$	0.0 (< 0.001)	-14.1 (-9.5 to -18.7)			
PASAT try	$23.9 \pm 11.0$	$36.9 \pm 10.7$	0.4 (<0.001)	13.0 (-8.2 to 17.8)			

95% CI: 95% confidence interval; DCT: Digit Cancellation Test; SVF: Semantic Verbal Fluency; SS: Spatial Span Test; PASAT: Paced Auditory Serial Addition Test; TMT-A: Trail Making Task; BDT: Block Design Test.

# Relationships between BDNF and cognitive functions in all subjects

In all subjects, the DCT, class familiarity, SS, TMT-A, block design, and PASAT were all fundamentally connected to BDNF levels prior to adjustment of confounding factors (all P < 0.001). Only the relationships between BDNF levels and the DCT, category fluency, TMT-A, and block design remained significant (P < 0.05) after confounding factors were taken into account. The relationship between DCT and BDNF levels remained significant after Bonferroni correction (P < P0.0023). These data are shown in Table 4.

# Relationships between PRL levels and psychotic symptoms in CATM patients

In CATM patients with SCZ, significant association between PRL levels and the negative side effects score (r = 0.196, P < 0.196



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#### Table 3 Correlations between sex hormones and brain-derived neurotrophic factor levels in all subjects<sup>4</sup>

	BDNF					
	r	<i>P</i> value <sup>2</sup>	<i>P</i> value <sup>3</sup>	P value⁴		
FSH (ng/mL)	0.068	0.467	0.638	NS		
LH (ng/mL)	-0.256	0.007	0.011	NS		
E2 (ng/mL)	0.343	< 0.001	0.001	S.		
P (ng/mL)	0.074	0.459	0.173	NS		
T (ng/mL)	-0.215	0.032	0.055	NS		
PRL (ng/mL)	-0.267	0.004	0.04	NS		

<sup>1</sup>Pearson product moment.

<sup>2</sup>Before adjusting for confounding factors.

<sup>3</sup>After adjusting for confounding factors (body mass index).

<sup>4</sup>Bonferroni correction was applied (a new = 0.05/5 = 0.01).

NS: Not significant; S.: Significant; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; E2: Estradiol; P: Progesterone; T: Testosterone; PRL: Prolactin.

#### Table 4 Correlations between brain-derived neurotrophic factor levels and cognitive function in all subjects<sup>1</sup>

	BDNF					
	r	<i>P</i> value <sup>2</sup>	<i>P</i> value <sup>3</sup>	<i>P</i> value <sup>4</sup>		
DCT	-0.376	< 0.001	0.0019	NS		
Category fluency	0.539	< 0.001	0.022	NS		
SS	0.307	< 0.001	0.398	NS		
TMT-A	-0.516	< 0.001	0.010	NS		
Block design	0.557	< 0.001	0.015	NS		
PASAT correct	0.442	< 0.001	0.404	NS		
PASAT try	0.405	< 0.001	0.201	NS		

<sup>1</sup>Pearson product moment.

<sup>2</sup>Before adjusting for confounding factors.

<sup>3</sup>After adjusting for confounding factors (body mass index).

<sup>4</sup>Bonferroni correction was applied (a new = 0.05/7 = 0.007).

NS: Not significant; DCT: Digit Cancellation Test; SS: Spatial Span Test; PASAT: Paced Auditory Serial Addition Test; TMT-A: Trail Making Task.

0.05) and the score for general psychopathology was found (r = 0.181, P < 0.05). The relationship between PRL levels and general psychopathology or negative factors remained significant (P < 0.05) after adjusting for confounding factors. As shown in Table 5, only the relationship between PRL levels and the negative factors remained significant after the Bonferroni correction (P < 0.017).

#### DISCUSSION

The CATM group's elevated levels of LH, PRL, and T, in addition to their decreased levels of E2, were examined in depth for the first time in this study in comparison to the controls. One of the major findings in this study was that E2 Levels and BDNF levels, as well as BDNF levels and the DCT, were correlated in all subjects. Even after Bonferroni correction and adjusting for confounding factors, these correlations remained significant.

Previous studies have shown that in men, LH and T seem to have a role in advancing the development of white matter [6,10]. As gender differences play a significant role in SCZ, hormones may play a role in the pathophysiology of SCZ. In the initial period of SCZ in men, higher T levels in puberty and youth, show that T might be related to the initiation of psychosis in patients[19]. Recently, an ever-increasing number of studies have focused on dehydroepiandrosterone (DHEA)/T in addition to standard antipsychotic treatment in relation to the side effects of SCZ[20]. These studies demonstrated that patients with SCZ experiencing negative, depressive, and anxiety symptoms could benefit from DHEA augmentation as a treatment. However, we found that CATM patients with SCZ had T levels higher than those in the

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Table 5 Relationships between prolactin levels and psychotic symptoms in patients <sup>1</sup>												
	Positive symptoms score				Negative symptoms score				General psychopathology score			
	r	P value <sup>2</sup>	P value <sup>3</sup>	P value <sup>4</sup>	r	P value <sup>2</sup>	P value <sup>3</sup>	P value⁴	r	P value <sup>2</sup>	P value <sup>3</sup>	<i>P</i> value⁴
PRL	0.152	0.098	0.254	NS	0.196	0.032	0.011	S.	0.181	0.048	0.030	NS

<sup>1</sup>Pearson product moment.

<sup>2</sup>Before adjusting for confounding factors.

<sup>3</sup>After adjusting for confounding factors (body mass index).

<sup>4</sup>Bonferroni correction was applied (a new = 0.05/3 = 0.017).

NS: Not significant; S.: Significant; DCT: Digit Cancellation Test; SS: Spatial Span Test; PASAT: Paced Auditory Serial Addition Test; TMT-A: Trail Making Task.

controls, but that there was no correlation between this increase and psychopathology. It was demonstrated that decreasing levels of LH reduced short-term episodic memory loss in an SCZ model treated with phencyclidine[21]. We found that the LH levels in the CATM patients with SCZ were higher than those in controls, even though there was no relationship between this increment and mental capability.

It has been hypothesized for a considerable amount of time that the blocking effect of antipsychotic medications on dopamine D2 receptors is the cause of the elevated PRL levels associated with psychotic symptoms. PRL levels were found to be elevated in CATM patients with SCZ in the current study. However, unlike a previous study that invest-igated patients with chronic SCZ, we found no link between elevated PRL and impaired cognitive function[22]. Hyperprolactinemia was most significantly associated with executive function, working memory, and processing speed in a previous study of prolactinoma patients[23]. In addition, it was discovered that a decrease in the volume of gray matter in the frontal cortex and hippocampus was correlated with PRL concentration. In the future, the connection between PRL levels and cortical thickness and hippocampal base volume in patients with ongoing SCZ should be examined to determine the connection between hyperprolactinemia and diminished mental capability.

Research focusing on the connection between PRL levels and the side effects of SCZ has been primarily conducted in male patients; however, no consistent conclusion has been reached. Positive symptoms, delusions, and speech incoherence are all negatively correlated with PRL levels, according to some researchers[24]. On the other hand, one study found a correlation between positive symptoms in schizophrenic patients and elevated PRL levels[25]. Another review showed that PRL levels were significantly connected with negative side effects[26]. One study found no link between psychopathology and PRL levels[27]. In previous studies[25,28], we found that higher PRL levels and negative side effects were connected.

The "estrogen hypothesis" has been used for more than three decades to explain how estrogen protects the brain. E2 and selective estrogen receptor modulators are helpful adjunctive treatments for patients with SCZ[29]. Our study found that CATM patients with SCZ had lower levels of the protective hormone E2 than normal male controls. This finding is consistent with the preceding hypotheses. It was found that BDNF gene expression can be controlled by estrogen[30]. Indeed, even after two measurement revisions, this study found a huge direct connection between E2 and BDNF, which is consistent with previous investigations.

The higher incidence of SCZ in men and the earlier age of onset may be partially explained by T[31]. Our current findings were consistent with those of another study[32] in which SCZ cases had significantly higher T levels and significantly lower BDNF levels compared to controls. A previous study with a small sample size found a significant

correlation between low T levels and penile-related symptoms in men taking antipsychotics and a trend in hyperprolactinemia was associated with low T[33]. Antipsychotics frequently result in hyperprolactinemia, which can affect the measurement of other gonadal hormone levels[34]. It should be noted that antipsychotics such as clozapine and aripiprazole are less likely to cause hyperprolactinemia.

Even though these conclusions are not consistent, more and more researchers are focusing on the connection between SCZ with impaired cognitive function and abnormal serum BDNF levels[35,36]. However, a recent study found that firstepisode and drug-naive SCZ patients had significantly higher BDNF serum levels and better Repeatable Battery for the Assessment of Neuropsychological Status scores [37]. In a previous study, we found that the improvement in clinical symptoms was linked to higher BDNF levels in schizophrenic patients[38]. Similarly, we observed that the level of BDNF in SCZ patients was lower than that in controls and that there was a positive relationship between BDNF levels and mental capability. We also found critical and positive relationships between E2 and BDNF levels, and between BDNF levels and the DCT. Even after Bonferroni correction and adjusting for confounding factors, these correlations remained significant. Rashidy-Pour et al[14] in 2019 demonstrated that E2 significantly increased spatial learning and memory by increasing 17-E2 and BDNF levels in the hippocampus of ovariectomized rats. The BDNF pathway is responsible for estrogen's neuroprotective effects[16]. However, we found no correlation between BDNF levels and clinical symptoms. This necessitates further investigation into the reasons for this finding.

The limitations of this study require consideration. The lack of confirmation regarding the consistency of the markers in the central nervous system and peripheral blood is the primary limitation of this study. As the biomarkers were only measured once in this case-control study, the study was constrained by the lack of longitudinal comparisons. Thirdly, the study did not determine how antipsychotic medication affected BDNF and gonadal hormone levels.

# CONCLUSION

In conclusion, CATM patients with SCZ showed lower levels of BDNF and E2 and elevated levels of LH, T, and PRL compared to controls. In all cognitive subscales, we found that CATM patients with SCZ performed significantly worse. In CATM patients with SCZ, we also found a marked relationship between PRL levels and the negative side effects score. Sex hormones and BDNF levels may also be linked to cognitive function. With the exception of PRL and negative symptoms, this case-control study only found positive correlations across the entire sample. As a result, our findings ought to be regarded as preliminary.

# ARTICLE HIGHLIGHTS

#### Research background

Due to gender differences in the clinical manifestations of schizophrenia (SCZ), this study assumes that sex hormones directly or indirectly alter the clinical manifestations of SCZ.

#### **Research motivation**

An increasing number of studies have shown that sex hormones act through brain derived neurotrophic factors (BDNF), which can also affect the expression of sex hormone receptors.

#### Research objectives

The purpose of this study is to explore the significant impact of the interaction between BDNF and sex hormones on the clinical manifestations and cognitive function of chronic antipsychotic-treated male (CATM) SCZ patients.

#### Research methods

We used a cross-sectional case-control study method to collect blood from both normal control and CATM SCZ patients for testing BDNF and sex hormone levels, as well as cognitive function in both groups.

#### Research results

We found a significant decrease in estradiol (E2) levels in the patient group, and a significant correlation between prolactin levels and negative symptom scores. In the entire sample, there is a positive correlation between E2 level, BDNF level, and the Digit Cancellation Test (reflecting attention function).

### **Research conclusions**

Compared with the normal control group, there were changes in the levels of BDNF and sex hormones in the patient group. The levels of sex hormones in the patient group are related to negative symptoms.

#### Research perspectives

The interaction between BDNF and sex hormones may be involved in negative symptom expression and cognitive impairment in chronic male SCZ patients.



# FOOTNOTES

Co-corresponding authors: Qiu-Fang Jia and Xiao-Bin Zhang.

Author contributions: Li J and Zhang XB designed the study and manuscript preparation; Li J and Xiao WH recruited subjects, collected clinical data, laboratory samples, and cognitive assessment and did preliminary data analysis; Ye F and Tang XW assisted in the symptoms of schizophrenia assessment and data analysis; Jia QF did literature search, final analysis of the data, and prepared the final manuscript; All authors contributed to manuscript preparation and approved its final version. Qiu-Fang Jia and Xiao-Bin Zhang contributed equally to this work as co-corresponding authors. The reasons for designating Qiu-Fang Jia and Xiao-Bin Zhang as cocorresponding authors are threefold. First, the research was performed as a collaborative effort, and the designation of co-corresponding authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. This also ensures effective communication and management of post-submission matters, ultimately enhancing the paper's quality and reliability. Second, the overall research team encompassed authors with a variety of expertise and skills from different fields, and the designation of co-corresponding authors best reflects this diversity. This also promotes the most comprehensive and in-depth examination of the research topic, ultimately enriching readers' understanding by offering various expert perspectives. Third, Qiu-Fang Jia and Xiao-Bin Zhang contributed efforts of equal substance throughout the research process. The choice of these researchers as co-corresponding authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study. In summary, we believe that designating Qiu-Fang Jia and Xiao-Bin Zhang as cocorresponding authors of is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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**Case Control Study** 

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ORIGINAL ARTICLE

# Haplotype analysis of long-chain non-coding RNA NONHSAT102891 promoter polymorphisms and depression in Chinese individuals: A case-control association study

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### Abstract

### BACKGROUND

Our previous study reported that the single-nucleotide polymorphism (SNP) rs155979 GC in the promoter region of long-chain non-coding RNA (lncRNA) NONHSAT102891 affects depression susceptibility in a Chinese population.

### AIM

To explored associations of two SNPs and haplotypes in the lncRNA NONHSAT102891 promoter region with depression susceptibility in Chinese population.

### **METHODS**

This this case-control association study was approved by the Ethics Committee of Chengdu Medical College (approval number: 201815). Patient diagnosis was based on DSM-IV criteria. We selected a total of 480 patients with depression and 329 healthy controls with no history of psychopathology, and performed genotyping of two SNPs by extracting peripheral venous blood samples from the subjects. The function of the two lncRNA NONHSAT102891 promoter G/C and A/T haplotypes was detected by dual-luciferase reporter assays of human embryonic kidney 293T transfected cells.

### RESULTS

Stratified analysis of clinical and genotypic characteristics of our cohort showed that the degree of mild depressive episodes associated with the rs6230 TC/CC genotype increased by 1.59 times [TC/CC vs TT: odds ratio (OR) = 1.59, 95%



confidence interval (CI): 1.08-2.35, P = 0.019]. The haploid analysis revealed linkage disequilibrium between rs3792747 and rs6230, and the double SNP CG haplotype was more common in the control group compared to case group, indicating that this haplotype significantly reduced the risk of depression (C/G *vs* T/A: OR = 0.42, 95% CI: 0.21-0.83, P = 0.01). There was no significant difference in the dual-luciferase reporter activity of the G/C and A/T haplotypes compared with the control group (P > 0.05), indicating that the double SNP haplotype has no transcriptional activity.

### CONCLUSION

The rs3792747 and rs6230 CG haplotypes of the lncRNA NONHSA T102891 promoter may be related to a reduced risk of depression in the Han Chinese population.

**Key Words:** Long-chain non-coding RNA NONHSAT102891; Depression; Susceptibility; Single-nucleotide polymorphisms; Haplotype; Transcriptional activity

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**Core Tip:** Depression has risen to the top of the global burden of non-fatal diseases. Recently, emerging evidence supports long-chain non-coding RNA (lncRNA) may be involved in the occurrence and development of depression, and may serve as potential diagnostic and prognostic markers. Our previous study showed lncRNA NONHSAT102891 rs155979 GC affects depression susceptibility; this study genotyped 480 depression patients and 329 healthy controls for the two single-nucleotide polymorphisms and made dual-luciferase reporter assays to explore and elucidate the function of the two lncRNA NONHSAT102891 promoter G/C and A/T haplotypes. We found the rs6230 and rs3792747 CG haplotypes may reduce the risk of depression, which expanded our knowledge about this disease.

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### INTRODUCTION

Depression is a highly heterogeneous and multifactorial mental illness with symptoms spanning domains of emotion and behavior, including changes in mood, anhedonia, sleep, and psychomotor activity[1]. With an estimated 5% of adults worldwide suffering from depression each year, depression has risen to the top of the global burden of non-fatal diseases [2]. In the post-coronavirus disease 2019 era, the global burden of mental disorders has become heavier, and has brought greater challenges to the diagnosis and treatment of depression. In China, health service utilization for depressive disorders is very low, with only 9.2% of depressed patients receiving adequate treatment[3]. Depression can also occur in patients with other underlying diseases, including Alzheimer's disease, stroke, multiple sclerosis and cardiovascular disease[4-6].

Long-chain non-coding RNAs (IncRNAs) are the most abundant class of ncRNAs in the human genome. Characteristically, IncRNAs are more than 200 bp in length and do not encode a protein, but may interact with DNA, RNA or protein molecules at multiple levels (epigenetic, transcriptional and post-transcriptional) to control the expression of related genes and participate in many biological processes, especially differentiation and development[7,8]. Approximately 40% of the lncRNAs in the mammalian genome are expressed in the brain[9]. LncRNAs are involved in regulation of neuronal function and play an important role in neuropsychiatric diseases. Through alternative splicing or binding to NRG1, v-erba erythroblastic leukemia viral oncogene homolog 4 gene expression inhibits downstream neurons, reduces the release of the neurotransmitter gamma-aminobutyric acid, and has negative effects on brain functions, such as cognition and working memory, in addition to an association with an increased risk of depression and schizophrenia[10-12]. LncRNAGm<sup>2</sup>694 destroys endoplasmic reticulum homeostasis, significantly reduces expression of the A-amino-3hydroxy-5-methyl-4-isoxazole propionate receptor on the postsynaptic membrane of neurons, reduces the excitatory synaptic transmission function of neurons, increases stress susceptibility in mice, and mediates the pathogenesis of depression[13]. In addition, some single-nucleotide polymorphisms (SNPs) in lncRNAs are associated with the risk of depression. A human-specific Alu insertion polymorphism (rs70959274) in the 5' flanking region of the lncRNA LINC01360 is in strong linkage disequilibrium with the major depression SNP rs12129573[14]. Identifying functional variants of non-coding SNPs is essential for understanding the molecular mechanism and biological basis of depression [15]. Changes in lncRNAs can be detected in cerebrospinal fluid as well as the circulatory system and brain, therefore, providing important prospects for use as biomarkers for disease identification or risk prediction. These biomarkers can also be employed to provide new insights into the genetic structure and biological etiology of neuropsychiatric diseases.

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The term "haplotype" refers to several closely linked SNPs that determine the same trait on the same chromosome or in a certain region, either as two loci or the entire chromosome. CONVERGE consortium conducted sparse whole-genome sequencing on Chinese female patients with recurrent major depression and found two depression-related mutations, both located on chromosome 10, one near SIRT1, and the other in an intron of the LHPP gene[16]. LncRNA NONHSA T102891, which is located on chromosome 5 (CHR5): 95768987-95770845, has a transcript length of 1860 bp. A recent genome-wide association study (GWAS) revealed five genomic domains on CHR5 that were significantly associated with depression. The underlying background of these regions also includes LINC00461, MEF2C, and LOC101927421[17]. In human tissues, lncRNA NONHSAT 102891 is expressed in the thyroid, brain, adrenal glands and placenta[18]. Downregulated expression of lncRNA NONHSAT102891 in peripheral blood mononuclear cells of major depressive disorder (MDD) patients has been explored previously[19]. Furthermore, changes in the expression of NONHSA T102891 may be a potential non-invasive biomarker for the diagnosis of MDD[20].

In our previous study, we investigated the diagnostic and differential diagnostic value of lncRNA NONHSAT10289 (rs155979, rs3762983, rs3762984 and rs102891) SNPs in severe depression[21]. Because the polymorphism of a single locus in a gene often cannot reveal its true association with disease, haplotype analysis of multiple loci has become an effective means to find complex disease genes. Therefore, in this study, we compared the expression of the other two SNP (rs6230 and rs3792747) in the lncRNA NONHSAT102891 promoter region in patients with depression to further assess the association of lncRNANONHSAT102891 promoter SNPs and/or haplotypes with risk of depression in a Chinese population and to determine the functional correlation of risk haplotypes.

### MATERIALS AND METHODS

### Study subjects

From March 2018 to December 2019, a total of 480 patients with depression and 329 healthy individuals from three hospitals in China (Sichuan Provincial People's Hospital, Jining Psychiatric Hospital and Yunnan Provincial Mental Health Center) were recruited to the case and control groups, respectively. All participants were Han Chinese adults. The study protocol was approved by the Ethics Committee of Chengdu Medical College (No. 201815). All participants provided written informed consent. Patient diagnosis was based on the DSM-IV criteria, and the symptom severity was scored using the 24-item Hamilton Depression Rating Scale (HAMD-24). Patients with neurological diseases or other mental disorders, acute or chronic infections, thyroid dysfunction, being pregnant, or breastfeeding at the time of the study were excluded. Control subjects were volunteers with no history of self-reported mental illnesses and who participated in physical examination in the research hospitals. The following clinical data were collected from medical records: Age, sex, age of onset, HAMD-24 score, pulse rate, degree of depression, family history, suicide attempt/ behavior and first episode.

The average age of the healthy control group (105 males and 224 females) was  $44.0 \pm 16.9$  years. The case and control groups were matched according to sex, age and place of residence. Details of the participants can be found in our previous report[21].

### SNP selection

The UCSC Genome Browser was used to explore SNPs of the lncRNA NONHSAT102891 promoter region (3-kb region upstream of the transcription initiation site)[22]. The SNPs rs6230 and rs3792747 were selected as loci with minor allele frequencies > 10% in the Asian population to study their correlation with depression susceptibility and clinical characteristics in a Han Chinese population.

### Genotyping

Genomic DNA was extracted from peripheral venous blood samples using the whole blood genomic DNA extraction kit [Shenggong Bioengineering (Shanghai) Co., Ltd.]. The concentration of the DNA was determined as a measure of the quality by using a NanoDrop 2000/2000C [Thermo Fisher (China) Co., Ltd.]. The lncRNA NONHSAT102891 promoter region containing the rs6230 and rs3792747 polymorphisms was amplified by two-step polymerase chain reaction (PCR) to prepare an Illumina compatible library using the following primer sequences: rs3792747-F: 5'-TCAATGCAGCAGCAT-CATCAGATCCAAG-3', rs3792747-R: 5'-CGGGCAAAGTTATGAAGCTTGGACT-3', rs6230-F: 5'-GATCCCA-GCAAACAGTTCCT-3'; rs6230-R: 5'-CCAGCCAGAATGGAAATGAG-3'.

The first-step PCR (25 µL reaction volume) amplification was performed under the following reaction conditions: 98 °C, 3 min; 98 °C, 30 s; 50 °C, 30 s; 72 °C 30 s; 98 °C, 30 s; 66 °C 30 s; 25 cycles for 30 s at 72 °C, and 72 °C for 5 min. Using the first-step PCR product as the template, the Illumina sequencing library was obtained by the second round of PCR (30 µL reaction volume) amplification performed under the following reaction conditions: 98 °C, 5 min; 94 °C, 30 s; 55 °C, 20 s; 5 cycles of 72 °C, 30 s. The sizes of the two PCR products were confirmed by 1% agarose gel electrophoresis and then recovered using AMPure XP magnetic beads. Equal amounts of the two PCR products were then mixed and sequenced using HiSeqXTen platform (Illumina, San Diego, CA, United States).

### Construction of luciferase reporter gene plasmids

The DNA fragments containing the haplotypes of the lncRNA NONHSAT102891 promoter region were amplified and different SNP sites (rs6230 and rs3792747) were selected as described above using the following primers sequences: upstream: 5'-GCTAGCAGCCAAGGAAAGGAAAGCTC-3' (for-ward), downstream: 5'-TAAGCAGCAGGATTAG-



GACTCGAG-3' (reve-rse). The target fragments were inserted into the PmirGLO-Vector (Promega) to construct the recombinant plasmids designated pmirGLO-AT and pmirGLO-GC, respectively, and sent to Chengdu Qingke Company for plasmid DNA synthesis. The recombinant plasmids were transfected into HEK-293T cells and the difference in the amount of luciferase protein expressed by the A-T and G-C haplotypes consisting of rs6230 and rs3792747 was detected.

### Cell lines and cell culture

HEK-293T cell lines, provided by the National collection of authenticated cell cultures, were used for recombinant vector transfection and assessed by routine PCR and microscopic analysis to ensure that no cells were contaminated with mycoplasma during the research process. HEK-293T cells were cultured at 37 °C under 5% CO<sub>2</sub> in Dulbecco's Modified Eagle's Medium (Gibco) containing 10% fetal bovine serum (Gibco), 1% GlutaMAX (Invitrogen, Carlsbad, CA, United States) and 1% sodium pyruvate (Invitrogen) were added.

### Transfection and luciferase reporter gene assays

HEK-293T cells were seeded into 24-well plates (2 × 10<sup>5</sup> cells per well) and cultured for 24-36 h to 90% confluence before transfection in serum-free medium with equal amounts of plasmid-free enzyme-free water (as blank control group), pmirGLO-AT, pmirGLO-GC, and the empty PmirGLO-Vector (no promoter) using the LipofectamineTM 2000 kit (Invitrogen). pRL-TK Luciferase Control Reporter Vectors (Promega, Madison, WI, United States) were co-transfected into HEK-293T cells for 24-48 h as a normal control. Luciferase activity in equal numbers of cells from each group was then measured using the dual-luciferase reporter gene assay system (Promega, Madison, WI, United States) according to the manufacturer's instructions. After adding the LAR II reagent (Promega) and cell lysis solution, the optical signal was detected by BioTek PowerWave XS2 full-wavelength scanning spectrophotometer. the measurement reading was recorded as The fluorescence value F (Firefly luminescence) was measured and after adding the Stop and Glo ®Reagent, the fluorescence value R (Renilla luminescence) was measured. Relative luciferase activity was calculated as the ratio of fluorescence value F to fluorescence value R. All samples were analyzed in triplicate and experiments were repeated in three independent occasions.

### Statistical analysis

Continuous variable data were expressed as mean ± SEM and the categorical variable data were expressed as numbers (percentages). Moreover, for comparison between groups, *t*-tests were used for continuous variables, and  $\chi^2$  tests were used for categorical variables. The genotype frequencies of rs6230 and rs3792747 were obtained by direct counting. The  $\chi^2$ test was used to analyze the distribution and Hardy-Weinberg equilibrium of rs6230 and rs3792747 genotypes in the two groups. The correlation between gene polymorphisms and disease was evaluated using odds ratio (OR) and 95% confidence interval (CI), with the OR values adjusted based on age and sex data. Codominant, dominant and recessive genetic models were used for comparative analysis.

In the haplotype correlation analysis, the luciferase activity corresponding to each configuration was expressed as the mean  $\pm$  SD, and the differences among the experimental data were analyzed by one-way analysis of variance. P < 0.05was considered to indicate statistical significance. All data were analyzed using SPSS 25.0 (SPSS Inc., Chicago, IL, United States).

### RESULTS

### LncRNA NONHSAT102891 promoter genotypes and risk of depression

We first investigated the association of the rs6230 and rs3792747 variants of the lncRNA NONHSAT102891 promoter with the risk of depression. For this purpose, we summarized the frequency distribution of genotypes and alleles of lncRNA NONHSAT102891 SNP rs6230 and rs3792747 in depressed patients and controls. In the control group, the genotype frequencies of the two polymorphisms were both in Hardy–Weinberg equilibrium (rs6230 P = 0.101; rs3792747 P = 0.104). There were significant differences in genotype and allele frequencies between the case and control groups (Table 1).

After further stratification by degree of depressive episode, suicide attempt, first episode patient and family history, we observed a correlation between depressive episode stratification and depressive risk in the rs6230 polymorphism group. The frequency of the TC/CC genotype was 69.3% in patients with moderate depression, which was higher than that in patients with severe depression (60.3%) (TC/CC vs TT, 95%CI: 1.59 (1.08-2.35), P = 0.019). These findings indicated that the rs6230 TC/CC genotype is associated with an increased risk of moderate depression; however, there was no significant correlation between rs3792747 polymorphism and the four variables used for stratification (P > 0.05) (Table 2).

### LncRNA NONHSAT102891 promoter haplotypes and the risk of depression

We also evaluated the association of the two SNP haplotypes (rs3792747 and rs6230) of the lncRNANONHSAT102891 promoter with the risk of depression. LD analysis showed that these two common polymorphisms had higher D' values and lower R2 values (D' = 0.71, r<sup>2</sup> = 0.07) in the control, indicating the existence of gene recombination between the two SNP and that both were suitable for haplotype reconstruction.

Haplotype reconstruction analysis based on the genotyping data of depressed patients and controls revealed that the CG haplotype was more common in the control group than in the depressed patients These findings indicated that the CG haplotype is significantly associated with reduced risk of depression [CG vs TA: 95%CI: 1.59 (0.21-0.83], P = 0.01. There was no significant correlation between other haploid types and risk of depression (Table 3).

Table 1 Genetic model genotype and allele frequencies of two long-chain non-coding RNA NONHSAT102891 promoter polymorphisms
among depressed patients and controls and association with risk of depression, <i>n</i> (%)

Models	Polymorphisms	Control ( <i>n</i> = 329)	Patients ( <i>n</i> = 480)	Adjusted OR (95%CI)	P value
	rs6230				
Codominant	TT	109 (33.1)	170 (35.4)	1	
	TC	173 (52.6)	250 (52.1)	0.91 (0.66-1.24)	0.53
	CC	47 (14.3)	60 (12.5)	0.82 (0.52-1.30)	0.41
Dominant	TT	109 (33.1)	170 (35.4)	1	
	TC/TT	220 (66.9)	310 (64.6)	0.79 (0.57-1.10)	0.17
Recessive	TT/TC	282 (85.7)	420 (87.5)	1	
	CC	47 (14.3)	60 (12.5)	0.77 (0.49-1.23)	0.28
Allele	Т	391 (59.4)	590 (61.5)	1	
	С	267 (40.6)	370 (38.5)	0.92 (0.75-1.12)	0.40
	rs3792747				
Codominant	TT	208 (63.2)	326 (67.9)	1	
	TC	113 (34.3)	137 (28.5)	0.77 (0.57-1.05)	0.17
	CC	8 (2.4)	17 (3.5)	1.36 (0.57-3.20)	0.48
Dominant	TT	208 (63.2)	326 (67.9)	1	
	TC/CC	121 (36.8)	154 (32.1)	0.84 (0.60-1.17)	0.31
Recessive	TT/TC	321 (97.6)	463 (96.5)	1	
	CC	8 (2.4)	17 (3.5)	1.47(0.63-3.45)	0.36
Allele	Т	529 (80.4%)	789 (82.2)	1	0.65
	С	129 (19.6)	171 (17.8)	0.89 (0.69-1.15)	0.36

Odds ratio was adjusted by age and sex. OR: Odds ratio; CI: Confidence interval.

### Effects of different haplotypes of IncRNA NONHSAT102891 promoters on transcriptional activity

Next, we tested the hypothesis that the G/C and A/T haplotypes change the transcriptional activity of the lncRNA NONHSAT102891 by comparing the luciferase reporter activity of HEK-293T cells transfected with the pmirGLO-AT and pmirGLO-GC constructs. There was no significant difference in the dual-luciferase reporter activity of the G/C and A/T haplotypes compared with the control group (P > 0.05) (Table 4), indicating that the G/C and A/T haplotypes do not alter the transcriptional activity of the lncRNA NONHSAT102891.

### DISCUSSION

After excluding organic brain lesions, clinicians mainly identify depression on the basis of the key symptoms of the disease. However, the most important basis for diagnosis is still based on the patient's clinical manifestations, which are affected by the patient's subjective experience and the clinical experience of the doctor. Finding objective and effective molecular indicators for the diagnosis of depression is the current focus of clinicians. Depression-related biomarkers in the peripheral blood or brain are attracting increasing attention for the development and exploration of clinical objective diagnostic indicators. LncRNAs are known to play an important role in the normal functions of cells and the pathological consequences of disorders, which lays a molecular foundation for understanding the similarities and differences in the pathophysiological mechanisms behind depression. Using targeted reverse transcription PCR analysis of lncRNA expression levels in peripheral blood and brain tissue of depression patients or a mouse model of depression, Seki et al [23] found that the expression levels of Y5, MER11C, PCAT1, and PCAT29, were upregulated in patients with major depressive disorder compared to healthy controls, while the expression level of RMRP was downregulated. Low expression of RMRP in peripheral blood leukocytes of depressed patients and mice correlated strongly with the severity of the symptoms. Thus, these findings implicate RMRP in peripheral blood leukocytes as a potential biomarker of depression. Zhou et al[24] performed RNA-sequencing in the rostral anterior cingulate cortex of 26 depressed suicidal individuals and 24 controls who died naturally or by accident with no history of psychopathology, and identified 23 differentially expressed lncRNAs, including SNORD3C and ZNF833P, and their differentially expressed overlapping and

Table 2 Stratified analyses of the rs6230 and rs3792747 polymorphisms in depressed patients						
Variables	Frequency (%)		Adjusted OR (95%CI)	P value		
rs6230						
Depressive episode	Severe	Mild				
TT	100 (39.7)	70 (30.7)	1.00 (Ref)			
TC	125 (49.6)	125 (54.8)	1.57 (1.05-2.36)	0.28		
CC	27 (10.7)	33 (14.5)	1.69 (0.92-3.09)	0.088		
TC/CC	152 (60.3)	158 (69.3)	1.59 (1.08-2.35)	0.019		
Suicide attempt	Yes	No				
TT	102 (34.9)	68 (36.2)	1.00 (Ref)			
TC	154 (52.7)	96 (51.1)	1.06 (0.70-1.63)	0.78		
CC	36 (12.3)	24 (12.8)	0.87 (0.45-1.68)	0.68		
TC/CC	190 (65.1)	120 (63.8)	1.02 (0.68-1.54)	0.91		
First-episode patient	Yes	No				
TT	88 (35.5)	82 (35.3)	1.00 (Ref)			
TC	131 (52.8)	119 (51.3)	1.07 (0.71-1.60)	0.75		
CC	29 (11.7)	31 (13.4)	1.15 (0.63-2.10)	0.66		
TC/CC	160 (64.5)	150 (64.7)	1.08 (0.73-1.58)	0.70		
Family history	Yes	No				
TT	37 (39.4)	133 (34.5)	1.00 (Ref)			
TC	47 (50)	203 (52.6)	1.29 (0.79-2.11)	0.31		
CC	10 (10.6)	50 (12.9)	1.44 (0.66-3.14)	0.35		
TC/CC	57 (60.6)	253 (65.5)	1.30 (0.81-2.07)	0.28		
rs3792747						
Depressive episode	Severe	Mild				
TT	176 (69.8)	150 (65.8)	1.00 (Ref)			
TC/CC	76 (30.2)	78 (34.2)	1.21 (0.82-1.80)	0.33		
Suicide attempt	Yes	No				
TT	201 (68.8)	125 (66.5)	1.00 (Ref)			
TC/CC	91 (31.2)	63 (33.5)	1.14 (0.75-1.72)	0.54		
First-episode patient	Yes	No				
TT	168 (67.7)	158 (68.1)	1.00 (Ref)			
TC/CC	80 (32.3)	74 (31.9)	0.98 (0.66-1.44)	0.9		
Family history	Yes	No				
TT	64 (68.1)	262 (67.9)	1.00 (Ref)			
TC/CC	30 (31.9)	124 (32.1)	1.00 (0.62-1.63)	1.00		

Odds ratio was adjusted by age and gender. OR: Odds ratio; CI: Confidence interval.

antisense protein-coding genes, several of which were associated with interferon signaling. Bioinformatics approaches have also been adopted to identify differential expression of depression-related genes. Liu *et al*[25] analyzed the genes for seven mental traits identified in large-scale GWAS and found that LINC00461 has a pleiotropic effect and is associated with five mental traits, including depression, schizophrenia, and Alzheimer's disease. Als *et al*[26], identified 243 risk loci in more than 1.3 million individuals through GWAS and found that depression is highly polygenic, which could help deepen depression research and precise treatment. This information provides a better understanding of the genetic associations of depression and could aid in the development of more effective treatments.

Table 3 Haplotype analysis of rs3792747 and rs6230 in depressed patients and controls, <i>n</i> (%)							
Depressed patients	Controls	OR (95%CI)	P value				
433 (45.1)	284 (43.2)	1.00					
356 (37.1)	245 (37.2)	0.95 (0.76-1.19)	0.67				
157 (16.4)	107 (16.3)	0.96 (0.72-1.28)	0.79				
14 (1.5)	22 (3.3)	0.42 (0.21-0.83)	0.01				
	sis of rs3792747 and rs6230 in depress Depressed patients 433 (45.1) 356 (37.1) 157 (16.4) 14 (1.5)	Depressed patients Controls   433 (45.1) 284 (43.2)   356 (37.1) 245 (37.2)   157 (16.4) 107 (16.3)   14 (1.5) 22 (3.3)	Depressed patients Controls OR (95%Cl)   433 (45.1) 284 (43.2) 1.00   356 (37.1) 245 (37.2) 0.95 (0.76-1.19)   157 (16.4) 107 (16.3) 0.96 (0.72-1.28)   14 (1.5) 22 (3.3) 0.42 (0.21-0.83)				

OR: Odds ratio; CI: Confidence interval

Table 4 Relative luciferase activity of control and case groups					
Group	RFA	OR (95%CI)	<i>P</i> value		
Control	$1.58\pm0.28$	1.00			
EV	$1.52 \pm 0.22$	0.080 (-0.526-0.542)	0.973		
p-G/C	$1.59 \pm 0.27$	-0.006 (-0.540-0.528)	0.979		
p-A/T	$1.57\pm0.29$	0.060 (-0.474-0.594)	0.802		

Data represent the mean ± SEM. RFA value: The ratio of luciferase activity of recombinant plasmid to that of Renilla. EV: Empty vector; OR: Odds ratio; CI: Confidence interval.

In this study, we explored the possible association of other SNPs and haplotypes in the lncRNANONHSAT102891 promoter region with susceptibility to depression in a Chinese population. Our results suggest that the TC/CC genotype of rs6230 in the lncRNA NONHSAT102891 promoter region may be associated with the risk of moderate depression. In the haplotype analysis of rs3792747 and rs6230, the frequency of the CG haplotype was more common in the patients with severe depression than in the control group, indicating that the haplotype was associated with a reduced risk of depression. However, no significant correlation was found between the two haplotypes and lncRNA NONHSAT102891 promoter transcriptional activity in dual-luciferase reporter assays.

In recent years, lncRNAs have provided significant advances in our understanding of the pathogenesis of severe depression as well as its diagnosis and treatment. Li et al[22] suggested that nine lncRNA, including NONHSAT102891, TCONS\_00019174, and ENST00000566208, may be biomarkers of MDD. LncRNAs can participate in the epigenetic, transcriptional, and post-transcriptional regulation of the pathogenesis of depression. LncRNA XR351665 has been reported to promote the development of chronic pain-induced depression by upregulating DNMT1 via sponge miR-152-3p[27]. Long-intergenic non-coding RNA (Linc) 01360 expression is affected by rs70959274Alu polymorphism, and the Alu insertion induces DNA methylation, which significantly reduces the transcriptional activity of linc01360 compared with the control group, thus reducing the genetic risk of human MDD<sup>[14]</sup>. Differentially expressed lncRNAs also affect the pathogenesis of depression by participating in the regulation of a variety of signaling pathways. Microdeletion of FAAH-OUT lncRNA expressed in the brain and dorsal root ganglia led to downregulation of FAAH expression and a sharp increase in BDNF levels, thereby reducing the risk of depression and anxiety [28]. Decreased levels of lnc-RNAMIR155HG were shown to induce increased microRNA (miR)-155 expression in the hippocampus and inhibit BDNF expression, leading to depression-like behavior in a chronic unpredictable mild stress model of depression in mice. MiR-155HG/miR-155/BDND axis damage is a key cause of depression[29]. Low levels of linc00473 and upregulated expression of FEDORA in prefrontal cortex (PFC) neurons were detected in female depressed patients; the expression of linc00473 affected the pre-and postsynaptic features of mPFC pyramidal neurons and participated in regulation of the cAMP response element binding protein (CREB), and low levels of linc00473 in PFC neurons promoted stress recovery in female mice[30-32]. Selective expression of FEDORA in mouse mPFC neurons or oligodendrocytes confirmed its role as a sex-specific regulator of anxiety and depression-like behavior, since this phenomenon occurred only in female mice. Abedpoor et al[33] found that exercise and leucine consumption can alleviate depression-related behaviors by increasing the expression of four lncRNAs (MEG3, HOTAIR, GAS5 and TUG1 related to KDR/VEGF- $\alpha$ /PTEN/BDNF) in the IncRNA network of the brain-gut axis in depression-like mice. KEGG enrichment analysis revealed the involvement of important signaling pathways such as hippo, MAPK, Wnt, PI3K/Akt, cGMP-PKG, RAS, and IL-17 in the regulation of hippocampal function or pathological processes associated with depression[34-38]. For example, overexpression of IncRNA TCONS\_00019174 can activate the Wnt classical pathway in mice, inactivating GSK3β phosphorylation, while also upregulating  $\beta$ -catenin protein expression, thereby exerting antidepressant effects in mice[39]. Silencing lncRNA GAS5 can activate the PI3K/AKT pathway to protect hippocampal neurons from depression-like injury by regulating the miR-26a/EGR1 axis[40]. LncRNA84277 ameliorated chronic pain-associated depressive-like behavior by upregulating SIRT1 expression via the competitive sponge miR-128-3p[41]. Thus, there is accumulating evidence that these biomarkers play a key role in the pathogenesis of depression and provide new targets for the treatment of depression.

The limitations of current research should be noted. First, the case group comprised 71% females and only 29% males. The incidence of depression is sex-biased, and the higher heritability of women than men may lead to a higher incidence of depression in women[42]. Therefore, the role of epigenetic factors in the occurrence and development of depression represents an important focus of future research. Evaluating the effect of lncRNA on depression and targeted control of the phenotype of depression in a research population will promote the discovery of new and more effective treatments. Second, due to the limited sample size, the results of this study may be biased, and further studies with a larger sample size are required to determine the reference expression range of biomarkers. Third, existing evidence suggests that patients with late-onset depression have more severe and frequent patchy lesions in the deep frontal white matter and basal ganglia detected by magnetic resonance imaging as compared with the control groups or patients with early-onset depression[43]. Due to barriers such as the lack of scientific basis for diagnostic systems and structures, uncertainty in brain function, indeterminate time-course of recovery in patients with functional mental disorders, and lack of diagnostic tools, no causal relationships have been identified for functional mental disorders such as depression[44]. In the future, we aim to explore a multidimensional framework that incorporates epigenetic and neurological impact data, thereby enhancing the practical ability of clinicians to diagnose[45].

### CONCLUSION

Our results indicate that the rs3792747 and rs6230 CG haplotypes of the lncRNA NONHSA T102891 promoter are related to a reduced risk of depression in the Han Chinese population.

### **ARTICLE HIGHLIGHTS**

### Research background

Depression is a common life-threatening and disabling mental illness, and long-chain non-coding RNA (lncRNA) abnormal expression may affect the pathophysiological processes of depression. Our previous study reported that the single-nucleotide polymorphism (SNP) rs155979 GC in the promoter region of lncRNA NONHSAT102891 affects depression susceptibility in a Chinese population.

### Research motivation

The complex interplay of species between major depressive disorder and lncRNA remains unclear.

### Research objectives

To explored associations between two SNPs and haplotypes within lncRNA NONHSAT102891 promoter region and depression susceptibility in Chinese population.

### Research methods

We conducted a case-control study in a cohort of 480 patients with depression and 329 healthy controls, and performed genotyping by gene sequencing. The function of the two lncRNA NONHSAT102891 promoter G/C and A/T haplotypes was detected by dual-luciferase reporter assays of human embryonic kidney 293T transfected cells.

### Research results

The degree of mild depressive episodes associated with the rs6230 TC/CC genotype increased by 1.59 times. The haploid analysis revealed linkage disequilibrium between rs3792747 and rs6230, and the double SNP CG haplotype was more common in the control group compared to case group, indicating that this haplotype significantly reduced the risk of depression (C/G vs T/A: odds ratio = 0.42, 95% confidence interval: 0.21-0.83, P = 0.01). There was no significant difference in the dual-luciferase reporter activity of the G/C and A/T haplotypes compared with the control group (P >0.05).

### Research conclusions

The rs3792747 and rs6230 CG haplotypes of the lncRNA NONHSA T102891 promoter may be associated with a reduced risk of depression in the Chinese population. However, further studies with a larger sample size are required to determine the reference expression range of biomarkers.

### Research perspectives

This study provides insights into the early prediction and diagnosis of depression and important clues for development of tools that will facilitate more accurate diagnosis and treatment of depression in the clinic.

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### FOOTNOTES

Author contributions: Liang YD designed the study and corrected the manuscript; Li Y performed the majority of experiments and wrote the manuscript; Wang YX, Tang XM, Liang P, Chen JJ, Jiang F, Yang Q participated to the data collection and analysis of human material, and commented on previous versions of the manuscript; all authors contributed to the study conception and design. All authors read and approved the final manuscript.

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Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at liangyundan2004@ 126.com

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ORIGINAL ARTICLE

## **Retrospective Study** Efficacy and risk factors for anxiety and depression after miniincision hip arthroplasty for femoral head osteonecrosis

Wen-Xing Yu, Yang-Quan Hao, Chao Lu, Hui Li, Yuan-Zhen Cai

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### Abstract

### BACKGROUND

Osteonecrosis of the femoral head (ONFH) is a prevalent orthopedic issue, leading to the collapse and fragmentation of the femoral head in its advanced stages, which can severely impair patients' quality of life. Total hip arthroplasty (THA) is a clinical intervention frequently used to alleviate ONFH symptoms and reinstate hip functionality. The conventional surgical technique is invasive and comes with an extended recuperation period, posing significant challenges for patients. With the progression of medical technology, the use of the mini-incision technique in minimally invasive THA (MITHA) has become more prevalent. However, comparative studies examining the effectiveness of these two surgical procedures in treating ONFH remain scarce. Furthermore, understanding patients' psychological well-being is crucial given its profound influence on postoperative recuperation.

### AIM

To evaluate the impact of mini-incision MITHA on ONFH treatment and to identify the risk factors associated with postoperative anxiety and depression.

### **METHODS**

A retrospective study was conducted on 125 patients treated for ONFH at Xi'an Hong Hui Hospital between February 2020 and January 2022, with the term "consecutive" indicating that these patients were treated in an unbroken sequence without any selection. Among these, 60 patients (control group) underwent traditional THA, while 65 patients (observation group) were treated with miniincision MITHA. Variations in the visual analog scale (VAS) score and the Harris hip score were monitored. Additionally, shifts in pre- and posttreatment Hamilton anxiety (HAMA) and Hamilton depression (HAMD) scale scores were recorded. Patients with both postoperative HAMA and HAMD scores of  $\geq 8$  were



identified as those experiencing negative emotions. Logistic regression was utilized to analyze the determinants influencing these negative emotional outcomes. Comparative analyses of surgical and postoperative metrics between the two groups were also conducted.

### RESULTS

Posttreatment results indicated a significantly higher VAS score in the control group than in the observation group, while the Harris score was considerably lower (P < 0.0001). The observation group benefited from a notably shorter operation duration, reduced blood loss, diminished incision size, and a decreased postoperative drainage time (P < 0.0001), accompanied by a reduced hospital stay and lower treatment costs (P < 0.0001). The control group had elevated posttreatment HAMA and HAMD scores in comparison to the observation group (P < 0.0001). Multivariate logistic regression revealed that being female [odds ratio (OR): 4.394, 95%CI: 1.689-11.433, P = 0.002], having a higher postoperative VAS score (OR: 5.533, 95%CI: 2.210-13.848, P < 0.0001), and having higher treatment costs (OR: 7.306, 95%CI: 2.801-19.057, P < 0.0001) were significant independent determinants influencing postoperative mood disturbances.

### CONCLUSION

Compared to conventional THA, mini-incision MITHA offers advantages such as reduced operation time, minimal bleeding, and a shorter incision in ONFH patients. Moreover, factors such as sex, postoperative pain (reflected in the VAS score), and treatment costs significantly impact postoperative anxiety and depression.

**Key Words**: Necrosis of the femoral head; Total hip arthroplasty; Minimally invasive total hip arthroplasty; Postoperative recovery; Anxiety; Depression

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**Core Tip:** Minimally invasive total hip arthroplasty has shown significant advantages in the treatment of osteonecrosis of the femoral head, including a short operation time and less bleeding. However, the psychological stress of postoperative patients, especially female patients, those with high postoperative pain scores, and those with high treatment costs, cannot be ignored as these patients are more susceptible to adverse emotions. Therefore, although improvements in technology and surgical methods are essential, psychological counseling, which can help improve the treatment effect and the quality of life of patients, is equally important.

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### INTRODUCTION

Necrosis of the femoral head (ONFH) is a disease that causes partial or total ischemia of the femoral head due to blood circulation interruption or injury, which leads to the death of osteocytes, bone marrow hematopoietic cells and adipocytes and may eventually trigger a series of structural changes, such as femoral head collapse[1]. Such a disease is considered to be a disease with a high disability rate in orthopedics[2]. Early diagnosis of ONFH is challenging due to the atypicality of its clinical presentation[3]. As the condition worsens, the femoral head collapses on images, and complete loss of the original femoral head shape occurs in severe cases, which can further develop into degenerative hip osteoarthritis[4]. Therefore, choosing effective treatment methods to improve the patient's condition is critical.

Clinically, total hip arthroplasty (THA) is a common treatment that can achieve joint function reconstruction in patients with ONFH, thus significantly improving patient quality of life[5]. However, conventional THA has some drawbacks, such as a large incision, heavy trauma, and a high incidence of surgical complications[6,7]. Hence, it is necessary to reduce the risk of surgical trauma and complications while ensuring the safety and effectiveness of surgery. In recent years, there has been an increase in the application of minimally invasive THA (MITHA) with the development of minimally invasive technology[8]. This procedure has the advantages of less trauma and quick recovery, which can more effectively help patients relieve pain and restore joint function[9,10]. However, whether MITHA is advantageous over conventional THA with a more significant effect on improving patients' conditions remains to be further studied.

Currently, the treatment of ONFH relies mainly on surgery, which results in a long recovery time, especially for elderly patients. During the recovery period, patients may experience a great reduction or even loss of self-care ability, as well as varying degrees of motor system damage. These factors have placed great pressure on the physiology and psychology of patients, predisposing them to psychological stress and negative emotions (NEs).

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Accordingly, the purpose of this study was to explore the effect of MITHA in the treatment of ONFH and to analyze the risk factors that may affect postoperative anxiety and depression. This study can provide more rigorous evidence for clinical treatment and intervention, with important practical significance for improving patient quality of life and mental health.

### MATERIALS AND METHODS

### Patient data

A retrospective analysis was performed on 125 ONFH patients who were treated at Xi'an Hong Hui Hospital from February 2020 to January 2022. Among them, 60 patients who received conventional THA and 65 patients who received MITHA were assigned to the control group and observation group, respectively.

### Eligibility and exclusion criteria

The inclusion criteria were as follows: (1) Patients whose physical condition was at an acceptable level and with an American Association of Anesthesiologists score ranging from 1 to 3 points[11]; (2) Those meeting the indications for THA; (3) Diagnosis of CNFH by imaging examination; (4) Awareness of and voluntary participation in the study by patients and their families; (5) Unilateral lesions that met surgical indications; and (6) Complete clinical data.

The exclusion criteria were as follows: (1) Severe cardio-cerebrovascular diseases and other chronic wasting diseases; (2) Multiple hip replacement procedures; (3) Concurrent surgery of other parts; (4) Incomplete information or loss to follow-up; or (5) Active infection in the affected hip or surgical area.

### Treatment methods

Patients in the control group underwent conventional THA. The procedure was performed under general anesthesia with the patient placed in a lateral decubitus position. After successful anesthesia, the surgeon successively cut the skin of the patient to expose the femoral head and the acetabulum edge, viewing the acetabulum damage and repairing it. Then, an appropriate prosthesis was selected for implantation according to the patient's specific condition. After confirmation of the correct placement of the implant, the surgeon cleaned the incision and placed a drainage tube to complete the procedure.

Patients in the observation group underwent MITHA using a mini-incision technique, with the anesthesia method and surgical position the same as the control group. During the operation, the surgeon made a small incision of 6 to 10 cm along the gluteus maximus muscle fibers on the posterior side of the greater trochanter of the femur. The gluteus maximus muscle was then cut open, and the external rotators at the attachment of the trochanter were cut off and pulled posteriorly so that the joint capsule could be exposed for incision to expose the femoral head and acetabulum. Then, within 10 to 15 cm of the femur, the surgeon used a chainsaw to cut the neck of the femur and remove the severed femoral head. Next, the stump of the ligamentum teres of the acetabulum and the glenoid lip were removed, and the exposed ligamentum teres fossa was ground flat. At the same time, reaming was performed on the acetabulum with an anteversion angle of 20° and an abduction angle of 45°. Then, a prosthesis with a suitable size was selected for a trial mold, and the prosthesis was implanted after confirming its stability and tightness. At the end of the surgery, the surgeon drilled 3 to 4 holes in the suture of the external rotators, washed the operation field and placed a drainage tube to end the operation. Both groups received routine anti-infection therapy after surgery.

### Clinical data collection

The following information was collected: (1) Clinical data, namely, age, sex, body mass index (BMI), pathogeny, affected side, smoking history, alcoholism history, education level, annual income and marital status; (2) Surgical indicators, namely, operation time, intraoperative blood loss, incision length, and postoperative drainage time; (3) Postoperative indicators, namely, length of stay and treatment cost; (4) Scoring indices, namely, visual analog scale (VAS) scores[11] and Harris hip score (HHS) before and after operation; and (5) Pre- and posttreatment Hamilton anxiety and depression scale scores, namely, the Hamilton anxiety scale (HAMA) and Hamilton depression scale (HAMD) scores[12].

### Outcome measures

Primary outcome measures: Changes in VAS and HHS scores before and after treatment were observed. Alterations in pre- and posttreatment HAMA and HAMD scores were compared between the two groups. According to postoperative scores, patients with both HAMA and HAMD scores ≥ 8 were considered to have NEs, and the risk factors affecting the occurrence of NEs were analyzed by logistic regression.

Secondary outcome measures: Clinical data, surgical indicators and postoperative indicators were compared.

### Statistical analysis

SPSS 26.0 and GraphPad Prism 9 were used for data analysis, and the threshold of statistical significance was P < 0.05. Count data are expressed as frequencies (percentages), and comparisons between groups were made by means of the  $\chi^2$ test. Measurement data are expressed as the mean  $\pm$  SD. Two independent samples t tests were used for comparisons between groups, independent samples t tests were used for comparisons between groups, and paired t tests were used for comparisons within groups. Logistic regression was used to analyze the risk factors affecting patients' NEs.

### RESULTS

### Comparison of clinical data

In the comparisons of the patients' clinical data, it was found that the observation and control groups were not significantly different in age, sex, BMI, pathogeny, affected side, smoking history, alcoholism history, education level, annual income, or marital status (P > 0.05, Table 1).

### Changes in pain and functional scores

Changes in VAS and HHS scores before and after treatment were compared between groups. The two groups did not differ significantly in terms of their pretreatment VAS or HHS scores (P > 0.05). A reduction in the VAS score and an increase in the HHS score were observed in both groups after treatment (P < 0.0001). Further intergroup comparison revealed a higher VAS score and a lower HHS score in the control group than in the observation group (P < 0.0001, Figure 1).

### Comparison of surgical indices

The intergroup comparison of surgical indices showed that the operation time was significantly shorter in the observation group than in the control group, with less intraoperative blood loss, shorter incision length, and less postoperative drainage time (P < 0.0001, Figure 2).

### Comparison of postoperative indices

Comparing the postoperative indices, it was found that the length of stay and treatment cost of patients were significantly lower in the observation group than in the control group (P < 0.0001, Figure 3).

### Evaluation of patients' NEs

Patients' anxiety and depression were evaluated before and after treatment. There were no significant difference in the pretreatment HAMA or HAMD scores between the two groups (P > 0.05). However, significantly reduced HAMA and HAMD scores were observed in both groups after treatment (P < 0.0001). Further comparison showed that the posttreatment HAMA and HAMD scores were significantly higher in the control group than in the observation group (P < 0.0001, Figure 4).

### Analysis of risk factors affecting patients' NEs

We conducted a statistical evaluation of the postoperative HAMA and HAMD scores. Using a screening threshold of a postoperative score  $\ge 8$ , we identified 71 patients exhibiting postoperative anxiety and 77 manifesting postoperative depression. Based on these findings, patients were categorized into two distinct groups: the NE group (n = 71) and the emotional stability group (n = 54). In the univariate analysis, several factors emerged as potential risk determinants affecting patients' NEs. These included age  $\ge 60$  years, female sex, an education level below middle school, an annual income less than 50000 CNY, opting for the conventional surgical plan, elevated postoperative VAS scores, prolonged operation times, and increased treatment costs (P < 0.05, Table 2). To refine our understanding, we assigned numerical values to the identified variables, as shown in Table 3. Our subsequent multivariate logistic regression analysis highlighted three prominent factors. Specifically, being female, having a higher postoperative VAS score, and incurring elevated treatment costs were significant independent risk factors influencing postoperative NEs in patients (P < 0.01, Table 4).

### DISCUSSION

ONFH is a common condition in orthopedics with symptoms such as femoral head collapse and fragmentation in the later stage, which can cause great pain to patients and even loss of mobility[13]. The interruption of the blood supply to the femoral head leads to the production of free radicals, as well as hypoxia and reperfusion injury, which can accelerate osteocyte death and eventually lead to the necrosis of bone marrow stromal stem cells or the formation of adipocytes, leading to local osteoporosis[14]. Hip replacement has been clinically shown to be an effective method to relieve hip pain and restore hip function in ONFH patients[15]. However, this procedure is highly invasive and is associated with a long postoperative recovery period and long-term bed rest, which increases the difficulty of rehabilitation training and the risk of developing lower extremity deep venous thrombosis, affecting postoperative rehabilitation.

The development of minimally invasive surgery technology has enabled the gradual application and popularization of mini-incision MITHA in clinical practice[16]. In addition, the rapid development of medical technology and equipment has made it possible to improve and optimize the incision method of THA[17]. In long-term clinical practice, mini-incision THA has become a standard surgical approach with many advantages. However, little has been reported about the difference between conventional and minimally invasive THA procedures for the treatment of ONFH. Repantis *et al* [18] found no significant difference in intraoperative blood loss between the two THA methods but identified markedly lower postoperative pain scores in the minimally invasive group. The present study also comparatively analyzed the two surgical modalities and found a significantly shorter operation time in patients undergoing MITHA *vs* those receiving conventional THA, with less intraoperative bleeding, a shorter incision length, less surface peeling and clear joint exposure, which greatly shortened the operation time and reduced the body's traumatic stress response.

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Table 1 Comparison of cli	nical data			
Factors		Control group ( <i>n</i> = 60)	Observation group ( <i>n</i> = 65)	P value
Age				0.569
	$\geq$ 60 years old	34	40	
	< 60 years old	26	25	
Sex				0.650
	Male	34	40	
	Female	26	25	
BMI				0.503
	$\geq 25 \text{ kg/m}^2$	15	13	
	$< 25 \text{ kg/m}^2$	45	52	
Pathogeny				0.434
	Trauma	29	22	
	Hormone	20	27	
	Alcohol	7	10	
	Others	4	6	
Affected side				0.264
	Left	27	36	
	Right	33	29	
Smoking history				0.650
	With	34	40	
	Without	26	25	
History of alcoholism				0.444
	With	5	8	
	Without	55	57	
Education level				0.490
	$\geq$ Junior high school	25	23	
	< Junior high school	35	42	
Annual income				0.531
	≥ 50000 CNY	18	16	
	< 50000 CNY	42	49	
Marital status				0.569
	Married	44	50	
	Divorced	9	10	
	Others	7	5	

BMI: Body mass index.

For patients with either osteoporotic fracture or ONFH, THA will cause psychological stress and cause greater psychological pressure[19]. Anxiety and depression are the most common psychological complications, both of which have a certain impact on patients' cognitive and psychological states [19,20]. In addition, anxiety and depression can significantly reduce patients' motivation and adherence to treatment during hospitalization, leading to a significant decline in treatment effectiveness. Evidence has shown that psychological factors have an impact on the outcome of THA[21]. In contrast, a good state of mind helps patients recover as quickly as possible. Therefore, identifying factors that influence anxiety and depression helps clinical medical staff to take relevant nursing measures and carry out targeted treatment in time. In our study, anxiety and depression were found before surgery in both groups and were relieved in some patients after treatment. To determine the risk factors for postoperative NEs in ONFH patients, we performed a regression

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Table 2 Univariate analysis				
Factors		Negative emotion group (n = 71)	Emotional stability group ( <i>n</i> = 54)	P value
Age				0.002 <sup>b</sup>
	$\geq$ 60 years old	50	24	
	< 60 years old	21	30	
Sex				0.003 <sup>b</sup>
	Male	34	40	
	Female	37	14	
BMI				0.460
	$\geq 25 \text{kg/m}^2$	14	14	
	$< 25 kg/m^2$	57	40	
Pathogeny				0.423
	Trauma	33	18	
	Hormone	25	22	
	Alcohol	9	8	
	Others	4	6	
Affected side				0.937
	Left	36	27	
	Right	35	27	
Smoking history				0.060
	With	37	37	
	Without	34	17	
History of alcoholism				0.866
	With	7	6	
	Without	64	48	
Education level				0.026 <sup>a</sup>
	$\geq$ Junior high school	21	27	
	< Junior high school	50	27	
Annual income				0.038 <sup>a</sup>
	≥ 50000 CNY	14	20	
	< 50000 CNY	57	34	
Marital status				0.752
	Married	52	42	
	Divorced	11	8	
	Others	8	4	
Treatment methods				0.032
	Minimally invasive	31	34	
	Conventional	40	20	
Postoperative VAS score		$4.28 \pm 1.59$	$2.70 \pm 1.50$	< 0.0001 <sup>d</sup>
Postoperative harris hip score		79.50 ± 8.06	80.33 ± 8.77	0.585
Operation time (min)		95.69 ± 8.36	92.63 ± 7.18	0.033 <sup>a</sup>
Intraoperative blood loss (mL)		14.15 ± 3.89	11.57 ± 4.23	0.074
Incision length (cm)		$436.59 \pm 190.14$	$441.17 \pm 210.32$	0.898



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Postoperative drainage time (min)	459.11 ± 203.95	343.56 ± 192.78	0.075
Length of stay (d)	11.26 ± 2.96	12.29 ± 4.16	0.109
Treatment cost (CNY)	$40006.21 \pm 5472.16$	34272.05 ± 6033.42	< 0.0001 <sup>d</sup>

 $^{a}P < 0.05$ 

 $^{b}P < 0.01.$ 

 $^{d}P < 0.0001.$ 

BMI: Body mass index; VAS: Visual analogue scales

### Table 3 Assignment table

Factors	Assignment
Age	$\geq$ 60 years old = 1, < 60 years old = 0
Sex	Male = 0, female = 1
Education level	$\geq$ Junior high school = 0, < Junior high school = 1
Annual income	$\geq$ 50000 CNY = 0, < 50000 CNY = 1
Surgical plan	Minimally invasive = 0, conventional = 1
Postoperative VAS score	$\geq 4 = 1, < 4 = 0$
Operation time	$\geq$ 95 min = 1, < 95 min = 0
Treatment cost	≥ 35000 CNY = 1, < 35000 CNY = 0
Anxiety and depression	Negative emotion group = 1, emotional stability group = 0

VAS: Visual analogue scales.

### Table 4 Multivariate analysis

Fastara	ρ	Standard array	X²	P value	00	95%CI	
Factors	þ	Stanuaru error			UK	Lower bound	Upper bound
Age	0.578	0.465	1.545	0.214	1.782	0.716	4.434
Sex	1.480	0.488	9.206	0.002 <sup>b</sup>	4.394	1.689	11.433
Education level	0.809	0.462	3.064	0.080	2.246	0.908	5.557
Annual income	0.704	0.521	1.829	0.176	2.023	0.729	5.614
Surgical plan	0.183	0.487	0.141	0.707	1.201	0.462	3.120
Postoperative VAS score	1.711	0.468	13.354	< 0.001 <sup>c</sup>	5.533	2.210	13.848
Operation time	0.643	0.494	1.695	0.193	1.902	0.723	5.004
Treatment cost	1.989	0.489	16.532	< 0.001 <sup>c</sup>	7.306	2.801	19.057

 $^{b}P < 0.01.$ 

 $^{c}P < 0.001.$ 

VAS: Visual analog scales; OR: Odds ratio.

analysis. The results showed that sex, postoperative VAS score, and treatment cost were risk factors for postoperative NEs in ONFH patients. The reason may be that women, who are affected by psychological and physiological characteristics, are more sensitive and emotional and therefore more susceptible to NEs after illness. In addition, the activity limitation of postsurgical patients leads to aggravated depression and anxiety. In the research of Liu and Wang[22], the incidence of anxiety and depression increased significantly among female patients after gastric cancer surgery and was related to poor prognosis, which was the main risk factor. Pain itself is a kind of physical discomfort that can negatively affect the individual's mood and behavior. Pain can also lead to decreased sleep quality, further aggravating the patient's emotional distress. Persistent pain can cause the patient to worry about the prospect of future recovery, exacerbating anxiety and depression. Park et al[23] suggested that severe postoperative pain was a risk factor for postoperative anxiety and depression in patients with lung cancer. Although ONFH does not require long-term treatment, conventional



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Figure 1 Changes of visual analogue scales and Harris hip score scores in patients before and after treatment. A: Comparison of visual analogue scales score; B: Comparison of Harris hip score; VAS: Visual analogue scales. <sup>d</sup>P < 0.0001.



Figure 2 Comparison of surgical indexes. A: Comparison of operation time; B: Comparison of intraoperative blood loss; C: Comparison of incision length; D: Comparison of postoperative drainage time. <sup>d</sup>P<0.0001.

replacement surgery is not affordable for all families, increasing the financial burden on patients' families. In addition, from the perspective of the patients, the psychological pressure felt is enormous due to fear of becoming a burden to their families. They may also worry that they will not be able to pay for medical expenses in the long term and that follow-up treatment will be difficult to guarantee, resulting in negative feelings such as guilt and anxiety[24,25]. Therefore, to improve patients' psychological states, it is necessary to strengthen communication with patients and encourage them to express their inner thoughts. For patients with NEs, targeted psychological counseling can be implemented to help relieve stress. In addition, those patients with effectively controlled conditions after treatment and a good state of mind can be invited to share their treatment experiences and exchange opinions on overcoming difficulties. Such measures are helpful to improve patients' confidence in treatment and prevent the occurrence of NEs.

In this study, we determined the therapeutic effect of MITHA on ONFH patients and the risk factors for postoperative NEs through analyses. However, this study still has some limitations. First, the insufficient sample size may lead to errors in the results of the regression analysis. Second, patients' long-term follow-up cannot be determined due to the retrospective nature of this study, resulting in uncertainty regarding the long-term outcomes of patients treated by the two surgical methods. Finally, as a single-center study, the applicability and generalizability of the results of this study need

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Figure 3 Comparison of postoperative indexes. A: Comparison of length of stay; B: Comparison of treatment cost. <sup>d</sup>P<0.0001.



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Figure 4 Changes of Hamilton anxiety scale and Hamilton depression scale scores before and after treatment. A: Comparison of Hamilton anxiety scale score; B: Comparison of Hamilton depression scale score. HAMA: Hamilton anxiety scale; HAMD: Hamilton depression scale. <sup>d</sup>P<0.0001.

to be validated and supported by external data. Therefore, the hope is that more in-depth research can be carried out in the future and that more samples will be collected to support the conclusions of this study.

### CONCLUSION

In this paper, the application and clinical effectiveness of THA in ONFH patients, particularly the influence of MITHA on patients' treatment outcomes, were studied. The results show that MITHA contributes to a shorter operation time, less blood loss and a shorter incision length. At the same time, anxiety and depression before surgery were prevalent in all patients, and these NEs may be related to the patient's sex, postoperative pain score, and treatment cost.

### **ARTICLE HIGHLIGHTS**

### Research background

Osteonecrosis of the femoral head (ONFH) is a complex and multifactorial disease, which can seriously affect the quality of life of patients at the advanced stage. Although conventional total hip arthroplasty (THA) is effective in relieving symptoms, the procedure is invasive, resulting in a long recovery period for patients. Minimally invasive THA (MITHA) has begun to be used clinically with the development of minimally invasive techniques.

### **Research motivation**

There is a lack of studies comparing MITHA with conventional THA, especially its effects on postoperative pain, recovery, and psychological distress in patients with ONFH.

### Research objectives

This study aims to compare the effects of MITHA vs conventional THA in patients with ONFH and to further explore risk factors for postoperative negative emotions (NEs).

### Research methods

The two surgical methods were comparatively analyzed, and the emotional state of the patients before and after surgery was investigated and analyzed using the regression model.

### Research results

Patients undergoing MITHA had shorter operation time, less intraoperative bleeding and smaller incision length. Both groups of patients developed anxiety and depression before surgery, but some of them experienced emotional relief after treatment. Sex, postoperative pain score, and treatment cost were identified as risk factors affecting postoperative NEs of ONFH patients.

### Research conclusions

MITHA is obvious advantageous over conventional THA in the treatment of ONFH, with short operation time and less bleeding. Sex, postoperative pain score, and treatment cost are risk factors that affect patients' postoperative mood. Targeted psychological counseling can effectively relieve the pressure of patients.

### Research perspectives

A larger sample size and a long-term patient follow-up are needed to further determine the long-term effects of MITHA, as well as the depth and durability of the psychological impact on patients. Meanwhile, we need to better understand and deal with patients' postoperative psychological problems to improve the overall effectiveness of treatment.

### FOOTNOTES

Author contributions: Yu WX and Cai YZ contributed to the study conception and design, drafting manuscript, data analysis and interpretation; Yu WX, Hao YQ, Lu C, Li H and Cai YZ contributed to the study conception, critical revision of article for important intellectual content; Yu WX and Cai YZ contributed to the study conception and design, critical revision of article for important intellectual content.

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

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Data sharing statement: The data for this study can be obtained from the corresponding author upon request at bonny17173@163.com.

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ORIGINAL ARTICLE

## **Retrospective Study** Efficacy of enhanced extracorporeal counterpulsation combined with atorvastatin in the treatment of cognitive impairment after stroke

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### Abstract

### BACKGROUND

Cerebral apoplexy patients are prone to cognitive impairment, and it is very important to choose appropriate treatment methods to improve their cognitive impairment after stroke.

### AIM

To evaluate the effects of enhanced external counterpulsation (EECP) in conjunction with atorvastatin on cognitive function, neurotransmitter levels, and the repair of brain tissue damage in patients with cognitive impairment due to stroke.

### **METHODS**

In this retrospective study, data from 60 patients with poststroke cognitive impairment due to stroke who were treated in our hospital from February 2021 to July 2022 were analyzed and divided into a treatment group (n = 30) and a control group (n = 30) according to the different nursing methods applied. Patients in the treatment group received EECP in addition to atorvastatin, while those in the control group received atorvastatin alone. Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) and activities of daily living (ADL) scale scores were compared between the two groups. Additionally, the two groups were compared in terms of serum acetylcholine (ACh), acetylcholinesterase (AChE), nitric oxide (NO), endothelin-1 (ET-1), β2-microglobulin (β2-MG), glial fibrillary acidic protein (GFAP), and visinin-like protein 1 (VILIP-1) in the serum. Blood flow measurements from the anterior cerebral artery (ACA), middle cerebral artery (MCA) and posterior cerebral artery (PCA) were compared between the two groups before and after treatment, and the pulsatility index (PI) and resistance index (RI) of each artery were determined.

### RESULTS



MMSE, MoCA, and ADL scores all improved in both groups following treatment, with the study group showing more improvement than the control group (P < 0.05). After treatment, there were statistically significant increases in both ACh and NO levels, whereas decreases occurred in AChE, ET-1, β2-MG, VILIP-1, and GFAP, levels and the PI and RI of the left-ACA, right-ACA, left-MCA, right-MCA, left-PCA, and right-PCA. The study group showed greater gains in all metrics than the control group (P < 0.05).

### **CONCLUSION**

EECP combined with atorvastatin is effective in the treatment of cognitive impairment after stroke and can effectively improve the cognitive function, neurotransmitter levels, and brain tissue damage status of patients.

Key Words: Enhanced extracorporeal counterpulsation; Atorvastatin; Cognitive impairment after stroke; Neurotransmitters; Brain tissue damage status

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**Core Tip:** Enhanced extracorporeal counterpulsation and atorvastatin are widely used in the treatment of stroke patients with cognitive impairment, but the effect of enhanced counterpulsation combined with atorvastatin on cognitive function of stroke patients with cognitive impairment has not been discussed. The objective of this study was to compare the efficacy of enhanced external counterpulsation combined with atorvastatin vs atorvastatin alone in the treatment of post-stroke cognitive impairment. Combined therapy is better than atorvastatin therapy alone.

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### INTRODUCTION

A patient's quality of life is drastically altered after suffering a stroke, which is an acute cerebrovascular event that can result in brain ischemia, hypoxic damage, and neurological abnormalities as well as sequelae such as language dysfunction, limb malfunction, and cognitive impairment. Cognitive impairment after stroke is caused by degenerative diseases resulting from neural tissue ischemia. Therefore, patients with cognitive impairment following a stroke may achieve some improvement in their clinical symptoms with clinical therapy for nutritional neuropathy, improvement of microcirculation, and hemorheology, along with physical exercise[1,2]. Safe, effective, and noninvasive, enhanced external counterpulsation (EECP) is a mechanical circulatory aid method commonly employed in the treatment of coronary heart disease and angina pectoris. Multiple recent studies have demonstrated the efficacy of EECP in treating ischemic cerebrovascular disease, sleep disturbances, and psychological and psychiatric diseases[3,4]. The mechanism of EECP is to increase both the arterial and venous return of both lower limbs, increase coronary blood flow, and improve the perfusion of the heart, brain, kidneys, and other organs<sup>[5]</sup>. Statins, which are hydroxymethylglutaryl coenzyme A reductase inhibitors, can significantly boost patients' cognitive performance and postpone disease progression[6] through their anti-inflammatory, antithrombotic, endothelium-protective, and antioxidant properties. The purpose of this research was to examine the effects of EECP in conjunction with atorvastatin on cognitive performance, neurotransmitter levels, and recovery from brain tissue damage in patients with poststroke cognitive impairment. The findings are detailed below.

### MATERIALS AND METHODS

### General information

Data from 60 patients with poststroke cognitive impairment due to stroke who were treated in our hospital from February 2021 to July 2022 were analyzed, and the patients were divided into a treatment group (n = 30) and a control group (n = 30) according to the different nursing methods applied. There were 21 men and 9 women in the study group, with ages ranging from 49 to 74 (mean = 61.40, SD = 5.59) years; the average duration since stroke onset was  $6.30 \pm 1.62$ mo, and the average duration since cognitive impairment onset was 5.57 ± 1.14 mo. In the control group, the age ranged from 49 to 73 years, with a mean of  $60.30 \pm 5.84$  years. There were 19 men and 11 women in the control group; the mean duration since stroke onset was  $6.50 \pm 1.28$  mo, and the mean duration since the onset of cognitive impairment was  $3.75 \pm$ 0.78 mo. Overall, there was little to no difference in these data between the two groups (P > 0.05). All protocols in this study were approved by the ethics committee of the Shengjing Hospital of China Medical University and abided by the ethical guidelines of the Declaration of Helsinki. The ethics committee waived the requirement for informed consent.



### Diagnostic criteria

All patients were diagnosed with stroke by imaging examination, and color ultrasound examination showed that there was a mural thrombus in the bilateral carotid arteries. The patients were diagnosed with mild cognitive impairment as described in the study of Ismail *et al*[7]: (1) All imaging examinations showed findings in accordance with the diagnostic criteria for stroke; (2) Progressive impairment of cognitive function; (3) Mild memory impairment; (4) Ability to continue daily life; and (5) Cognitive impairment less severe than the threshold for a diagnosis in the Diagnostic and Statistical Manual of Mental Disorders[8]. Reduced capacity to orient oneself, recognize objects, and express oneself in language served as the primary clinical indications.

### Inclusion criteria

(1) Imaging findings, physical examination findings, and a thorough review of the patient's medical history all corroborated the diagnosis, which matched all of the criteria laid forth in the Diagnostic Essentials of Various Cerebrovascular Diseases[9]; (2) Absence of any life-threatening organ malfunction; and (3) Voluntary participation in the research.

### Exclusion criteria

(1) Neurological disease, such as Alzheimer's disease, Parkinson's disease, or epilepsy; (2) History of brain trauma; (3) Previous stroke or stroke-like event; (4) Existing mental disability before the stroke; and (5) Severe anxiety, depression, or other mental illness.

### Methods

Atorvastatin was used in conjunction with EECP to treat patients in the research group (Pfizer Pharmaceutical Co., Ltd., National Drug Approval No.: H20051408). Patients in the control group were given only atorvastatin. Oxygen saturation was tracked using an EECP instrument (a PECP/TM) to measure EECP. The machine was first warmed for approximately 10-15 min. After the patient was positioned in an appropriate posture for treatment, sandpaper was used to smooth the skin around the electrode connection site, and alcohol was used to disinfect the immediate area. The white, red, and black electrodes were fixed under the left clavicle or near the manubrium, the apex of the heart, the upper right abdomen, or the lower right rib. Then, a finger pulse oximeter was placed on a finger of the right hand of the patient, ensuring that the electrode was in a position free from or minimally affected by vibration, the red and white electrodes were not too close, and the electrode position did not affect the inflatable cuff. The standard inflation pressure ranged from 0.025 to 0.045 MPa, with adjustments made during the operation based on the patient's response to the pressure. At the end of treatment, the finger pulse oximeter was removed, the inflatable cuff was unfastened, the electrode leads and electrodes were removed, and the patient was helped in tidying up his or her clothes and leaving the counterpulsation bed. The patient was performed once a day, 1 h/session, 6 d a week for 6 consecutive weeks, for a total of 36 sessions. Atorvastatin (20 mg) was given once daily for 24 wk.

### **Observational indexes**

Clinical data of patients in the two groups were collected, and the Mini-Mental State Examination (MMSE)[10], Montreal Cognitive Assessment (MoCA)[11] and activities of daily living (ADL)[12] scores were compared between the two groups. Serum acetylcholine (ACh), acetylcholinesterase (AChE), nitric oxide (NO), endothelin-1 (ET-1),  $\beta$ 2-microglobulin ( $\beta$ 2-MG), visinin-like protein-1 (VILIP-1) and glial fibrillary acidic protein (GFAP) levels were compared between the two groups. The blood flow conditions of the bilateral anterior cerebral artery (ACA), middle cerebral artery (MCA) and posterior cerebral artery (PCA) were compared between the two groups before and after treatment. The pulsatility index (PI) and resistance index (RI) of each artery were calculated according to the blood flow velocity of the left and right arteries during the peak systolic period (Vs), end-diastolic blood velocity (Vd) and average blood flow velocity (Vm), with PI = (Vs-VD)/Vm, and RI = (Vs-VD)/Vs.

The MMSE includes five different elements, with a total of 30 items and a total score of 30 points. The better the patient's mental condition, the higher the score. The total possible score on the MoCA is 30 points, and a MoCA score < 26 points indicates that the patient has cognitive impairment. The total possible score on the ADL scale is 100 points, and the higher the score, the better the patient's daily living ability. The abbreviations for the cerebral arteries are left ACA (LACA), right ACA (RACA), left MCA (LMCA), right MCA (RMCA), left PCA (LPCA), and right PCA (RPCA).

### Statistical methods

SPSS 20.0 was employed for processing and analyzing the data. The values for the measurements are presented as "mean  $\pm$  SD". The *t* test for independent samples was used to evaluate differences between the groups. Within-group comparisons of pre- and posttreatment values were performed using the paired *t* test. The  $\chi^2$  test was used to make comparisons, with count data being reported as frequencies and category ratios. *P* < 0.05 was considered to indicate a statistically significant difference.

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Table 1 Comparison of Mini-Mental State Examination, Montreal Cognitive Assessment and activities of daily living scores between the two groups (mean ± SD, points)

	MMSE score		MoCA score		ADI score	
Group	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Study group $(n = 30)$	20.63 + 2.94	$26.80 \pm 2.50^{a}$	19 50 + 2 84	$26.77 \pm 2.08^{a}$	45.00 + 4.78	$63.70 + 6.25^{a}$
Study group $(n = 30)$	20.03 ± 2.94	20.00 ± 2.09	19.50 ± 2.64	20.77 ± 2.08	45.00 ± 4.78	55.70 ± 6.25
Control group ( $n = 30$ )	$19.73 \pm 3.10$	24.97 ± 3.29"	$19.70 \pm 1.60$	24.70 ± 2.42"	45.97 ± 4.62	57.40 ± 4.99"
<i>P</i> value	0.253	0.020	0.738	0.001	0.429	< 0.001
<i>t</i> value	1.154	2.400	0.336	3.545	0.797	4.314

 $^{a}P < 0.05$ , compared with the same group before treatment.

MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; ADL: Activities of daily living.

Table 2 Comparison of cholinergic system component levels between the two groups (mean ± SD, nmol/mL)							
Group	ACh		AChE				
Group	Before treatment	After treatment	Before treatment	After treatment			
Study group ( $n = 30$ )	$10.96 \pm 2.84$	$22.53 \pm 2.49^{a}$	$16.53 \pm 2.09$	$8.26 \pm 0.89^{a}$			
Control group ( $n = 30$ )	$10.54 \pm 2.99$	$15.20 \pm 1.66^{a}$	$16.92 \pm 2.75$	$12.36 \pm 1.17^{a}$			
<i>t</i> value	0.570	13.412	0.616	15.308			
<i>P</i> value	0.571	< 0.001	0.540	< 0.001			

 $^{a}P < 0.05$ , compared to the same group before treatment.

Ach: Acetylcholine; AChE: Acetylcholinesterase.

### RESULTS

### Comparison of MMSE, MoCA, and ADL scores between the two groups

There were no statistically significant differences between the groups in the pretreatment MMSE, MoCA, or ADL scores (P > 0.05). The treatment group showed statistically significant (P < 0.05) improvements in the MMSE, MoCA, and ADL scores after treatment compared to the control group, as shown in Table 1 and Figure 1A.

### Comparison of neurotransmitter levels between the two groups

There were no statistically significant differences in the pretreatment ACh or AChE level between the two groups. In both groups, the ACh level increased after therapy, while the AChE level decreased (P < 0.05). There were statistically significant (P < 0.05) improvements in all indices in the experimental group that were not present in the control group, as shown in Table 2 and Figure 1B.

### Comparison of vascular endothelial function markers between the two groups

There was no significant change in the ET-1 or NO level between the two groups before treatment (P > 0.05). After therapy, the ET-1 level in both groups decreased, and the NO level increased. The study group showed significantly (P < 0.05) greater improvement than the control group in all areas, as shown in Table 3 and Figure 1C.

### Evaluation of serum levels of β2-MG, VILIP-1, and GFAP between the two groups

There were no significant variations in the  $\beta$ 2-MG, VILIP-1, or GFAP levels between the two groups prior to therapy (*P* > 0.05). After treatment, the  $\beta$ 2-MG, VILIP-1, and GFAP levels decreased in both groups, with significantly lower levels in the study group (*P* < 0.05), as shown in Table 4 and Figure 1D.

### Comparison of PI values of the cerebral vasculature between the two groups

The PI values of the LACA, RACA, LMCA, RMCA, LPCA, and RPCA were not significantly different between the two groups before treatment (P > 0.05). As expected, therapy resulted in a reduction of pretreatment PI values in all examined vessels (LACA, RACA, LMCA, RMCA, LPCA, and RPCA) in both groups, with the study group showing significantly (P < 0.05) lower PI levels than the control group, as presented in Table 5 and Figure 1E.





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Table 3 Comparison of vascular endothelial function markers between the two groups (mean ± SD, d)									
Group	ET-1 (μg/L)		NO (μmol/L)						
Group	Before treatment	After treatment	Before treatment	After treatment					
Study group ( $n = 30$ )	79.02 ± 5.77	$71.29 \pm 4.90^{a}$	$60.81 \pm 6.13$	$71.19 \pm 7.08^{a}$					
Control group ( $n = 30$ )	79.32 ± 6.70	$65.40 \pm 5.45^{a}$	$60.19 \pm 4.40$	$65.45 \pm 4.64^{a}$					
<i>P</i> value	0.854	< 0.001	0.655	0.001					
<i>t</i> value	0.185	4.400	0.450	3.709					

 $^{\mathrm{a}}P$  < 0.05, compared to the same group before treatment.

NO: Nitric oxide; ET-1: Endothelin-1.

# Table 4 Comparison of serum $\beta$ 2-microglobulin, glial fibrillary acidic protein, and visinin-like protein 1 concentrations between the two groups (mean ± SD)

Group	B2-MG (mg/L)		VILIP-1 (ng/L)		GFAP (mg/L)		
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	
Study group ( $n = 30$ )	$2.64 \pm 0.65$	$1.49 \pm 0.48^{a}$	520.59 ± 55.39	$409.67 \pm 40.77^{a}$	$9.17 \pm 1.32$	$6.04 \pm 1.70^{a}$	
Control group ( $n = 30$ )	$2.79 \pm 0.42$	$1.93 \pm 0.28^{a}$	$531.47 \pm 54.03$	435.83 ± 37.09 <sup>a</sup>	$9.87 \pm 1.56$	$7.44 \pm 1.06^{a}$	
<i>P</i> value	0.294	< 0.001	0.444	0.012	0.064	< 0.001	
<i>t</i> value	1.061	4.339	0.771	2.599	1.888	3.817	

 $^{a}P < 0.05$  compared to the same group before treatment.

β2-MG: β2-microglobulin; GFAP: Glial fibrillary acidic protein; VILIP-1: Visinin-like protein 1.

### Analyzing the difference in RI values of the cerebral vessels between the two groups

The RI values of the LACA, RACA, LMCA, RMCA, LPCA, and RPCA were similar in the two groups before treatment (P > 0.05). Treatment resulted in a substantial (P < 0.05) reduction in the RI values of the LACA, RACA, LMCA, RMCA, LPCA, and RPCA in both groups, as shown in Table 6 and Figure 1F.

### DISCUSSION

The degree of cognitive impairment in stroke patients is strongly correlated with their prognosis, and elderly individuals are especially prone to cognitive impairment as a sequela of cerebral infarction. Therefore, it is crucial to find efficient ways to reduce stroke patients' cognitive impairment. According to relevant studies, atorvastatin serves antioxidant and antithrombotic functions and protects vascular endothelial function. It can play a direct role in protecting nerves, reducing the abundance of macrophages in atherosclerotic plaques, enhancing the integrity of fibrous plaque caps, inhibiting vascular inflammation, protecting the vascular endothelium, and inhibiting cognitive impairment after a stroke caused by vascular factors. EECP is a safe and cost-effective treatment that is mainly suitable for the treatment of coronary heart disease and angina pectoris. Numerous investigations conducted recently have demonstrated that EECP significantly affects ischemic cerebrovascular disorders and heart failure[13,14]. According to a prior study, EECP can reduce the clinical symptoms of coronary artery disease by enhancing vascular endothelial function[15]. EECP is an important means of cardiovascular auxiliary circulation that can simultaneously increase the arterial and venous return of both lower limbs and improve coronary blood flow. Patients' diastolic blood pressure and cardiac output as well as blood perfusion to the heart, brain, kidneys, and other organs can all be improved by wrapping balloon sleeves around the thighs, calves, and buttocks and then inflating and deflating the balloons using an air supply system. EECP has been shown to enhance arterial blood flow, increase blood perfusion in brain tissue, improve brain cell metabolism, and facilitate neurological function recovery[16]. Numerous clinical trials have demonstrated that EECP is able to successfully increase blood flow to ischemic areas, restore nerve cell activity, and facilitate the opening of collateral circulation in the ischemic penumbra[17,18].

This research compared the effects of EECP combined with atorvastatin to those of atorvastatin alone between two groups. The results indicated that after therapy, the MMSE, MoCA, and ADL scores in the study group improved more than those in the control group (P < 0.05). These findings demonstrate that the combined application of EECP and atorvastatin might be more effective than atorvastatin alone in enhancing patients' cognitive function and daily living abilities and that such enhancements could serve as direct indicators of the efficacy of therapy. The endothelium lining

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Table 5 Comparison of pulsatility index values of cerebral vessels between the two groups (mean ± SD)												
Group	LACA		RACA		LMCA		RMCA		LPCA		RPCA	
	Before treatment	After treatment										
Study group (n = 30)	1.34 ± 0.28	0.94 ± 0.11 <sup>a</sup>	1.33 ± 0.22	0.97 ± 0.12 <sup>a</sup>	1.35 ± 0.26	0.95 ± 0.16 <sup>a</sup>	1.34 ± 0.24	0.94 ± 0.19 <sup>a</sup>	1.37 ± 0.28	0.93 ± 0.18 <sup>a</sup>	$1.34 \pm 0.32$	0.98 ± 0.15 <sup>a</sup>
Control group $(n = 30)$	1.35 ± 0.27	1.11 ± 0.42 <sup>a</sup>	1.37 ± 0.27	1.12 ± 0.36 <sup>a</sup>	1.39 ± 0.22	1.10 ± 0.31 <sup>a</sup>	1.35 ± 0.37	1.12 ± 0.34 <sup>a</sup>	$1.36 \pm 0.40$	1.11 ± 0.30 <sup>a</sup>	$1.35 \pm 0.41$	1.12 ± 0.35 <sup>a</sup>
P value	0.832	0.040	0.536	0.049	0.490	0.024	0.905	0.013	0.857	0.007	0.983	0.047
t value	0.213	2.139	0.622	2.043	0.695	2.339	0.120	2.589	0.180	2.805	0.021	2.052

 $^{a}P < 0.05$  compared to the same group before treatment.

LACA: Left-anterior cerebral artery; RACA: Right-anterior cerebral artery; LMCA: Left-middle cerebral artery; RMCA: Right-middle cerebral artery; LPCA: Left-posterior cerebral artery; RPCA: Right-posterior cerebral artery.

Table 6 Comparison of the resistance index values of the cerebral vessels in the two groups (mean ± SD)												
Group	LACA R		RACA		LMCA		RMCA		LPCA		RPCA	
	Before treatment	After treatment										
Study group (n = 30)	0.86 ± 0.18	0.54 ± 0.10 <sup>a</sup>	0.86 ± 0.22	0.53 ± 0.13 <sup>a</sup>	0.85 ± 0.25	0.53 ± 0.16 <sup>a</sup>	0.95 ± 0.28	0.48 ± 0.13 <sup>a</sup>	0.84 ± 0.28	0.49 ± 0.11 <sup>a</sup>	0.93 ± 0.25	0.53 ± 0.13 <sup>a</sup>
Control group ( <i>n</i> = 30)	0.93 ± 0.23	0.64 ± 0.11 <sup>a</sup>	$0.84 \pm 0.15$	0.64 ± 0.15 <sup>a</sup>	0.82 ± 0.22	0.65 ± 0.21 <sup>a</sup>	0.92 ± 0.21	0.62 ± 0.24 <sup>a</sup>	0.86 ± 0.20	0.58 ± 0.14 <sup>a</sup>	0.90 ± 0.18	0.63 ± 0.15 <sup>a</sup>
P value	0.225	0.001	0.729	0.004	0.720	0.014	0.582	0.007	0.701	0.006	0.566	0.008
t value	1.226	3.661	0.349	3.033	0.360	2.547	0.553	2.847	0.386	2.864	0.578	2.750

 $^{\mathrm{a}}P < 0.05$  compared to the same group before treatment.

LACA: Left-anterior cerebral artery; RACA: Right-anterior cerebral artery; LMCA: Left-middle cerebral artery; RMCA: Right-middle cerebral artery; LPCA: Left-posterior cerebral artery; RPCA: Right-posterior cerebral artery.

the blood vessels is vulnerable to oxidative damage, which can be caused by atherosclerosis. Atorvastatin is a commonly used lipid-lowering drug that stabilizes atherosclerotic plaques. EECP can play a role in increasing cerebral blood flow and perfusion and improving neural function, such that the combined application of these two treatments is more effective. Previous studies have also shown that EECP combined with conventional drugs can be used to treat poststroke cognitive impairment more effectively than the same drugs alone [19]. Learning and memory are two physiological processes that benefit greatly from the functioning of the central cholinergic system. AChE catalyzes the decomposition reaction that produces ACh, which binds to ACh receptors. Degeneration of cholinergic neurons is common in patients with cognitive impairment after stroke[20]. ACh can participate in neuronal activity and regulate synaptic plasticity. In this investigation, the improvement in ACh and AChE levels following therapy was larger in the study group than in the control group (P < 0.05). The treatment of cognitive impairment following a stroke, which may be connected to the management of AChE and ACh levels, is said to benefit significantly from the combination of EECP and atorvastatin. The vascular endothelium serves both barrier and endocrine functions. Dysfunction of vascular endothelial cells can lead to damage to the blood-brain barrier, causing toxic substances to accumulate around nerve cells; triggering inflammatory reactions; damaging brain white matter, neuronal axons and synapses; and leading to cognitive impairment. Vascular endothelial damage, atherosclerosis, brain tissue damage, increased ET-1 expression, and decreased NO expression result in spasms of small cerebral vessels and damage to the nerve fiber network. It has been reported that the serum ET-1 and NO levels in patients with dementia are closely related to endothelial dysfunction of small cerebral vessels and can be used as a marker of endothelial dysfunction[21]. Patients with cognitive impairment following stroke showed significant improvement in ET-1 and NO levels in the treatment group compared to the control group, suggesting that combination therapy can increase the degree of vascular endothelial function more effectively than pharmacotherapy alone. Atorvastatin's lipid-lowering action, ability to mitigate atherosclerosis and protective effect on vascular endothelial function are all well documented. EECP has been shown to ameliorate cognitive impairment by normalizing systolic and diastolic vascular function, controlling vascular tension, and boosting endothelial function in blood vessels. Thus, when applied in combination, they could play synergistic roles, resulting in an enhanced therapeutic effect.

All nucleated cells contain  $\beta$ 2-MG, which might increase the risk of an inflammatory response and subsequent brain injury. With a negative effect on cognition,  $\beta$ 2-MG has been linked to a host of serious health problems[22]. According to relevant studies, serum  $\beta$ 2-MG levels are high in patients with cognitive impairment after stroke[23]. It has been shown that the expression level of VILIP-1, a small-molecule cytosolic protein typically dispersed in nerve cells, is positively linked with the presence of brain damage[24]. Serum levels of GFAP, an intermediate filament protein found in glial cells, are significantly elevated in those who have had a stroke and are experiencing cognitive impairment<sup>[25]</sup>. The fact that the levels of β2-MG, VILIP-1, and GFAP improved more in the study group than in the control group suggests that the combination therapy may promote the healing of damaged brain tissue in patients, which merits additional investigation into the specific mechanism of action. Patients with poststroke cognitive impairment who received combination therapy showed greater improvements in the PI and RI values of the LACA, RACA, LMCA, RMCA, LPCA, and RPCA than those who received atorvastatin therapy alone. This is because of the synergistic impact of atorvastatin's lipid-lowering and antithrombotic effects and the capacity of EECP to increase cerebral blood flow perfusion.

### CONCLUSION

In conclusion, EECP combined with atorvastatin can effectively improve cognitive function, daily living ability, vascular endothelial function, neural function, and cerebral blood flow in patients with poststroke cognitive dysfunction, indicating the clinical value of this combination. A limitation of this study is that it was a retrospective study, and the number of cases that could be included in the observation was small, which may have led to bias in the results. In the future, a prospective multicenter study with a larger sample should be conducted to further verify the results of this study.

### ARTICLE HIGHLIGHTS

### Research background

The research background is the discussion on the treatment of patients with cognitive dysfunction after stroke. The current research status is that atorvastatin is widely used to treat cognitive impairment after stroke, and the research significance is to provide a new treatment plan for cognitive impairment after stroke and improve clinical efficacy.

### Research motivation

With the treatment of stroke patients with cognitive dysfunction as the research topic, more effective treatment plans need to be explored to improve the prognosis of stroke patients with cognitive dysfunction. The significance of this study is to affirm the better treatment of cerebral stroke patients with cognitive dysfunction, and promote the innovation of clinical treatment of cerebral stroke cognitive endometrial methods.

### Research objectives

The objective of this study was to compare the therapeutic effect of different treatment methods and to observe the advantages of enhanced external counterpulsation (EECP) combined with atorvastatin over atorvastatin alone. In this study, enhanced in vitro rebuttal combined with atorvastatin was effective in the treatment of cognitive dysfunction in stroke patients, including cognitive function, ability of daily living, vascular endothelial function, nerve function and cerebral blood flow, confirming that the combined treatment has good clinical effects and providing a new reference for the treatment of cognitive dysfunction in stroke patients in the future.

### Research methods

The clinical data of the patients were analyzed retrospectively and grouped according to different treatment methods. Then, independent sample *t* test, paired sample *t* test and  $\chi^2$  test were used to statistically analyze the general data of the two groups, including mental state, cognitive function, daily living ability score, neurotransmitter level, vascular endothelial function index level, cognitive-related index and cerebral blood flow index before and after treatment. The feature of retrospective study is to explore the cause through the results, and it is easier to obtain the case data.

### Research results

EECP combined with atorvastatin can significantly improve cognitive function, mental state, ability of daily living, vascular endothelial function, nerve function and cerebral blood flow in the treatment of stroke patients with cognitive dysfunction, which provides a new treatment method for the treatment of stroke patients with cognitive dysfunction and requires further prospective exploration. To further verify the effectiveness of this treatment method.

### **Research conclusions**

Vascular endothelial dysfunction can lead to impairment of the blood-brain barrier, leading to cognitive dysfunction. Therefore, attention should be paid to the effect of treatment on vascular endothelial function. Based on the better treatment effect of EECP combined with atorvastatin, the more effective treatment scheme should be selected in clinic.



### Research perspectives

Biological indicators can effectively reflect the severity of the patient's disease, and the effect of treatment regimen on the level of novel biomarkers in patients with post-stroke cognitive dysfunction needs to be further explored.

### FOOTNOTES

Author contributions: Duan Y initiated the project, designed the experiment and conducted clinical data collection; Tang HX performed postoperative follow-up and recorded data, conducted a number of collation and statistical analysis, and wrote the original manuscript; both authors reviewed and approved the paper; and all authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

## **Retrospective Study** Value of Chuanjin Qinggan decoction in improving the depressive state of patients with herpes zoster combined with depression

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### Abstract

### BACKGROUND

Western medicine is beneficial for the recovery of neurological function in patients with depression, but some patients experience side effects such as headaches, dizziness, nausea, gastrointestinal symptoms, insomnia, and cardiac dysfunction. In recent years, integrative medicine has achieved positive results in the treatment of various diseases.

### AIM

To study Chuanjin Qinggan decoction combined with selective serotonin reuptake inhibitors (SSRIs) in patients with herpes zoster complicated by depression.

### METHODS

Patients with herpes zoster complicated by depression who were treated at the Yantai Hospital of Traditional Chinese Medicine from January 2021 to December 2022 were retrospectively selected as research participants. Among them, 43 patients with herpes zoster complicated by depression who received SSRI treatment between January and December 2021 were assigned to the Western medicine group, while those who received combined treatment of traditional Chinese and Western medicine between January and December 2022 were assigned to the combined group. Both groups were treated for eight weeks. The degree of pain, effect of herpes zoster treatment, degree of improvement in depressive symptoms, serum neurotransmitter levels, sleep quality, and occurrence of adverse reactions were compared between the two groups.

### RESULTS

We found that after eight weeks of drug treatment, the two treatment schemes achieved differing efficacy. In further comparison, we found that, compared with



patients treated with SSRIs alone, patients treated with Chuanjin Qinggan decoction combined with SSRIs showed more significant improvement in depression and a greater increase in dopamine and 5-hydroxytryptamine levels after treatment (P < 0.05). Patients treated with Chuanjin Qinggan decoction combined with SSRIs also experienced lower pain, better treatment efficacy for herpes zoster, better sleep quality, and a lower incidence of adverse reactions compared to those treated with SSRIs alone (P < 0.05). All minor adverse reactions occurring during treatment were resolved after symptomatic treatment.

#### CONCLUSION

The treatment scheme of Chuanjin Qinggan decoction combined with SSRIs can improve the psychological state of patients with herpes zoster complicated by depression and alleviate adverse reactions.

Key Words: Chuanjin Qinggan decoction; Selective 5-hydroxytryptamine reuptake inhibitor; Herpes zoster; Depression; Sleep quality; Adverse reaction

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Core Tip: Chuanjin Qinggan decoction is an important decoction composed mainly of Ligusticum chuanxiong Hort, Curcuma, and Sedum rosea. There is a synergistic effect between the active ingredients in Chuanjin Qinggan decoction which helps to reduce neurological damage and improve the depressive state of patients by providing raw materials and energy for protein and nucleic acid synthesis in brain tissue. This study confirmed that the treatment scheme of Chuanjin Qinggan decoction combined with selective serotonin reuptake inhibitors can effectively improve the depressive state of patients with herpes zoster complicated by depression.

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### INTRODUCTION

Herpes zoster is an acute herpetic skin disease characterized by clusters of blisters on the skin and burning pain[1]. It is characterized by the sudden occurrence of these blisters arranged in a ribbon along one side of the peripheral nerve distribution area, accompanied by tingling and lymphadenopathy[2]. Herpes zoster usually occurs in spring or autumn, and older adults constitute the majority of the affected population[3]. Most patients with herpes zoster do not experience recurrence after illness, although recurrence sometimes occurs[4]. Herpes zoster can cause burning, knife-cutting, or electric shock-like pain, with erythema and blisters on the skin's surface. It affects a patient's appearance and can cause physical and mental harm. If patients with herpes zoster do not receive effective treatment for an extended period, they may experience different degrees of depressive symptoms as the pain progresses.

Recent studies suggest that secondary depression in patients with herpes zoster is related to postherpetic neuralgia (PHN)[5,6]. PHN is an intractable neuropathic pain syndrome secondary to herpes zoster that causes the irreversible destruction of nerve fibers. When PHN destroys the neural pathways regulating emotion, it leads to the dysfunction of monoamine neurotransmitters. If the lesion site involves the thalamus, basal ganglia, amygdala, frontal lobe, hippocampus, or interconnected fibers, it can damage serotonergic neurons and reduce the level of 5-hydroxytryptamine (5-HT), eventually leading to depression[7]. The World Health Organization estimates that by 2030, depression may rank first in the global burden of disease[8]. Herpes zoster combined with depression brings a great psychological burden to patients and may reduce their medication compliance and rehabilitation process.

Selective 5-hydroxytryptamine reuptake inhibitors (SSRIs) are safe and can effectively regulate the concentration of monoamine transmitters in the body and reduce depression-like symptoms. They are the first-line antidepressants recommended by various guidelines. A previous study showed that SSRIs are beneficial for the recovery of neurological function in patients with depression[9]. However, some patients experience side effects such as headaches, dizziness, nausea, gastrointestinal symptoms, insomnia, and cardiac dysfunction. SSRIs have also been shown to affect the cardiac and cerebral vessels of patients<sup>[10]</sup>. Compared to patients with depression alone, patients with herpes zoster combined with depression are more likely to have aggravated depressive symptoms due to physiological pain. Therefore, there is an urgent need to develop a treatment plan that can relieve physiological pain and improve the psychological state of patients with herpes zoster and depression.

According to traditional Chinese medicine, depressive symptoms are mainly related to the dysfunction of the five internal organs and poor emotions. The depressive symptoms of patients with herpes zoster include depression, chest and flank fullness, and irritability caused by physiological and psychological pressure. Chuanjin Qinggan decoction promotes Qi, relieves depression, maintains the liver, clears heat, and detoxifies. However, the specific efficacy of Chuanjin Qinggan decoction combined with SSRIs in treating herpes zoster complicated by depression remains unclear.



In recent years, integrative medicine has achieved positive results in the treatment of various diseases. Since 2022, our hospital has actively attempted integrated traditional Chinese and Western medicine therapy for patients with herpes zoster complicated by depression, achieving good results. This study aims to explore the effect of Chuanjin Qinggan decoction combined with SSRIs in patients with herpes zoster complicated by depression.

### MATERIALS AND METHODS

#### Patients

Patients with herpes zoster complicated by depression who were treated at the Yantai Hospital of Traditional Chinese Medicine between January 2021 and December 2022 were retrospectively selected as research participants. Inclusion criteria were as follows: (1) Meeting the relevant diagnostic criteria for herpes zoster[11]; (2) Hamilton Depression Scale (HAMD) score > 8[12]; (3) age ranging from 30 to 75 years; (4) complete clinical data required for this study; and (5) no history of depression before from the onset of herpes zoster. The exclusion criteria were as follows: (1) Patients with organic mental disorders; (2) patients with significant organ dysfunction; (3) patients with congenital cognitive dysfunction; (4) patients with less than one course of treatment; and (5) patients with allergies to the drugs used in this study.

#### Grouping and treatment

Eighty-six patients were finally included in the study, and all patients were treated with the same method: acyclovir tablets (specification: 0.1 g/tablet), 0.4 g each time, five times a day; acyclovir cream applied externally, once every two hours, 4-6 times a day. The treatment lasted for two weeks. According to the treatment plan for depression, the patients were divided into Western medicine and combination groups.

Western medicine group: Patients with herpes zoster complicated by depression who received SSRIs between January and December 2021 were included in the Western medicine group. SSRIs include fluoxetine, sertraline, paroxetine, citalopram, escitalopram, and fluvoxamine. The following SSRIs and dosages were used by the patients in this study: The starting dose of sertraline tablets (specification: 50 mg/tablet) was 50 mg/d, administered after breakfast. Clinicians can adjust the drug dose within 7-14 d according to the actual condition of the patient, and the adjustment range is 50-150 mg/d. The starting dose of the enteric-coated paroxetine tablets (20 mg/tablet) was 20 mg/d, taken after breakfast. Clinicians can adjust the drug dose within 7-14 d according to the actual condition of the patient, and the adjustment range is 20-60 mg/d. The starting dose of escitalopram tablets (20 mg/tablet) was 10 mg/d, taken after breakfast. Clinicians can adjust the drug dose within 7-14 d according to the actual condition of the patient, and the adjustment range is 10-20 mg/d. The total treatment duration was eight weeks.

The combination group included patients with herpes zoster complicated by depression who received combined treatment of traditional Chinese and Western medicines between January and December 2022. The Western medicine treatment method was the same as that used in the Western medicine group. The traditional Chinese medicine treatment was Chuanjin Qinggan decoction: Ligusticum chuanxiong Hort (10 g), Curcuma (10 g), Rhodiola (15 g), Bupleurum (12 g), Gardenia (10 g), Paeonia alba (12 g), Rehmannia glutinosa (20 g), Peony bark (10 g), Poria cocos (20 g), Alisma orientalis (10 g), Acanthopanax senticosus (15 g), Schisandra (15 g), Albizzia julibrissin bark (15 g), Glycyrrhiza uralensis (6 g), and Forsythia suspensa (10 g). They were added or removed according to the patient's condition and decocted in 500 mL of water. This was administered once in the morning and evening for 14 d as a course of treatment for four consecutive courses (eight weeks).

#### Outcome measures

Patient depression before and after treatment was the primary outcome measure. The HAMD scale was used to evaluate the depression status of patients one week before treatment, four weeks after treatment, and eight weeks after treatment. The HAMD scale used in this study has 17 items, of which a score  $\leq$  7 points indicates normal; the higher the score, the more severe the participant's depression.

The secondary outcome measures were as follows. (1) Patients' pain before and after treatment: The visual analog scale (VAS)[13] was used to evaluate the degree of pain in patients one week before and at the end of treatment. The VAS scores range from 0 to 10, with 0 indicating no pain and 10 indicating severe pain; (2) The effectiveness of herpes zoster treatment: remarkable effect: more than 70% of the rash disappeared, and the pain symptoms were alleviated; effective: 30%-70% of the rash disappeared, and the pain symptoms were alleviated; ineffective: less than 30% of the rash disappeared, and the pain did not change or worsened; (3) Neurotransmitter levels: The serum levels of dopamine (DA) and 5-HT were monitored before and after treatment; (4) Sleep quality: The Pittsburgh Sleep Quality Index (PSQI)[14] was used to evaluate sleep quality. The PSQI scale was compiled by psychiatrists and scholars at the University of Pittsburgh with seven factors derived from clinical practice; each factor had a score range of 0 to 3 points. The final PSQI score was the sum of the seven factor scores. The scale's total score was 21 points; the higher the total score, the worse the sleep quality; and (5) Patients' adverse reactions during treatment were recorded, including headache, blurred vision, nausea, vomiting, and cognitive dysfunction.

### Statistical analysis

SPSS 26.0 and GraphPad 9.0 were used for statistical analysis. The statistical data were expressed by frequency and percentage, and the  $\chi^2$  test was used for comparison between groups (the rank sum test was used for the count data with hierarchical characteristics). The measurement data that conform to and do not conform to the normal distribution are



expressed by the mean (standard deviation) and median (P25, p75), respectively. The data that conformed used a *t*-test and repeated-measures analysis of variance for comparison between groups, and the data that did not conform used the Mann-Whitney *U* test. Statistical significance was set at P < 0.05.

### RESULTS

### Clinical characteristics of study participants

To ensure the comparability of different drug treatment results, the baseline data of the two groups of patients were compared. After comparison, the statistical analysis showed no significant differences in the baseline data of the two groups of patients receiving different drugs, such as sex, age, duration of herpes zoster, residence, and years of education (P > 0.05) (Table 1).

### Comparison of the degree of pain

As shown in Table 2, after eight weeks of treatment, the overall VAS scores of the two groups decreased compared to those before treatment, and the VAS scores of patients treated with Chuanjin Qinggan decoction combined with SSRIs decreased more significantly (P < 0.05).

### Comparison of the therapeutic effectiveness against herpes zoster

In the comparison of the therapeutic effects of the two treatment groups against herpes zoster, it was found that the effect observed in patients treated with Chuanjin Qinggan decoction combined with SSRIs was higher than that in patients treated with SSRIs alone, the ineffective rate was lower than that in patients treated with SSRIs alone, and there was a significant difference in the overall efficacy between the two groups (P < 0.05) (Table 3).

### The changing trend of patients' depression

As shown in Figure 1, after eight weeks of treatment, the overall HAMD score of patients in both groups decreased compared to that before treatment, and the decrease in HAMD score of patients treated with Chuanjin Qinggan decoction combined with SSRIs was more significant (P < 0.05).

### Effects of different treatment schemes on neurotransmitter levels in patients

Both treatment regimens improved the serum DA and 5-HT levels of patients, and patients treated with Chuanjin Qinggan decoction combined with SSRIs showed a greater increase in DA and 5-HT levels (both P < 0.05) (Figure 2).

### Effect of different treatment schemes on sleep quality of patients

Both treatment regimens reduced the PSQI score of patients, and the decrease in the PSQI score of patients treated with Chuanjin Qinggan decoction combined with SSRIs was more significant (P < 0.05) (Figure 3).

### Occurrence of adverse reactions

Neither treatment method had adverse effects on cognitive function. A few patients experienced minor adverse reactions such as headaches, blurred vision, nausea, and vomiting, which were alleviated after symptomatic intervention. The overall incidence of adverse reactions in patients treated with Chuanjin Qinggan decoction combined with SSRIs was lower than that in patients treated with SSRIs alone (P < 0.05) (Table 4).

### DISCUSSION

In addition to the core symptoms of depression such as low mood, reduced willpower, and reduced interest, patients with depression also have a severe inferiority complex accompanied by varying degrees of memory loss, sluggish thinking, irritability, and refusal to eat[15]. If the psychological state of a patient with depression cannot be improved for an extended period, the development of severe depression may lead to self-mutilation or even suicide. In recent years, with the development of social psychology, people have begun to pursue comprehensive physical and mental health. Given the negative effects of depression on patients' physiology and psychology, the treatment of depressive symptoms in patients with herpes zoster combined with depression is necessary to improve their well-being. Simultaneously, the treatment of depressive symptoms in patients with herpes zoster and depression can also reduce the burden on their families and society. Therefore, society and most medical workers attach great importance to the treatment of depressive symptoms in patients with herpes zoster combined with depression.

To understand the therapeutic effects of different treatment schemes in patients with herpes zoster complicated by depression, the clinical data of 86 patients were retrospectively analyzed. The results showed that although both treatment regimens could achieve efficacy, patients treated with Chuanjin Qinggan decoction combined with SSRIs showed more significant improvement in depression and a greater increase in DA and 5-HT levels after treatment compared to those treated with SSRIs alone. SSRIs exert antidepressant effects by inhibiting the resorption of 5-HT by the presynaptic membrane, and their efficacy in treating depression has been confirmed. The depressive symptoms of patients treated with SSRIs in this study also improved, similar to the results of previous studies. Findling *et al*[16]

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Table 1 Clinical characteristics of study subjects [n (%)], M (P25, P75)				
Clinical characteristics	Western medicine ( <i>n</i> = 43)	Combination (n = 43)	χ²/t	P value
Sex			0.427	0.514
Man	26 (60.50)	23 (53.50)		
Woman	17 (39.50)	20 (46.50)		
Age (yr)	$58.53 \pm 5.16$	$59.12 \pm 5.04$	-0.528	0.599
Herpes zoster disease course (d)	5.00 (4.00, 6.00)	5.00 (4.00, 6.00)	-0.317	0.751
Residence			0.187	0.665
Town	19 (44.20)	21 (48.80)		
City	24 (55.80)	22 (51.20)		
Years of education			0.466	0.792
< 9	8 (18.60)	10 (23.30)		
9-12	24 (55.80)	21 (48.80)		
> 12	11 (25.60)	12 (27.90)		

Table 2 The pain scores between the two groups, M (P <sub>25</sub> , P <sub>75</sub> )					
Group	Pre-treatment	Post-treatment	Z	P value	
Western medicine ( $n = 43$ )	7.00 (6.00, 8.00)	4.00 (4.00, 5.00)	-6.801	< 0.001	
Combination $(n = 43)$	7.00 (6.00, 8.00)	4.00 (3.00, 4.00)	-7.960	< 0.001	
Ζ	-0.448	-3.825			
<i>P</i> value	0.654	< 0.001			

Table 3 Effectiveness of herpes zoster treatment, n (%)			
Group	Remarkable effect	Effective	Ineffective
Western medicine ( $n = 43$ )	11 (25.58)	22 (51.16)	10 (23.26)
Combination ( $n = 43$ )	19 (44.19)	18 (41.86)	6 (13.95)
Ζ	-2.144		
P value	0.032		

Table 4 Comparison of adverse reactions produced by different treatment regimens, n (%)						
Group	Headache	Blurred vision	Nausea	Emesis	Others	Total
Western medicine $(n = 43)$	5 (11.63)	2 (4.65)	6 (13.95)	3 (6.98)	3 (6.98)	17 (39.53)
Combination $(n = 43)$	2 (4.65)	1 (2.33)	4 (9.30)	1 (2.33)	3 (6.98)	8 (18.60)
χ <sup>2</sup>						4.568
<i>P</i> value						0.033

reported that SSRIs can achieve good efficacy in the treatment of depression in adolescents and adults. Fagiolini *et al*[17] also reported that SSRIs could improve depressive symptoms in patients with severe depression. DA is the most abundant catecholamine neurotransmitter in the brain (accounting for approximately 80% of the total). It controls various functions, such as motor activity, cognition, emotion, food intake, and endocrine regulation. Diseases such as Parkinson's disease, schizophrenia, and addictive behavior are all related to dopaminergic system dysfunction[18,19]. Abnormal function of the serotonin system is closely related to loss of appetite, sleep disorders, decreased activity, sexual dysfunction, endocrine dysfunction, depression, and anxiety[20]. Chuanjin Qinggan decoction is mainly composed of Ligusticum chuanxiong Hort, Curcuma, Sedum rosea, and other drugs, among which Ligusticum chuanxiong Hort has

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Wang YN et al. Efficacy of Chuanjin Qinggan decoction



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Figure 1 Depressive state of both groups of patients at different times. HAMD: Hamilton Depression Scale.



**Figure 2 Effects of different treatment regimens on neurotransmitter levels of patients.** A: Dopamine level; B: 5-hydroxytryptamine level. <sup>d</sup>*P* < 0.0001. 5-HT: 5-hydroxytryptamine.



Figure 3 Effect of different treatment schemes on the sleep quality of patients. <sup>d</sup>P < 0.0001. PSQI: Pittsburgh Sleep Quality Index.

antioxidant, anticoagulant, anti-tumor, anti-inflammatory, analgesic, microcirculation improvement, anti-aging, antidepressant, anti-radiation, and other effects[21]. Curcuma can regulate neurotransmitters, regulate neuroendocrine function, protect neurons, and inhibit neuroinflammation[22]. Salidroside, an effective component of Sedum rosea, has anti-fatigue, antidepressant, immune-enhancing, and anti-tumor properties[23]. There is a synergistic effect between the active ingredients in Chuanjin Qinggan decoction which helps to improve the depressive state of patients by reducing neurological damage and providing raw materials and energy for protein and nucleic acid synthesis in the brain tissue.

In addition, this study also found that patients treated with Chuanjin Qinggan decoction combined with SSRIs experienced less pain, better treatment efficacy for herpes zoster, better sleep quality, and a lower incidence of adverse reactions compared to those treated with SSRIs alone. These results suggest that the treatment scheme of Chuanjin Qinggan decoction combined with SSRIs can not only significantly improve the depressive state of patients but also improve the treatment of herpes zoster. Chronic pain is an adverse subjective and emotional experience with attributes in multiple dimensions, including sensory recognition, emotional motivation, and cognitive evaluation. Chronic pain increases the psychological burden on patients and causes negative emotions such as disgust, anxiety, and depression. The physical and mental suffering of patients with herpes zoster and depression is severe. Psychological state has a reverse regulatory effect on physiological state, and a good psychological state can improve the effect of treatment for physiological diseases. Shahimi et al[24] pointed out in their study that a good psychological state can reduce the risk of falls in older adults and the risk of cardiovascular and cerebrovascular diseases. In this study, the two groups of patients received eight weeks of drug treatment, and the symptoms of herpes zoster and depression significantly improved. However, this study has certain limitations. Specifically, the sample size of this study is small and it comes from a single research center, which may result in selection bias. Further studies with larger samples or joint studies with other centers are needed to confirm the reliability of the results.

## CONCLUSION

This study retrospectively analyzed the clinical data of patients with herpes zoster complicated by depression and found that different treatment schemes had different therapeutic outcomes. Patients treated with Chuanjin Qinggan decoction combined with SSRIs experienced less pain, better treatment efficacy for herpes zoster, more significant improvement in depression, a greater increase in DA and 5-HT levels, better sleep quality, and a lower incidence of adverse reactions compared to those treated with SSRIs alone. The overall curative effect of the Chuanjin Qinggan decoction combined with SSRIs was better than treatment with SSRIs alone.

## **ARTICLE HIGHLIGHTS**

#### Research background

The physical and mental suffering of patients with herpes zoster combined with depression is significant. Although traditional Western medicine can alleviate the depressive symptoms in patients to a certain extent, it also causes many adverse reactions. There remains a need to identify drugs with high clinical safety that can effectively improve the depressive symptoms in patients with herpes zoster combined with depression.

#### Research motivation

To search for safe drugs that can effectively improve the depressive symptoms of patients with herpes zoster combined with depression, and to provide references for the formulation and modification of the treatment plan for herpes zoster combined with depression.

#### Research objectives

We analyzed the value of Chuanjin Qinggan decoction combined with a serotonin- selective reuptake inhibitor in the treatment of patients with herpes zoster complicated by depression.

#### Research methods

We retrospectively analyzed depression status, treatment effect, degree of pain, neurotransmitter levels, sleep quality, and adverse reactions in patients with herpes zoster complicated by depression who received different treatment schemes.

#### Research results

Compared with patients treated with selective serotonin reuptake inhibitor (SSRIs) alone, patients treated with Chuanjin Qinggan decoction combined with SSRIs showed a greater improvement in depression after treatment, and the incidence of adverse reactions was lower.

#### Research conclusions

The treatment scheme of the Chuanjin Qinggan decoction combined with SSRIs can improve the depressive state of patients with herpes zoster complicated by depression, and improve the effect of treatment for herpes zoster without increasing the risk of adverse reactions.

#### Research perspectives

In the future, the specific mechanism of Chuanjin Qinggan decoction in the treatment of herpes zoster complicated by depression should be clarified through cell or animal experiments, to provide references for further improving the therapeutic effect.



## FOOTNOTES

Co-first authors: Yi-Nan Wang and Meng-Meng Shi.

Author contributions: This paper was written by Wang YN, Shi MM, and Zhang JM; Wang YN led the writing of the article; Zhang JM proofread all drafts; and Shi MM, the director of the paper, provided the first guidance; all authors contributed to revision of this paper and made constructive suggestions to ensure accurate expression of the research results. Wang YN and Shi MM contributed equally to this work and are co-first authors.

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**Retrospective Study** 

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ORIGINAL ARTICLE

# Impact of an emergency department nursing intervention on continuity of care, self-care, and psychological symptoms

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## Abstract

#### BACKGROUND

The emergency department plays a crucial role in providing acute care to patients. Nursing interventions in this setting are essential for improving the continuity of care, enhancing patients' self-care abilities, and reducing psychological symptoms.

## AIM

To evaluate the effect of nursing interventions in the emergency department on these indicators in an emergency department.

#### METHODS

A retrospective analysis was conducted on 120 patients admitted to the emergency department between January 2022 and May 2023. The patients were divided into two groups: The control group (conventional nursing intervention) and the observation group (conventional nursing intervention + emergency department nursing intervention). The two groups were compared regarding continuity of care, self-care ability, psychological symptoms, and satisfaction with care.

## RESULTS

The emergency department nursing interventions significantly improved the continuity of care, enhanced patients' self-care abilities, and reduced psychological symptoms such as anxiety and depression.

## CONCLUSION

Nursing interventions in the emergency department positively impact continuity of care, self-care, and psychological symptoms. However, it is important to acknowledge the limitations of this study, including the small number of studies, variable methodological quality, and the heterogeneity of the study population. Future research should address these limitations and further explore the effects of



different types of nursing interventions in the emergency department. Additionally, efforts should be made to enhance the application and evaluation of these interventions in clinical practice.

Key Words: Emergency department; Nursing interventions; Continuity of care; Self-care; psychological symptoms

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**Core Tip:** Future research should address these limitations and further explore the effects of different types of nursing interventions in the emergency department. Targeted nursing interventions can alleviate psychological symptoms and improve patients' psychological well-being.

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#### INTRODUCTION

The emergency department is crucial for providing treatment for acute illnesses and trauma. Nursing interventions in this setting are essential for improving the continuity of care, enhancing self-care abilities, and alleviating psychological symptoms[1-5]. Emerging evidence from clinical practice indicates that these interventions positively impact the patients' overall health status[6-9]. Therefore, conducting a comprehensive study of these effects can enhance the quality of care and improve patient outcomes.

Continuity of care in the emergency department involves providing uninterrupted care throughout the patient's stay, including monitoring their condition, implementing care measures, and assessing outcomes. It has been shown that good continuity of care can effectively reduce complications and improve patient outcomes[10-15]. Self-care refers to a patient's ability to independently perform activities of daily living (ADL) and self-care while in the emergency department. Nursing interventions can improve patients' self-care abilities, reduce their reliance on healthcare professionals, and enhance their quality of life[16-23]. Psychological symptoms such as anxiety, depression, and fear are common among emergency department patients. These symptoms can negatively affect patient recovery and prolong the hospital stay [24]. Targeted nursing interventions can help alleviate psychological symptoms and improve patients' psychological well-being.

#### MATERIALS AND METHODS

#### General information

We retrospectively analyzed the data of 120 patients admitted to our hospital's emergency department between January 2022 and May 2023. The inclusion criteria were as follows: (1) Age range: Patients in the emergency department were adults aged 18 years and older; (2) primary diagnosis: patients with acute illness, trauma, or other acute medical problems requiring emergency department nursing intervention; (3) self-care: patients had some ability to care for themselves and could understand and follow instructions for nursing intervention; and (4) consent to participate: patients or their legal representatives agreed to participate in the study and signed an informed consent form. Exclusion criteria were as follows: (1) Age restriction: patients under the age of 18 years were excluded from the study; (2) critical status: severe illness or trauma requiring urgent intensive care or surgical treatment; (3) state of consciousness: patients with impaired consciousness or an unstable mental status who were unable to cooperate with the nursing intervention assessment; (4) unable to provide informed consent: patients unable to understand, express, or sign an informed consent form; and (5) previously received similar interventions: patients who had previously received an emergency department nursing intervention or a similar research intervention. The study design considered the feasibility, ethical requirements, and practicalities to ensure scientific validity and reliability.

The control group consisted of 60 patients who received conventional nursing intervention, whereas the observation group received both conventional nursing intervention and emergency department nursing intervention. The control group consisted of 30 males and 30 females, with an age range of 43-75 years (58. 41 ± 3. 17), and the length of hospital stay ranged from 7-20 d (10. 54 ± 2. 57). The observation group consisted of 29 males and 31 females, aged 44-77 years (58. 47 ± 3. 22).

The duration of hospitalization ranged from 8 to 22 d [(mean: 10.  $68 \pm 2$ . 61) d]. There were no statistically significant differences between the two groups in terms of sex, age, or duration of hospitalization (P > 0.05).

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#### Methodology

In the control group, routine care was provided, including maintaining a constant room temperature, regularly opening windows and doors, providing a balanced diet based on the patient's preferences, guiding the patient to change positions, and providing psychological care.

In the observation group, emergency department nursing interventions were carried out in addition to conventional nursing care: (1) Optimizing the nursing process: Improving the efficiency and quality of patient care by optimizing the nursing process and operational specifications in the emergency department. This includes the rapid assessment of patients, prioritization of treatment for critically ill patients, and prompt examinations and treatments; (2) personalized care plans: developing personalized care plans based on each patient's specific situation and diagnosis. Considering the patients' conditions, needs, and preferences, nursing interventions were tailored to their individual situations; (3) nursing education: providing relevant health education and nursing guidance to patients and their family members. This includes educating patients about the disease, treatment plans, and medication to help them better understand and cope with acute medical problems; (4) psychological support: recognizing that patients in the emergency department often experience psychological symptoms such as anxiety, fear, and stress. Nursing staff can reduce patients' psychological burdens and provide positive psychological support through active listening, reassurance, and emotional support; (5) pain management: effectively addressing and managing pain in patients with pain in the emergency department. The nursing staff assessed pain, managed medication, and provided physiotherapy to alleviate pain; (6) critical care: providing close monitoring of patients in critical conditions, including continuous monitoring of vital signs, ongoing assessment of the patient's condition, and timely intervention to ensure patient safety and stability; (7) rehabilitation and referral arrangements: Offering relevant rehabilitation advice and referral to other departments. Nursing staff can provide relevant rehabilitation advice, referral arrangements, and follow-up for patients who require rehabilitation care or need to be referred to other departments; and (8) establishing a nursing team to summarize key considerations in nursing care and improve emergency care foresight by reviewing and summarizing nursing care.

#### Indicators of observation

(1) The observation indicators for continuity of care include re-attendance rate into the emergency department after a visit: This indicator assesses the frequency at which patients return to the emergency department within a certain period after their initial visit; hospitalization rate: This indicator assesses whether patients require hospitalization or not. Outpatient follow-up rate: This indicator measures the proportion of patients requiring further treatment or follow-up in the outpatient clinic; and (2) Self-care ability observation indicators include assessment of ADL (0-100 points, the higher the score, the stronger the ability): This assessment evaluates the patient's ability to perform daily activities, such as eating, washing, dressing, toileting, and walking; and self-assessment scales: Patients self-report their level of self-care ability through self-assessment scales, such as the Barthel Index and Lawton Self-care Ability Scale. The observation indicators for psychological symptoms include the Symptom Self-Rating Scale (SCL-90): This scale assesses the severity of the patient's psychological symptoms.

#### RESULTS

The observed indicators of continuity of care were compared between the two groups of patients. Based on the data presented in Table 1, patients in the observation group demonstrated significantly lower rates of re-attendance at the emergency department after their initial visit than patients in the control group (P < 0.05). The ADL scores of both groups were compared before and after the intervention. Furthermore, after the intervention, the ADL scores of the patients in both groups were significantly higher than those before the intervention (P < 0.05), and the ADL scores of the patients in the observation group were significantly higher than those in the control group (P < 0.05) (Table 2). The self-care abilities of the two groups were compared before and after the intervention. The Barthel index scores of the patients in the observation group were significantly higher than those in the control group (P < 0.05) (Table 3). After the intervention, there was a significant decrease in the SCL-90 scores for both groups compared to those before the intervention (P < 0.05) (Figure 1). Additionally, the SCL-90 scores of the patients in the observation group were significantly lower than those in the control group (P < 0.05). The SCL-90 scores of patients in the observation group were significantly lower than those in the control group (P < 0.05) (Table 4).

#### DISCUSSION

With global economic development, the overall quality of life has improved, leading to an increase in accidents and acute diseases. Consequently, the number of patients admitted to hospitals increased annually. Patients in the emergency department commonly present severe functional disorders of the limbs, including motor, sensory, and autonomic dysfunction. These impairments significantly reduce the patient's self-care ability and can result in complications such as autonomic reflex disorders, deep vein thrombosis, and pressure sores. These complications not only cause physical and psychological harm to the patients but also impose a significant economic burden on their families.

In the emergency department, the primary treatment principle is to save the lives of patients. Additionally, efforts would be made to prevent or minimize the loss of function, reduce the occurrence of complications, and achieve the best possible recovery in the shortest time to enhance the quality of life. Although most patients are generally stable after



Table 1 The observed indicators of continuity of care between the two groups of patients are compared				
Group	Re-visit rate	Hospitalization rate	Recurrence rate	
Observation group ( $n = 60$ )	10 (16.67)	15 (25.00)	20 (33.33)	
Control group ( $n = 60$ )	40 (66.67)	50 (83.33)	54 (90.00)	
$\chi^2$	7.281	6.310	5.431	
<i>P</i> value	< 0.001	< 0.001	< 0.001	

#### Table 2 Comparison of activities of daily living scores between the two groups before and after the intervention

Group	Pre-intervention	Post-intervention
Observation group ( $n = 60$ )	44.37 ± 7.32	$96.74 \pm 9.91^{a}$
Control group ( $n = 60$ )	43.28 ± 6.24	85.66 ± 8.78 <sup>a</sup>
T value	0.124	8.732
<i>P</i> value	0.938	< 0.001

<sup>a</sup>P < 0.05 vs pre-intervention group.

#### Table 3 Comparison of self-care ability between the two groups before and after intervention (mean ± SD, points)

Group	Pre-intervention	Post-intervention	Barthel index rating scale score difference
Observation group ( $n = 60$ )	52.34 ± 6.85	$78.63 \pm 5.44^{a}$	26.28 ± 6.62
Control group ( $n = 60$ )	$52.00 \pm 6.32$	$69.72 \pm 5.81^{a}$	17.72 ± 4.55
T value	0.209	6.330	6.032
<i>P</i> value	0.835	< 0.001	< 0.001

<sup>a</sup>P < 0.05 vs pre-intervention group.

#### Table 4 Comparison of Symptom Self-Rating Scale scores before and after the intervention in the two groups (mean ± SD, points)

Group	Pre-intervention	Post-intervention	Poor SCL-90 score
Observation group ( $n = 60$ )	234.69 ± 25.35	$162.44 \pm 15.48^{a}$	$72.25 \pm 20.00$
Control group ( $n = 60$ )	235.50 ± 26.29	187.41 ± 16.53 <sup>a</sup>	$48.09 \pm 17.45$
T value	-0.126	6.236	5.149
<i>P</i> value	0.900	< 0.001	< 0.001

<sup>a</sup>P < 0.05 vs pre-intervention group. SCL-90: Symptom Self-Rating Scale.

treatment, they still require long-term care. Studies have confirmed that emergency department nursing, in addition to routine nursing, can improve patients' motor functions, reduce the incidence of complications, and improve their quality of life.

The impact of emergency department nursing interventions on continuity of care, self-care, and psychological symptoms is an area of considerable research interest[25]. The literature review presented here highlights the fact that numerous studies have explored the impact of various emergency department nursing interventions on these aspects. In the cardiovascular field, interventions, such as home environment interventions and telephone support, have been found to enhance patient self-care and quality of life. These interventions empower patients to manage their condition better and provide them with support, thereby improving their understanding and ability to cope with their illness. Additionally, studies have focused on emergency department nursing interventions for critically ill patients and those with heart failure, indicating the potential of these interventions in improving patients' self-care and psychological symptoms. In addition, for patients with heart failure and severe infections, the implementation of early fluid resuscitation in the emergency department has shown potential benefits in improving self-care and reducing psycho-



Figure 1 Impact of emergency department nursing intervention on continuity of care, self-care and psychological symptoms. A: Before intervention; B: After intervention. ROC: Receiver operating characteristic; AUC: Area under the curve.

logical symptoms. These interventions can improve the physiological status of patients and facilitate their recovery and rehabilitation. Taken together, emergency department nursing interventions have a positive impact on the continuity of care, self-care, and psychological symptoms.

## CONCLUSION

Emergency department care can help patients improve their caregiving capacity, reduce psychological symptoms, and improve their quality of life through individualized nursing interventions, self-management support, and early interventions. However, further research is needed to explore the impact of different types of emergency department nursing interventions on diverse populations and conditions to provide more accurate guidance and best practices. This study has limitations in terms of sample size, diversity of interventions, and time constraints. Additionally, the complexity of the emergency department settings may introduce other uncontrolled interventional factors.

## ARTICLE HIGHLIGHTS

#### Research background

The emergency department plays a crucial role in providing acute care to patients, and nursing interventions in this setting are essential for improving continuity of care, enhancing patients' self-care abilities, and reducing psychological symptoms.

#### Research motivation

To evaluate the impact of nursing interventions in the emergency department on these indicators in an emergency department.

#### Research objectives

This study examined various indicators of continuity of care, self-care, and psychological symptoms.

#### Research methods

A retrospective analysis was conducted on 120 patients admitted to the emergency department between January 2022 and May 2023. The patients were divided into two groups: The control group (conventional nursing intervention) and the observation group, which received both conventional nursing and emergency department nursing interventions. Patients in both groups were compared in terms of continuity of care, self-care ability, psychological symptoms, and satisfaction with care.



#### Research results

The emergency department nursing interventions significantly positively impacted various aspects. Specifically, these interventions improved the continuity of care, enhanced patients' self-care abilities, and reduced psychological symptoms such as anxiety and depression.

#### Research conclusions

Additionally, the complexity of the emergency department settings introduces the possibility that other uncontrolled intervention factors may have an impact.

#### Research perspectives

Emergency department nursing interventions have the potential to improve patients' self-care and psychological symptoms, suggesting their effectiveness. Furthermore, the implementation of early fluid resuscitation in the emergency department has shown potential benefits for patients with heart failure and severe infections, leading to improved selfcare and reduced psychological symptoms. These interventions can improve the patient's physiological status and facilitate recovery and rehabilitation.

## FOOTNOTES

Author contributions: XU S and Gu YF contributed equally to this work; XU S designed the study; Gu YF and Dong AH contributed to the analysis of the manuscript; XUS and GuYF were involved in the data and writing of this article; and all authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

## **Retrospective Study** Effect of cognitive behavior therapy training and psychological nursing on the midwifery process in the delivery room

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## Abstract

## BACKGROUND

The severe physical and psychological impact of pain on the physical and mental health of women during labor leads to increased risks and complications during childbirth, presenting a major public health concern. Some studies have shown that cognitive behavioral therapy (CBT) has a positive effect on maternal psychology during delivery, reducing stress and shortening labor time. Thus, CBT training for mothers and delivery room staff may be beneficial in minimizing complications and adverse effects during natural birth.

## AIM

To investigate the clinical effects of CBT training and psychological care during delivery, and their therapeutic effects on women in labor.

#### **METHODS**

This study used a retrospective analysis and included 140 mothers admitted to the maternity ward between January 2021 and January 2023. The study subjects were randomized into two groups: control (n = 70) and observation (n = 70). Routine care, CBT training, and psychological care were provided to mothers in both groups. Psychological status scores, delivery time, and satisfaction with care preand post-delivery were compared, and the incidence of complications after receiving care was analyzed between the two groups.

## RESULTS

Although the psychological state of both groups improved significantly in the late stages of labor, the psychological state scores of the mothers in the observation group were significantly lower than those of the mothers in the control group (P <0.05). The duration of labor and incidence of complications in the observation group were significantly lower than those in the control group (P < 0.05). The mothers in the observation group were significantly more satisfied with nursing care during the course of labor than those in the control group (P < 0.05).



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#### CONCLUSION

CBT training and psychological care for mothers in the midwifery process can effectively improve anxiety and depression, shorten labor duration, reduce postnatal complications, and improve nursing satisfaction and nursepatient relationships. Its clinical application is effective and has popularization value, providing a new way to protect maternal mental health.

Key Words: Cognitive behavior therapy; Cognitive behavior therapy training; Psychological care; Childbirth; Mental health

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**Core Tip:** The application of cognitive behavior therapy training and psychological care in the delivery process can effectively improve the psychological condition of mothers, shorten labor duration, reduce the incidence of complications, and improve nurse-patient relationships and nursing satisfaction. Compared to either approach alone, the effect of the combined intervention was more significant.

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## INTRODUCTION

During labor, the resulting pain causes strong psychological stimulation in women, often leading to accidents due to excessive mental stress[1,2]. Psychological factors have a strong influence on childbirth and are considered to be the fourth stage after the dilation, expulsion, and placental stages[3]. Mild anxiety is a normal psychological stress that can be accompanied by moderate activation of the sympathetic nervous system, improving the body's ability to adapt to the environment; however, the following question arises: How can excessive anxiety or stress lead to physiological alterations during labor[4,5]? First, excessive anxiety leads to a decrease in norepinephrine production, resulting in weak uterine contractions, which can, in turn, lead to obstructed labor and is a possible factor in increasing the risk of postpartum hemorrhaging[6]. Second, stress and anxiety may exacerbate contraction pain by causing a relative decrease in the mother's pain threshold. Severe pain and poor maternal mood also promote catechol secretion in the body, causing uncoordinated uterine contractions, thus impeding the ongoing labor process and increasing the chances of obstructed childbirth as well as decreasing uterine blood flow, which can also cause fetal hypoxia[7,8].

Previous surveys have shown that more than 90% of pregnant women experience labor pain, physiological changes during pregnancy, and anxiety prior to delivery. Mothers who are fearful of a natural birth are more likely to develop other psychological conditions after birth, such as postnatal depression, than those who are not[9]. Incidences of obsessive-compulsive disorder and generalized anxiety disorder are also much higher in postpartum women than in those who have not given birth[10]. Especially in China, since the implementation of the two-child policy, the incidence of postpartum depression has increased significantly. Statistics show that the annual incidence of postpartum depression in China is 5.36%-11.09% [11]. However, numerous studies have demonstrated that timely and effective psychological interventions during labor can significantly reduce maternal fear and tension and increase the rate of successful delivery. Natural childbirth, led by midwives, reduces the risks of pregnancy[12]. Midwives are primarily responsible for providing health education to mothers and their families during labor and delivery, increasing mothers' confidence in a smooth delivery through constant encouragement and reassurance, and by reducing fear, pain, and anxiety[13]. A previous study found that cognitive behavioral therapy (CBT) training before childbirth can help reduce anxiety and tension, decrease the duration of childbirth, and improve mothers' quality of life[14]. Psychological care, however, is aimed at changing the mother's psychological condition during childbirth and is targeted to help improve her mood and reduce fear of a natural birth, thus reducing the incidence of adverse birth events. However, to the best of our knowledge, only a few studies have combined CBT training and psychological care to provide childbirth assistance.

This study used a retrospective approach to investigate the clinical effects of CBT training and psychological care for mothers during assisted delivery and provide new insights into reducing labor complications as well as safeguarding mothers' physical and mental health.

## MATERIALS AND METHODS

#### Study design, setting, and participants

This retrospective study included 140 women who had previously received CBT training and psychological care from midwives as study subjects in the hospital. Subjects who received combined care were included in the observation group



(n = 70), and those who received either psychological care or CBT training alone were included in the control group (n = 70). The psychological status scores, delivery time, and satisfaction with nursing care were compared pre- and postdelivery and the rate of complications after receiving nursing care were analyzed in both groups. The study subjects met the following criteria: (1) Single full-term vaginal births; (2) complete, true, and valid clinical data; (3) signed informed consent form subjects and their families after being informed of the study purpose and content; (4) no history of psychiatric or psychological disorders, or language or cognitive impairment; and (5) no serious comorbidities. The attending physicians met the guidelines for vaginal delivery.

The control group was selected from among the subjects who received either CBT training or psychological care only during the midwifery process, whereas the observation group received both. Except for the noted cognitive and/or psychological interventions, the same care model was applied to both groups.

Regarding routine nursing care, the nursing staff conducted consistent routine nursing care for all mothers, including the following: (1) Providing health education to the mothers and their families (*i.e.*, informing them of the relevant precautions and popular knowledge related to childbirth); (2) assisting the mother in the correct position during labor, instructing her to breathe and exert herself reasonably, and answering her questions about the childbirth process; and (3) enhancing the monitoring of maternal vital signs during labor, instructing family members and mothers to implement postnatal care, and instructing mothers to pay attention to rest, scientific diet, and good hygiene.

Regarding CBT training, when a mother is admitted to the hospital for delivery, the nursing staff learn about her cognitive and comprehension abilities. This, in turn, allows for the adoption of various informational approaches, such as lectures, videos, props and models, and health education manuals to help her grasp the delivery-related knowledge, making her comprehensively aware of the advantages and disadvantages of vaginal delivery and cesarean section, and helping enhance her confidence in delivery. The following is an overview of the instructions: (1) During the first stage of labor, close attention is paid to the mother's labor contractions, instructing her to conduct breathing training and leading her to a free position where she chooses to stand, squat, sit, or lay down while waiting for delivery to provide favorable conditions for the fetus's head to descend, rotate, and be delivered; (2) During the second stage of labor, when the vagina is fully dilated, the recorded video is played back to correctly guide exertion, while changes in the vital signs are closely observed. If abnormalities are found, the doctor is promptly informed and helps in strictly implementing an aseptic operation to avoid infection during labor and the contraction period, to guide the food and water, and to maintain good stamina to lead the head of the fetus to the crown; and (3) During the third stage of labor, when the placenta is delivered, the presence of soft birth canal laceration is checked and, if present, timely suture treatment is provided. At the end of childbirth, the mother is closely monitored, especially for any instances of vaginal bleeding, and guidance for perineal cleansing, supplemented by abdominal massage, is provided to promote contractions and reduce bleeding. If a vaginal delivery is not possible, the mode of delivery should be changed according to the actual situation to avoid irreversible and serious consequences.

Regarding psychological care, prior to delivery, women often experience negative psychological emotions, such as anxiety and depression, due to labor pain and fear for fetal safety. Nursing staff must comprehensively assess changes in their psychological emotions, determine the influencing factors, and provide targeted guidance and encouragement, allowing mothers to maintain a normal or positive state of mind prior to delivery. During labor, an entire process of encouragement and guidance for women is implemented to alleviate such adverse emotions and emotional stress. Post-delivery, the mother is informed promptly of the successful completion of the delivery process to eliminate her worries. Simultaneously, the mother and baby are placed in the same room as soon as possible, and breastfeeding is started as early as possible to help with breast milk secretion and support the mother's adaptation to motherhood.

#### Measurement of variables

The psychological state score, delivery time, and satisfaction with nursing care before and after delivery in both patient groups were compared, and rates of complications after receiving nursing care were analyzed. The psychological state score is comprised of the self-rating anxiety scale (SAS) and self-rating depression scale (SDS); the lower the score, the better the psychological state of the patient. The duration of childbirth in both groups included the average duration of the first, second, and third stages. Incidence of postpartum complications in the two groups included weak contractions, postpartum hemorrhage, and postpartum depression. Satisfaction with nursing care was assessed using a self-developed scale with four dimensions: basic nursing care, nursing methods, nursing intervention, and nursing care attitude. The scores showed a positive correlation with satisfaction with nursing care; the higher the scores, the higher the satisfaction with nursing care.

#### Statistical analysis

Data in this study were statistically analyzed using SPSS 26.0. Continuous data conformed to the normal distribution described by means and percentages, median range (interquartile range) was used to describe continuous variables with skewed distributions, and categorical variables were summarized as numbers and percentages (%). Differences between two groups of quantitative data were analyzed using *t*-tests, and multiple groups of data were analyzed using chi-square tests. Analyses were set to a significance level of  $\alpha$  = 0.05, and differences were specified as statistically significant at *P* < 0.05.

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#### RESULTS

#### Baseline data and pathological characteristics

A total of 140 subjects were included in the study. The baseline data of the study subjects were collected for comparison, which showed no statistically significant difference between age, weight, domicile, number of births, or gestational weeks between the two study groups (P > 0.05), and the data of the two groups were comparable. The mean age of the study subjects in the observation group was 27.23 ± 1.46 years, the mean weight was 72.91 ± 5.44 kg, the gestational period was 39.41 ± 1.22 wk, and the number of births was 1.23±0.30. In the control group, the mean age of the study subjects was 27.25 ± 1.25 years, the mean weight was 72.91 ± 5.44 kg, the gestational period was 39.25 ± 1.30 wk, and the number of births was 1.18 ± 0.21. The characteristics of the study subjects are presented in Table 1.

#### Mental status scores before and after delivery in both groups

The psychological state scores of the mothers before and after delivery were assessed in both groups, and the results showed no statistically significant differences from those of the mothers before delivery. After childbirth, the SAS and SDS scores of the observation group were significantly higher than those of the control group (P < 0.05). The mental status results are presented in Table 2.

#### Comparative analysis of delivery time in the two groups

Labor duration was recorded in both groups, showing differences from the first stage of childbirth onwards, with a significant decrease in childbirth time in the observation group compared with the control group (P < 0.05). The findings show that the combined intervention was effective in shortening childbirth time (Table 3).

#### Incidence of complications in both groups

Statistics on the incidence of complications during delivery in both groups showed that in the observation group, two (2.86%) women had postpartum depression, three (4.29%) had postpartum hemorrhage, three (4.29%) had weak contractions, and the total incidence of complications was eight (11.43%). In the control group, 10 (14.29%) mothers developed postpartum depression, seven (10.0%) had postpartum hemorrhage, and 11 (15.71%) developed contraction weakness; the overall complication rate was 28 (40.0%). There was a statistically significant difference in the incidences of complications between the two groups (P < 0.05). The complications results are presented in Table 4.

#### Comparative analysis of nursing satisfaction

Both groups of mothers were asked to rate their satisfaction with nursing care during childbirth. Subjects rated their satisfaction in four dimensions: basic nursing care, nursing methods, nursing intervention, and nursing care attitude. The results show that nursing care satisfaction in the observation group was higher than that in the control, and the difference was statistically significant (P < 0.05). The results are presented in Table 5.

### DISCUSSION

This study compared the clinical effects of combined CBT training and psychological care for mothers during the process of assisted delivery with those of a single psychological intervention. The results demonstrated that, although the psychological state of mothers in both groups improved significantly in the later stages of labor, the psychological state scores in the observation group were significantly lower than those in the control group. The duration of labor and incidence of complications in the observation group were significantly lower than those in the control, and the satisfaction of mothers with care during the process of labor in the observation group was significantly higher than that in the control. In addition, labor duration and complication rates in the observation group were significantly lower than those in the control group, and the satisfaction rate in the observation group was significantly higher than that in the control group.

Childbirth is an important physiological process that mothers must undergo[15]. During childbirth, many mothers experience greater stress and emotional fluctuations accompanied by anxiety and fear. This leads to sympathetic nerve excitation, resulting in an increased small rate, respiratory frequency, and insufficient gas exchange in the lungs. These changes can cause uterine hypoxia and slow expansion of the uterine opening, causing difficulty in childbirth, prolonging labor duration, and increasing the rate of obstructed labor, as well as the risk of postpartum complications. Previous studies have demonstrated that both CBT training and psychological care can significantly reduce maternal anxiety and fear during labor and improve postnatal quality of life[16,17]. That is, the use of CBT training is effective in reducing maternal anxiety during the postpartum period. It has also been shows to reduce the complications of postpartum stress and depression, with follow-up showing improvements in family well-being and parent-child relationships during the postpartum period[18,19]. The results of this study show that compared to either CBT training or psychological care alone, a combination of the two is more effective in improving the psychological state of mothers after delivery and in reducing the incidence of postpartum depression.

Labor duration has been associated with childbirth complications in previous studies, and maternal anxiety during labor significantly affects its duration[20,21]. The present study showed that CBT training and psychological care during assisted labor were effective in reducing labor duration. The study also found a relative reduction in the incidence of post-delivery complications in the observation group. Moreover, increased satisfaction with care was effective in improving the relationship between mothers and caregivers, leading to mothers' increased trust in midwives during

Table 1 General information about the study population					
		Observation group ( <i>n</i> = 70)	Control group <i>n</i> = 70)	t/χ <sup>2</sup>	P value
Age (yr)		$27.23 \pm 1.46$	27.25 ± 1.25	0.982	0.902
Weight (kg)		72.91 ± 5.44	$72.91 \pm 5.44$	1.973	0.981
Domicile	Urban	56	55		0.214
	Rural	14	15		
Weeks of pregnancy (wk)		39.41 ± 1.22	39.25 ± 1.30	0.712	0.131
No. of deliveries		$1.23 \pm 0.30$	$1.18\pm0.21$	0.561	0.056

## Table 2 Maternal psychological state score before and after delivery

	Before childbirth		After childbirth	
	SAS	SDS	SAS	SDS
Observation group	$57.25 \pm 1.68$	57.57 ± 2.55	$51.35 \pm 1.23$	$50.41 \pm 1.33$
Control group	$57.39 \pm 1.87$	$57.49 \pm 2.61$	$48.78 \pm 1.15$	$47.88 \pm 1.21$
t	1.241	0.987	7.812	6.902
<i>P</i> value	0.521	0.712	< 0.001	< 0.001

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

Table 3 Comparative analysis of two groups of maternal labor time					
	The first stage of labor (h)	The second stage of labor (min)	The third stage of labor (min)		
Control group	$8.26 \pm 1.76$	45.32 ± 7.25	9.29 ± 1.37		
Observation group	$6.15 \pm 1.21$	33.19 ± 5.35	6.33 ± 0.91		
t	7.193	14.210	11.021		
<i>P</i> value	< 0.001	< 0.001	< 0.001		

#### Table 4 Comparative analysis of the incidence of post-delivery complications between both groups

	Postpartum depression	Postpartum hemorrhage	Weak contractions	Total incidence of complications
Observation group, <i>n</i> (%)	2 (2.86)	3 (4.29)	3 (4.29)	8 (11.43)
Control group, <i>n</i> (%)	10 (14.29)	7 (10.0)	11 (15.71)	28 (40.0)
<i>x</i> <sup>2</sup>				23.914
<i>P</i> value				< 0.001

## Table 5 Comparative analysis of maternal nursing satisfaction between both groups

	Basic nursing care	Nursing methods	Nursing intervention	Nursing care attitude
Observation group	94.24 ± 2.81	96.91 ± 2.92	94.45 ± 1.91	97.89 ± 3.14
Control group	$90.89 \pm 1.12$	91.21 ± 1.14	$90.14 \pm 0.94$	92.94 ± 1.58
t	7.193	14.210	11.021	8.931
<i>P</i> value	< 0.001	< 0.001	< 0.001	< 0.001



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labor[22].

The strength of this study is in its combined use of CBT training and psychological care, evaluated in terms of psychological status scores, labor duration, postpartum complications, and satisfaction with care. However, due to the retrospective nature of the study, the extent of support for the exact efficacy and safety of the intervention was not as high as that of a prospective study. Nonetheless, we obtained complete clinical data and avoided errors caused by incomplete data.

## CONCLUSION

In conclusion, CBT training and psychological care for mothers in the midwifery process can effectively improve maternal anxiety and depression, shorten labor duration, reduce postnatal complications, and improve nursing satisfaction and nurse-patient relationships. Its clinical application is effective and has popularization value, offering a new way to protect maternal mental health.

## ARTICLE HIGHLIGHTS

#### Research background

The severe physical and psychological impact of pain on the physical and mental health of women during childbirth, leads to increased risks and complications, presenting a major public health issue.

#### Research motivation

During childbirth, labor pain causes strong psychological stimulation in women, which often leads to accidents due to excessive mental stress.

#### Research objectives

To provide new insights into reducing accidents during childbirth and safeguarding mothers' physical and mental health.

#### Research methods

This study used a retrospective analysis and included 140 mothers admitted to the maternity ward between January 2021 and January 2023. The two groups were randomized: Routine care, cognitive behavior therapy (CBT) training, and psychological care were, respectively, provided to mothers in the control (n = 70) and the observation (n = 70) groups.

#### Research results

The results showed that although the psychological state of mothers in both groups improved significantly in the late stage of labor, that of the mothers in the observation group was significantly lower than that of mothers in the control group. The labor duration and incidence of complications in the observation group were significantly lower than those in the control group, and the satisfaction of mothers with care during the process of labor in the observation group was significantly higher than that in the control group. In addition, labor duration and complication rates in the observation group were significantly lower than those in the control group, and the satisfaction rate in the observation group was significantly higher than that in the control group.

#### Research conclusions

CBT training and psychological care for mothers in the midwifery process can effectively improve maternal anxiety and depression, shorten labor duration, reduce postnatal complications, and improve nursing satisfaction and nurse-patient relationships. Its clinical application is effective and has popularization value, providing a new way to protect the mental health of mothers.

#### Research perspectives

CBT training and psychological care were administered during the delivery process, and the clinical effects were assessed by evaluating the psychological state scores of the mothers after delivery, observing labor duration, incidence of postdelivery complications, and satisfaction with nursing care.

## FOOTNOTES

Author contributions: Shi Q and Gu LY contributed equally to this work; Shi Q, Wang J, Zhao D and Gu LY designed the research study; Shi Q, Wang J, Zhao D and Gu LY performed the research; Shi Q and Gu LY contributed new reagents and analytic tools; Shi Q and Gu LY analyzed the data and wrote the manuscript; all authors have read and approve the final manuscript.

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ORIGINAL ARTICLE

## **Retrospective Study** Meteorological factors, ambient air pollution, and daily hospital admissions for depressive disorder in Harbin: A time-series study

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## Abstract

## BACKGROUND

The literature has discussed the relationship between environmental factors and depressive disorders; however, the results are inconsistent in different studies and regions, as are the interaction effects between environmental factors. We hypothesized that meteorological factors and ambient air pollution individually affect and interact to affect depressive disorder morbidity.

## AIM

To investigate the effects of meteorological factors and air pollution on depressive disorders, including their lagged effects and interactions.

## **METHODS**

The samples were obtained from a class 3 hospital in Harbin, China. Daily hospital admission data for depressive disorders from January 1, 2015 to December 31, 2022 were obtained. Meteorological and air pollution data were also collected during the same period. Generalized additive models with quasi-Poisson regression were used for time-series modeling to measure the non-linear and delayed effects of environmental factors. We further incorporated each pair of environ-



mental factors into a bivariate response surface model to examine the interaction effects on hospital admissions for depressive disorders.

#### RESULTS

Data for 2922 d were included in the study, with no missing values. The total number of depressive admissions was 83905. Medium to high correlations existed between environmental factors. Air temperature (AT) and wind speed (WS) significantly affected the number of admissions for depression. An extremely low temperature (-29.0 °C) at lag 0 caused a 53% [relative risk (RR)= 1.53, 95% confidence interval (CI): 1.23-1.89] increase in daily hospital admissions relative to the median temperature. Extremely low WSs (0.4 m/s) at lag 7 increased the number of admissions by 58% (RR = 1.58, 95% CI: 1.07-2.31). In contrast, atmospheric pressure and relative humidity had smaller effects. Among the six air pollutants considered in the time-series model, nitrogen dioxide (NO<sub>2</sub>) was the only pollutant that showed significant effects over non-cumulative, cumulative, immediate, and lagged conditions. The cumulative effect of NO<sub>2</sub> at lag 7 was 0.47% (RR = 1.0047, 95%CI: 1.0024-1.0071). Interaction effects were found between AT and the five air pollutants, atmospheric temperature and the four air pollutants, WS and sulfur dioxide.

#### **CONCLUSION**

Meteorological factors and the air pollutant NO<sub>2</sub> affect daily hospital admissions for depressive disorders, and interactions exist between meteorological factors and ambient air pollution.

Key Words: Mental health; Depressive disorder; Hospital admissions; Meteorological factors; Air pollution; Time-series

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**Core Tip:** This retrospective study assessed the influence of environmental factors on depressive disorders. Daily hospital admissions for depressive disorders at a hospital in Harbin, China from 2015 to 2022 were obtained. Four meteorological factors and six air pollutants were considered predictors in the time-series models. Air temperature, atmospheric pressure, wind speed, relative humidity, and nitrogen dioxide have effects on daily hospital admissions for depressive disorders, and interactions exist between meteorological factors and ambient air pollution.

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#### INTRODUCTION

Depressive disorder (also known as depression) is a common mental disorder that involves depressed mood and loss of pleasure or interest in activities for long periods of time[1]. Approximately 280 million people (3.8%) worldwide experience depression[2]. Depressive disorder is a complex phenomenon that represents the interplay between social, psychological, and biological mechanisms<sup>[1]</sup>. The crucial biochemical mechanism underlying depression lies in the disruption of synaptic chemical transmission, which leads to a functional deficiency in the brain's monoaminergic transmitters including norepinephrine, serotonin (5-hydroxytryptamine), and/or dopamine[3]. These mechanisms have become targets of antidepressant action; for example, selective serotonin reuptake inhibitors such as fluoxetine are typical antidepressant medications<sup>[1]</sup> used for regulating serotonergic transmission.

In the last couple of years, accumulated evidence suggests that depressive disorder is also affected by environmental factors[4], including meteorological factors[5-8], ambient air pollution[9-13], light exposure[14-16], and access to green space[17,18]. An increase in temperature has been found to exacerbate psychiatric disease hospitalizations[19] in Greece, deteriorate mental well-being, and increase depressive language and suicide rates<sup>[20]</sup> in North America. Exposure to fine particles ( $PM_{15}$ ), inhalable particles ( $PM_{10}$ ), nitrogen dioxide ( $NO_2$ ), sulfur dioxide ( $SO_2$ ), and carbon monoxide (CO) was positively associated with depression, and the risk of depression increased with exposure to high levels of these pollutants[21]. Sunlight intensity may also be associated with depressive symptoms[22]. People reporting inadequate natural light in their dwellings were more likely to report depression[15]. This strongly suggests that environmental factors play a role in altering serotonin levels, leading to depression. Corresponding therapies, such as bright-light therapy, have been developed and used, and have evolved into effective treatments that act on serotonin and other monoaminergic pathways[16].

While the literature has discussed the relationship between environmental factors and depressive disorders, the interactions between different environmental factors have rarely been considered. Moreover, the results of different studies have been inconsistent. This study aimed to investigate the effects of environmental factors on depressive disorders. We obtained environmental data containing four meteorological factors and six air pollutants and modeled the



interactions between these environmental factors simultaneously to gather more precise evidence and obtain a regional supplement for this research field.

## MATERIALS AND METHODS

#### Study design

To measure the precise effects of and the interaction between meteorological factors and air pollution on depressive disorders, we obtained as our sample daily hospital admission data for depressive disorders at a class 3 hospital in Harbin, China from January 1, 2015 to December 31, 2022. Data on the meteorological factors and air pollution for each day of admission were also collected to construct a predictive model.

#### Data collection

Data from 2922 d were obtained from the information management system developed and used by the hospital. Patient information included the visit time and diagnosis. Individual identifiers were excluded. Patients with permanent residence in Harbin were selected, and those with other mental disorders were excluded. Daily depressive disorder admission data equaled the sum of depressive outpatient and hospitalization data. The diagnosis of depressive disorder (coded as F32-F33 ICD-10 diagnoses) refers to GB/T 14396-2016", classification and Code of Diseases" [23].

Meteorological data for the same period from 2015 to 2022 for Harbin, China, were collected from the China meteorological data service centre<sup>[24]</sup>, including daily mean air temperature (AT), daily mean atmospheric pressure (AP), wind speed (WS), and relative humidity (RH).

Ambient air pollution data included six international standard air pollutants that have been extensively investigated previously [12]:  $PM_{2.5}$ ,  $PM_{10'}$ ,  $SO_{2'}$ , CO,  $NO_{2'}$ , and ozone ( $O_{3'}$ , usually measured at maximum 8-h average concentrations). The pollutant data were collected from the China Air Quality Online Monitoring and Analysis platform [25]. For all ambient air pollutants, we averaged all valid monitoring measurements each day to obtain their daily mean concentrations, in line with previous studies [12,26].

To conduct a time-series analysis, information on time-related variables was collected for modeling, such as the day of admission and public holidays. A sequence of calendar times was generated to indicate the time trends.

#### Statistical analysis

All data were inspected and preprocessed using Microsoft excel and IBM SPSS 25.0. No missing values or outliers were identified. Descriptive analysis, correlation calculations, time-series modeling, and plotting were conducted using R version 4.2.3. The mean value; SD; and minimum, maximum, median, and quartile ( $P_{25}$  and  $P_{75}$ ) were used to describe the data. The correlation coefficients between variables were calculated using Spearman's correlation analysis with the R package psych. We conducted a time-series analysis using the R packages dlnm[27], mgcv[28], rsm[29], and splines, modeling the effects of and interactions between various environmental factors. The R package ggplot2[30] was used to visualize the results. All statistical tests were two-tailed probability tests,  $\alpha = 0.05$ . Statistical results with P < 0.05, such as associations and differences, were considered statistically significant.

We used generalized additive models with quasi-Poisson regression to estimate the meteorological effects of each factor. The covariates in the models included a natural cubic spline of calendar time with 14 degrees of freedom, which modeled time trends in hospital admissions for depressive disorders, and two indicator variables for the day of the week and public holidays, accounting for potential variations in hospital admissions over weekdays, weekends, and holidays. Natural cubic splines of the daily AT, AP, WS, and RH with three degrees of freedom were included as predictors. To assess the potential lagged effects of meteorological factors, we included lags of up to seven days in the model for non-cumulative effects, similar to the methodology of a previously published study[31]. The choice of calendar time *df* was determined by calculating the minimum sum of the absolute values of the partial autocorrelation function based on the residuals of the underlying model, consistent with the residual independence principle[31]. Choices of meteorological factors *df* have been recommended by papers on time-series analyses[32] and have been adopted by most studies. The time-series analysis model for a single meteorological factor is as follows:

$$Y_t \sim quasiPoisson(\mu_t)$$

 $log E ([Y_t]) = \alpha + ns_t (calendar time, df = 14) + DOW_t + holiday_t + \beta_{it} \\ \times ns_{it} (meteological factor, df = 3)$ 

Where E (Y<sub>t</sub>) denotes the expected number of depressive disorder admissions on day t;  $\alpha$  is the intercept; ns represents the natural cubic spline function; and  $\beta_{it}$  is the exposure coefficients of meteorological factors and their lagged effects. We included the immediate and lagged effects of each air pollutant in the model and used meteorological factors as covariates. The time-series analysis model for a single air pollutant is as follows:

 $Y_t \sim quasiPoisson(\mu_t)$ 

 $log E ([Y_t]) = \alpha + ns_t (calendar time, df = 14) + DOW_t + holiday_t + \beta_{it} \\ \times ns_{it} (meteological factor, df = 3) + \beta_{jt} \times (air pollutant)_{jt}$ 

Where (air pollutant) represents lags of 0 to 7 for cumulative and non-cumulative exposures. Finally, we incorporated each meteorological factor and air pollutant into a bivariate response surface model to inspect the interaction effects of each pair of meteorological factors and air pollutants on hospital admissions for depressive disorders. The model for interaction effects is as follows:



Figure 1 Effects of air temperature on hospital admissions for depressive disorder. A: 3D plot of relative risk (RR) along air temperature and lags, with reference to the median temperature of 7.8 °C; B: Overall RR of lags 1-7 by air temperature, with reference at 7.8 °C. RR: Relative risk.

 $Y_t \sim quasiPoisson(\mu_t)$ 

Where  $t_e$  is the interaction effect of meteorological factors and air pollutants (on the day with the strongest lag effect) on daily hospital admissions for depressive disorders. Results are expressed as relative percentage change (%) and estimated 95% confidence intervals (CIs) at hospital admissions for depressive disorders of certain meteorological factor levels or per unit increment of air pollutants.

#### RESULTS

#### Descriptive statistics and correlation

The general features of all the variables are summarized in Table 1. The total number of hospital admissions for depressive disorders from January 1, 2015 to December 31, 2022 included in the study was 83905, with a daily average admissions of 28.7. During the studied period, the daily average AT in Harbin was 5.4 °C, and the daily average AP was 749.3 mmHg. The average WS was 2.9 m/s. The mean RH was 66.2%. The climate in Harbin is cold but mild, which means that it is not excessively windy or dry most times of the year, and the AP remains slightly lower than the standard. The daily average concentrations of  $PM_{2.5}$ ,  $PM_{10}$ ,  $SO_{2}$ , CO,  $NO_{2}$ , and  $O_{3}$ \_8h (the maximum 8-h average concentration of ozone) were 47.2 µg/m<sup>3</sup>, 71.3 µg/m<sup>3</sup>, 22.0 µg/m<sup>3</sup>, 0.9 mg/m<sup>3</sup>, 36.7 µg/m<sup>3</sup>, and 75.8 µg/m<sup>3</sup>, respectively. There is relatively high variability in air pollution, although the concentration levels are usually low according to the quartiles.

The correlation coefficients between the meteorological factors and air pollutants are shown in Table 2. All Spearman's correlation coefficients were statistically significant, except for the correlation between RH and CO. There was a moderate correlation among AT, AP, and air pollutants. Relatively high correlations among the air pollutants (except for  $O_3$ ) were found.

#### Time-series analysis modeling

In the single meteorological factor model for AT, AP, WS, and RH, we reported relative risks (RRs) with 95%CIs of the depressive disorder admissions for each level of the meteorological factor. The overall relationships between each meteorological factor and hospital admissions for depressive disorders are summarized in Figures 1-4. As shown in Figure 1A, there was a sharp effect of extremely low temperature, although, in Figure 1B, the overall low temperature had no positive effect on RR. Figure 2 shows the mild effect of AP on RR, which is close to zero. Figure 3 shows a larger effect of low WS and a smaller effect of high WS. As shown in Figure 4, both moderate and high RH appeared to have relatively small effects.

To provide more certainty and precision in the estimates, we further investigated the effect of each meteorological factor by calculating and plotting the RRs by these factors at lags 0-7, as shown in Figures 5-8. The results for AT showed significant increases at lags 0-2 and 5-6. Figure 5 shows that an extremely low temperature (-29.0 °C) at lag 0 increased daily hospital admissions for depressive disorders by 1.53 times (95%CI: 1.23-1.89) relative to median temperature (7.8 °C), which was the largest effect of AT. As shown in Figure 6, the effect of AP was significant only at lags 5 and 6. A moderately high AP (762 mmHg) at lag 5 increased the number of admissions by 1.13 times (95%CI: 1.00-1.27) relative to the median AP (748.9 mmHg). Figure 7 shows that WS had a significant effect at lags 2-7. The largest effect was at lag 7, where an extremely low WS (0.4 m/s) increased the number of admissions by 1.58 times (95%CI: 1.07-2.31) relative to the median WS (2.6 m/s). Relatively high RHs at lags 4-7 had statistically significant effects, and the largest effect of RH





Figure 2 Effects of atmospheric pressure on hospital admissions for depressive disorder. A: 3D plot of relative risk (RR) along atmospheric pressure (AP) and lags, with reference to the median AP of 748.9 mmHg; B: Overall RR of lags 1-7 by atmospheric pressure, with reference at 748.9 mmHg. RR: Relative risk; AP: Atmospheric pressure.



Figure 3 Effects of wind speed on hospital admissions for depressive disorder. A: 3D plot of relative risk (RR) along wind speed (WS) and lags, with reference to the median WS of 2.6 m/s; B: Overall RR of lags 1-7 by wind speed, with reference at 2.6 m/s. RR: Relative risk; WS: Wind speed.

resulted from a moderately high RH (86%) at lag 7, which increased the number of admissions by 1.09 times (95% CI: 1.01-1.17) relative to the median RH (67.9%), as shown in Figure 8.

Next, the concentrations on the same day (lag 0) and 1-7 d ago (lag 1-7) of the six air pollutants were included in the time-series model. The results are shown in Figure 9. Among these air pollution variables, only NO<sub>2</sub> showed significant effects, and the effects of concentration increases in NO<sub>2</sub> at lags 0-7 were all statistically significant, despite their weakness. The cumulative exposure to air pollution was also modeled and plotted, as shown in Figure 10. Consistent with the non-cumulative results, only NO<sub>2</sub> exhibited a significant cumulative effect. As NO<sub>2</sub> accumulated, the exposure effect on daily hospital admissions for depressive disorders increased slightly and smoothly, reaching its highest value at lag 7, where RR = 1.0047 (95%CI: 1.0024-1.0071).

A bivariate response surface model was generated to analyze the interactions between environmental factors. AT significantly interacted with all pollutants included in this study, except for  $NO_2$ . As shown in Figure 11, extremely low ATs combined with high concentrations of PM<sub>2.5</sub> and PM<sub>10</sub> increased the number of admissions for depressive disorders. Combination of low temperature, low SO<sub>2</sub>, and of high temperature and high SO<sub>2</sub> affected hospital admissions. Extremely low temperatures at any CO concentration increased the admission rate. When hot, a low CO concentration had an increasing effect, whereas a high CO concentration did not. Low temperatures and high  $O_3$  concentrations had decreasing effects. Figure 12 shows the interactions between the AP and air pollutants. The interactions between the AP and PM<sub>25</sub>, CO, NO<sub>2</sub>, and O<sub>3</sub>–8h were statistically significant. Low APs combined with low CO, low NO<sub>2</sub>, or high O<sub>3</sub> had increasing effects, whereas high APs combined with high  $PM_{25}$  high CO, or low  $O_3$  increased hospital admissions for depressive disorders. The interaction patterns of AP and  $PM_{25}/CO/NO_2$  were similar; however, the pattern between AP and  $O_3$  was the opposite. The interactions between WS and air pollutants are shown in Figure 13.  $SO_2$  had the only significant

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Figure 4 Effects of relative humidity on hospital admissions for depressive disorder. A: 3D plot of relative risk (RR) along relative humidity (RH) and lags, with reference to the median RH of 67.9%; B: Overall RR of lags 1-7 by RH, with reference at 67.9%. RR: Relative risk; RH: Relative humidity.



Figure 5 Plots of relative risk by air temperature at lags 0-7. A: Relative risk (RR) by air temperature (AT) at lag 0; B: RR by AT at lag 1; C: RR by AT at lag 2; D: RR by AT at lag 3; E: RR by AT at lag 4; F: RR by AT at lag 5; G: RR by AT at lag 6; H: RR by AT at lag 7. Reference at 7.8 °C. RR: Relative risk.

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Table 1 Descriptive statistics of variables (sample size = 2922 d)								
Variable (	mean ± SD	Percentile						
Variable (unit)		Min	<b>P</b> <sub>25</sub>	Median	P <sub>75</sub>	Max		
Admissions for depressive disorder ( <i>n</i> )	28.7 ± 21.2	0	9	28	42	130		
AT (°C)	$5.4 \pm 15.1$	-29.2	-8.4	7.8	19.0	30.6		
AP (mmHg)	749.3 ± 7.0	727.9	743.7	748.9	754.8	768.0		
WS (m/s)	$2.9 \pm 1.2$	0.4	2.0	2.6	3.5	9.8		
RH (%)	$66.2 \pm 15.6$	14.9	56.1	67.9	77.8	100.0		
$PM_{2.5} (\mu g/m^3)$	$47.2\pm54.6$	0.0	16.0	29.0	58.0	906.0		
$PM_{10} (\mu g/m^3)$	71.3 ± 59.3	0.0	35.0	53.0	87.0	644.0		
$SO_2 (\mu g/m^3)$	$22.0 \pm 23.6$	3.0	9.0	13.0	26.0	222.0		
CO (mg/m <sup>3</sup> )	$0.9 \pm 0.4$	0.3	0.6	0.8	1.0	4.3		
$NO_2 (\mu g/m^3)$	$36.7 \pm 17.8$	8.0	24.0	33.0	44.0	145.0		
$O_{3}_{8}h (\mu g/m^{3})$	$75.8\pm34.1$	0.0	50.0	71.0	96.0	253.0		

AT: Air temperature; AP: Atmospheric pressure; WS: Wind speed; RH: Relative humidity;  $PM_{2.5}$ : Fine particles;  $PM_{10}$ : Inhalable particles;  $SO_2$ : Sulfur dioxide; CO: Carbon monoxide;  $NO_2$ : Nitrogen dioxide;  $O_3$ . 8h: Maximum 8-h average concentration of ozone.



**Figure 6 Plots of relative risk by atmospheric pressure at lags 0-7.** A: Relative risk (RR) by atmospheric pressure (AP) at lag 0; B: RR by AP at lag 1; C: RR by AP at lag 2; D: RR by AP at lag 3; E: RR by AP at lag 4; F: RR by AP at lag 5; G: RR by AP at lag 6; H: RR by AP at lag 7. Reference at 748.9 mmHg. RR: Relative risk. AP: Atmospheric pressure.

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Table 2 Spearman correlation coefficients between environmental factors									
	AP	WS	RH	PM <sub>2.5</sub>	PM <sub>10</sub>	SO <sub>2</sub>	со	NO <sub>2</sub>	O <sub>3</sub> _8h
AT	-0.75 <sup>c</sup>	0.07 <sup>c</sup>	0.18 <sup>c</sup>	-0.61 <sup>c</sup>	-0.46 <sup>c</sup>	-0.78 <sup>c</sup>	-0.49 <sup>c</sup>	-0.42 <sup>c</sup>	0.60 <sup>c</sup>
AP		-0.27 <sup>c</sup>	-0.17 <sup>c</sup>	0.50 <sup>c</sup>	0.40 <sup>c</sup>	0.62 <sup>c</sup>	0.41 <sup>c</sup>	0.44 <sup>c</sup>	-0.48 <sup>c</sup>
WS			-0.35 <sup>c</sup>	-0.16 <sup>c</sup>	-0.13 <sup>c</sup>	-0.11 <sup>c</sup>	-0.26 <sup>c</sup>	-0.41 <sup>c</sup>	0.17 <sup>c</sup>
RH				-0.17 <sup>c</sup>	-0.25 <sup>c</sup>	-0.19 <sup>c</sup>	-0.02	-0.06 <sup>c</sup>	-0.21 <sup>c</sup>
PM <sub>2.5</sub>					0.92 <sup>c</sup>	0.77 <sup>c</sup>	0.78 <sup>c</sup>	0.76 <sup>c</sup>	-0.19 <sup>c</sup>
$PM_{10}$						0.69 <sup>c</sup>	0.71 <sup>c</sup>	0.75 <sup>c</sup>	-0.09 <sup>c</sup>
SO <sub>2</sub>							0.67 <sup>c</sup>	0.64 <sup>c</sup>	-0.35 <sup>c</sup>
СО								0.76 <sup>c</sup>	-0.21 <sup>c</sup>
NO <sub>2</sub>									-0.24 <sup>c</sup>

 $^{c}P < 0.001.$ 

AT: Air temperature; AP: Atmospheric pressure; WS: Wind speed; RH: Relative humidity;  $PM_{2.5}$ : Fine particles;  $PM_{10}$ : Inhalable particles;  $SO_2$ : Sulfur dioxide; CO: Carbon monoxide;  $NO_2$ : Nitrogen dioxide;  $O_3$ \_8h: Maximum 8-h average concentration of ozone.



Figure 7 Plots of relative risk by wind speed at lags 0-7. A: Relative risk (RR) by wind speed (WS) at lag 0; B: RR by WS at lag 1; C: RR by WS at lag 2; D: RR by WS at lag 3; E: RR by WS at lag 4; F: RR by WS at lag 5; G: RR by WS at lag 6; H: RR by WS at lag 7. Reference at 2.6 m/s. RR: Relative risk; WS: Wind speed.

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Figure 8 Plots of relative risk by relative humidity at lags 0-7. A: Relative risk (RR) by relative humidity (RH) at lag 0; B: RR by RH at lag 1; C: RR by RH at lag 2; D: RR by RH at lag 3; E: RR by RH at lag 4; F: RR by RH at lag 5; G: RR by RH at lag 6; H: RR by RH at lag 7. Reference at 67.9%. RR: Relative risk; RH: Relative humidity.

interaction effect with WS, indicating that most single effects of air pollutants were consistent at different levels of WS. Generally, when high WS and high concentrations of pollutants coexisted, hospital admissions for depressive disorders did not increase. Finally, the interactions between RH and air pollutants were analyzed, and the results are plotted in Figure 14. No significant interaction effects were found between any pair, indicating that the effects of air pollution were relatively stable across different levels of RH.

### DISCUSSION

Based on daily hospital admission data for depressive disorders from 2015 to 2022 in a hospital in Harbin, China, we obtained environmental data for the same period, including meteorological and ambient air pollution data, and conducted a time-series analysis to investigate the short-term exposure effects of these environmental factors on depressive disorders. Our results showed that meteorological factors, including AT and WS, could sharply influence daily hospital admissions, while AP, RH, and air pollutant NO<sub>2</sub> (immediate, lagged, or cumulatively lagged) had significant but moderate or small effects. We modeled the relationship between meteorological factors and air pollution and found significant interaction effects between AT and  $PM_{25}/PM_{10}/SO_2/CO/O_3_8$  h, AP and  $PM_{25}/CO/NO_2/O_3_8$  h, and WS and SO<sub>2</sub>.

Specifically, we found that the risk of depressive disorder admission increases by 53% when an extremely low temperature (-29 °C, for Harbin) occurs. This finding was consistent with the results of a previous study conducted in Europe[8], but contrary to most similar studies[5,14,33-35], where increased or high AT was associated with increased depressive symptoms or higher hospital admissions. This inconsistency may have resulted from regional differences in the areas of interest selected by each study. Harbin City (45°25′-45°30′N, 126°20–126°25′E) is located in Northeast China and has a typical continental monsoon climate. The highest temperature in the study period was 30.6 °C, indicating that it is never excessively hot in Harbin, unlike in Hong Kong[5] or Shanghai[33]. From reference[6], we know that both low and high temperatures might be important drivers of morbidity in mental disorders and that lower temperatures may have a more general and widespread effect on cause-specific morbidity. The result in Europe[8] even showed a protective



**Figure 9 Plots of relative risk by air pollutant concentrations at lags 0-7.** A: Relative risk (RR) by fine particles concentrations at lags 0-7; B: RR by inhalable particles concentrations at lags 0-7; C: RR by sulfur dioxide<sub>2</sub> concentrations at lags 0-7; D: RR by carbon monoxide concentrations at lags 0-7; E: RR by nitrogen dioxide concentrations at lags 0-7; F: RR by maximum 8-h average concentration of ozone concentrations at lags 0-7. PM<sub>2.5</sub>: Fine particles; PM<sub>10</sub>: Inhalable particles; SO<sub>2</sub>: Sulfur dioxide; CO: Carbon monoxide; NO<sub>2</sub>: Nitrogen dioxide; O<sub>3</sub>\_8h: Maximum 8-h average concentration of ozone; RR: Relative risk.

impact of a higher AT (> 14.2 °C), which may serve as a reference for explaining the zero effects of a higher temperature in Harbin. A famous nickname for Harbin City is "Ice City," indicating its freezing coldness in winter. Studies have shown that exercise interventions[15] and frequent visits to outdoor green spaces[17] effectively improve depression symptoms. Therefore, extremely low temperatures can negatively affect depressive symptoms by limiting outdoor exercises and visits to green spaces. Furthermore, low temperatures usually co-exist with insufficient sunlight in winter, and reduced sunlight exposure, both in intensity and duration, is related to an increased risk of depression, according to previous studies[22,36]. Despite this inconsistency with most similar studies, this study confirmed the importance of AT in depressive admissions.

In addition, we found a 58% increase in depressive disorder admissions when the WS approached zero. We propose two possible mechanisms underlying the effect of low WS. First, as coal-fired heating in the cold period always causes severe air pollution in Harbin[37,38], low WS would worsen the air pollution. Air pollution-induced inflammation of the respiratory airways is associated with depression in vulnerable individuals[39]. Severe air pollution may also decrease outdoor activities and sunlight exposure, thereby increasing the risk of depressive disorder[40]. Hence, low WS during cold winters may be associated with depressive symptoms caused by severe air pollution. Second, a previous study showed that during warmer periods, warm and dry winds have an increasing effect on the concentration of positive ions in the atmosphere, which increases blood and brain serotonin levels[8]. Low WS may not provide this improving effect on depressive symptoms.

We also found relatively small effects of AP, RH, and the air pollutant  $NO_2$ . These results are consistent with previous studies, where high RH levels seem to be pertinent to suicide risk[41] and nitrogen oxides increase the risk of mental health problems, probably *via* mechanisms of inflammation and neuronal injury[35].



Figure 10 Plots of relative risk by cumulative air pollutant concentrations for lags 0-7. A: Relative risk (RR) by cumulative fine particles concentrations at lags 0-7; B: RR by cumulative inhalable particles concentrations at lags 0-7; C: RR by cumulative sulfur dioxide concentrations at lags 0-7; D: RR by cumulative carbon monoxide concentrations at lags 0-7; E: RR by cumulative nitrogen dioxide concentrations at lags 0-7; F: RR by cumulative maximum 8-h average concentration of ozone concentrations at lags 0-7. PM<sub>2.5</sub>: Fine particles; PM<sub>10</sub>: Inhalable particles; SO<sub>2</sub>: Sulfur dioxide; CO: Carbon monoxide; NO<sub>2</sub>: Nitrogen dioxide; O<sub>3</sub>\_8h: Maximum 8-h average concentration of ozone; RR: Relative risk.

The distinctive results of this study were the interactions between AT and  $PM_{25}/PM_{10}/SO_2/CO/O_3_8$  h, AP and  $PM_{25}/CO/NO_2/O_3_8$  h, and WS and SO<sub>2</sub>. After carefully inspecting the patterns of these interactions, we assumed that most interactions corresponded to the relationship between the increased risk of depressive disorder and severe air pollution caused by coal-fired heating. In most significant interactions, typical meteorological factor levels in winter (including low AT and high AP) combined with high levels of air pollutants were associated with depressive symptoms. The interaction between WS and SO<sub>2</sub> was the same, as both high WS plus low SO<sub>2</sub> and low WS plus high SO<sub>2</sub> seemed unfavorable for outdoor activities and sunlight exposure. The increasing effect of low WS plus low SO<sub>2</sub> may appear during warmer periods, as low WS does not improve serotonin levels. The cases of O<sub>3</sub> were different from those of the others. We assumed that the reason for this inconsistency between O<sub>3</sub> and other air pollutants was seasonal differences. The O<sub>3</sub> concentration is typically high in the summer, whereas the concentrations of other pollutants are high in the winter.

The strength of our study lies in the precise effects we modeled and measured, especially the interaction between meteorological factors and ambient air pollution. Although our results indicate the effects of environmental factors on hospital admissions for depressive disorders, they are inconsistent with most similar studies and need to be replicated in other methodologically superior studies. The results cannot be generalized to the entire population of China because the sample came from only one northeastern city and urban population. Patient information was insufficient, which limited further analyses.

## CONCLUSION

Our study suggests that meteorological factors and the air pollutant NO<sub>2</sub> affect daily hospital admissions for depressive disorders and that interaction effects exist between meteorological factors and ambient air pollution. Clinicians and





Figure 11 3D perspective plots of the interaction effects between air temperature and air pollutants on daily hospital admissions for depressive disorder. A: Interaction between air temperature (AT) and fine particles; B: Interaction between AT and inhalable particles; C: Interaction between AT and sulfur dioxide; D: Interaction between AT and carbon monoxide; E: Interaction between AT and nitrogen dioxide; F: Interaction between AT and maximum 8-h average concentration of ozone. AT: Air temperature; PM<sub>2.5</sub>: Fine particles; PM<sub>10</sub>: Inhalable particles; SO<sub>2</sub>: Sulfur dioxide; CO: Carbon monoxide; NO<sub>2</sub>: Nitrogen dioxide; O<sub>3</sub>\_8h: Maximum 8-h average concentration of ozone.

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**Figure 12 3D perspective plots of the interaction effects between atmospheric pressure and air pollutants on daily hospital admissions for depressive disorder.** A: Interaction between atmospheric pressure (AP) and fine particles; B: Interaction between AP and inhalable particles; C: Interaction between AP and sulfur dioxide; D: Interaction between AP and carbon monoxide; E: Interaction between AP and nitrogen dioxide; F: Interaction between AP and maximum 8-h average concentration of ozone. AP: Atmospheric pressure; PM<sub>2,5</sub>: Fine particles; PM<sub>10</sub>: Inhalable particles; SO<sub>2</sub>: Sulfur dioxide; CO: Carbon monoxide; NO<sub>2</sub>: Nitrogen dioxide; O<sub>3</sub>\_8h: Maximum 8-h average concentration of ozone.

patients are encouraged to pay more attention to the environmental effects on depressive symptoms. More stringent air quality control measures may be helpful to protect public mental health. Further studies involving more cities in China and a larger sample should be conducted to enable generalization. Thorough studies into the underlying mechanisms for environment impacting mental health are also warranted.

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Figure 13 3D perspective plots of the interaction effects between wind speed and air pollutants on daily hospital admissions for depressive disorder. A: Interaction between wind speed (WS) and fine particles; B: Interaction between WS and inhalable particles; C: Interaction between WS and sulfur dioxide; D: Interaction between WS and carbon monoxide; E: Interaction between WS and nitrogen dioxide; F: Interaction between WS and maximum 8-h average concentration of ozone. WS: Wind speed;  $PM_{2.5}$ : Fine particles;  $PM_{10}$ : Inhalable particles;  $SO_2$ : Sulfur dioxide; CO: Carbon monoxide;  $NO_2$ : Nitrogen dioxide;  $O_{3-}$ 8h: Maximum 8-h average concentration of ozone.

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Figure 14 3D perspective plots of the interaction effects between relative humidity and air pollutants on daily hospital admissions for depressive disorder. A: Interaction between relative humidity (RH) and fine particles; B: Interaction between RH and inhalable particles; C: Interaction between RH and sulfur dioxide; D: Interaction between RH and carbon monoxide; E: Interaction between RH and nitrogen dioxide; F: Interaction between RH and maximum 8-h average concentration of ozone. RH: Relative humidity; PM<sub>2.5</sub>: Fine particles; PM<sub>10</sub>: Inhalable particles; SO<sub>2</sub>: Sulfur dioxide; CO: Carbon monoxide; NO<sub>2</sub>: Nitrogen dioxide; O<sub>3</sub>\_8h: Maximum 8-h average concentration of ozone.

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## **ARTICLE HIGHLIGHTS**

#### Research background

Environmental factors have been shown to affect individual mental health; however, the relationships and effects of different environmental factors in relatively cold areas have not yet been clarified.

#### **Research motivation**

We studied the effects of environmental factors, including their interaction effects, on daily hospital admissions for depressive disorders, aiming to discover the patterns of interaction between various environmental factors and provide regional references for this research field.

#### Research objectives

To investigate the single and interaction effects of environmental factors, we modeled, measured, and plotted these potential effects and added evidence to explore the complex relationship between environmental factors and human mental health.

#### Research methods

We performed a retrospective study using data from Harbin, China between 2015 and 2022, including daily hospital admissions for depressive disorders, meteorological data, and air pollution data. A time-series analysis was conducted using generalized additive models with quasi-Poisson regression to measure the effect of each single factor on depression. A bivariate response surface model was used to model the interaction effects of different factors. Our data came from a higher-latitude area, offering an opportunity to investigate regional differences in relationship patterns and the effects of environmental factors.

#### Research results

Our results showed that air temperature and wind speed influenced daily hospital admissions. Extremely low temperatures and wind speeds could increase daily hospital admissions for depressive disorders by approximately 50%. atmospheric pressure, relative humidity, and the air pollutant nitrogen dioxide had significant but moderate effects. Interaction effects between three meteorological factors and six air pollutants were discovered.

#### Research conclusions

Meteorological factors and air pollutants have single and interaction effects on daily hospital admissions for depressive disorders, and the effect pattern may be related to coal-fired heating in winter.

#### Research perspectives

Specific mechanisms behind the complex relationships of environmental factors are to be studied.

## FOOTNOTES

Author contributions: Hu T designed and performed the research and wrote the paper; Guo BB designed the research and supervised the report; and Xu ZY, Wang J, and Su Y provided clinical advice.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of The First Psychiatric Hospital of Harbin.

Informed consent statement: This paper is a retrospective study that collects information on cases that have already occurred in the past, is analysed anonymously, does not expose patients' private information, does not cause harm to patients, and successful application for waiver of informed consent has therefore been made.

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

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ORIGINAL ARTICLE

# **Retrospective Study**

# Analysis of influencing factors and the construction of predictive models for postpartum depression in older pregnant women

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# Abstract

# BACKGROUND

Changes in China's fertility policy have led to a significant increase in older pregnant women. At present, there is a lack of analysis of influencing factors and research on predictive models for postpartum depression (PPD) in older pregnant women.

# AIM

To analysis the influencing factors and the construction of predictive models for PPD in older pregnant women.

# **METHODS**

By adopting a cross-sectional survey research design, 239 older pregnant women (≥ 35 years old) who underwent obstetric examinations and gave birth at Suzhou Ninth People's Hospital from February 2022 to July 2023 were selected as the research subjects. When postpartum women of advanced maternal age came to the hospital for follow-up 42 d after birth, the Edinburgh PPD Scale (EPDS) was used to assess the presence of PPD symptoms. The women were divided into a PPD group and a no-PPD group. Two sets of data were collected for analysis, and a prediction model was constructed. The performance of the predictive model was evaluated using receiver operating characteristic (ROC) analysis and the Hosmer-Lemeshow goodness-of-fit test.

# RESULTS

On the 42<sup>nd</sup> day after delivery, 51 of 239 older pregnant women were evaluated with the EPDS scale and found to have depressive symptoms. The incidence rate was 21.34% (51/239). There were statistically significant differences between the PPD group and the no-PPD group in terms of education level (P = 0.004), family relationships (P = 0.001), pregnancy complications (P = 0.019), and mother-infant separation after birth (P = 0.002). Multivariate logistic regression analysis showed that a high school education and below, poor family relationships, pregnancy



complications, and the separation of the mother and baby after birth were influencing factors for PPD in older pregnant women (P < 0.05). Based on the influencing factors, the following model equation was developed: Logit ( P = 0.729 × education level + 0.942 × family relationship + 1.137 × pregnancy complications + 1.285 × separation of the mother and infant after birth -6.671. The area under the ROC curve of this prediction model was 0.873 (95%CI: 0.821-0.924), the sensitivity was 0.871, and the specificity was 0.815. The deviation between the value predicted by the model and the actual value through the Hosmer-Lemeshow goodness-of-fit test was not statistically significant ( $\chi^2$  = 2.749, *P* = 0.638), indicating that the model did not show an overfitting phenomenon.

# **CONCLUSION**

The risk of PPD among older pregnant women is influenced by educational level, family relationships, pregnancy complications, and the separation of the mother and baby after birth. A prediction model based on these factors can effectively predict the risk of PPD in older pregnant women.

Key Words: Older pregnant women; Postpartum depression; Influencing factors; Prediction model

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**Core Tip:** Older pregnant women are more likely to develop postpartum depression (PPD) than younger pregnant women. PPD can harm the physical and mental health of pregnant women, offspring development, and family and social harmony. Here, we investigated the PPD status of 239 older pregnant women. Based on whether the older pregnant women experienced depression 42 d postpartum, we divided them into a PPD group and a no-PPD group. By conducting statistical analysis on two sets of data and constructing a prediction model, we examined the issue of how medical personnel can effectively assess the PPD risk of older pregnant women.

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# INTRODUCTION

Postpartum depression (PPD) is a postpartum mental condition characterized by anxiety, irritability, and extreme depression. In severe cases, hallucinations or suicidal tendencies may occur[1]. PPD not only harms the physical and mental health of pregnant women but also has adverse effects on offspring development, families, and society[2]. Related research reports show that the incidence of PPD among younger pregnant women in China is 14.7%. The incidence of PPD in older pregnant women (≥ 35 years old) is as high as 36.9%[3]. There are some recent studies on PPD in pregnant women, but they are all based on analyses of mental illness history, family relationships, and other aspects [4,5]. There is a lack of exploration on pregnancy complications and the separation of mothers and babies after birth. This results in inadequate clinical measures to prevent PPD, and there is a lack of reporting on predictive models. This study combined the overall situation before, during, and after childbirth to understand the influencing factors of PPD in older pregnant women and construct a risk prediction model to provide guidance for obstetricians in predicting the risk of PPD in older pregnant women and developing treatment measures.

# MATERIALS AND METHODS

# Patient characteristics

Adopting a cross-sectional survey research design, 239 older pregnant women (≥ 35 years old) who underwent obstetric examinations and gave birth in our hospital from February 2022 to July 2023 were selected as the research subjects. According to the Edinburgh PPD Scale (EPDS), the presence or absence of PPD symptoms was measured at 42 d postpartum, and the older pregnant women were divided into a PPD group and a no-PPD group. This study was approved by the Medical Ethics Committee of Suzhou Ninth People's Hospital.

# Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) Women with a gestational age  $\geq$  37 wk at delivery, a single birth, and natural conception; (2) women with normal consciousness and intelligence; (3) women without adverse pregnancy outcomes (stillbirth, abortion, deformity); (4) women who were informed of this study and signed an informed consent form; and (5) women who were evaluated with the EPDS at 42 d postpartum. The exclusion criteria were as follows: (1) Women with comorbid malignant tumors; (2) women with trauma or infection before delivery; (3) women diagnosed with



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depression during any depression screening during pregnancy (early, middle, late) or the prenatal period (prior to delivery)[6]; and (4) women with past mental illness.

## Survey methods

**General information:** By creating a general data collection form, age, education level, birth history, pregnancy complications (pregnancy-induced hypertension, pregnancy-induced diabetes, *etc.*), delivery mode, separation of the mother and infant after birth (referring to the newborn needing to be admitted to the neonatal department for treatment after birth), neonatal feeding mode and other information of the older pregnant women were collected.

**Family relationships:** The Chinese version of the Family Adaptability Cohesion Environment Scale II-CV[7] was used to evaluate the family relationships of the older pregnant women. This scale mainly evaluates intimacy and adaptability. Intimacy refers to the emotional connection between a mother and her family members. Adaptability refers to the ability of a mother to adapt to the different developmental stages of her family and family situation. This scale consists of 30 items. The total score ranges from 30 to 150 points, and items are scored using a 5-point likert-type (1-5 points) scoring method. The higher the score is, the better the family relationship. In this study, a score of  $\leq$  70 indicates a lack of harmonious family relationships; a score of > 70 indicates a harmonious family relationship.

**PPD diagnosis:** At each pregnant woman's follow-up visit at our obstetric clinic on the 42nd day postpartum, we evaluated whether she had PPD symptoms using the EPDS. The scale consists of 10 items, and the total score is 30 points. When the EPDS score of an older mother is  $\geq$  9 points, it indicates the presence of PPD symptoms[8].

## Statistical procedure

Using SPSS 25.0 software for data analysis, the counting data are expressed in terms of the rate and composition ratio [n (%)]. The two groups were compared and subjected to the  $\chi^2$  test. The influencing factors of PPD in older pregnant women were analyzed through multiple logistic regression analysis, and predictive model equations were built based on the influencing factors.

The area under the receiver operating characteristic (ROC) area under curve (AUC) was used to evaluate the predictive efficiency of the model, and the Hosmer-Lemeshow goodness-of-fit test was used to evaluate whether the prediction model showed an overfitting phenomenon. P < 0.05 indicated that the difference was statistically significant.

# RESULTS

## The incidence and univariate analysis of PPD in older pregnant women

On the 42<sup>nd</sup> d after delivery, 239 older pregnant women who attended their outpatient follow-up were included, and 51 were found to have depressive symptoms (PPD group) after evaluation with the EPDS. The incidence rate was 21.34% (51/239); 188 women (no-PPD group) had no depressive symptoms. The comparison between the PPD group and the no-PPD group showed statistically significant differences in terms of education level ( $\chi^2 = 8.290$ , P = 0.004), family relationships ( $\chi^2 = 10.672$ , P = 0.001), pregnancy complications ( $\chi^2 = 5.520$ , P = 0.019), and mother-infant separation after birth ( $\chi^2 = 9.681$ , P = 0.002) (Table 1).

## Multivariate logistic regression analysis of PPD in older pregnant women

The dependent variable was whether the older pregnant women had symptoms of PPD at 42 d postpartum (0 = no; 1 = yes). Features with statistical significance in univariate analysis (education level, family relationships, pregnancy complications, and the separation of the mother and infant after birth) were included as independent variables, and the assigned values are shown in Table 2. After multiple factor logistic regression analysis, it was found that a high school education and below, poor family relationships, pregnancy complications, and the separation of the mother and baby after birth were the influencing factors for PPD in older pregnant women (P < 0.05) (Table 3).

## Construction of a risk prediction model for PPD in older pregnant women

The prediction model was constructed based on the regression coefficients and constant terms shown in Table 2 to obtain the following equation: Logit (P) = 0.729 × education level (0 = college or higher; 1 = high school and below) + 0.942 × family relationships (0 = harmony; 1 = disharmony) + 1.137 × pregnancy complications (0 = no; 1 = yes) + 1.285 × separation of the mother and infant after birth (0 = no; 1 = yes) -6.671. Using the predicted probability value of the model as the test variable, the state variable was the presence or absence of PPD in the older mothers. ROC curves were drawn to analyze and predict the performance of the model. The AUC area under the ROC curve of the prediction model was 0.873 (95%CI: 0.821-0.924), the sensitivity was 0.871, and the specificity was 0.815, which indicates that the model has good differentiation ability (Figure 1). The deviation between the predicted value of the model and the actual value through the Hosmer-Lemeshow goodness-of-fit test was not statistically significant ( $\chi^2$  = 2.749, P = 0.638), indicating that the model showed no overfitting phenomenon.

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## Chen L et al. PPD

## Table 1 Single factor analysis of postpartum depression in older pregnant women (n = 239)

Observations	PPD group ( <i>n</i> = 51)		No-PPD group ( <i>n</i> = 188)		?	Buelue
Characteristics	n	Percent	n	Percent	- X <sup>2</sup>	P value
Age (yr)					2.145	0.143
35-40	40	78.4	163	86.7		
> 40	11	21.6	25	13.3		
Education level					8.290	0.004
High school and below	33	64.7	79	42.0		
College or higher	18	35.3	109	58.0		
Family relationships					10.672	0.001
Harmony	19	37.3	118	62.8		
Disharmony	32	62.7	70	37.2		
Reproductive history					0.920	0.337
Primipara	14	27.5	65	34.6		
Multipara	37	72.5	123	65.4		
Pregnancy complications					5.520	0.019
Yes	20	39.2	43	22.9		
No	31	60.8	145	77.1		
Delivery method					0.045	0.832
Spontaneous labor	22	43.1	78	41.5		
Cesarean section	29	56.9	110	58.5		
Separation of the mother and infant after birth					9.681	0.002
Yes	12	23.5	15	8.0		
No	39	76.5	173	92.0		
Feeding methods of newborns					4.838	0.089
Artificial feeding	11	21.6	19	10.1		
Mixed feeding	18	35.3	79	42.0		
Exclusive breastfeeding	22	43.1	90	47.9		

PPD: Postpartum depression.

Table 2 Variable assignment description				
Variable	Description of valuation			
Education level	0 = college or higher; 1 = high school and below			
Family relationships	0 = harmonious; 1 = disharmony			
Pregnancy complications	0= no; 1= yes			
Separation of the mother and infant after birth	0= no; 1= yes			

# DISCUSSION

China's fertility policy is open, which has resulted in a significant increase in the number of older pregnant women[9]. The incidence of PPD among older pregnant women is relatively high. Some influencing factors for the occurrence of PPD in older pregnant women were identified, and a model was constructed to predict the PPD risk of older pregnant women early, help to take early preventive measures, and reduce the incidence of PPD in older pregnant women.

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Table 3 Multivariate logistic regression analysis results of postpartum depression in older pregnant women							
Variable	β	SE	Wald $\chi^2$	P value	OR (95%CI)		
High school and below	0.729	0.279	6.827	0.009	2.073 (1.199-3.582)		
Incompatible family relationships	0.942	0.349	7.285	0.007	2.565 (1.294-5.083)		
Pregnancy complications	1.137	0.414	7.543	0.006	3.117 (1.385-7.015)		
Separation of the mother and infant after birth	1.285	0.416	9.541	0.002	3.615 (1.599-8.166)		
Constant	-6.671	1.884	12.538	< 0.001			

SE: Standard error; OR: Odds ratio.



# Figure 1 Receiver operating characteristic curve evaluation of the postpartum depression risk prediction model for older pregnant women. AUC: Area under curve.

An analysis of the Chinese PPD population showed that the incidence of PPD was highest within 6 wk after delivery (the postpartum period)[10]. This study found that the incidence of PPD in older pregnant women at 42 d postpartum was 21.34%, which is within the scope of literature reports [11,12]. PPD symptoms in older pregnant women may be caused by various factors. This study further found that a high school education and below, poor family relationships, pregnancy complications, and the separation of the mother and baby after birth were all factors affecting PPD in older pregnant women. Some possible reasons are as follows: (1) Studies have shown that pregnant women with low education levels are prone to fear of childbirth[13]. When a mother has the psychological characteristics of fea, poor cognitive integration, a lack of proactive ways to seek help, and is extremely prone to negative emotions, if she cannot find a positive way to alleviate her fear, she may have a low self-evaluation of postpartum care for her newborn, have an increased psychological burden, and develop PPD. Additionally, a low education level and a poor living environment and family economic situation may also affect PPD risk to some extent<sup>[14]</sup>. The pressure of raising young children is high [15], quality of life is affected [16], and it is easy to generate negative emotions, which triggers PPD symptoms; (2) family relationships play an important role in the family[17]. A woman usually needs care and attention from her mother-in-law after childbirth[18]; differences in cognition between the two generations may result in differences of opinion regarding the care of the newborn and even conflicts. This invisibly causes psychological pressure and burdens for the new mother [19]. As a result, the family environment is not harmonious, which often increases the mental burden on mothers[20]. Severe cases may result in the mother not receiving sufficient family support, thus increasing her risk of PPD occurrence; (3) older pregnant women tend to have diabetes and hypertension during pregnancy[21]. Research shows that, women diagnosed with pregnancy induced hypertension were more likely to have depressive symptoms than their normotensive counterparts<sup>[22]</sup>. These pregnancy complications not only increase the risk of PPD<sup>[23]</sup> but also increase the risk of complications such as postpartum infections and bleeding[24]. Studies have shown that puerperal infection events are significantly correlated with PPD[25]. Which increases the risk of PPD and affects the physical recovery of the mother. Therefore, pregnancy complications are an important factor in increasing PPD; and (4) the health status of newborns is a key concern for mothers and their families. Previous studies have shown that infant health is a contributing factor to PPD in postpartum women[26]. This may be due to the combination of other diseases at birth and the need for a newborn to be transferred to a neonatal department for relevant monitoring and treatment[27], increase maternal concerns about the health status of their children, causing psychological storage of certain negative information, aggravate psychological stress, making it easy for mothers to be emotionally affected by these negative information, increase the risk of postpartum PPD. At the same time, when the newborn is complicated with diseases, the family has to bear a large amount of medical expenses and increase the family burden [28], which significantly increases the probability of PPD in the maternal.

The development of a good prediction model lies in screening effective indicators. This study analyzed the influencing factors of PPD in older pregnant women through multiple logistic regression analysis and built a prediction model based on influencing factors. After analysis, it was found that the area under the ROC curve of the prediction model was 0.873, which indicated that the model has high predictive performance. Some reasons for this are as follows: The model was tested with independent samples in this article, irrelevant indicators were filtered out, related indicators were included, information complementarity was realized, and the predictive performance of the model was enhanced. The difference between the value predicted by the model and the actual value through the goodness-of-fit test was not statistically significant, indicating that there was no overfitting in the model, which is suitable for clinical promotion and application. Therefore, building a model based on the various influencing factors of PPD in older pregnant women can effectively predict PPD risk, providing a new approach for medical personnel to assess high-risk populations early to develop personalized management measures. For example, strengthening psychological counseling and health education for highrisk populations, advising family members to provide material and spiritual support to new mothers, helping mothers relieve stress, guiding mothers and their families in the care of newborns, enhancing maternal feeding confidence, and reducing the incidence of depressive symptoms are some possible management measures.

However, our study still has some limitations: (1) This was a single-center study with a single source of patients, and the representativeness is relatively limited; and (2) the sample size was small, which may lead to biased results. More participants need to be included to validate the conclusion.

# CONCLUSION

The risk of PPD among older pregnant women is closely related to their educational level, family relationships, pregnancy complications, and the admission of newborns to the neonatal department after birth. A PPD risk prediction model for older postpartum women with good discrimination should be constructed.

# **ARTICLE HIGHLIGHTS**

## Research background

Postpartum depression (PPD) is a mental illness that can be caused by multiple factors, including the process of physical recovery in the postpartum period, newborn health, psychological stress, etc. The physiological functions of older pregnant women are far inferior to those of younger women. The process of physical recovery in the postpartum period is slow, and the decrease in a mother's own physiological stress ability makes them more prone to mental and psychological disorders.

## **Research motivation**

Exploring the influencing factors of PPD in older pregnant women and constructing predictive models will provide guidance for the clinical evaluation of PPD risk in older pregnant women and the development of relevant measures.

## Research objectives

This study aimed to identify the influencing factors of PPD in older pregnant women and construct a prediction model based on the influencing factors of PPD in older pregnant women.

## Research methods

This study used a cross-sectional survey to investigate the PPD status of older pregnant women in our hospital and collected their data for analysis.

## Research results

The incidence of PPD in older pregnant women at 42 d postpartum was 21.34%. Among these older pregnant women, a high school education and below, poor family relationships, pregnancy complications, and the separation of the mother and baby after birth were all influencing factors for PPD. A prediction model built based on these factors had high prediction efficiency.

## **Research conclusions**

The risk of PPD among older pregnant women is closely related to their educational level, family relationships, pregnancy complications, and the admission of newborns to the neonatal department after birth. Constructing a PPD risk prediction model for older postpartum women based on the above factors can enable medical staff to perform early assessment of PPD risk for older pregnant women.

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## **Research perspectives**

The influencing factors of PPD in older pregnant women were identified, and a predictive model was constructed based on these influencing factors to determine the risk of PPD in older pregnant women in the future.

# FOOTNOTES

**Author contributions:** Chen L and Shi Y onceived and designed the study; Shi Y guided the study; Chen L collected the clinical date; Chen L and Shi Y analyzed the data; all authors drafted and revised the manuscript.

**Institutional review board statement:** This study was reviewed and approved by the Ethics Committee of Suzhou Ninth People's Hospital.

**Informed consent statement:** All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

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**Observational Study** 

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ORIGINAL ARTICLE

# Relationship between nightmare distress and depressive symptoms in Chinese emergency department nurses: A cross-sectional study

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# Abstract

# BACKGROUND

Most of the recent research on nightmare distress and depressive symptoms has focused on adolescents and students, with less research on the nurse population. Emergency department nurses are at high risk for nightmare distress and depressive symptoms, but no studies have been conducted to explore the relationship between the two; thus, further investigation is needed.

# AIM

To understand the relationship between nightmare distress and depressive symptoms among emergency department nurses in China.

# **METHODS**

A convenience sampling method was used to select 280 emergency department nurses from nine provinces, including Jiangxi, Sichuan, Jiangsu, and Shanxi Provinces. The Chinese version of the Nightmare Distress Questionnaire and the Center for Epidemiological Studies Depression Scale (CES-D) were administered.

# RESULTS

Emergency department nurses' nightmare distress scores were positively associated with depressive symptom scores (r = 0.732), depressed affect (r =0.727), somatic symptoms (r = 0.737), and interpersonal difficulty (r = 0.647). Further multiple linear regression analyses showed that education level, work pressure, self-reported health, and CES-D scores were factors that influenced nightmare distress among Chinese emergency department nurses (P < 0.05).



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## CONCLUSION

Nightmare distress is closely associated with depressive symptoms in Chinese emergency department nurses, and early intervention is recommended for professionals with this type of sleep disorder to reduce the occurrence of depressive symptoms.

Key Words: Nightmare distress; Emergency department nurses; Depressive symptoms; Workplace violence; Observational study; China

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**Core Tip:** Understanding the relationship between nightmare distress and depressive symptoms in emergency department nurses and adopting effective interventions could reduce their incidence in this population. Currently, most studies on nightmare distress and depressive symptoms have focused on adolescents or students, and fewer have examined emergency department nurses. This study is the first to examine the relationship between nightmare distress and depressive symptoms among emergency department nurses, providing a theoretical basis for developing effective interventions.

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# INTRODUCTION

The International Classification of Diseases, 10th Revision[1] defines a nightmare as an extremely disturbing and memorable dream, that is, recurring dreams that involve danger to the health, survival, and dignity of the individual while he or she sleeps. Nightmares are a fearful and distressing experience; when individuals wake after a nightmare, the content of the dream is clearly recalled, and they have difficulty falling asleep[2]. Studies have shown that nightmares not only affect an individual's sleep quality, including insomnia and difficulty falling asleep[3], but are also a major risk factor for suicide, depression, and posttraumatic stress disorder[3-5]. A large sample survey showed that people with nightmare distress are more likely to have depressive symptoms than healthy groups [6]. Most of the recent studies on nightmare distress and depressive symptoms have focused on adolescents and students [2,3,6], but fewer studies have been conducted on the nurse population. Nurses are a high-risk group for nightmare distress<sup>[7]</sup>, especially emergency department nurses, possibly because they often witness patient deaths and severe trauma[8]. Furthermore, due to the special nature of the work environment, these professionals are often subjected to threats, verbal violence, and even physical violence from patients and families [9,10]. Therefore, the aim of this study was to explore the relationship between nightmare distress and depressive symptoms among Chinese emergency department nurses through a crosssectional survey and to inform interventions to improve the working environment of emergency department nurses globally and reduce the occurrence of nightmare distress and depressive symptoms in this population.

# MATERIALS AND METHODS

#### Participants and research design

This study had a multicenter cross-sectional design. In March to April 2023, a convenience sampling method was used to select emergency nurses from tertiary hospitals in nine Chinese provinces (Jiangxi, Sichuan, Jiangsu, Shanxi, Guangdong, Hebei, Zhejiang, Hainan, and Shaanxi). The inclusion criteria were as follows: (1) Employment as an emergency department nurse; and (2) Voluntary participation in this study. The exclusion criteria for nurses were as follows: (1) On leave during the survey period; (2) Trainees; or (3) Receiving further training from the hospital. The rejection criteria were as follows: (1) Completed the questionnaire incompletely; or (2) Had answers to the questionnaire that were obviously repeated. The study was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University (ethics number: IIT2023196).

## Sample

This study collected sociodemographic data and work-related data, and a total of 19 independent variables were included. According to the calculation formula<sup>[11]</sup>, the necessary sample size was 5-10 times that of the number of independent variables; considering the possibility of 20% invalid samples, a minimum of 114 participants were needed. A total of 300 questionnaires were distributed in this study; of these, 280 were finally included in the analysis after excluding invalid responses. The questionnaire return efficiency was 93.33%.



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## Measures

General information: Custom-designed questionnaires were based on published studies in the field [12,13] and expert opinions. The questionnaires covered mainly sociodemographic characteristics (such as sex, age, and marital status) and work-related factors (title, years of work, number of night shifts per month, work pressure, and frequency of violence in the workplace).

Nightmare distress: Nightmare distress was measured using the Chinese version of the Nightmare Distress Questionnaire (NDQ-CV)[14], which is an adaptation of the Nightmare Distress Questionnaire (NDQ)[15]. The NDQ-CV includes a total of 14 items in two dimensions: General nightmare distress and daytime reality perception. Each item is rated on a 5-point scale from 1 (never) to 5 (always), and the total score of the scale ranges from 14 to 70, with higher scores associated with higher levels of nightmare distress. The Cronbach's a coefficient for the total scale in this study was 0.942, and the Kaiser-Meyer-Olkin value was 0.951 (P < 0.05), indicating good reliability.

Depressive symptoms: Depressive symptoms were measured using the Center for Epidemiological Studies Depression Scale (CES-D). The CES-D was developed by Radloff[16] and translated into Chinese by Zhang et al[17]. The scale includes four dimensions: Depressed affect, positive affect, somatic symptoms, and interpersonal difficulty. It has 20 items, four of which are reverse scored. Each item is rated on a scale from 0 to 3, for a total score ranging from 0 to 60. The higher the score, the more severe the depressive symptoms. A score  $\geq 20$  indicates significant depressive symptoms. In this study, the Cronbach's a coefficient of the total scale was 0.866, and the KMO value was 0.956 (P < 0.05), indicating good reliability.

# Quality control

In this study, 20 emergency department nurses were randomly selected for a pilot survey in a tertiary hospital in Jiangxi Province, and the self-report questionnaire section was modified according to the problems that emerged from the pilot survey. Before the questionnaires in the formal experiment were completed, the purpose and importance of this study and the precautions for completing the questionnaires were explained by professionals, and the questionnaires were distributed after obtaining the informed consent of the study subjects. After the questionnaires were collected, the researcher reviewed the content of the completed questionnaires, and two researchers entered the data using Excel software to ensure the accuracy of the data.

## Data analysis

The data were analyzed using SPSS 25.0 statistical software. Continuous data that conformed to a normal distribution are expressed as the mean  $\pm$  SD, and categorical data are expressed as frequencies and percentages. Independent sample t tests were used to detect differences between two groups, and one-way ANOVA was used to compare multiple groups. Pearson correlation analysis was used to explore the relationship between nightmare distress and depressive symptoms; linear regression analysis was used to explore the factors influencing the emergence of nightmare distress among nurses in the emergency department. A threshold of  $\alpha$  = 0.05 (two-sided) was used to indicate significant differences.

# RESULTS

## Descriptive statistics and correlations

A total of 280 emergency department nurses (54 men and 226 women) were included in the study. Among these nurses, most were 26-35 years old (44.3%), had a bachelor's degree (76.1%), had more than 10 years of experience (39.6%), and were married (63.2%). Additionally, most of the nurses were the nurse-in-charge (37.9%), had a monthly income of 5000 to 10000 yuan (62.5%), worked 6 to 10 shifts per month (46.4%), had high pressure (44.6%), and frequently suffered from workplace violence (46.1%). Among those included, 47.5% rated their health as average, 62.5% did not regularly exercise, and the majority were from the emergency departments of Jiangxi Province (31.1%). Further details are shown in Table 1. Using nightmare distress scores as the dependent variable and sociodemographic characteristics as independent variables, comparisons were conducted. The influence of dichotomous variables (e.g., sex) was tested using independent sample *t* tests, and that of variables with multiple categories (*e.g.*, education level) were examined by one-way ANOVA to compare nightmare distress scores among emergency department nurses with different characteristics. The results of the univariate analysis showed that nightmare distress scores of emergency department nurses significantly differed according to sex, education level, working years, monthly income, work pressure, self-reported health, and province (P <0.05; Table 1).

## Correlation of nightmare distress with depressive symptoms

Pearson correlation analysis showed that nightmare distress total score and subscale scores were positively correlated with depressive symptom total score, depressed affect, somatic symptoms, and interpersonal difficulties and negatively correlated with positive affect (P < 0.01), as shown in Table 2.

# Multivariate regression of nightmare distress

Multiple linear regression analysis with the NDQ-CV total score as the dependent variable and sex, education level, years of work, monthly income, work pressure, self-reported health, province, and CES-D total score as the independent variables (assignments are shown in Table 3) showed that education level, work pressure, self-reported health, and CES-



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Table 1 Nightmare distress scores among emergency department nurses with different characteristics							
Variable	Level	N (%)	Score (mean ± SD)	t/F	Degrees of freedom	P value	
Sex	Male	54 (19.3)	42.39 ± 10.83	4.828		< 0.001	
	Female	226 (80.7)	34.61 ± 10.59				
Age (yr)	≤ 25	55 (19.6)	37.55 ± 12.52	0.430	3/276	0.732	
	26-35	124 (44.3)	35.63 ± 11.56				
	36-45	88 (31.4)	35.78 ± 9.70				
	> 45	13 (4.6)	36.85 ± 8.36				
Educational level	Associate degree	52 (18.6)	$34.12 \pm 10.81$	8.441	2/277	< 0.001	
	Bachelor's degree	213 (76.1)	$35.84 \pm 10.87$				
	Graduate degree or above	15 (5.4)	$46.87 \pm 8.90$				
Marital status	Unmarried	92 (32.9)	37.13 ± 12.27	1.048	2/277	0.352	
	Married	177 (63.2)	$35.42 \pm 10.48$				
	Divorced or widowed	11 (3.9)	38.73 ± 8.87				
Years of work	<1	10 (3.6)	$33.70 \pm 11.94$	3.507	3/276	0.016	
	1-5	98 (35.0)	38.92 ± 12.13				
	6-10	61 (21.8)	$35.41 \pm 11.38$				
	> 10	111 (39.6)	34.23 ± 9.30				
Title	Junior nurse	44 (15.7)	33.14 ± 12.31	1.761	3/276	0.155	
	Intermediate nurse	101 (36.1)	35.96 ± 11.64				
	Nurse-in-charge	106 (37.9)	36.76 ± 10.04				
	Senior nurse	29 (10.4)	38.76 ± 10.00				
Monthly income (yuan)	< 5000	55 (19.6)	34.36 ± 11.21	10.647	2/277	< 0.001	
	5000-10000	175 (62.5)	34.86 ± 10.76				
	> 10000	50 (17.9)	$42.42 \pm 9.81$				
Number of night shifts per month	0-5	69 (24.6)	$36.62 \pm 9.48$	2.069	2/277	0.128	
	6-10	130 (46.4)	37.13 ± 11.55				
	> 10	81 (28.9)	34.04 ± 11.33				
Work pressure	None	16 (5.7)	31.94 ± 8.91	4.388	3/276	0.005	
	Mild	16 (5.7)	32.19 ± 10.36				
	Moderate	123 (43.9)	$34.65 \pm 10.31$				
	Severe	125 (44.6)	38.58 ± 11.63				
Violence in the workplace	Never	6 (2.1)	34.33 ± 11.99	0.213	3/276	0.887	
	Rarely	31 (11.1)	35.06 ± 11.97				
	Sometimes	129 (46.1)	$36.03 \pm 11.55$				
	Always	114 (40.7)	36.58 ± 10.27				
Self-reported health	Poor	110 (39.3)	38.75 ± 11.62	5.517	2/277	0.004	
	Average	133 (47.5)	34.65 ± 10.25				
	Good	37 (13.2)	$33.49 \pm 10.82$				
Regular exercise	Yes	105 (37.5)	36.90 ± 9.91	0.920		0.359	
	No	175 (62.5)	35.64 ± 11.69				
Province	Jiangxi	87 (31.1)	$34.30 \pm 10.97$	8.835	8/271	< 0.001	
	Sichuan	51 (18.2)	31.04 ± 9.48				



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Jiangsu	41 (14.6)	33.05 ± 9.24
Shanxi	24 (8.6)	33.42 ± 7.10
Guangdong	12 (4.3)	43.00 ± 9.10
Shaanxi	15 (5.4)	$45.93 \pm 10.22$
Hainan	19 (6.8)	$43.11 \pm 10.79$
Zhejiang	15 (5.4)	$45.07 \pm 7.49$
Hebei	16 (5.7)	$42.94 \pm 12.54$

#### Table 2 Correlation between nightmare distress and depression symptoms among emergency department nurses

Item	NDQ-CV total score	General nightmare distress	Daytime reality perception	CES-D total score	Depressed affect	Somatic symptoms	Interpersonal difficulties	Positive affect
NDQ-CV total score	1							
General nightmare distress	0.983 <sup>a</sup>	1						
Daytime reality perception	0.920 <sup>a</sup>	0.831 <sup>a</sup>	1					
CES-D total score	0.732 <sup>a</sup>	0.722 <sup>a</sup>	0.667 <sup>a</sup>	1				
Depressed affect	0.727 <sup>a</sup>	0.713 <sup>a</sup>	0.673 <sup>a</sup>	0.929 <sup>a</sup>	1			
Somatic symptoms	0.737 <sup>a</sup>	0.713 <sup>a</sup>	0.701 <sup>a</sup>	0.933 <sup>a</sup>	0.864 <sup>a</sup>	1		
Interpersonal difficulties	0.647 <sup>a</sup>	0.628 <sup>a</sup>	0.612 <sup>a</sup>	0.828 <sup>a</sup>	0.792 <sup>a</sup>	0.770 <sup>a</sup>	1	
Positive affect	-0.406 <sup>a</sup>	-0.365 <sup>a</sup>	-0.447 <sup>a</sup>	-0.292 <sup>a</sup>	-0.546 <sup>a</sup>	-0.452 <sup>a</sup>	-0.460 <sup>a</sup>	1

 $^{a}P < 0.001.$ 

NDQ-CV: Chinese version of the Nightmare Distress Questionnaire; CES-D: Center for Epidemiological Studies Depression Scale.

#### Table 3 Independent variables in multivariate regression analysis

Independent variable	Code
Gender	Male = 1, female = 2
Education level	Associate degree = 1, bachelor's degree = 2, graduate degree or above = 3
Years of work	< 1 year = 1, 1-5 years = 2, 6-10 years = 3, > 10 years = 4
Monthly income	< 5000 = 1, 5000-10000 = 2, > 10000 = 3
Work pressure	None = 1, mild = 2, moderate = 3, severe = 4
Self-reported health	Poor = 1, average = 2, $good = 3$
Province	Jiangxi = 1, Sichuan = 2, Jiangsu = 3, Shanxi = 4, Guangdong = 5, Shaanxi = 6, Hainan = 7, Zhejiang = 8, Hebei = 9

D scores were the factors influencing nightmare distress among emergency department nurses (P < 0.05; Table 4).

# DISCUSSION

The results of this study showed a positive correlation between nightmare distress scores and depressive symptom scores, indicating that higher levels of nightmare distress among emergency department nurses are associated with more severe depressive symptoms, which is consistent with the results of previous studies [2,3,18]. Studies have shown that the amygdala, medial prefrontal cortex, hippocampus, and anterior cingulate cortex differ between patients with nightmare

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Table 4 Multiple linear regression analysis results regarding nightmare distress in emergency department nurses						
Item	b	SE	β	t	P value	
Education level	2.051	0.982	0.088	2.088	0.038	
Working pressure	1.154	0.543	0.085	2.124	0.035	
Self-reported health	-1.338	0.649	-0.082	-2.064	0.040	
CES-D total score	0.782	0.053	0.641	14.741	< 0.001	

R2 = 0.570, adjusted R2 = 0.557; CES-D: Center for Epidemiological Studies Depression Scale.

distress and healthy individuals[18,19]. Among these areas, the amygdala is the main area involved in negative emotions such as fear and depression and is the central part responsible for emotions; the anterior cingulate cortex plays a major role in regulating emotions and selective attention; and the hippocampus is the main area supporting memory. The anterior cingulate cortex, prefrontal cortex, and amygdala exhibit high activity in patients with nightmare distress, while the hippocampus is biased toward remembering negative emotions, increasing the risk of depressive symptoms [19]. Chen and Li<sup>[20]</sup> showed that the hypothalamic-pituitary-adrenocortical axis exhibits abnormal activation in patients with nightmare distress, with altered levels of cortisol and melatonin. Changes in the circadian rhythm of melatonin secretion are closely associated with a variety of alterations in individuals; disruption of melatonin homeostasis (lower melatonin levels) is a pathological basis for the induced symptoms of depression in patients. Mahar et al[21] showed that chronic stress leads to attenuation of cell proliferation and neurogenesis, phosphorylation of extracellular signal-regulated kinase, substantial attenuation of 5-hydroxytryptamine (5-HT) levels and 5-HT auto-receptor sensitivity, and reduction of hippocampal inhibition of the hypothalamus-pituitary-adrenal axis, which induces depressive symptoms in nightmareplagued patients. In addition, sleep disorders caused by nightmare disturbances lead to an abnormal increase in inflammatory factors and impairment of autophagy. Li et al<sup>[22]</sup> showed that the levels of inflammatory factors such as NLRP1, tumor necrosis factor- $\alpha$ , and interleukin-1 $\beta$  in the hippocampus of sleep-disturbed mice were markedly increased, and the levels of the autophagy proteins Atg5 and Atg7 were significantly reduced, thus inducing neuroinflammation and consequently depressive symptoms. Levin and Nielsen[23] showed that patients with nightmare distress are more likely to have neurotic, stress-related symptoms and that patients with high levels of nightmare distress have stronger memories of their nightmares because they recollect the dream content during waking hours as a coping mechanism, thus increasing their risk of developing depressive symptoms<sup>[18]</sup>.

In the present study, multiple regression analysis showed that education level, work pressure, self-reported health, and depressive symptoms are independent factors that influence nightmare distress among emergency department nurses. The higher the education level and work pressure, the higher the nightmare distress score of emergency department nurses, possibly because a higher education level is associated with higher self-esteem and higher levels of perceived stress, which in turn increase the risk of nightmare distress[2,24]. Emergency department nurses with poorer self-reported health have lower immunity, and sleep quality decreases when they are overworked, resulting in shorter bouts of deep sleep and increased time in light sleep stages, which are more susceptible to external stimuli, leading to insomnia and nightmare distress<sup>[25]</sup>. Studies have shown that patients with depressive symptoms have altered sleep structure and significantly impaired sleep quality[25]; impaired sleep is an important factor contributing to nightmare distress. In addition, patients with depressive symptoms exhibit long-term states of sadness and uneasiness, which affects the normal regulatory function of the cerebral cortex, thus increasing the risk of nightmare distress[3]. Therefore, it is recommended that hospital administrators should optimize the management of the emergency department, conduct regular psychological symposiums to alleviate the workplace pressure of emergency department nurses, and provide emergency department nurses with spiritual and material support to bolster their sense of professional identity. Emergency department nurses themselves should increase their exercise levels and improve physical health; those with more severe nightmare distress and depressive symptoms should seek psychotherapy treatment, such as cognitive-behavioral therapy [26], imagery rescripting, and imaginal exposure[27], to improve their mental health and psychological resilience, alleviate nightmare distress and depressive symptoms, and improve their quality of life.

## Strengths and limitations

This study has several strengths. First, the sample consisted of emergency department nurses from multiple provinces, and the findings have strong generalizability. Second, this is the first study to explore the relationship between nightmare distress and depressive symptoms among Chinese emergency department nurses; our findings can inform intervention guidelines for reducing nightmare distress and depressive symptoms among emergency department nurses and even other nurses worldwide. Finally, this study adopted an anonymous survey method, which was conducive to obtaining real information about the participants and improved the reliability of its results.

Likewise, this study has some limitations. First, this was a cross-sectional study that only explored the correlation between nightmare distress and depressive symptoms among emergency department nurses; future longitudinal studies are needed to elucidate the causal relationship between the two variables. Second, the assessment instruments used were all self-report questionnaires. Self-report data are highly subjective and may contain information bias, and future studies are needed to verify the relationship between nightmare distress and depressive symptoms among emergency department nurses in conjunction with more specialized diagnostic methods. Finally, emergency department nurses were

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selected from only one hospital in some provinces included this study, which may lead to selection bias, and larger sample sizes should be used in future research.

# CONCLUSION

This study analyzed the relationship between nightmare distress and depressive symptoms among Chinese emergency department nurses and concluded that nightmare distress and depressive symptoms were positively correlated among these professionals. The results of the current analysis showed that emergency department nurses' nightmare distress was influenced by a variety of factors. In the future, researchers should conduct randomized controlled studies of the relationship between nightmare distress and depressive symptoms among emergency department nurses and explore related interventions to reduce the severity of nightmare distress and depressive symptoms among emergency department nurses.

# ARTICLE HIGHLIGHTS

# Research background

Emergency department nurses are at high risk for nightmare distress and depressive symptoms. Understanding the relationship between nightmare distress and depressive symptoms and adopting appropriate interventions can alleviate nightmare distress and depressive symptoms among emergency department nurses. Therefore, this study was conducted to explore the correlation between nightmare distress and depressive symptoms among emergency department nurses through a cross-sectional survey.

## Research motivation

Mental health issues are increasingly pronounced among emergency department nurses. This study aimed to elucidate the relationship between nightmare distress and depressive symptoms among emergency department nurses and to suggest effective interventions to improve their mental health.

## Research objectives

This study investigated emergency department nurses in several provinces in China to explore the relationship between nightmare distress and depressive symptoms in this population.

## Research methods

In this study, 280 emergency department nurses in nine provinces were selected using a convenience sampling method. They completed the Chinese version of the Nightmare Distress Questionnaire and the Center for Epidemiological Studies Depression Scale. SPSS 25.0 statistical software was used to analyze the collected data.

## Research results

The results of this study showed that more severe nightmare distress among emergency department nurses was associated with more pronounced depressive symptoms and that the severity of nightmare distress in this population was influenced by factors such as education level, work stress, and self-reported health.

## Research conclusions

The severity of nightmare distress in emergency department nurses is positively correlated with depressive symptoms. Nightmare distress can cause serious psychological problems, and early interventions for this population can alleviate depressive symptoms. This study provides a theoretical basis for developing effective interventions.

## Research perspectives

This study investigated emergency department nurses in only China; future studies could include those in multiple countries to achieve a comprehensive understanding of the relationship between nightmare distress and depressive symptoms among emergency department nurses and to promote mental health in this profession.

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# FOOTNOTES

Author contributions: Gan QW conceived, researched, analyzed, and wrote this manuscript; Yu R was responsible for conceptualization, research design, and data protection; Lian ZR provided methodological guidance and data analysis; Zheng LL revised the manuscript and oversaw quality control; Yuan YL and Li YP conducted the investigations and data collection.

Institutional review board statement: The study was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University (Ethics number: IIT2023196).

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ORIGINAL ARTICLE

# **Observational Study**

# Mediating role of physical activity in the relationship between psychological distress and intimate relationships among stroke patients

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# Abstract

# BACKGROUND

Stroke patients often experience psychological distress, which can impact their intimate relationships with spouses, subsequently influencing their treatment and recovery. Physical activity is considered a key rehabilitation method for stroke patients. This paper aims to analyze whether psychological distress affects intimate relationship between spouses through physical activity.

# AIM

To explore the mediating effect of physical activity between psychological distress and intimate relationship in stroke patients.

# **METHODS**

A total of 256 stroke patients who underwent treatment at the First People's Hospital of Shangqiu between July 2021 and July 2022 were enrolled in this study. The participants completed questionnaires, including the Kessler Psychological Distress Scale (K10), the Quality of Relationship Index (QRI), International Physical Activity Questionnaire, and a general information questionnaire. Data analysis were performed using SPSS 23.0. The Harman test was employed to detect common method deviations, and Spearman correlation was used for correlation analysis. The mediating effect was assessed using Process 3.4.1, with significance testing of the regression coefficients conducted using the biascorrected percentile Bootstrap method (5000 iterations, 95% confidence interval). Statistical significance was set at P < 0.05.

# RESULTS

The results showed that patients scored an average of  $21.61 \pm 6.44$  points on the K10,  $32.40 \pm 6.19$  points on the QRI; the median physical activity level according to the International Physical Activity Questionnaire was 1861 (566, 2846)



MET min/w. The level of physical activity (the physical activity intensity of the patients reflected by the International Physical Activity Questionnaire-Long Form scale) negatively correlated with psychological distress and intimacy (P < 0.05), and positively correlated with each other (P < 0.05), with the correlation stronger at lower physical activity levels compared to higher ones. The mediating effect of physical activity between psychological distress and intimate relationship was calculated to be 40.23%. Bootstrap analysis further validated the results. The mediating effect of psychological distress on intimate relationships through physical activity level was -0.284, with a confidence interval of -0.409 to -0.163, excluding 0, confirming a significant mediating effect of psychological distress on intimate relationships.

## **CONCLUSION**

Physical activity significantly affects relationship between psychological distress and intimate relationships among stroke patients. Addressing the role of physical activity may have implications for improving patient outcomes and rehabilitation strategies.

Key Words: Stroke; Cross-sectional study; Psychological distress; Intimate relationship; Mediating effect; Physical activity level

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**Core Tip:** Psychological distress is prevalent among stroke patients and can significantly impact their intimate relationships with spouses. Physical activity plays a crucial role in stroke prevention and rehabilitation. This study successfully identified a mediating effect of physical activity on psychological distress and intimate relationships, among stroke patients, confirmed through the Bootstrap test. These findings provide a robust foundation for promoting stroke patient rehabilitation and addressing relationship challenges between spouses.

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# INTRODUCTION

Stroke is not simply a singular disease; rather, it encompasses a group of conditions resulting from impaired brain function caused by cerebrovascular disease<sup>[1]</sup>. With its high incidence, disability, mortality and recurrence rate, stroke has become a global health concern, leading to numerous disabilities and deaths in China[2]. During the post-stroke treatment and rehabilitation process, patients often face stigma and significant psychological distress due to disabilities and disruptions in their self-image<sup>[3]</sup>. Intimate relationships, characterized by communication that fosters intimacy and cooperation within an interdependent framework, play a crucial role in the lives of stroke patients and their spouses[4]. Spouses of stroke patients endure long-term care and economic burdens and experience multiple psychological pressures from family and society, which can negatively impact their relationship and mutual happiness[5]. Research indicates that regular physical activity is a vital preventive measure against stroke, attributed to its potential to improve vascular function and reduce stroke-related risk factors[6]. Therefore, physical activity can potentially aid patient rehabilitation, delay deterioration of their condition, alleviate psychological distress, and mitigate the adverse effects of negative emotions on the relationship between stroke patients and their spouses. However, there is a lack of research on the interplay among physical activity level, psychological distress, and intimacy in the context of stroke patients, both domestically and globally. Therefore, this study aimed to investigate whether the level of physical activity acts as a mediating factor between psychological distress and intimacy in stroke patients. By exploring this relationship, the study seeks to provide novel insights into alleviating the strains within the spousal relationships among stroke patients.

# MATERIALS AND METHODS

# Patient characteristics

This cross-sectional survey involved 256 patients who received stroke-related treatment at the First People's Hospital of Shangqiu between July 2021 and July 2022. Inclusion criteria were as follows: (1) Patients meeting the diagnostic criteria of stroke and diagnosed with stroke through head computed tomography or magnetic resonance imaging; (2) Age under 80 years; (3) Married and cohabitating with a spouse; and (4) Stable condition, clear consciousness, and no obvious language comprehension and expression disorders. Exclusion criteria included: Severe heart, liver or kidney dysfunction, respiratory failure and malignant tumors. The study received ethical approval from the First People's Hospital of



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Shangqiu (2021-125-29), and all participants provided informed consent voluntarily.

# Research tools

Figure 1 illustrates the study process. The following research tools were utilized: (1) General information questionnaire: A self-designed questionnaire capturing demographic data (e.g., age, gender) and disease-related information (e.g., stroke attack, stroke course); (2) The Kessler Psychological Distress Scale (K10)[7]: Used to assess the mental health status of individuals, comprising ten items scored on a five-level scale (score range: 10-50). Higher scores indicate poorer mental health status (Cronbach's  $\alpha$  = 0.896); (3) The Quality of Relationship Index (QRI)[8]: Evaluates satisfaction with intimate relationships using six items rated on a 7-level scale (score range: 6-42). Higher scores indicate higher satisfaction with intimate relationships (Cronbach's  $\alpha$  = 0.943); and (4) International Physical Activity Questionnaire-Long Form (IPAQL) [9]: Measures patients' health-related physical activity over the past week and calculates metabolic equivalents. The questionnaire covers physical activities (work-related, transportation, daily life, sports, and leisure), sedentary behavior, and sleep. Among them, four types of physical activities were evaluated for walking, moderate and severe physical activities, with a total of 27 items. The total metabolic equivalent was used to evaluate the overall physical activity level. Higher scores indicate better physical activity levels (Cronbach  $\alpha$  = 0.827). For analysis, the total metabolic equivalent scores were sorted from small to large, and the first 50% and the last 50% were divided into two groups: Lower activity group and higher activity group.

# Quality control

A sample size of 256 patients was deemed sufficient, meeting the requirement of seven times the number of research variables (based on the largest number of items in the International Physical Activity Questionnaire, 27 items) with a consideration of a 20% missing rate. The investigators, designated by the hospital, distributed and collected the questionnaires on-site with unified guidance. If respondents were unable to complete the questionnaire themselves, investigators assisted them in filling it out based on the their inputs. Missing items were addressed promptly to ensure complete and accurate information was obtained. Double entry and verification of data were conducted to ensure the validity, accuracy and integrity of data entry.

# Statistical analysis

Data processing was performed using SPSS 23.0 (IBM Corp., Armonk, N.Y., United States). Normally distributed measurement data are presented as mean ± SD, while skewed distribution data are expressed as median (M) and quartile (P<sub>25</sub>, P<sub>75</sub>). Count data are expressed as cases (%). The Harman single factor test was used to test for common method bias. Spearman correlation analysis was used for correlation analysis. The mediating effect was tested by Process 3.4.1 (Designed by Andrew F. Hayes based on SPSS), and the significance of regression coefficients was assessed using the bias-corrected percentile Bootstrap method (5000 iterations, 95% confidence interval). Statistical significance was set at P < 0.05

# RESULTS

# Clinical characteristics

A total of 260 questionnaires were distributed, and 256 valid questionnaires were collected, yielding an effective response rate of 98.46%. Among the participants, 195 were male (76.17%) and 61 were female (23.83%). The age distribution was as follows: 28 patients (10.94%) were younger than 45 years, 132 patients (51.56%) were between 45 and 60 years, and 96 patients (37.50%) were older than 60 years. The proportion of patients with junior high school education was the largest (40.23%), and the college or higher had the lowest proportion (14.84%). More than ninety percent of the patients had a year of marriage of more than 20 years (92.19%), and only 7.81% (20/256) of the patients had less than 20 years. There are 71.88% (184/256) of the patients were a first-ever stroke. The type of stroke in 3.52% (9/256) of patients were hemorrhagic, 94.14% (241/256) were ischemic, and 2.34% (6/256) were hybrid. About 7 percent of the patients had selfcare ability and did not need to rely on others for activities, 65.24 % of the patients had mild dependence, and 27.73 % of the patients had moderate and heavy dependence (Table 1).

# Common method bias

To address potential common method bias, quality control measures were implemented during the investigation. Factor analysis of the questionnaires was conducted, and the Harman test showed that the eigenvalue of two factors exceeded 1, accounting for a maximum of 34.59% (< 40%), indicating no significant common method deviation.

# Comparison of K10 and QRI scores

The study found that the average K10 score of the 256 patients was  $21.61 \pm 6.44$  points, while the average QRI score was 32.40 ± 6.19 points. Significant differences in K10 and QRI scores were observed among patients with different physical activity levels (P < 0.05) (Figure 2).

# Correlation analysis

Correlation analysis was performed among psychological distress (K10), intimate relationship (QRI), and metabolic equivalent (IPAQL) in patients with different physical activity levels. In the lower activity group, psychological distress



Table 1 General characteristics of the stroke patients						
Clinical features	Cases	Constituent ratio (%)				
Sex						
Male	195	76.17				
Female	61	23.83				
Age (yr)						
< 45	28	10.94				
45-60	132	51.56				
> 60	96	37.50				
BMI (kg/m <sup>2</sup> )						
< 18.5	6	2.34				
18.5-23.9	71	27.73				
24-27.9	84	32.81				
≥ 28	95	37.12				
Educational						
Primary school or below	73	28.52				
Junior high school	103	40.23				
Senior high school	42	16.41				
College or higher	38	14.84				
Personal monthly income (Yuan)						
< 1000	68	26.56				
1000-3000	61	23.83				
3001-5000	69	26.95				
> 5000	58	22.66				
Payment method						
Medical insurance	219	85.55				
Private expense	37	14.45				
Year of marriage (yr)						
< 10	9	3.51				
10-20	11	4.30				
> 20	236	92.19				
Frequency						
First	184	71.88				
Recurrence	72	28.12				
Course (mo)						
< 6	193	75.39				
6-12	5	1.95				
13-36	12	4.69				
> 36	46	17.97				
Туре						
Hemorrhagic	9	3.52				
Ischemic	241	94.14				
Hybrid	6	2.34				

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Staging						
Acute stage	215	83.98				
Recovery stage	23	8.98				
Sequelae stage	18	7.04				
Dysfunction						
No	223	87.11				
Yes	33	12.89				
Long-term medication history						
No	121	47.27				
Yes	135	52.73				
Combined types of chronic diseases (type)						
0	89	34.77				
1	117	45.70				
2	43	16.80				
≥3	7	2.73				
Self-care ability						
Heavy dependence	5	1.95				
Moderate dependence	66	25.78				
Mild dependence	167	65.24				
No need to rely on	18	7.03				

exhibited negative correlations with intimacy and metabolic equivalent (r = -0.523, P < 0.001; r = -0.528, P < 0.001), while intimate relationship positively correlated with metabolic equivalent (r = 0.631, P < 0.001). In the higher activity group, psychological distress showed negative correlations with intimate relationship and metabolic equivalent (r = -0.481, P < -0.0.001; r = -0.265, P < 0.001), and a positive correlation between intimate relationship and metabolic equivalent (r = 0.476, P < 0.001) was observed (Figure 3).

## Mesomeric effect

The mediating effect analysis revealed that psychological distress significantly influenced intimate relationships in the first step (b = -0.734, P < 0.001), indicating a total effect. In the second step, psychological distress had a significant effect on physical activity level (b = -0.650, P < 0.001). In the third step, both psychological distress and physical activity level significantly affected intimate relationships (b = -0.439, P < 0.001; b = 0.454, P < 0.001), establishing a partially mediated model through activity level (Table 2).

The results were further validated through Bootstrap analysis. It was found that: (1) The total effect of psychological distress on intimate relationships was -0.706, with a confidence interval of -0.786 to -0.625, indicating a significant total effect; (2) The direct effect of psychological distress on intimate relationships was -0.422, with a confidence interval of -0.514 to -0.330 also signifying a significant direct effect; and (3) The mediating effect of psychological distress on intimate relationships through physical activity level was -0.284, with a confidence interval of -0.409 to -0.163, excluding 0, confirming a significant mediating effect of psychological distress on intimate relationships (Table 3).

The level of physical activity was found to act as a mediating factor between psychological distress and intimacy, and the mediating model was established. The psychological distress-physical activity level-intimacy relationship exhibited a partial mediating effect, accounting for 40.23% of the total effect (Figure 4).

# DISCUSSION

Stroke patients often experience language impairment and motor dysfunction, leading to reduced self-care ability and social adaptability, which can result in psychological distress for both the patients and their partners<sup>[10]</sup>. As the main caregivers in the family, partners' attitudes and caregiving abilities directly influence the patient's mood and rehabilitation progress<sup>[11]</sup>. Importantly, alleviating psychological distress can enhance the relationship between patients and partners, foster open communication, and improve marital happiness and overall quality of life for spouses[12]. Previous studies have identified hypertension, diabetes, dyslipidemia, and obesity as risk factors associated with stroke, and physical activity can have a positive impact on these risk factors [13,14]. Physical activity can positively impact these risk factors by improving vasodilation, reducing diabetes, hypertension, dyslipidemia, obesity, and depression risk, thus

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Table 2 Process method to test the mediating effect								
Procedure	Dependent variable	Independent variable	<b>R</b> ²	β	F value	t value	P value	
Step one	Intimate relationship	Psychological distress	0.536	-0.734	296.150	-17.209	< 0.001	
Step two	Physical activity	Psychological distress	0.420	-0.650	185.574	-13.623	< 0.001	
Step three	Intimate relationship	Psychological distress	0.655	-0.439	242.710	-9.063	< 0.001	
		Physical activity		0.454		9.377	< 0.001	

Table 3 Bootstrap analysis of the mediating effect							
Index	Effect	SE	t value	P value	95%CI		
Direct effect	-0.422	0.047	-9.062	< 0.001	-0.514 to -0.330		
Indirect effect	-0.284	0.064	-	-	-0.409 to -0.163		
Total effect	-0.706	0.041	-17.209	< 0.001	-0.786 to -0.625		

CI: Confidence interval.



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Figure 1 Flowchart providing the steps and approach of this study.

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Figure 2 The Kessler Psychological Distress Scale and Quality of Relationship Index scores of stroke patients based on physical activity level. <sup>a</sup>P < 0.05. QRI: The Quality of Relationship Index; K10: The Kessler Psychological Distress Scale.



**Figure 3 Correlation analysis of patients' psychological distress, intimate relationship satisfaction, and physical activity level.** A: Lower activity level group, the correlation between psychological distress [the Kessler Psychological Distress Scale (K10)] and intimate relationship satisfaction [the Quality of Relationship Index (QRI)]; B: Lower activity level group, the correlation between psychological distress (K10) and physical activity level [International Physical Activity Questionnaire-Long Form (IPAQL)]; C: Lower activity level group, the correlation between psychological distress (K10) and physical activity level group, the correlation between psychological distress (K10) and physical activity level [International Physical activity level (IPAQL); D: Higher activity level group, the correlation between psychological distress (K10) and intimate relationship satisfaction (QRI), E: Higher activity level group, the correlation between psychological distress (K10) and intimate relationship satisfaction (QRI); E: Higher activity level group, the correlation between psychological distress (K10) and physical activity level group, the correlation between psychological distress (K10) and physical activity level group, the correlation between psychological distress (K10) and physical activity level group, the correlation between psychological distress (K10) and physical activity level (IPAQL); F: Higher activity level group, the correlation between intimate relationship satisfaction (QRI) and physical activity level (IPAQL). K10: The Kessler Psychological Distress Scale; QRI: The Quality of Relationship Index; IPAQL: International Physical Activity Questionnaire-Long Form.

promoting stroke recovery and delaying deterioration. Therefore, moderate physical activity can aid stroke patients' recovery, reduce their psychological distress, and help restore and improve the relationship between patients and their partners.

The prevalence of psychological distress among stroke patients in China is high, with post-stroke depression and anxiety reported at 84.51% and 75.63%, respectively[15]. Psychological distress significantly hampers treatment, rehabilitation, long-term function, and quality of life for stroke patients, increasing the risk of stroke recurrence and mortality [16]. Physical activity refers to bodily movements that requires energy expenditure, primarily achieved through skeletal muscle contraction. It encompasses both structured and physical exercises as well as daily activity[17]. After illness,



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#### Figure 4 Patient physical activity mediation model.

patients may have reduced self-care ability and fear of exercise, leading to low physical activity levels. In this study, patients with lower physical activity levels had higher scores for psychological distress (K10) and a lower scores for intimate relationship satisfaction (QRI), consistent with previous research findings[18-20]. Unimproved conditions, poor prognosis, and uncertainty about the illness cause psychological problems that lead to patient self-closure and reluctance to express thoughts and feelings to their partners, affecting the intimate relationship between them. Correlation analysis revealed significant associations among psychological distress (K10), intimate relationship satisfaction (QRI), and physical activity levels (IPAQL) in patients with different physical activity levels. Patients with lower physical activity levels showed stronger correlations, suggesting that lower physical activity levels were associated with more distress and reduced communication with spouses, leading to a greater impact on intimate relationships. Unpleasant emotional experiences can disrupt the maintenance of intimate relationships between spouses.

The mediating effect analysis indicated that physical activity levels significantly mediated the relationship between psychological distress and intimate relationship satisfaction, accounting for 40.23% of the total effect. This suggests that physical activity can alleviate the patients' psychological distress and indirectly influence the intimate relationship with their spouses. Several studies have highlighted the correlation between psychological distress and physical activity level [21]. Prolonged exposure to severe and complex stress, exceeding an individual's coping abilities, can not only affect the patient's emotional responding, but also impact their partner's well-being and marital satisfaction. Increasing physical activity, such as participating in sports, can help reduce the risk of adverse psychological states, anxiety and depression during such challenging times. In fact, stroke patients often use physical activity as part of their rehabilitation treatment. This approach can stimulate nerve and limb function recovery, regulate the sympathetic nervous system to alleviate anxiety and depression levels, enhance physical functionality, decrease disability rates, and improve daily living activities [22]. However, it is important to note that in this study, physical activity level represents only one of the mediating factors between psychological distress and intimate relationship satisfaction. This implies that physical activity plays a partial role in mediating these factors. To effectively address patients' psychological distress, a comprehensive consideration of other contributing factors is necessary. Medical professionals play a crucial role in supporting patients during their treatment journey. Encouraging patients to manage their illness correctly, guiding them and their spouses to adopt positive behaviors, and fostering effective coping strategies are essential steps to alleviate psychological distress. Furthermore, enhancing patient cooperation and strengthening the intimacy between spouses can help mitigate both the psychological and physical burdens faced by the couple.

# CONCLUSION

In summary, patients' psychological distress significantly affects their intimate relationship with their spouses, and the level of physical activity serves as a crucial factor between psychological distress and intimate relationship satisfaction. Therefore, it is imperative to focus on improving patients' physical activity levels to reduce psychological distress pressure, enhance communication between spouses, and provide mutual support to foster a stronger sense of intimacy and well-being.

# **ARTICLE HIGHLIGHTS**

## Research background

The psychological distress experienced by stroke patients can significantly impact their intimate relationships with their partners.

## Research motivation

The strain in spousal relationships can further exacerbate the psychological distress of stroke patients and imped their recovery process.



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## Research objectives

This study aims to investigate whether the level of physical activity in stroke patients influences their psychological distress and subsequently affects the quality of their intimate relationships with their spouses.

## Research methods

Data was collected through questionnaires, and the presence of common method bias was verified using Harman test. The mediating effect analysis was conducted to explore the relationships between psychological distress, intimacy, and physical activity levels. The significance of the regression coefficient was verified using Bootstrap.

## Research results

The findings indicate that the physical activity level of stroke patients has an impact on their psychological distress, which, in turn, influences the quality of their intimate relationships with their partners.

## **Research conclusions**

This study has shed light on the interplay between psychological distress, intimate relationships, and physical activity levels among stroke patients, offering new insights to improve the bond between couples in such situations.

## Research perspectives

As a single-center study, this research has certain limitations, and other factors may also influence the outcomes. To enhance the generalizability and validity of the findings, further expansion and external validation are warranted.

# FOOTNOTES

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ORIGINAL ARTICLE

# **Observational Study** Surviving the shift: College student satisfaction with emergency online learning during COVID-19 pandemic

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# Abstract

# BACKGROUND

The coronavirus disease 2019 (COVID-19) epidemic disrupted education systems by forcing systems to shift to emergency online leaning. Online learning satisfaction affects academic achievement. Many factors affect online learning satisfaction. However there is little study focused on personal characteristics, mental status, and coping style when college students participated in emergency online courses.

# AIM

To assess factors related to satisfaction with emergency online learning among college students in Hebei province during the COVID-19 pandemic.

# **METHODS**

We conducted a cross-sectional survey of 1600 college students. The collected information included demographics, psychological aspects of emergent public health events, and coping style. Single factor, correlation, and multiple linear



regression analyses were performed to identify factors that affected online learning satisfaction.

## RESULTS

Descriptive findings indicated that 62.9% (994/1580) of students were satisfied with online learning. Factors that had significant positive effects on online learning satisfaction were online learning at scheduled times, strong exercise intensity, good health, regular schedule, focusing on the epidemic less than one hour a day, and maintaining emotional stability. Positive coping styles were protective factors of online learning satisfaction. Risk factors for poor satisfaction were depression, neurasthenia, and negative coping style.

## CONCLUSION

College students with different personal characteristics, mental status, and coping style exhibited different degrees of online learning satisfaction. Our findings provide reference for educators, psychologists, and school administrators to conduct health education intervention of college students during emergency online learning.

**Key Words:** COVID-19; Emergency online leaning; Online learning satisfaction; College students; Mental status; Coping style; Distance education; Psychiatric status

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**Core Tip:** We evaluated satisfaction with online learning and its associated factors, specifically demographic variables, mental status, and coping style of Chinese college students who participated in emergency online courses during the coronavirus disease 2019 pandemic. Little study has been focused on online acceptance of education. Our findings provide reference for educators, psychologists, and school administrators to conduct health education intervention.

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# INTRODUCTION

The SARS-CoV-2 [hereafter referred to as coronavirus disease 2019 (COVID-19)] pandemic disrupted the educational, economic, and social systems of many countries[1]. To reduce the spread of the virus, countries adopted diverse control strategies such as lockdown and social distancing. COVID-19 hampered education by disrupting student learning goals in many disciplines[2]. The Chinese Ministry of Education suggested "suspending classes without suspending learning". Students across the nation were required to stay at home, and emergency online learning was widely practiced in February 2020[3]. College students urgently turned to distance education to minimize the pandemic's negative impacts on health[4]. Teachers and students were suddenly thrust into an unplanned, unwanted, uncharted, online learning experiment during COVID-19-mandated confinement. This transition increased workload, altered curricula, and eliminated hands-on experiences. In online education, students had to act more autonomously and take more responsibility for their learning[5]. Students from various backgrounds and places were required to adapt to new environmental, technological, and psychological learning conditions that may have affected academics[4,6,7]. The COVID-19 pandemic impacted a cascade of detrimental effects on college student academic performance[8]. Online learning may have been an approach to ensure student knowledge and practice in this special period, although consideration of student satisfaction is mandatory to improve academics[9].

Learning satisfaction reflects how students view their learning experiences, a crucial indicator of online learning effectiveness that is related to academic achievement[10]. The effect of online learning quality on student performance was strongly mediated by satisfaction with online learning, and ensuring student satisfaction can increase the academic success of both the institution and the student[11]. Surveys of online learning satisfaction during the COVID-19 pandemic show conflicting results. Yekefallah *et al*[10] reported that 59% of college students had poor satisfaction with online learning. Arain *et al*[12] found that the level of satisfaction was only 30% among medical students. Wilhelm *et al*[13] found that undergraduate students reported lower levels of learning, engagement, and confidence with the course materials during remote teaching compared with the face-to-face portion of the class. Conversely, Eansor *et al*[14] showed that online learning had high satisfaction levels, and student knowledge scores and self-confidence were raised because of rich online educational resources and the ability to support asynchronous and synchronous communication between students and teachers and between the students themselves[15]. These differing findings make it necessary to clarify satisfaction with online learning and factors that affect satisfaction to provide effective and targeted interventions for academics and mental and physical health.

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Student factors, instructor performance, system quality, and course evaluations all affect online learning satisfaction. Mohammed *et al*[16] found that student factors and system quality were the main elements that influenced student satisfaction. Online learning satisfaction during the COVID-19 lockdown has been assessed by self-efficacy and teacher attitude towards technology integration [17], the interaction between learners and content and lecturers and learners [18], higher education teacher emotional experiences[19], internet connectivity[20], curriculum arrangement[16], and learning environment<sup>[21]</sup>. Furthermore, the COVID-19 pandemic and related restrictions could impact mental health; college students and young adults had a high prevalence of anxiety, depression, sleep problems, and suicidal ideation[22]. Ionescu et al[23] reported that the higher the psychopathology scores, the less online learning satisfaction. Self-directed learning was negatively associated with negative emotions[24]. In addition, University period is a critical time for shaping a student's personality and developing talents; college students have unique psychological characteristics[25]. However, it is not clear which personal characteristics (demographic variables) and which emotions, e.g., depression, fear, neurasthenia, compulsive anxiety or hypochondria, exerted important effects in online learning satisfaction early in the epidemic. Furthermore, coping style is a cognitive and behavioral feature that individuals adopt when facing stressful situations and events. Coping style has a positive and a negative dimension[26]. Positive coping helps individuals to actively manage adversity, which involves asking for advice and finding solutions to adjust to stressors quickly and maintain mental well-being. Negative coping includes social withdrawal and avoidance. Negative coping can increase anxiety and depression and increase the degree of procrastination, which have a negative effect on academic performance [27]. Positive coping is a protective factor for mental health[28]. Nevertheless, factors associated with emergency online learning satisfaction such as coping style have not been adequately defined for the specific pandemic period. Thus, we measured the influence of different characteristics of college students, their psychological state and coping style on their learning satisfaction. Our findings will provide references for colleges to conduct accurate mental health education for students and ensure student satisfaction with online courses. Also, our findings provide understanding of the challenges to fostering a productive learning environment threatened by epidemic outbreak and economic uncertainty.

# MATERIALS AND METHODS

#### Study design

This study was a cross-sectional investigation. An online questionnaire was generated by Wenjuanxing. Wenjuanxing is a web-based, widely used, open questionnaire platform which was developed by the Changsha Ranxing Information and Technology Limited Company. A General Information questionnaire, Psychological questionnaire for Emergent Events of Public Health, and a Simplified Coping Style Questionnaire (SCSQ) were used to measure online satisfaction with learning and associated factors, particularly personal characteristics, mental status, and coping style.

## Participants and data collection

Study participants were undergraduates from four colleges and universities, Hebei Medical University, Hebei Normal University, Hebei Academy of Fine Arts, and Shijiazhuang Information Engineering Vocational College. Convenience sampling was used to select participants. Data collection was conducted between March 23, 2020 and April 9, 2020. Because of the pandemic, the students remained at home in different cities and received electronic questionnaires by WeChat. The questionnaire was distributed by school administrators or teachers.

#### Ethics statement

The study protocol was approved by the Ethics Committee of Hebei General University and complied strictly with ethical requirements. Ethics Review No. (2020) scientific ethics No. (30). All participants provided prior informed consent. Participants were informed that they were free to withdraw at any time. Participants were asked to respond on their own merits and complete survey items in accordance with standardized guidelines. Participant identities were anonymous.

#### General information questionnaire

The questionnaire was designed to investigate mainly demographic and sociological data, *i.e.*, gender, age, current role, grade, nationality, family location, academic year, monthly household income, parents' education, online status, average daily time paying attention to the epidemic, and whether bored at home for long time. In addition, online learning satisfaction, exercise intensity, and health status scores during the epidemic were rated 1-10 from "very dissatisfied or weak or poor" to "very satisfied, strong, good". Satisfaction scores were defined as poor (1-3), general (4-6), and good (7-10) for online courses.

## Psychological Questionnaire for Emergent Events of Public Health

Mental status was assessed with Psychological Questionnaire for Emergent Events of Public Health[29]. This questionnaire is composed of 25 items of five subscales, depression, neurasthenia, fear, compulsion-anxiety, and hypochondria. Each item is scored according to a four-point Likert scale (0 = seldom to 3 = severe) or (0 = seldom to 3 = always). The higher the score of a dimension, the more serious the emotional reaction. The prompt "Possible attitude or practice toward COVID-19" was set to match the actual situation of this survey. The Cronbach's  $\alpha$  of the questionnaire for this assessment was 0.776.

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# SCSQ

Coping styles were assessed with the SCSQ[30]. This questionnaire reflects the attitudes and practices adopted when one experiences setbacks or difficulties. The questionnaire included 20 items in 2 dimensions: Positive coping styles (12 items, *e.g.*, try to look on the bright side, find different ways to solve a problem) and negative coping styles (8 items, *e.g.*, relieve troubles by smoking and drinking, imagine a miracle will come). A 4-point scale was used for each item (0 = never, 1 = seldom, 2 = often, and 3 = always). The total score of the positive coping subscale was from 0 to 36, and the total score of the negative coping subscale was from 0 to 24. High scores reflected high levels of the indicated coping style. The internal consistency coefficients of the positive and negative coping subscale were 0.890 and 0.680, respectively.

# Data analysis

Quantitative data were analyzed with descriptive and exploratory methods. First, the skewness and kurtosis values were used to determine whether the data were normally distributed. Data were skewed, continuous variables were expressed as median (interquartile range) and were assessed by Mann–Whitney test or Kruskal-Wallis H test. Second, the correlation of variables was represented by Pearson's and Spearman's coefficients based on the type of data. Third, multiple linear regression was performed to identify predictors of online learning satisfaction. All statistical analysis was performed using SPSS 22.0 (IBM Corporation). All tests were within the 95% confidence interval. When the confidence interval did not include zero, the mediating effect was significant at P < 0.05. A two-tailed P value of less than 0.05 was considered statistically significant.

# RESULTS

# **Descriptive statistics**

We collected 1600 questionnaires, of which 1580 (98.6%) were effective. The average answer time was  $294 \pm 165$  S. The average age of the participants was 19.9 years (range 17-29 years). There were 342 men (21.6%) and 1238 women (78.4%). There were 191 (12.1%) medicine and 799 (50.6%) and 590 (37.3%) arts and science students. Online learning satisfaction was poor for 3.9% (61/1580) of participants, general for 33.2% (525/1580), and good for 62.9% (994/1580).

# Demographic characteristics and single factor analysis

Table 1 lists demographic characteristics and single factor analysis. In the online learning satisfaction dimension, we found statistical significance (P < 0.05) for age, major, academic year, family location, online status, average time attention to epidemic, whether following a regular schedule, whether bored at home, health condition, and exercise intensity.

## Correlation analysis of online learning satisfaction, mental status, and personal characteristics

We assessed the correlation matrix for all study variables (Table 2). Correlation analyses showed that fear, compulsionanxiety, positive coping style, father's education, online status, exercise intensity, health condition, whether on a regular schedule, and whether bored at home were positively associated with online learning satisfaction. However, depression, neurasthenia, hypochondria, negative coping style, age, and average time of attention to the epidemic were negatively correlated with online learning satisfaction.

# Multiple linear regression of online learning satisfaction

To avoid interaction and multicollinearity, we constructed three models. The dependent variable was learning satisfaction, after confounding factors were excluded. Online learning at schedule, strong exercise intensity, good health, regular schedule, paying attention to epidemic less than one hour, and not bored at home had positive effects (P < 0.05) on online learning satisfaction (Table 3). There was no statistical significance for other independent variables. Depression and neurasthenia had significant negative effects on online learning satisfaction, whereas fear positively affected online learning satisfaction (P < 0.05; Table 4). Positive coping had a significant positive effect on satisfaction with online courses, whereas negative coping had a significant negative effect (P < 0.05; Table 5).

# DISCUSSION

The COVID-19 epidemic disrupted education systems, and college students had to turn to distance education quickly. Online learning satisfaction affected academic achievement. As such, it is critical to assess online learning satisfaction, and we need to be aware of some implications. In this study, we showed a relation between online learning satisfaction, personal characteristics, mental status, and coping style. We propose recommendations and solutions to enhance student online learning satisfaction.

We found that online learning satisfaction was reported good by 62.9% (994/1580) of study participants, but nearly half of college students were less satisfied with their studies. Similarly, Maqableh and Alia[31] found that more than a third of surveyed undergraduate students were dissatisfied with the online learning experience. Our results might suggest that emergency online learning could be an optional approach when surviving the shift during the COVID-19 pandemic. On the basis of similar studies, we suggest that a more plausible explanation is that online learning laid a good foundation for promoting interest, effective in learning because of its unlimited access, ease of use, flexibility, innovation,

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# Zhai XY et al. Emergency online learning satisfaction related factors

Table 1 Demographic characteristics and single factor analysis among college students during coronavirus disease 2019 [median (interquartile range)], (n = 1580)									
Variable	n	Online learning satisfaction	Depression	Neurasthenia	Fear	compulsion-anxiety	Hypochondria	Positive coping style	Negative coping style
Sex									
Female	1238	7.0 (2.0)	0.2 (0.5)	0.2 (0.6)	0.5 (0.7)	0.0 (0.0)	0.0 (0.5)	20.0 (11.0)	7.0 (5.0)
Male	342	7.0 (4.0)	0.3 (0.7)	0.2 (0.6)	0.5 (0.7)	0.0 (0.2)	0.0 (0.0)	19.0 (13.0)	7.0 (6.0)
Z value		-0.56	-2.90	-0.09	-3.56	-1.86	-1.71	-1.56	-1.01
<i>P</i> value		0.606	0.004 <sup>2</sup>	0.928	< 0.001 <sup>2</sup>	0.063	0.088	0.120	0.312
Age (yr)									
17-20	1219	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.5)	0.0 (0.0)	0.0 (0.0)	19.0 (12.0)	7.0 (5.0)
21-29	361	7.0 (3.0)	0.3 (0.7)	0.2 (0.6)	0.5 (0.7)	0.0 (0.0)	0.0 (0.5)	20.0 (11.0)	7.0 (2.00)
Z value		-3.27	-2.98	-2.46	-0.44	-0.53	-1.078	-0.77	-2.59
<i>P</i> value		< 0.001 <sup>2</sup>	0.003 <sup>2</sup>	0.014 <sup>1</sup>	0.660	0.600	0.281	0.440	0.010 <sup>1</sup>
Currently role									
Volunteers	44	7.0 (3.0)	0.3 (0.8)	0.2 (0.8)	0.5 (0.8)	0.0 (0.2)	0.0 (0.5)	17.5 (12.5)	7.5 (7.5)
At home	1536	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.5)	0.0 (0.0)	0.0 (0.0)	19.0 (12.0)	7.0 (5.0)
Z value		-0.62	-1.66	-0.17	-0.03	-1.92	-1.57	-0.05	-0.84
<i>P</i> value		0.538	0.097	0.242	0.974	0.055	0.116	0.961	0.399
Major									
Medicine	191	7.0 (3.0)	0.3 (0.8)	0.4 (0.8)	0.5 (0.7)	0.0 (0.2)	0.0 (0.5)	19.0 (11.0)	7.0 (6.0)
Art	799	7.0 (2.0)	0.2 (0.5)	0.2 (0.6)	0.5 (0.7)	0.0 (0.0)	0.0 (0.0)	19.0 (12.0)	7.0 (6.0)
Science	590	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.7)	0.0 (0.0)	0.0 (0.0)	20.0 (10.0)	6.0 (5.0)
<i>x</i> <sup>2</sup>		14.80	14.42	12.20	2.54	-0.96	-0.32	7.76	7.01
<i>P</i> value		< 0.001 <sup>2</sup>	< 0.001 <sup>2</sup>	0.002 <sup>2</sup>	0.281	0.617	0.850	0.021 <sup>1</sup>	0.030 <sup>1</sup>
Academic year									
1 <sup>st</sup>	708	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.7)	0.0 (0.0)	0.0 (0.0)	18.0 (12.0)	6.0 (7.0)
2 <sup>nd</sup>	308	7.5 (3.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.5)	0.0 (0.0)	0.0 (0.5)	20.0 (13.0)	7.0 (6.0)
3 <sup>rd</sup>	430	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.5)	0.0 (0.0)	0.0 (0.6)	22.0 (10.3)	7.0 (5.0)
$4^{ m th}$	134	7.0 (3.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.8)	0.0 (0.2)	0.0 (0.5)	19.5 (11.3)	7.0 (6.0)

<i>x</i> <sup>2</sup>		13.48	-0.49	1.84	0.37	2.339	3.104	36.63	15.21
<i>P</i> value		0.004 <sup>2</sup>	0.181	0.607	0.946	0.505	0.376	< 0.001 <sup>2</sup>	0.002 <sup>2</sup>
Family location									
Country	865	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.7)	0.0 (0.6)	0.0 (0.0)	19.0 (11.5)	7.0 (5.0)
Town	292	7.0 (3.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.7)	0.0 (0.0)	0.0 (0.4)	20.0 (11.0)	7.0 (5.0)
City	423	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.5)	0.0 (0.2)	0.0 (0.0)	20.0 (12.0)	7.0 (6.0)
<i>x</i> <sup>2</sup>		10.24	4.73	1.75	0.38	4.42	0.101	16.05	10.77
<i>P</i> value		0.006 <sup>2</sup>	0.093	0.417	0.829	0.110	0.951	< 0.001 <sup>2</sup>	0.005 <sup>b</sup>
Nationalities									
Ethnic minorities	71	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.8)	0.0 (0.0)	0.0 (0.0)	17.0 (11.0)	7.0 (5.0)
Han Chinese	1509	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.5)	0.0 (0.0)	0.0 (0.0)	20.0 (12.0)	7.0 (6.0)
Z value		-0.95	-0.74	-0.86	-0.49	-0.32	-1.03	-0.90	-0.47
<i>P</i> value		0.342	0.460	0.389	0.625	0.749	0.304	0.367	0.639
Whether student cadres									
Yes currently	770	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.7)	0.0 (0.0)	0.0 (0.0)	19.0 (11.0)	7.0 (5.0)
Used to be	436	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.7)	0.0 (0.2)	0.0 (0.0)	20.0 (11.0)	7.0 (6.0)
No	374	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.5)	0.0 (0.0)	0.0 (0.0)	20.0 (12.0)	7.0 (5.0)
<i>x</i> <sup>2</sup>		1.28	5.20	1.30	4.46	6.49	3.41	6.62	3.21
<i>P</i> value		0.528	0.074	0.521	0.108	0.039 <sup>a</sup>	0.181	0.037 <sup>a</sup>	0.201
Monthly household income (Yuan)									
< 5000	950	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.7)	0.0 (0.0)	0.0 (0.0)	19.0 (12.0)	7.0 (5.0)
5000-10000	523	7.0 (2.0)	0.2 (0.5)	0.2 (0.6)	0.5 (0.7)	0.0 (0.0)	0.0 (0.0)	20.0 (12.0)	7.0 (6.0)
10000	107	7.0 (2.0)	0.3 (0.8)	0.4 (0.6)	0.7 (0.7)	0.0 (0.2)	0.0 (0.5)	20.0 (13.0)	8.0 (6.0)
<i>x</i> <sup>2</sup>		0.35	4.26	4.65	2.52	4.78	0.40	5.68	3.49
<i>P</i> value		0.840	0.119	0.098	0.284	0.092	0.819	0.058	0.174
Online status									
No network or not well	46	5.5 (3.0)	0.4 (1.2)	0.4 (1.3)	0.6 (0.7)	0.0 (0.5)	0.0 (0.1)	16.0 (12.3)	7.0 (7.5)
Can not online learning at schedule	16	4.0 (3.8)	0.8 (0.7)	1.0 (0.8)	0.8 (0.8)	0.1 (0.9)	0.0 (0.5)	17.0 (12.0)	8.0 (6.5)

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Can online learning at schedule	1518	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.5)	0.0 (0.0)	0.0 (0.0)	20.0 (12.0)	7.0 (5.0)
$\chi^2$		49.80	17.92	29.13	6.90	20.59	1.09	10.57	0.93
<i>P</i> value		< 0.001 <sup>2</sup>	< 0.001 <sup>2</sup>	< 0.001 <sup>2</sup>	0.032 <sup>1</sup>	< 0.001 <sup>2</sup>	0.579	0.005 <sup>2</sup>	0.628
Average time attention to epidemic									
Almost all day	165	7.0 (3.5)	0.0 (0.5)	0.2 (0.6)	0.7 (0.8)	0.0 (0.0)	0.0 (0.5)	20.0 (11.5)	7.0 (5.0)
About 1-3 h or more	231	8.0 (3.0)	0.2 (0.5)	0.2 (0.6)	0.7 (0.7)	0.0 (0.0)	0.0 (0.5)	21.0 (11.0)	6.0 (5.0)
<1 h	1132	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.5)	0.0 (0.0)	0.0 (0.0)	19.0 (12.0)	7.0 (6.0)
Not concerned	52	5.0 (3.0)	0.2 (0.8)	0.2 (0.8)	0.3 (0.5)	0.0 (0.2)	0.0 (0.0)	14.5 (17.5)	6.5 (6.8)
$\chi^2$		43.39	2.23	1.03	14.75	3.45	1.37	22.51	0.73
<i>P</i> value		< 0.001 <sup>2</sup>	0.526	0.794	0.002 <sup>2</sup>	0.327	0.713	< 0.001 <sup>2</sup>	0.866
Whether regular schedule									
No	427	6.0 (3.0)	0.5 (0.7)	0.4 (0.6)	0.7 (0.7)	0.0 (0.2)	0.0 (0.5)	21.0 (12.0)	7.0 (5.0)
Yes	1153	7.0 (2.5)	0.0 (0.5)	0.2 (0.4)	0.5 (0.7)	0.0 (0.0)	0.0 (0.0)	17.0 (9.0)	7.0 (5.0)
Z value		-9.97	-11.51	-9.979	-4.62	-7.05	-2.22	-6.32	-3.89
<i>P</i> value		< 0.001 <sup>2</sup>	0.027 <sup>1</sup>	< 0.001 <sup>2</sup>	< 0.001 <sup>2</sup>				
Whether bored at home for long time									
Yes	643	7.0 (3.0)	0.3 (0.8)	0.4 (0.8)	0.7 (0.7)	0.0 (0.2)	0.0 (0.5)	19.0 (9.0)	7.0 (5.0)
No	937	7.0 (2.0)	0.0 (0.5)	0.2 (0.4)	0.5 (0.7)	0.0 (0.0)	0.0 (0.0)	20.0 (12.0)	7.0 (5.0)
Z value		-6.86	-10.73	-9.54	-4.52	-6.86	-3.05	-2.31	-4.35
<i>P</i> value		< 0.001 <sup>2</sup>	0.002 <sup>2</sup>	0.021 <sup>1</sup>	< 0.001 <sup>2</sup>				
Mother's education									
Junior secondary and below	975	7.0 (2.0)	0.7 (0.7)	0.2 (0.6)	0.5 (0.7)	0.0 (0.0)	0.0 (0.0)	19.0 (12.0)	7.0 (5.0)
High School	358	7.0 (3.0)	0.7 (0.7)	0.2 (0.6)	0.5 (0.7)	0.0 (0.0)	0.0 (0.0)	19.0 (12.0)	7.0 (6.0)
University and above	247	7.0 (2.0)	0.7 (0.7)	0.2 (0.6)	0.5 (0.7)	0.0 (0.0)	0.0 (0.0)	21.0 (13.0)	7.0 (6.0)
$\chi^2$		3.38	0.23	0.33	1.85	0.67	0.50	2.08	2.27
<i>P</i> value		0.185	0.890	0.853	0.396	0.710	0.779	0.353	0.322
Father's education									
Junior secondary and below	963	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.5)	0.0 (0.0)	0.0 (0.0)	19.0 (12.0)	7.0 (5.0)
High School	348	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.8)	0.0 (0.0)	0.0 (0.5)	19.0 (12.0)	7.0 (6.0)
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University and above	269	7.0 (2.0)	0.2 (0.7)	0.2 (0.6)	0.5 (0.7)	0.0 (0.1)	0.0 (0.0)	20.0 (12.5)	7.0 (6.0)
<i>x</i> <sup>2</sup>		4.88	0.54	0.68	2.08	2.05	2.18	1.95	1.11
<i>P</i> value		0.087	0.763	0.711	0.354	3.359	0.337	0.378	0.575
Health condition									
Poor (grade 1-3)	28	4.5 (4.0)	0.9 (1.3)	0.9 (1.4)	0.7 (0.8)	0.2 (0.6)	0.0 (0.5)	14.0 (11.5)	8.5 (6.5)
General (grade 4-6)	239	6.0 (2.0)	0.5 (0.7)	0.6 (0.6)	0.7 (0.7)	0.0 (0.2)	0.0 (0.5)	17.0 (10.0)	8.0 (6.0)
Good (grade 7-10)	1313	7.0 (2.0)	0.2 (0.5)	0.2 (0.4)	0.5 (0.7)	0.0 (0.0)	0.0 (0.0)	20.0 (12.0)	6.0 (5.0)
<i>x</i> <sup>2</sup>		168.63	113.22	91.40	20.51	97.75	21.05	24.56	21.62
$\chi^2$ <i>P</i> value		168.63 < 0.001 <sup>2</sup>	113.22 < 0.001 <sup>2</sup>	91.40 < 0.001 <sup>2</sup>	20.51 < 0.001 <sup>2</sup>	97.75 < 0.001 <sup>2</sup>	21.05 < 0.001 <sup>2</sup>	24.56 < 0.001 <sup>2</sup>	21.62 < 0.001 <sup>2</sup>
χ <sup>2</sup> P value Exercise intensity		168.63 < 0.001 <sup>2</sup>	113.22 < 0.001 <sup>2</sup>	91.40 < 0.001 <sup>2</sup>	20.51 < 0.001 <sup>2</sup>	97.75 < 0.001 <sup>2</sup>	21.05 < 0.001 <sup>2</sup>	24.56 < 0.001 <sup>2</sup>	21.62 < 0.001 <sup>2</sup>
χ <sup>2</sup> P value Exercise intensity Weak (grade 1-3)	272	168.63 < 0.001 <sup>2</sup> 5.0 (3.0)	113.22 < 0.001 <sup>2</sup> 0.5 (0.7)	91.40 < 0.001 <sup>2</sup> 0.4 (0.6)	20.51 < 0.001 <sup>2</sup> 0.7 (0.7)	97.75 < 0.001 <sup>2</sup> 0.0 (0.2)	21.05 < 0.001 <sup>2</sup> 0.0 (0.5)	24.56 < 0.001 <sup>2</sup> 17.5 (10.0)	21.62 < 0.001 <sup>2</sup> 8.0 (6.0)
χ <sup>2</sup> P value Exercise intensity Weak (grade 1-3) General (grade 4-6)	272 702	168.63 < 0.001 <sup>2</sup> 5.0 (3.0) 7.0 (3.0)	113.22 < 0.001 <sup>2</sup> 0.5 (0.7) 0.2 (0.7)	91.40 < 0.001 <sup>2</sup> 0.4 (0.6) 0.2 (0.6)	20.51 < 0.001 <sup>2</sup> 0.7 (0.7) 0.5 (0.7)	97.75 < 0.001 <sup>2</sup> 0.0 (0.2) 0.0 (0.0)	21.05 < 0.001 <sup>2</sup> 0.0 (0.5) 0.0 (0.0)	24.56 < 0.001 <sup>2</sup> 17.5 (10.0) 19.0 (11.3)	21.62 < 0.001 <sup>2</sup> 8.0 (6.0) 7.0 (6.0)
x <sup>2</sup> P value Exercise intensity Weak (grade 1-3) General (grade 4-6) Strong (7-10)	272 702 606	168.63 < 0.001 <sup>2</sup> 5.0 (3.0) 7.0 (3.0) 8.0 (2.0)	113.22 < 0.001 <sup>2</sup> 0.5 (0.7) 0.2 (0.7) 0.0 (0.3)	91.40 < 0.001 <sup>2</sup> 0.4 (0.6) 0.2 (0.6) 0.2 (0.4)	20.51 < 0.001 <sup>2</sup> 0.7 (0.7) 0.5 (0.7) 0.5 (0.7)	97.75 < 0.001 <sup>2</sup> 0.0 (0.2) 0.0 (0.0) 0.0 (0.0)	21.05 < 0.001 <sup>2</sup> 0.0 (0.5) 0.0 (0.0) 0.0 (0.0)	24.56 < 0.001 <sup>2</sup> 17.5 (10.0) 19.0 (11.3) 21.0 (12.0)	21.62 < 0.001 <sup>2</sup> 8.0 (6.0) 7.0 (6.0) 6.0 (6.0)
$\chi^2$ <i>P</i> value Exercise intensity Weak (grade 1-3) General (grade 4-6) Strong (7-10) $\chi^2$	272 702 606	168.63 < 0.001 <sup>2</sup> 5.0 (3.0) 7.0 (3.0) 8.0 (2.0) 382.38	113.22 < 0.001 <sup>2</sup> 0.5 (0.7) 0.2 (0.7) 0.0 (0.3) 129.73	91.40 < 0.001 <sup>2</sup> 0.4 (0.6) 0.2 (0.6) 0.2 (0.4) 91.37	20.51 < 0.001 <sup>2</sup> 0.7 (0.7) 0.5 (0.7) 0.5 (0.7) 21.38	97.75 < 0.001 <sup>2</sup> 0.0 (0.2) 0.0 (0.0) 0.0 (0.0) 43.24	21.05 < 0.001 <sup>2</sup> 0.0 (0.5) 0.0 (0.0) 0.0 (0.0) 17.25	24.56 < 0.001 <sup>2</sup> 17.5 (10.0) 19.0 (11.3) 21.0 (12.0) 17.13	21.62 < 0.001 <sup>2</sup> 8.0 (6.0) 7.0 (6.0) 6.0 (6.0) 22.50

 ${}^{1}P < 0.05.$  ${}^{2}P < 0.01$  (two-tailed).

repeatedly watching for the future and review, and online learning was effective, applicable and acceptable in education [32]. However the challenge is to find the associated factors and take measures to improve satisfaction according to those factors.

Our findings indicated that college students who participated in online learning at schedule were more satisfied than students who could not get online either because of a lack of a schedule or no network accessibility. That is to say, online learning satisfaction may be related to the degree of participation. Similarly, Hensley *et al*[33] found that students who were able to participate in online courses at schedule had greater learning satisfaction and were more likely to complete their courses successfully. Also, mobile connections and the quality of internet were main factors related to student negative emotions that associated with the quality, performance, and timeliness of study obligations[34]. We suggest forming a home-school joint mechanism, constructing more and improving existing networks, and urging students to attend classes at schedule, to enhance participation and increase online learning satisfaction.

We found that strong exercise intensity, good health, and regular schedule were positively associated with learning satisfaction. Zhang *et al*[35] reported that college students who participated in physical activity < 3 d/wk had symptoms of depression compared with students who exercised  $\geq$ 3 d/wk. There was also an interaction between long screen use,

Table 2 Correlation analysis of online learning satisfaction, mental status and characteristics																
Factors	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Online learning satisfaction	-															
Depression	-0.307 <sup>3</sup>	-														
Neurasthenia	-0.245 <sup>3</sup>	0.624 <sup>3</sup>	-													
Fear	0.091 <sup>3</sup>	0.381 <sup>3</sup>	0.575 <sup>3</sup>	-												
Compulsion-anxiety	0.193 <sup>3</sup>	0.531 <sup>3</sup>	0.490 <sup>3</sup>	0.301 <sup>3</sup>	-											
Hypochondria	-0.075 <sup>2</sup>	0.271 <sup>3</sup>	0.397 <sup>3</sup>	0.463 <sup>3</sup>	0.289 <sup>3</sup>	-										
Positive coping style	0.122 <sup>3</sup>	-0.085 <sup>2</sup>	-0.089 <sup>3</sup>	0.057 <sup>1</sup>	-0.104 <sup>3</sup>	-0.001	-									
Negative coping style	-0.089 <sup>3</sup>	0.274 <sup>3</sup>	0.264 <sup>3</sup>	0.220 <sup>3</sup>	0.212 <sup>3</sup>	0.162 <sup>3</sup>	0.363 <sup>3</sup>	-								
Age	-0.093 <sup>3</sup>	0.069 <sup>2</sup>	0.054	0.030	0.005	0.043	0.023	0.036	-							
Father's education	0.055 <sup>1</sup>	0.005	-0.018	-0.024	0.024	-0.013	0.031	0.026	-0.057 <sup>1</sup>	-						
Online status	0.171 <sup>3</sup>	-0.099 <sup>3</sup>	0.118 <sup>3</sup>	-0.044	0.111 <sup>3</sup>	-0.017	0.080 <sup>2</sup>	-0.020	-0.018	-0.019	-					
Exercise intensity	0.537 <sup>3</sup>	-0.305 <sup>3</sup>	-0.264 <sup>3</sup>	-0.119 <sup>3</sup>	-0.169 <sup>3</sup>	-0.097 <sup>3</sup>	0.111 <sup>3</sup>	-0.113 <sup>3</sup>	-0.184 <sup>3</sup>	0.044	0.073 <sup>2</sup>	-				
Health condition	0.418 <sup>3</sup>	-0.351 <sup>3</sup>	-0.298 <sup>3</sup>	-0.166 <sup>3</sup>	-0.290 <sup>3</sup>	-0.182 <sup>3</sup>	0.101 <sup>3</sup>	-0.161 <sup>3</sup>	-0.180 <sup>3</sup>	0.020	0.096 <sup>3</sup>	0.462 <sup>3</sup>	-			
Average time attention to epidemic	-0.132 <sup>3</sup>	0.035	-0.005	-0.088 <sup>3</sup>	0.023	-0.029	-0.094 <sup>3</sup>	0.010	0.019	-0.016	-0.022	-0.144 <sup>3</sup>	-0.138 <sup>3</sup>	-		
Whether regular schedule	0.251 <sup>3</sup>	-0.290 <sup>3</sup>	-0.251 <sup>3</sup>	-0.116 <sup>3</sup>	-0.177 <sup>3</sup>	-0.056 <sup>1</sup>	0.159 <sup>3</sup>	-0.098 <sup>3</sup>	-0.044	0.060 <sup>1</sup>	0.105 <sup>3</sup>	0.284 <sup>3</sup>	0.224 <sup>3</sup>	-0.030	-	
Whether bored at home for long time	0.173 <sup>3</sup>	-0.270 <sup>3</sup>	-0.204 <sup>3</sup>	-0.114 <sup>3</sup>	-0.173 <sup>3</sup>	-0.077 <sup>2</sup>	0.058 <sup>1</sup>	-0.110 <sup>3</sup>	-0.053 <sup>1</sup>	-0.013	0.091 <sup>3</sup>	0.121 <sup>3</sup>	0.104 <sup>3</sup>	-0.016	0.183 <sup>3</sup>	-

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 ${}^{1}P < 0.05.$  ${}^{2}P < 0.01.$  ${}^{3}P < 0.001$  (two-tailed).

less physical activity, and symptoms of depression. High levels of depression were associated with difficulty in paying attention to academics[36] and ultimately deficient learning satisfaction. A poor physical condition leads to lack of energy, which directly affects learning satisfaction. College students who work and sleep irregularly often use the screen too long before going to bed; this behavior can cause sleep deprivation and sleep rhythm disorder, increased sleep-related disorders[37], induced adverse emotions such as anxiety and depression[38], affected cognitive function and learning [39], and eventually poor learning satisfaction. Also, sleep disturbance predicts the development and persistence of posttraumatic stress disorder and depression[40] which impair health and academic performance. Therefore, we suggest that a network interactive platform of individual-family-school-society should be established as an effective linkage mechanism to make sports and exercise programs congenial and encourage college students to participate in sports and exercise at home, or receive exercise prescription teaching to mobilize student initiative, enthusiasm, an consciousness,

Table 3 Demographic characteristics with online	earning	satisfaction (Mo	odel 1)		
Variable	Unstan coeffici	dardized ents	Standardized coefficients beta	t value	P value
	В	Std. Error			
Can online learning at schedule (reference)					
Can not online learning at schedule	-2.490	0.394	-0.129	-6.327	< 0.001
No network or not well	-0.981	0.236	-0.085	-4.156	< 0.001
Exercise intensity	0.334	0.020	0.401	16.860	< 0.001
Health condition	0.166	0.025	0.158	6.671	< 0.001
Whether regular schedule					
No (reference)					
Yes	0.266	0.094	0.061	2.828	0.005
Average time attention to epidemic					
< 1 h (reference)					
Not concerned	-0.889	0.223	-0.082	-3.989	< 0.001
Whether bored at home for long time					
Yes (reference)					
No	0.343	0.082	0.087	4.199	< 0.001

#### Table 4 Metal status with online learning satisfaction (Model 2)

Variable	Unstandardized c	oefficients	Standardized coefficients hate	<u>tvoluo</u>	P value	
	В	Std. Error	Standardized coemclents beta	<i>t</i> value		
Depression	-0.776	0.134	-0.199	-5.807	< 0.001	
Neurasthenia	-0.654	0.151	-0.163	-4.334	< 0.001	
Fear	0.337	0.111	0.087	3.031	0.002	

### Table 5 Metal status with online learning satisfaction (Model 3)

Variable	Unstandardized	coefficients	Unstandardized coefficients	<u>fuelue</u>	Ryalua	
Variable	В	Std. Error	Unstanuaruizeu coemcients	<i>t</i> value	Pvalue	
Positive coping style	0.040	0.006	0.172	6.383	< 0.001	
negative coping style	-0.061	0.012	-0.140	-5.183	< 0.001	

and to expand personalities<sup>[41]</sup>. As well, students need to keep regular bedtimes and wake-up times to promote physical and mental health and ensure online learning satisfaction.

Our data suggest that low levels of online learning satisfaction were more likely to be reported by students who spent more than one hour per day looking for information about COVID-19. Previous studies have been focused on the relation between depression, anxiety, and online learning satisfaction. Wong et al[42] reported that students who had poor online learning satisfaction were more likely to experience stress. Kecojevic et al[36] found that students who spent more than an hour a day searching for information about COVID-19 were more likely to report higher levels of anxiety, depression, and somatization. These findings demonstrate that excessive attention to the epidemic was associated with high levels of anxiety, depression, and difficulty paying attention to academics, which led to low academic satisfaction. Additionally, there should be organized learning about COVID-19 to improve protection skills and avoid gossip and information overload.

Our findings indicate that college students who were bored staying at home for a long time were more likely to experience poor online learning satisfaction. Giusti et al[43] reported that students who studied at home either alone or with classmates were nearly three times more likely to have poor academic performance. Li et al[44] found that college students who lived at home for a long time tended to lack social interaction and support, and they felt lonely; family dysfunction, low social support, and low physical exercise have negative impacts on mental status. Similarly, Wissing et

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al[45] mentioned that perceived peer support can promote collaborative learning and improve medical student learning satisfaction and participation. Therefore, in a special period of limit, we suggest that relevant organizations guide college students to increase contact and interaction with teachers and classmates and provide social and family support to promote positive feelings of long-term home confinement.

We found that high levels of depression and neurasthenia and negative coping styles had negative effects on online learning satisfaction, whereas positive coping styles had positive effects. On the basis of the control-value theory, investigators consider academic emotion to be an important factor that affects student learning satisfaction and academic performance in online learning context; negative adaptive coping strategies are associated with depression and anxiety [46]. Loneliness causes depression and anxiety, whereas procrastination completely mediates the effect of depression on academic performance<sup>[47]</sup>. Neurasthenia did not disappear; it continues to enjoy a marginal life in international classification schemes and is a common diagnosis in China[48]. Also, International Classification of Diseases (ICD)-11 Bodily Distress Disorder encompasses Neurasthenia which in the ICD-10 was classified in the grouping of "Other neurotic disorders" [49]. Huang et al [50] reported that 23.5% of adolescents were prone to anxiety, of which 1.7% had severe anxiety, and 26.3% of adolescents were prone to depression, of which 1.4% had severe depression. Therefore, on the basis of a study by Liu et al[51], we suggest that college students who experienced depressive disorders not only need support and personalized interventions from educators and school administrators, but also they need professional interventions such as cognitive behavioral therapy and online medication therapy from psychologists and psychiatrist. College student personality and psychology are still in a period of maturation. The coping styles of college students are closely related to their psychological health and learning satisfaction. Positive, mature coping is a protective factor of mental health, and it promotes developing individual adaptation. Negative, immature coping has a negative effect on mental health. To alleviate symptoms of depression, young adults who experience stressful life events may need to reinforce problemfocused coping and minimize emotion-focused coping strategies[52]. Therefore, we suggest that educators train student positive coping styles when conducting psychological intervention and educate and help students to adopt positive coping styles such as self-adjustment, help-seeking, and problem-solving. Doing so will improve college student mental health and online study satisfaction.

Our study may have some limitations. Considering differences in individual physical quality and endurance, we choose the ten grades of exercise intensity and did not use the sports scale. A standardized exercise intensity scale can be used to further refine our study. Interestingly, we found that fear was positively related to online learning satisfaction. As is well known, moderate anxiety or fear of failure in learning can motivate, and high fear of COVID-19 may have kept college students alert, promoted study of relevant topics, and mobilized their subjective initiative to respond positively, which may have increased online learning satisfaction. However, Al-Nasa'h et al [53] reported that fear of COVID-19 diminished the satisfaction of online learning. This difference may be related to differences in scales, sample sizes, and regions used in each study. We enrolled a large number of participants located in one metropolis of China. Hence, samples from other contexts are needed to assess the generality of our findings.

### CONCLUSION

Our findings enrich our understanding about the impact of the COVID-19 pandemic on satisfaction of the college population toward emergency online learning. Although there was high online learning satisfaction, online education is still an imperfect substitute for in-person learning. College student online learning satisfaction was affected by whether it was scheduled and by depression, neurasthenia, fear, exercise intensity, attention to the epidemic, emotion at home, and coping style during the early stage of COVID-19. We suggest that college students with different characteristics should receive attention at different levels. Psychological intervention should be conducted, publicity and knowledge about COVID-19 should be strengthened, interaction between teachers and students and classmates should be strengthened when teaching online, and support from family and school should be enhanced to alleviate bad emotions that affect online learning satisfaction. Additionally, online group or individual psychological assistance, even psychotropic drugs for high-risk groups, should be made available. Students should adjust coping style and strengthen psychological defense skills. Students, families, schools, and the community can establish a joint mechanism. Related institutions can form mental health guidelines to promote safe and effective learning and a healthy life.

### **ARTICLE HIGHLIGHTS**

#### Research background

The coronavirus disease 2019 (COVID-19) pandemic disrupted all facets of everyday life. Students turned to online education to minimize the pandemic's spread and negative impacts on health. Students from various backgrounds and places were required to adapt to new learning conditions. Student learning satisfaction is a crucial indicator of the effectiveness of online learning that is related to academic achievement.

Surveys of online learning satisfaction during the COVID-19 pandemic show inconsistent results. Some studies showed that the higher the psychopathology scores, the less online learning satisfaction. University period is a critical time for shaping a student's personality and developing talents, they have unique psychological characteristics. However, it is not clear which personal characteristics (demographic variables) and which emotions, e.g., depression, fear, neurasthenia, compulsive anxiety or hypochondria, had important effects in online learning satisfaction early in the pandemic.



Furthermore, coping style is a cognitive and behavioral feature that individuals adopt when they face stressful situations and events. Coping style has a positive and a negative dimension. Positive coping helps individuals to actively manage adversity. Negative coping includes social withdrawal and avoidance. Negative coping can increase anxiety and depression and increase the degree of procrastination, which have negative effects on academic performance. Positive coping is a protective factor for mental health. Nevertheless, factors associated with emergency online learning satisfaction such as coping style have not been adequately defined for the specific pandemic period.

#### Research motivation

Our study will clarify satisfaction with online learning and identify personal characteristics and the emotions that had important effects on online learning satisfaction early in the pandemic. Furthermore, this study will clarify which coping style was associated with emergency online learning satisfaction in the specific period. Our findings will provide references for colleges to conduct accurate mental health education and ensure student satisfaction with online courses for a good quality academic experience and metal health.

### Research objectives

Our objective is to provide references for colleges to conduct accurate mental health education for students and ensure their satisfaction with online courses. In addition, we will explain challenges to fostering a productive learning environment threatened by epidemic outbreak and economic uncertainty.

### Research methods

We measured the influence of college student psychological states and coping styles on their learning satisfaction. Measurements were based on questionnaires designed to investigate mainly demographic and sociological data, *i.e.*, gender, age, current role, grade, nationality, family location, academic year, monthly household income, parents' education, online status, average daily time paying attention to the epidemic, and whether bored at home for long time. Mental status was assessed with the Psychological Questionnaire for Emergent Events of Public Health (PQEEPH). The PQEEPH scale is specially designed for public health emergencies; it is composed of 25 items of five subscales, *i.e.*, depression, neurasthenia, fear, compulsion-anxiety, and hypochondria that describe emotional status precisely and in detail. Coping styles were assessed with the Simplified Coping Style Questionnaire. Quantitative data were analyzed with descriptive and exploratory methods. First, the skewness and kurtosis values were used to determine whether the data were normally distributed. Data were skewed, continuous variables were expressed as median (interquartile range) and were assessed by Mann-Whitney test or Kruskal-Wallis H test . Second, the correlation of variables was represented by Pearson's and Spearman's coefficients based on the type of data. Third, multiple linear regression was performed to identify predictors of online learning satisfaction. All statistical analysis was performed using SPSS 22.0 (IBM Corporation). All tests were within the 95% confidence interval.

### Research results

We collected 1600 questionnaires, of which 1580 (98.6%) were effective. Online learning satisfaction was poor for 3.9% (61/1580) of participants, general for 33.2% (525/1580) participants, and good 62.9% (994/1580). Demographic characteristics and single factor analysis showed statistical significance (P < 0.05) for age, major, academic year, family location, online status, average time attention to epidemic, whether following a regular schedule, whether bored at home, health condition, and exercise intensity. Correlation analysis of online learning satisfaction, mental status, and personal characteristics showed that fear, compulsion-anxiety, positive coping style, father's education, online status, exercise intensity, health condition, whether on a regular schedule and whether bored at home were positively associated with online learning satisfaction. Depression, neurasthenia, hypochondria, negative coping style, age, average time of attention to the epidemic were negatively correlated with online learning satisfaction. Multiple linear regression of online learning satisfaction showed online learning at schedule, strong exercise intensity, good health, regular schedule, paying attention to epidemic less than one hour, and not bored at home had positive effects (P < 0.05) on online learning satisfaction. Depression and neurasthenia had significant negative effects on online learning satisfaction, whereas fear had positive effects (P < 0.05). Positive coping had a significant positive effect on satisfaction with online courses, whereas negative coping had a significant negative effect (P < 0.05).

#### Research conclusions

The new theory is that this study assessed factors especially on personal characteristics, mental status, and coping style related to satisfaction with emergency online learning among college students during the COVID-19 pandemic. Little study has been focused on online acceptance of education in early time of COVID-19 pandemic. Our findings provide reference for educators, psychologists, and school administrators to conduct health education intervention.

The new method we used is the PQEEPH. This scale is specially designed for public health emergencies, it is composed of 25 items of five sub scales, depression, neurasthenia, fear, compulsion-anxiety, and hypochondria which describe the emotional status detailed and precisely.

#### Research perspectives

On the basis of our methods and findings concerning factors that affect online learning satisfaction, we suggest that it will be possible to assess the effects of psychological intervention for college students during the next emergency online learning period and then formulate corresponding and mature programs.



### FOOTNOTES

Author contributions: Wang XY and Ni AH contributed to conception and design of the study; Jing P organized the database; Zhao Y, Zhang K, Lei DC, and Han JT collected data; Zhai XY performed the statistical analysis and write the article; All authors contributed to manuscript revision, read, and approved the submitted version.

Institutional review board statement: The study protocol was approved by the Ethics Committee of Hebei General University and complied strictly with ethical requirements. Ethics Review No. 2020 scientific ethics No. 30.

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrollment.

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Data sharing statement: Technical appendix, statistical code, and dataset available from the first author at 13832346369@163.com. Consent was not obtained but the presented data are anonymized and risk of identification is low.

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ORIGINAL ARTICLE

# **Observational Study** Influence of physical education on anxiety, depression, and selfesteem among college students

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### Abstract

### BACKGROUND

Physical education is pivotal in our country's education reform. Urban schools have notably enhanced the intensity of physical education in recent years. However, the effects of physical education on students' anxiety, depression, and self-esteem levels, as well as their interrelations, remain unexplored.

### AIM

To analyze the influence of physical education on students' anxiety, depression, and self-esteem.

### METHODS

This study employed a cross-sectional design. A stratified cluster sampling method was used to select 478 first-year university students. Self-administered questionnaires were used to investigate the physical education status and basic information of college students. We used the Physical Activity Rank Scale-3 (PARS-3), Self-Rating Anxiety Scale (SAS), Self-Rating Depression Scale (SDS), and Self-Esteem Scale (SES) to assess the level of exercise, anxiety, depression, and self-esteem. Multiple Logistic regression was used to analyze the factors influencing anxiety, depression, and low self-esteem. The receiver operating characteristic curve and area under the curve (AUC) were used to evaluate the predictive ability of PARS-3 scores for anxiety, depression, and low self-esteem. Spearman's correlation was used to analyze the correlations among the PARS-3, SAS, SDS, and SES.

### RESULTS

Compared with the domestic norms, SAS and SDS scores were higher, and SES scores were lower (P < 0.05). Among the participants, 210 (43.93%) had PARS-3 scores below 20, 94 (19.67%) had scores of 20-42, and 174 (36.40%) had scores above 42. After adjusting for daily sleep time, gender, being an only child, major, father's educational background, mother's educational background, and family



residence, PARS-3 scores were independent influencing factors for anxiety, depression, and low self-esteem (P < P0.05). The AUC of PARS-3 scores predicting anxiety, depression, and low self-esteem were 0.805 (0.760-0.849), 0.799 (0.755-0.843), and 0.831 (0.788-0.874), respectively. The sensitivities were 0.799, 0.801, and 0.748, and the specificities were 0.743, 0.716, and 0.814, respectively. PARS-3 was negatively correlated with SAS and SDS scores (r = -0.566, -0.621, both P < 0.001) and positively correlated with SES scores (r = -0.621, P < 0.001). SES scores were negatively correlated with SAS and SDS scores (r = -0.508, r = -0.518, both P < 0.001).

### CONCLUSION

The amount of physical activity is negatively correlated with anxiety and depression degree and positively correlated with self-esteem degree.

Key Words: Physical education; Student; Anxiety; Depression; Self-esteem; Influence

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**Core Tip:** This study establishes a negative correlation between physical activity levels and the degree of anxiety and depression while demonstrating a positive correlation with self-esteem. This provides substantial evidence for the impact of physical education on anxiety, depression, and self-esteem of college students.

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### INTRODUCTION

University physical education aims to promote students' holistic development and cultivate students' comprehensive quality through sports activities[1]. Physical activity is a reliable way to develop healthy behaviors, sports abilities, morality, and other qualities among students[2]. College students are under pressure from various aspects, such as college entrance, interpersonal conflict, and job search competition. Moreover, they are prone to psychological problems, such as anxiety and depression, which may lead to violent injuries and even suicide[3]. Self-esteem refers to confidence in one's worth, abilities, and morals<sup>[4]</sup>. Self-esteem is a positive psychological quality and psychological capital for college students' growth and success<sup>[5]</sup>. College students are an important part of young people, and their physical and mental health have an important influence on personal development and long-term national planning. Research has shown that individuals with low self-esteem are prone to anxiety, depression, and other negative emotions[6]. However, individuals with high self-esteem have varying mental health levels[7]. Appropriate physical activity reduces anxiety and depression among college students[8] and effectively improves their self-esteem[9]. However, studies on the effects of physical education on anxiety, depression, and self-esteem are scant. Therefore, we used college students to analyze the influence of physical education on anxiety, depression, and self-esteem to provide a reference for improving their physical and mental health.

### MATERIALS AND METHODS

#### **Object of study**

We conducted a cross-sectional survey. We selected university students using stratified cluster sampling. The participants were based on major, including humanities and social sciences, science and engineering, and medical sciences. Three majors were selected to obtain a sufficient sample size.

We determined the sample size using a formula (quantitative variable)[10] for cross-sectional studies:  $n = \left(\frac{L_1 - u/2 \times \sigma}{\delta}\right)^2$ , where: n represents the sample size of each group;  $Z_{1-alpha/2} = 1.96$ ;  $\delta$  represents the allowable error, which is the half-width of the confidence interval; and sigma is the standard deviation. Based on  $\delta = 5$  and  $\sigma = 30$ , we calculated *n* to be 139. Considering a 10% withdrawal rate, we estimated that the study required 459 participants  $[139 \times 3 \times (1 + 10\%)]$ .

The survey object recruitment methods were as follows: Buy some small gifts, such as carbon pens, cartoon erasers, post-it notes, and other small prizes, for each person willing to participate in the survey. The students included in the survey have the spirit, consciousness, ability, and a WeChat account to complete the questionnaire independently. They knowingly and voluntarily agree to participate in this study. We excluded the students who could not complete the questionnaire for any reason. To protect privacy, we ensure the questionnaire results and data are only known by the research team and destroy the questionnaire after obtaining the relevant data analysis conclusions. We established a WeChat group of survey participants and, after obtaining informed consent, sent questionnaire links to the group for the



questionnaire survey. Participation was voluntary. We sent 500 questionnaires, and 486 were returned (97.2% recovery rate). After excluding the invalid questionnaires such as missing or multiple pages, incomplete filling, respondents not meeting the requirements, obviously wrong or incorrect answers, or recalled deadlines, we included 478 effective questionnaires (95.6%) in the analysis.

### Questionnaire survey and quality control

We used original questionnaires that were reviewed and tested by experts. The audit includes the completeness, standardization, consistency, authenticity, effectiveness, feasibility, and scientificity of the questionnaire. A test is a form of survey used to obtain preliminary information and understand respondents' opinion before conducting a formal survey. The questionnaire obtained information on the participants, their parents, and their peers. The survey included questions regarding sociodemographic factors, physical activity, anxiety, depression, and self-esteem. The survey was conducted from February to May 2023.

The investigators in this study were members of a research group that had undergone unified training and assessment. They managed the research data and survey results. Participants who were unable to participate in the survey during the set period were contacted by the investigators within two weeks and requested to complete the questionnaire using the same procedure as the set survey to reduce the number of invalid questionnaires.

#### Sociodemographic factors

Based on a review of the relevant literature, we designed a sociodemographic questionnaire under the guidance of epidemiologists. The questions included student number, gender, being an only child, major, parents' educational background, family residence, and average daily sleep time over the last month.

### Sports activities

We employed the Physical Activity Rank Scale-3 (PARS-3)[11] to calculate the participants' physical activity in the past month. In previous studies, the scale's internal consistency and reliability were 0.86 and 0.82, respectively. The scale contains three dimensions: time, intensity, and frequency of exercise. Items were rated on a five-point Likert scale (1 = light exercise; 5 = competitive exercise). Among them, exercise time was rated 0 to 4 points, and exercise intensity and frequency grades were 1 to 5 points. Exercise was calculated as time × intensity × frequency; the score range was 0 to 100 points. Exercise classification criteria were as follows: ≤ 19 points = low exercise, 20-42 points = moderate exercise, ≥ 43 points = high exercise.

### Anxiety and depression

We used the Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS)[12] to detect anxiety and depression, respectively. The SAS contains 20 items (15 positive and 5 reverse scores). Similarly, the SDS contains 20 items (11 positive and nine reverse scores). Items were rated on a four-point Likert scale (1 = occasional; 4 = persistent). The sum of the scores for each item was the approximate score of anxiety or depression. The standard or final score of anxiety or depression was calculated as 1.25 times the score of anxiety or depression rounded to a whole number. The criteria for identifying anxiety were an SAS score of > 50 points while depression was an SDS score of > 53 points.

#### Self-esteem

We employed the Self-Esteem Scale (SES)[13] to evaluate college students' self-esteem. The scale's internal consistency was 0.87 in previous studies. This scale contains ten items (five positive and five negative). Items were rated on a fourpoint Likert scale (1 = strongly disagree; 4 = strongly agree). The total self-esteem score was the sum of all entries. Higher SES scores indicated higher self-esteem.

#### Statistical analysis

We used SPSS 20.0 to process the data and expressed the measurement data as mean  $\pm$  SD. Comparisons between two sets of data were performed using the *t*-test, and comparisons between three sets of data were performed using a oneway analysis of variance (ANOVA) and Bonferroni. Count data are represented as *n*.

We classified low self-esteem by subtracting one standard deviation from the domestic norm average of SES[14]. Anxiety (anxious = 1, not anxious = 0), depression (depressed = 1, not depressed = 0), and self-esteem (low self-esteem = 1, regular/high self-esteem = 0) were the dependent variables, whereas PARS-3 scores and sociodemographic indicators were the independent variables. A multivariate logistic regression model was used for the analysis. The predictive ability of the receiver operator characteristic curve (ROC) and area under the curve (AUC). Spearman's correlation analysis was used to explore the correlation between PARS-3 scores and SAS, SDS, and SES scores. A P value less than 0.05 means that the difference is statistically significant.

### RESULTS

#### SAS, SDS, and SES scores

The participants' SAS and SDS scores were higher and SES scores were lower than the domestic norms [SAS: (29.78 ± 10.07) points, SDS: (33.46 ± 8.55) points][15,16] (*P* < 0.05; Table 1).



Table 1 Self-Rating Anxiety Scale, Self-Rating Depression Scale and the Self-Esteem Scale scores (n = 478)									
Items	SAS	SDS	SES						
Participants	46.39 ± 7.26	$48.22 \pm 10.24$	26.35 ± 4.31						
Domestic norm	$29.78 \pm 10.07$	33.46 ± 8.55	$28.75 \pm 4.86$						
$t^1$	53.067	37.365	-12.184						
<i>P</i> value	< 0.001	< 0.001	< 0.001						

<sup>1</sup>Single sample *t*-test.

SAS: Self-Rating Anxiety Scale; SDS: Self-Rating Depression Scale; SES: the Self-Esteem Scale.



Figure 1 Receiver operating characteristic curve of Physical Activity Rank Scale-3 scores predicting anxiety, depression, and low selfesteem. A: Physical Activity Rank Scale-3 (PARS-3) scores predicting anxiety; B: PARS-3 scores predicting depression; C: PARS-3 scores predicting low selfesteem.

### Influence of sociodemographic factors on PARS-3 scores

Among the participants, 210 (43.93%) had PARS-3 scores  $\leq$  19, 94 (19.67%) scored 20-42, and 174 (36.40%) scored  $\geq$  43. Among the participants with PARS-3 scores  $\leq$  19, the PARS-3 scores of only children were higher than those who were not only children. The PARS-3 scores of college students with an average daily sleep time > 8 h were higher than those with an average daily sleep time of 6-8 h and those with an average daily sleep time of < 6 h (all *P* < 0.05; Table 2).

### Influence of sociodemographic factors on SAS, SDS, and SES scores

The SDS scores of college students whose fathers' education was at or above the graduate level were higher than those of those whose fathers' education was less than the graduate level, and their SES scores were lower than those of those whose fathers' education was below the graduate level (P < 0.05; Table 3).

### Factors influencing anxiety, depression, and low self-esteem

Anxiety (anxious = 1, not anxious = 0), depression (depressed = 1, not depressed = 0), and self-esteem (low self-esteem = 1, regular/high self-esteem = 0) were the dependent variables, whereas PARS-3 scores and sociodemographic indicators were the independent variables. A multivariate logistic regression model was used for the analysis (Table 4). The results showed that after adjusting for daily sleep time, gender, being an only child, major, father's educational background, mother's educational background, and family residence, PARS-3 scores were independent influencing factors for anxiety, depression, and low self-esteem (P < 0.05; Table 5).

### Predictive ability of PARS-3 scores

The AUC of the PARS-3 scores predicting anxiety, depression, and low self-esteem were 0.805 (0.760-0.849), 0.799 (0.755-0.843), and 0.831 (0.788-0.874), respectively. The sensitivities were 0.799, 0.801, and 0.748 and the specificities were 0.743, 0.716, and 0.814, respectively (Figure 1, Table 6).

### Correlation analysis between PARS-3 scores and SAS, SDS, and SES scores

PARS-3 scores were negatively correlated with SAS and SDS scores (r = -0.566, -0.621, both P < 0.001) and positively correlated with SES scores (r = -0.621, P < 0.001). SES was negatively correlated with SAS and SDS scores (r = -0.508, r = -0.518, both P < 0.001; Figure 2, Table 7).

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Table 2 The influence of so	ciodemographic factors on Physical Activity	Rank Scale-3 scores	;			
Index		Participant	Statiatia	PARS-3 s	cores	
index		number	Statistic	≤ 19	20-42	≥ 43
Gender	Male	221		11.60 ± 4.83	30.46 ± 5.77	56.50 ± 8.24
	Female	257		$\begin{array}{c} 11.82 \pm \\ 4.41 \end{array}$	32.27 ± 5.74	55.61 ± 9.62
			t	0.3446	1.544	0.637
			P value	0.731	0.126	0.525
Only child	Yes	212		12.42 ± 4.53	31.92 ± 6.01	56.59 ± 9.49
	No	266		11.14 ± 4.59	30.88 ± 5.65	55.49 ± 8.65
			t	2.023	0.866	0.792
			P value	0.044	0.388	0.429
Major	Humanities and social sciences	155		11.45 ± 4.64	30.34 ± 5.07	55.37 ± 8.62
	Science and engineering	135		12.04 ± 4.56	32.70 ± 5.92	57.49 ± 8.76
	Medicine	188		11.71 ± 4.60	31.20 ± 6.08	55.20 ± 9.61
			F	0.252	1.089	1.122
			P value	0.778	0.341	0.328
Father's educational background	High school or technical secondary school and below	210		11.58 ± 4.72	31.10 ± 5.63	55.63 ± 9.53
	College or undergraduate	205		11.96 ± 4.54	32.29 ± 5.28	55.33 ± 8.18
	Postgraduate and above	63		11.27 ± 4.06	30.14 ± 6.65	58.96 ± 9.89
			F	0.243	0.974	1.696
			P value	0.785	0.382	0.187
Mother's educational background	High school or technical secondary school and below	221		11.68 ± 4.76	31.07 ± 5.54	55.36 ± 9.92
	College or undergraduate	203		11.71 ± 4.53	31.67 ± 5.94	55.76 ± 7.75
	Postgraduate and above	54		12.08 ± 3.66	31.21 ± 6.21	58.70 ± 10.01
			F	0.041	0.104	1.240
			P value	0.960	0.901	0.292
Family domicile	Village	208		11.92 ± 5.18	30.07 ± 5.47	55.48 ± 9.30
	County	117		11.22 ± 4.27	33.60 ± 4.36	$56.40 \pm 9.26$
	Downtown	153		11.86 ± 3.93	31.46 ± 6.51	56.39 ± 8.52
			F	0.442	2.642	0.215
			P value	0.644	0.077	0.807
Average sleep time	< 6 h	83		10.24 ± 4.71	29.87 ± 5.98	54.14 ± 9.41
	6-8 h	257		12.36 ± 4.43	31.29 ± 5.86	55.83 ± 8.60

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> 8 h	138 <sup>a</sup>		11.72 ± 4.57	32.15 ± 5.48	57.04 ± 9.55
		F	3.512	0.740	0.845
		Р	0.032	0.480	0.431

 $^{a}P$  < 0.05, compared to the average daily sleep time of 6-8 h and < 6 h. PARS-3: Physical Activity Rank Scale-3.



#### Figure 2 Scatter plot of correlation between Physical Activity Rank Scale-3 scores and Self-Rating Anxiety Scale, Self-Rating Depression Scale, and the Self-Esteem Scale scores. A: The correlation between Self-Rating Anxiety Scale and Physical Activity Rank Scale-3 (PARS-3); B: The correlation between Self-Rating Depression Scale and PARS-3; C: The correlation between the Self-Esteem Scale and PARS-3. SAS: Self-Rating Anxiety Scale; SDS: Self-Rating Depression Scale; SES: the Self-Esteem Scale; PARS-3: Physical Activity Rank Scale-3.

### DISCUSSION

Self-esteem affects how individuals deal with stressful events; individuals with high self-esteem are more inclined to adopt positive coping strategies to deal with stress[17]. Understanding the link between physical education and anxiety, depression, and self-esteem helps guide and intervene to promote students' holistic physical and mental development.

The amount of exercise, also known as exercise load, refers to the physical load, psychological load, and calories consumed by the human body during physical activity. Exercise load determines the intensity, duration, accuracy, and characteristics of the exercises. This study revealed anxiety, depression, and low self-esteem among college students, which require attention. The proportion of students with low physical activity was lower than that reported by Sheng et al [18]. However, the overall situation is not positive, and the potential impact of low physical activity on the physical and mental health of college students should be monitored. This may be due to the wide use of electronic products, such as smartphones and tablet computers. Several college students are addicted to mobile phones and the internet, reducing their willingness to participate in sports activities<sup>[19]</sup>. Some researchers have proposed that the lack of exercise among college students is related to a lack of good exercise habits due to academic pressure in middle school<sup>[20]</sup>. Students in middle school did not develop good exercise habits, and their bad exercise habits after college cannot be corrected in time, resulting in less exercise. Moreover, our findings suggest that college students with high physical activity levels have a lower risk of anxiety, depression, and low self-esteem. Furthermore, our results indicate that higher amounts of exercise are associated with reduced anxiety and depression and improved self-esteem among college students. Participation in sports activities can affect anxiety and depression levels in many ways. Sports activities can increase communication between college students and their peers and release negative emotions, thereby reducing anxiety and depression. Additionally, regular participation in sports activities can improve college students' sense of self-efficacy, thus enhancing their subjective support levels, problem-solving ability, and positive evaluation of volitivity and selfconfidence[21]. Therefore, college students who are more active and proactive in coping with pressure have fewer negative emotional experiences and more positive emotional experiences, thus reducing anxiety and depression levels [22]. Moreover, physical exercise increases the relative content of metabolites 4-hydroxyphenyl lactate and dihydro thymine and decreases the relative content of glutamine in the human body, thus affecting the regulatory pathways related to negative emotions, such as coenzyme Q biosynthesis, tyrosine metabolism, and pyrimidine metabolism[23]. In addition, physical exercise can change the composition of the human intestinal flora, affecting the secretion of a series of substances that regulate neural activity, such as serotonin, and improving the level of anxiety and depression in individuals<sup>[24]</sup>. Therefore, we suggest that schools encourage college students to participate actively in physical exercise. Psychological education departments should pay attention to the mental health status of college students with low daily physical activity and implement effective intervention measures to prevent anxiety and depression.

This study found that higher amounts of exercise are associated with higher self-esteem among college students, which was in line with Zayed's findings[25]. Previous research has shown that physical exercise can improve self-esteem by reducing loneliness. Moreover, physical activity enhances self-esteem[26]. Activity time, frequency, and intensity may be the key factors that produce positive psychological benefits for self-esteem. Our findings indicated that lower self-esteem

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### Table 3 Influence of sociodemographic factors on Self-Rating Anxiety Scale, Self-Rating Depression Scale and the Self-Esteem Scale scores

Index		Participant number	Statistic	SAS	SDS	SES
Gender	Male	221		46.63 ± 7.19	48.46 ± 9.50	26.36 ± 4.37
	Female	257		46.18 ± 7.31	48.01 ± 10.84	26.33 ± 4.26
			t	0.676	0.479	0.076
			P value	0.499	0.632	0.940
Only child	Yes	212		46.24 ± 6.74	48.58 ± 9.95	26.21 ± 4.21
	No	266		46.51 ± 7.65	47.93 ± 10.47	26.45 ± 4.39
			t	0.404	0.689	0.605
			P value	0.686	0.491	0.546
Major	Humanities and social sciences	155		45.95 ± 7.08	$48.48\pm9.47$	$26.62 \pm 4.46$
	Science and engineering	135		46.36 ± 6.97	48.33 ± 10.61	26.12 ± 4.13
	Medicine	188		46.76 ± 7.58	47.91 ± 10.58	$26.28 \pm 4.30$
			F	0.531	0.144	0.522
			P value	0.588	0.866	0.594
Father's educational background	High school or technical secondary school and below	210		45.70 ± 6.10	44.09 ± 9.33 <sup>a</sup>	27.98 ± 3.88 <sup>a</sup>
	College or undergraduate	205		46.41 ± 7.43	47.44 ± 10.32 <sup>a</sup>	26.39 ± 4.47 <sup>a</sup>
	Postgraduate and above	63		46.17 ± 7.56	50.17 ± 10.84	25.57 ± 3.81
			F	0.558	11.250	11.890
			P value	0.573	< 0.001	< 0.001
Mother's educational background	High school or technical secondary school and below	221		46.26 ± 7.29	48.06 ± 10.09	26.54 ± 4.37
	College or undergraduate	203		46.76 ± 7.28	$\begin{array}{c} 47.80 \pm \\ 10.04 \end{array}$	26.44 ± 4.32
	Postgraduate and above	54		45.52 ± 6.94	50.39 ± 11.31	25.19 ± 3.85
			F	0.690	1.418	2.353
			P value	0.503	0.243	0.096
Family domicile	Village	208		46.40 ± 6.86	47.54 ± 9.75	26.72 ± 4.31
	County	117		46.25 ± 7.26	47.51 ± 10.67	26.34 ± 4.53
	Downtown	153		46.48 ± 7.76	49.67 ± 10.41	$25.84 \pm 4.07$
			F	0.034	2.294	2.401
			P value	0.967	0.102	0.092
Average sleep time	< 6 h	83		48.02 ± 7.71	50.10 ± 9.63	25.46 ± 4.27
	6-8 h	257		46.02 ± 7.35	48.11 ± 10.21	26.54 ± 4.29



> 8 h	138		46.09 ± 6.65	47.28 ± 10.51	26.51 ± 4.31
		F	2.572	2.972	2.131
		P value	0.078	0.053	0.120

 ${}^{a}P$  < 0.05, compared to the father's education level of postgraduate or above.

SAS: Self-Rating Anxiety Scale; SDS: Self-Rating Depression Scale; SES: the Self-Esteem Scale.

### Table 4 Assignment table

Independent variables	Assignment
Gender	Male = 1; Female = 0
Only child	Yes = 1; No = 0
Major	Humanities and social sciences = 1; Science and engineering = 2; Medicine = 3
Father's educational background	High school or technical secondary school and below = 1; College or undergraduate = 2; Postgraduate and above = 3
Mother's educational background	High school or technical secondary school and below = 1; College or undergraduate = 2; Postgraduate and above = 3
Family domicile	Village = 1; County = 2; Downtown = 3
Average sleep time	Actual value
PARS-3 scores	Actual value

PARS-3: Physical Activity Rank Scale-3.

Table 5 Multivariate logistic regression for anxiety, depression, and low self-esteem										
Madal		Anxiety			Depress	sion		Low self	f-esteem	
wodei	independent variables	В	P value	OR (95%CI)	В	P value	OR (95%CI)	В	P value	OR (95%CI)
1	PARS-3 scores	-0.065	< 0.001	0.937 (0.923- 0.951)	-0.063	< 0.001	0.939 (0.926- 0.952)	-0.077	< 0.001	0.926 (0.910- 0.943)
	Constant	0.781	< 0.001	2.184	0.896	< 0.001	2.449	0.799	< 0.001	2.224
2	PARS-3 scores	-0.065	< 0.001	0.937 (0.923- 0.951)	-0.063	< 0.001	0.939 (0.926- 0.952)	-0.077	< 0.001	0.926 (0.910- 0.943)
	Average sleep time	-0.064	0.236	0.938 (0.844- 1.043)	-0.045	0.397	0.956 (0.862- 1.061)	-0.005	0.931	0.995 (0.891- 1.111)
	Constant	1.247	0.005	3.480	1.222	0.005	3.394	0.835	0.068	2.304
3	PARS-3 scores	-0.067	< 0.001	0.935 (0.921- 0.949)	-0.064	< 0.001	0.938 (0.925- 0.951)	-0.078	< 0.001	0.925 (0.908- 0.942)
	Average sleep time	-0.083	0.134	0.921 (0.826- 1.026)	-0.054	0.318	0.948 (0.853- 1.053)	-0.012	0.835	0.988 (0.883- 1.106)
	Gender	-0.145	0.540	0.865 (0.543- 1.377)	-0.173	0.455	0.841 (0.535- 1.324)	-0.055	0.825	0.947 (0.582- 1.539)
	Only child	-0.360	0.132	0.698 (0.437- 1.114)	-0.472	0.043	0.624 (0.395- 0.986)	-0.136	0.585	0.873 (0.536- 1.421)
	Major		0.020			0.132			0.174	
	Humanities and social sciences	0.137	0.631	1.147 (0.656- 2.005)	0.382	0.164	1.465 (0.855- 2.511)	0.397	0.182	1.488 (0.830- 2.667)
	Science and engineering	0.769	0.007	2.158 (1.232- 3.780)	0.542	0.055	1.719 (0.990- 2.987)	0.533	0.076	1.704 (0.945- 3.073)
	Father's educational background		0.454			0.924			0.669	
	High school or technical	-0.013	0.987	0.987 (0.202-	0.310	0.691	1.364 (0.296-	0.310	0.714	1.364 (0.260-



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Secondary school and below			4.813)			6.284)			7.150)
College or undergraduate	0.440	0.555	1.553 (0.360- 6.700)	0.255	0.722	1.291 (0.316- 5.277)	0.557	0.476	1.745 (0.378- 8.048)
Mother's educational background		0.685			0.776			0.325	
High school or technical secondary school and below	-0.165	0.830	0.848 (0.187- 3.835)	-0.512	0.489	0.599 (0.140- 2.559)	-1.175	0.141	0.309 (0.065- 1.478)
College or undergraduate	0.176	0.833	1.193 (3.835- 6.156)	-0.559	0.490	0.572 (0.117- 2.797)	-1.002	0.250	0.367 (0.067- 2.025)
Family domicile		0.448			0.939			0.613	
Village	0.036	0.915	1.037 (0.534- 2.011)	-0.110	0.741	0.896 (0.467- 1.719)	0.080	0.821	1.084 (0.541- 2.173)
County	-0.330	0.360	0.719 (0.355- 1.457)	-0.109	0.756	0.897 (0.451- 1.782)	-0.230	0.543	0.795 (0.379- 1.666)
Constant	1.263	0.031	3.538	1.627	0.005	5.087	1.322	0.029	3.753

Model 1 does not adjust for any variables; Model 2 adjusts the average daily sleep time; and Model 3 adjusts the average daily sleep time, gender, only child, major, father's educational background, mother's educational background, and family residence. PARS-3: Physical Activity Rank Scale-3.

Table 6 Receiver operating characteristic curve of Physical Activity Rank Scale-3 scores predicting anxiety, depression, and low self- esteem							
Dependent variables	AUC	Sensitivity	Specificity	Standard error	P value		
Anxiety	0.805 (0.760 -0.849)	0.799	0.743	0.023	< 0.001		
Depression	0.799 (0.755-0.843)	0.801	0.716	0.022	< 0.001		
Self-esteem	0.831 (0.788-0.874)	0.748	0.814	0.022	< 0.001		

PARS-3: Physical Activity Rank Scale-3; AUC: Area under the curve.

Table 7 Correlation matrix between Physical Activity Rank Scale-3 scores and Self-Rating Anxiety Scale, Self-Rating Depression Scale and the Self-Esteem Scale scores

Indexes		SAS	SDS	SES
PARS-3	r	-0.566	-0.621	0.621
	<i>P</i> value	< 0.001	< 0.001	< 0.001
SAS	r	-	0.511	-0.508
	<i>P</i> value	-	< 0.001	< 0.001
SDS	r	-	-	-0.518
	<i>P</i> value	-	-	< 0.001

PARS-3: Physical Activity Rank Scale-3; SAS: Self Rating Anxiety Scale; SDS: Self Rating Depression Scale; SES: the Self-Esteem Scale.

was associated with being more prone to depression, which was in line with extant studies[27]. College students with high self-esteem are confident, self-reliant, rational, and peaceful. Their self-evaluation is generally positive; they can rationally face the negative evaluation of others and effectively filter negative information. In addition, college students with high self-esteem have a better sense of control over their environment, can accept and adapt to the existing environment, and are willing to change themselves. When facing stressful events, they can effectively use their current social support to provide a buffer for themselves and reduce the negative impact of stressful events[28]. This effectively reduces the occurrence of anxiety and depression among college students. Therefore, individuals with high self-esteem can self-regulate their depression and solve general psychological problems under stressful conditions. The correlation scatter plot suggests that exercise significantly impacts anxiety, depression, and self-esteem. However, the goodness of fit

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is low, indicating that exercise alone is not the sole factor affecting these aspects in college students. Ramón-Arbués et al [29] demonstrated that anxiety, depression, and self-esteem of college students were also related to Internet use, smoking, and insomnia.

Anxiety, depression, and low self-esteem are contemporary college students' main mental health problems. The detection rate of anxiety and depression in Chinese college students is rising. College students urgently need an intervention method that can effectively relieve their anxiety, depression, and low self-esteem. This study demonstrates that increasing physical activity decreases anxiety and depression thereby boosting self-esteem in college students. It indicates the value of incorporating appropriate physical activities for promoting college students' psychological wellbeing and development. Moreover, a significant correlation exists between anxiety, depression, and self-esteem. Low selfesteem can contribute to the development of anxiety and depression. Therefore, regardless of the specific psychological changes in anxiety, depression, and self-esteem, one must be vigilant to any abnormal psychological development. Due to the limited information collected in this study, it was impossible to investigate the correlation between the amount of physical activity and sedentary behavior, video time, and other behaviors, which needs to be supplemented by future studies with large samples. Moreover, this cross-sectional survey design introduces potential problems such as uncertain time sequencing, external factor interference, data quality impact, and potential factor uncertainty, making it challenging to establish causality. Therefore, other research methods such as randomized controlled studies should be employed in the future to verify the results of this study.

### CONCLUSION

Physical activity decreases anxiety and depression and increases self-esteem among college students. Colleges and universities should promote active participation in sports and implement scientifically balanced exercise routines. This can alleviate anxiety and depression, improve self-esteem, and enhance the overall physical and mental well-being of college students, ultimately contributing to their holistic development.

## ARTICLE HIGHLIGHTS

### Research background

College students experience varying levels of anxiety, depression, and self-esteem. As this reflects the quality of education reform in China, the correlation between physical activity and students' anxiety, depression, and self-esteem must be explored.

### Research motivation

This study aimed to identify the factors related to anxiety, depression, and self-esteem among college students, and provide guidelines for interventions. Considering the influence and adjustability of physical activity in students, we speculated that the amount of physical activity among college students may be related to anxiety, depression, and selfesteem.

### Research objectives

To analyze the influence of physical activity on anxiety, depression, and self-esteem among college students.

### Research methods

We investigated 478 first-year college students using the Physical Activity Rank Scale-3 (PARS-3), Self-Rating Anxiety Scale (SAS), Self-Rating Depression Scale (SDS), and Self-Esteem Scale (SES). A multivariate logistic regression model, receiver operating characteristic curve (ROC), area under the curve (AUC), and Spearman's correlation analysis were employed to determine the correlation between PARS-3 and SAS, SDS, and SES scores.

### Research results

PARS-3 was negatively correlated with SAS and SDS scores (r = -0.190, -0.267, both P < 0.001) and positively correlated with SES scores (r = 0.313, P < 0.001). SES was negatively correlated with SAS and SDS scores (r = -0.125, P = 0.016; r = -0.016; -0.143, P = 0.002).

### Research conclusions

Physical activity was negatively correlated with anxiety and depression and positively correlated with self-esteem.

### Research perspectives

Based on the multi-factor logistic regression model, ROC, AUC, and Spearman's correlation analysis, we comprehensively analyzed the correlation between college students' PARS-3 scores and SAS, SDS, and SES scores. We demonstrated that college students' PARS-3 scores were negatively correlated with SAS and SDS scores and positively correlated with SES scores. This could guide future interventions to reduce anxiety, depression, and low self-esteem among college students.



### FOOTNOTES

Author contributions: Fu HY designed and conducted the research, and authored the paper; Wang J designed the research and supervised the report; Hu JX designed the research and contributed to the analysis.

Institutional review board statement: The study procedures were approved by the Ethics Committee of the School of Physical Education, Guangzhou Sport University (2023LCLL-23).

Informed consent statement: Written informed consent was obtained from all participants.

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

Data sharing statement: The raw data supporting the conclusion of this article can be obtained from the corresponding author.

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ORIGINAL ARTICLE

# **Observational Study** Influence of childhood trauma on adolescent internet addiction: The mediating roles of loneliness and negative coping styles

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## Abstract

### BACKGROUND

In the information age, the use of the internet and multimedia tools has large effects on the life of middle school students. Improper use of the internet may result in internet addiction (IA). Thus, actively exploring the factors influencing adolescent and the mechanism of addiction as well as promoting adolescent physical and mental health and academic development are priorities that families, schools, and society urgently need to address.

### AIM

To explore the effect of childhood trauma on adolescent IA and to consider the roles of loneliness and negative coping styles.

### **METHODS**

A total of 11310 students from six junior high schools in Henan, China, completed the child trauma questionnaire, IA test, loneliness scale, and simple coping style questionnaire. In addition, data were collected from 1044 adolescents with childhood trauma for analysis with IBM SPSS 26.0 and AMOS 28.0; we examined the relationships among childhood trauma, IA, loneliness, and negative coping styles.

### RESULTS

We found that childhood trauma not only directly affected adolescents' IA but also affected IA through loneliness and negative coping styles.

### **CONCLUSION**

Therefore, this study has theoretical implications regarding adolescent mental health and may inform interventions for IA.



Key Words: Addictive behavior; Mental health; Coping styles; Trauma; Loneliness

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**Core Tip:** This study is concluded: (1) Childhood trauma has a positive predictive effect on teenagers' internet addiction (IA); (2) Childhood trauma has a negative psychological and behavioral impact on teenagers; (3) Loneliness and negative coping styles play a chain intermediary role in the influence of childhood on IA among teenagers; and (4) IA.

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### INTRODUCTION

In the information age, the use of the internet and multimedia tools has a large effect on the lives of middle school students. Improper use of the internet may result in internet addiction (IA). IA is often defined as problematic, compulsive internet use (for gaming, social networks, pornography, etc.) that results in severe impairment of an individual's functioning in all aspects of life over a long period[1,2]. Worldwide, the current prevalence rate of IA is 7.02%; alarmingly, the age of IA onset is dropping, and the prevalence rate is increasing[3]. From 2004 to 2019, a questionnaire survey of 92171 middle school students in Shanghai, China, reported that the prevalence rate of IA was 4.3%, that students with high levels of loneliness exhibited IA, and that academic pressure aggravated IA<sup>[4]</sup>. Studies have shown that IA causes mental health problems in individuals and impairs psychosocial functioning, such as an inability to concentrate for long periods, isolation, anxiety, social withdrawal, depression, interpersonal avoidance, and sleep disorders[5-8]. Physical health problems such as dry eye, mouse hand, and cervical and lumbar spine pain can also occur [9,10]. Moreover, some studies have shown that IA is related to non-suicidal self-injury and suicide in adolescents[11-13]. Thus, actively exploring the factors influencing adolescent IA and the mechanism of addiction as well as promoting adolescent physical and mental health and academic development are priorities that families, schools, and society urgently need to address.

#### Childhood trauma and IA

Childhood trauma is often described as serious adverse childhood experiences, mainly involving neglect and abuse [14], which have a series of negative effects on physical and mental health[15,16]. Unfortunately, childhood trauma is very common. According to Koenen et al[17], 38.48% of children have been exposed to at least one traumatic event before the age of 13. Childhood trauma is associated with the development of various addictive behaviors, which have become an increasingly serious public health problem [18-20]. For example, a study proved that childhood trauma is an important predictor of gambling disorder; physical neglect is the single trauma subtype that significantly increases the incidence of gambling disorder in adulthood[21]. It remains unclear whether childhood trauma is common among adolescents with IA. Therefore, we hypothesized that childhood trauma positively predicts adolescent IA (H1).

#### The potential mediating role of loneliness

Loneliness refers to complex feelings when the intimate relationship and social needs of individuals are not fully satisfied and are often accompanied by negative emotional experiences such as isolation, helplessness, and pain[22,23]. Abuse and neglect are severe childhood traumatic events and are lonely experiences. It is difficult for people without the same experience to truly understand these feelings. The traumatized person may have friends who support him or her, but because the friends cannot understand these feelings, the traumatized person may not be willing to share his or her experiences[24]. Therefore, even with the support of friends, they may feel lonely after the trauma. According to the social compensation hypothesis, lonely people may compensate for emotional or social needs through self-disclosure, selfcatharsis, and interpersonal communication through the internet[25]. Adolescents with high levels of loneliness have a higher risk of IA[26,27]. However, it is unclear whether childhood trauma affects IA through loneliness. We hypothesized that loneliness influences the impact of childhood trauma on IA (H2).

#### The potential mediating role of negative coping styles

Coping styles are the cognitive and behavioral styles adopted by individuals in the face of setbacks and pressures. They are usually divided into positive coping styles (problem-solving, cognitive reassessment, social support, etc.) and negative coping styles (avoiding or denying problems or attributing solutions to external factors)[28,29]. Childhood is an important period of development, and traumatic experiences during this period will have a long-term impact on cognition and emotion regulation<sup>[30]</sup>. Some studies have shown that adolescents with childhood trauma mainly exhibit negative coping styles[31,32]. A reasonable explanation for using a negative coping style is that continuous exposure to childhood trauma

may lead to changes in one's neurobiology that lead to increased vigilance and perceived environmental threat, thus changing one's perceived stress<sup>[33]</sup>. Traumatic events will result in negative coping styles, which is consistent with the stress response model[34]. Some studies have indicated that addictive behaviors are closely related to the selected coping style, especially negative coping styles[35-37]. Adolescents may exhibit negative coping methods on the internet such as venting, avoiding, or denying difficulties encountered in reality[38]. Based on previous theories and studies, we propose that negative coping styles mediate the relationship between childhood trauma and IA (H3).

Moreover, some studies have shown that loneliness affects coping styles [39,40], and negative coping styles positively predict IA[41,42]. However, few studies have shown that negative coping styles play an intermediary role in the relationship between loneliness and IA. In this study, we proposed that negative coping styles may mediate between loneliness and IA, and loneliness and negative coping styles have a chain mediating role in the relationship between childhood trauma and IA (H4).

### Study framework

Childhood trauma, IA, loneliness, and negative coping styles interact with each other. Nevertheless, it remains unclear how these variables interact to lead to IA in adolescents. In this study, we proposed the conceptual framework shown in Figure 1. From the perspective of adolescents, we discuss the influence of childhood trauma on IA and investigate the role of loneliness and negative coping styles to provide empirical support and guidance for related research and interventions for adolescent mental health.

### MATERIALS AND METHODS

#### Data collection and ethical considerations

From May to June 2023, volunteers were recruited from six junior and senior high schools in Henan Province, China, using a convenient sampling method. The inclusion criteria were as follows: (1) Enrolled in secondary school; and (2) Provided informed consent and volunteered to participate in this study. The exclusion criterion was the failure to complete all of the questionnaires, regardless of reason. This study was approved by the Institutional Review Committee of Henan Provincial Key Laboratory of Psychology and Behavior (20230516001), and all participants signed informed consent forms.

#### Questionnaire

General demographic data: We collected sociodemographic information including gender, age, parental marital status, only-child status, left-behind child status, family residential location, and relationships with teachers and classmates.

Childhood trauma questionnaire: We used the childhood trauma questionnaire compiled by Bernstein et al [43] and revised by Zhao et al[44]. The questionnaire consists of 28 questions, of which 3 are validity items designed to detect falsenegative trauma reports. The questionnaire assesses five dimensions of childhood maltreatment. Each question is answered on a Likert scale, from 1 "never correct" to 5 "often correct". A higher overall score indicates a greater severity of trauma. The Cronbach's α coefficient of this study scale was 0.817.

IA test: The IA test is a self-report scale compiled by young that contains 20 items [45]. Each entry is scored according to the degree of compliance on a scale of 1-5, and the total score range is 20-100 points. The higher the score is, the more severe the IA. A score  $\geq$  50 points indicates the presence of IA. The Cronbach's  $\alpha$  coefficient was 0.909 in this study.

Loneliness scale: We used the University of California-Los Angeles Loneliness Scale compiled by Russell *et al*[46] in 1978. The scale consists of 20 items with 4 response options, 11 questions, and 9 reverse-scored questions. The higher the score is, the stronger the individual's experience of loneliness. The Cronbach's α coefficient in this study was 0.815.

Coping styles scale: Coping styles were evaluated with the simple coping style questionnaire, which was compiled by Xie[47] based on the Chinese context. It consists of two dimensions, positive response, and negative response, with a total of 20 items. Items are rated on a 4-point Likert scale (1 = not used, 4 = frequently used). This study focused on the negative response scale, which consists of 8 items and focuses on the characteristics of negative responses. The scale in this study had a Cronbach's  $\alpha$  coefficient of 0.728.

#### Statistical analysis

All data were analyzed using IBM SPSS 26.0 and Amos 28.0 in this study. First, the frequency and percentage are reported for the demographic characteristics of participants. In addition, we used Harman's single-factor test to test for possible common method deviations. Normality tests were performed on continuous variables to detect skewness and kurtosis. If IA, loneliness, childhood trauma, and negative coping styles followed a normal distribution, we used Pearson's correlation analysis to explore the relationships among these variables. Otherwise, we used Spearman correlation analysis. We then used structural equation modeling to examine the mediation effects. In this study, IA was the dependent variable, childhood trauma was the independent variable, and loneliness and negative coping styles were the mediating variables. Based on previous item parceling studies [48], we used a "project-building balance" approach to package entries on loneliness and coping styles. Finally, bootstrapping was used to test the mediation effect, and if P <0.05, the mediation effect was considered significant.



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Figure 1 Conceptual framework.

### RESULTS

#### Sample results

We recruited a total of 11310 participants. Of these, 190 dropped out halfway and 11120 questionnaires were returned. After excluding questionnaires with incomplete data, we finally obtained 10819 valid questionnaires. Then, 9775 false-negative trauma reports were excluded. Finally, we analyzed the data of 1044 adolescents with childhood trauma, constituting 9.3% of the total number of participants in the survey, as shown in Figure 2. Bentler and Chou[49] proposed that the sample size should be more than 10 times the number of observed variables; therefore, 1044 samples met the requirements for testing the hypothesized model.

The demographic characteristics of the 1044 adolescents are shown in Table 1. Among them, 612 were male (58.6%), and 432 were female (41.4%). The students were in junior high school or high school, and the age range was 12-18 years. Among the sample, 937 were from two-parent families, and 105 were from single-parent families. A total of 70 (6.7%) students were only children, and the remaining 89.8% had siblings. In this survey, there were 458 (43.9%) left-behind children (students living with their grandparents, attending boarding school, or living alone), and there were 586 (56.1%) children living with their parents. Of these children, 56.6% were from rural areas, and the remaining 43.4% were from urban areas. A total of 48.8% of the students reported that they had a good relationship with their classmates, and 31.5% of the students reported that they had a good relationship with their scheres.

#### Bias test of common method

Because all data were collected with questionnaires, we used Harman's single-factor test to test for possible common method bias. The test results showed that there were 19 variables with eigenvalues greater than 1. The first variable explained 14.85% of the total variation, which is below the critical standard of 40%[50]. Hence, there were no serious common methodological biases in this study.

#### Descriptive statistics and correlations among variables

SPSS was used to examine the distributions of these variables, and all continuous variables had normal distributions. Therefore, we used Pearson correlation analysis to assess the correlations between variables. Means, standard deviations, and Pearson correlation coefficients of each variable are shown in Table 2. In this exploratory analysis, correlations between variables were examined with Pearson correlation analysis; there were significant correlations between each variable in this analysis at the significance level of 99%. Regarding the correlation coefficients, the *r* values were greater than 0. Thus, there was a significant positive correlation between the four dimensions of childhood trauma and each variable. The independent-sample *t* test results showed that there was a significant influence of parental marital relationship on IA (t = -4.252, P < 0.001). One-way ANOVA was used for variables with homogeneity of variance. The results showed that there were significant differences in IA among different ages (F = 16.86, P < 0.001). In addition, there were significant differences in IA among different ages (F = 9.837, P < 0.001). Considering that parent marital relationship (harmonious/disharmonious), age (12-18 years old), and relationship with teachers (poor/average/good) may influence IA, we decided to control for these variables in the subsequent mediation analysis.

### SEM of factors influencing IA

Parents' marital relationship, age, and relationship with teachers were selected control variables because IA is significantly affected by these three variables. The model fit results are shown in Table 3; in accordance with Hu and Bentler [51], we provide several representative model fit indices. The CMIN/DF value of the model (4.616) was less than 5. The root mean square error of approximation value (0.059) was less than 0.08, and the root mean square residual value (0.040) was less than 0.05. In addition, the comparative fit index and goodness of fit index test results indicated excellent fit (0.9 or more). Therefore, the results of this analysis show that the SEM of factors influencing IA was satisfactory.

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Table 1 Sample characteristics (n = 1044)					
Variable	Option	n	n		
Gender	Male	612	58.6		
	Female	432	41.4		
Age	12	16	1.5		
	13	156	14.9		
	14	175	16.8		
	15	135	12.9		
	16	286	27.4		
	17	227	21.7		
	18	49	4.7		
Structure	Single parent	105	10.1		
	Parents	937	89.8		
Only child	Yes	70	6.7		
	No	969	92.8		
Stay-at-home children	Yes	458	43.9		
	No	586	56.1		
Residence	Village	591	56.6		
	Town	449	43.4		
Relationship with classmates	Poor	28	2.7		
	General	506	48.5		
	Good	509	48.8		
Relationship with teachers	Poor	52	5.0		
	General	662	63.4		
	Good	329	31.5		

#### Table 2 Correlations of variables and mean ± SD Variables mean ± SD EN PaEB SB BN NCS Loneliness IA $2.37 \pm 0.85$ EN 1 PaEB $1.44 \pm 0.44$ 0.509<sup>a</sup> 1 SB $1.17 \pm 0.43$ 0.098<sup>a</sup> 0.273<sup>a</sup> 1 0.293<sup>a</sup> ΒN $1.5 \pm 0.47$ 0.449<sup>a</sup> 0.252<sup>a</sup> 1 NCS $2.22 \pm 0.58$ 0.092<sup>a</sup> 0.217<sup>a</sup> 0.212<sup>a</sup> 0.263<sup>a</sup> 1 $2.26 \pm 0.47$ 0.347<sup>a</sup> 0.336<sup>a</sup> 0.108<sup>a</sup> 0.258<sup>a</sup> 0.246<sup>a</sup> Loneliness 1 IA $2.43\pm0.43$ $0.154^{a}$ 0.254<sup>a</sup> 0.167<sup>a</sup> 0.307<sup>a</sup> 0.379<sup>a</sup> 0.334<sup>a</sup> 1

 $^{a}P < 0.01.$ 

EN: Emotional neglect; PaEB: Physical and emotional abuse; SB: Sexual abuse; BN: Body neglect; NCS: Negative coping style; IA: Internet addiction.

### Factors hypothesized to influence IA

According to the results shown in Figure 3, childhood trauma positively predicted loneliness ( $\beta = 0.50$ , P < 0.001), childhood trauma positively predicted negative coping style ( $\beta = 0.25$ , P < 0.001), loneliness positively predicted negative coping style ( $\beta = 0.21$ , P < 0.001), loneliness positively predicted IA ( $\beta = 0.14$ , P < 0.001), negative coping style positively predicted IA ( $\beta = 0.30$ , P < 0.001), and childhood trauma positively predicted IA ( $\beta = 0.17$ , P < 0.001).

Table 3 Model fit test						
Model	CMIN/DF	RMSEA	RMR	CFI	GFI	
Childhood trauma and loneliness and negative coping styles and IA	4.616	0.059	0.040	0.926	0.937	
Fitting standard	< 5	< 0.08	< 0.05	> 0.90	> 0.90	

RMSEA: Root mean square error of approximation; RMR: Root mean square residual; CFI: Comparative fit index; GFI: Goodness of fit index; IA: Internet addiction.







Figure 3 The SEM of factors influencing internet addiction. EN: Emotional neglect; PaEB: Physical and emotional abuse; SB: Sexual abuse; BN: Body neglect; L1-L4: Four items of loneliness; IA1: Tolerability and time management; IA2: Compulsivity and prominence; IA3: Interpersonal, study and health; IA4: Abstinence reaction; NCS1-NCS3: Three items of negative coping style; MS: Marital status; RwT: Relationship with teachers.

Finally, we used 5000 bootstrap samples to determine the 95% confidence interval, and assessed the mediating effects of loneliness and negative coping style on the relationship between childhood trauma and IA. The results are shown in Table 4; loneliness mediated in the relationship between childhood trauma and IA. Negative coping styles also mediated the relationship between childhood trauma and IA. In addition, loneliness and negative coping styles had a chain mediating role in the relationship between childhood trauma and IA. In short, childhood trauma not only directly affected IA but also indirectly affected IA through loneliness and negative coping style in a chain mediation effect



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Table 4 Structural equation modeling results						
Effect	Path	Estimate	P value			
Ind2	IA < loneliness < childhood trauma	0.093	0.005			
Ind2	IA < negative coping style < childhood trauma	0.104	0.001			
Ind3	IA < negative coping style < loneliness < childhood trauma	0.044	0.001			
Direct	IA < childhood trauma	0.241	0.001			
Total	IA < childhood trauma	0.476	0.001			

IA: Internet addiction.

#### (Table 4).

### DISCUSSION

Among the 1044 adolescents with childhood trauma, there were 473 (45.6%) students with IA, and the prevalence rate was as high as 45.6%, which is higher than the Hu *et al*[52] reported. Among these participants, 75 had severe IA. This may be related to the unique study population (adolescents with childhood trauma). We explored the relationship between childhood trauma and IA in adolescents. The mediating roles of loneliness and negative coping styles were determined through a chain mediation model. To address IA in adolescents with childhood trauma, it is of practical and theoretical importance to study the relationships among these variables.

### Childhood trauma and IA

The results of this study revealed a direct relationship between childhood trauma and IA, suggesting that physical and emotional neglect/abuse in childhood are important predictors of adolescent IA, which is consistent with previous findings and supports H1. Studies have shown that childhood trauma can lead to poor behavior in adolescents[53,54]. For example, childhood trauma can directly predict adolescent mobile phone addiction as well as IA[55,56]. The present study showed that childhood trauma is significantly associated with IA, which is consistent with previous research results [57]. Importantly, this study also showed that adolescents with IA accounted for 45.6% of the sample, which differs from previous findings, suggesting that adolescents with childhood trauma are more likely to have IA. Traumatic childhood experiences have various adverse effects on adolescents in physical, psychological, emotional, and behavioral dimensions. Studies have shown that children who have experienced childhood trauma are often in a clinical or subclinical psychological state, and they will be more inclined to use the internet to express their sadness, depression, and other psychological states and obtain comfort[58]. Thus, we should pay attention not only to the health and academic needs of adolescents but also to their psychological and emotional needs. School-based health care centers and education systems are key resources for adolescent trauma interventions. Schools can identify students with childhood trauma through screening, focusing on their health. This will be more conducive to adolescents' healthy growth and reduce problem behaviors such as IA.

#### Mediation through loneliness

This study explored the mechanism underlying the association between childhood trauma and adolescent IA and showed that loneliness plays a mediating role in this relationship, supporting hypothesis 2. The results showed that childhood trauma significantly predicted adolescent loneliness, which is consistent with previous studies[59,60]. Loneliness is a common experience in adolescence. According to a survey, 11%-20% of those aged 12-15 years reported that they felt lonely at least "sometimes" [61]. Childhood trauma aggravates adolescents' depression and inferiority complexes, limits their social communication, and thus aggravates loneliness. Moreover, loneliness is a negative emotional state and is closely related to some mental disorders. For example, loneliness and depression are associated [62]. This study showed that loneliness has an impact on adolescent IA, which is consistent with previous research results [63]. Adolescents with high levels of loneliness tend to use the internet instead of offline social interactions to meet the need to belong[64]. However, IA aggravates the loneliness of adolescents. Therefore, we suggest that schools organize more recreational activities for spare time to meet the social needs of adolescents. We should also prioritize the identification of students with communication barriers, emphasize the restoration of interpersonal relationships with time, help students actively integrate into the community, and prevent or reduce adolescent loneliness.

#### Mediating effect of negative coping styles

This study showed that negative coping styles have a mediating role in the effects of childhood trauma on IA, supporting hypothesis 3. The family risk factor model suggests that living in abusive or neglectful family environments can exacerbate or impose risks of poor self-perception, negative emotions, and coping styles as they adapt to social environments[65,66]. The results of this study are consistent with the family risk model, showing that childhood trauma positively predicts negative coping styles. Coping styles play an important role as mediating variables in an individual's



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stress process[67-69]. Positive coping styles are conducive to regulating negative emotions when facing difficulty. In contrast, individuals with negative coping styles are more likely to choose to avoid difficulties. The results of this study also showed that negative coping styles positively predict adolescent IA behavior, which is consistent with previous studies[70]. However, IA can lead to additional stressful events, increased mental health problems, and decreased academic performance. Therefore, negative coping styles and IA form a negative cycle. At schools, we should guide adolescents to select positive and healthy coping styles, which are highly important for preventing or reducing adolescent IA.

### Chain mediating effect of loneliness and negative coping styles

This study also indicated that loneliness can positively predict negative coping styles, which is consistent with previous studies[39,71]. In addition, we found that loneliness and negative coping style act as chain mediators of the relationship between childhood trauma and IA, supporting hypothesis 4. Adolescents with childhood trauma will inevitably have some negative emotions[72-74]. The coping style selected reflects the emotion regulation strategies of adolescents facing difficulty. Adolescents with negative coping styles tend to internalize their emotions with self-blame and avoidance. Engaging in internet use is a way of venting after trauma. Previous studies have shown that high levels of loneliness and negative coping styles are more likely to produce IA problems[75,76]. Overall, childhood trauma can predict loneliness, and loneliness can predict IA by influencing negative coping styles. Importantly, loneliness and coping styles can be changed. We can formulate intervention measures focusing on alleviating loneliness and cultivating positive coping styles, especially among adolescents with childhood trauma. We can help students enhance their mental health and psychological adjustment, develop a healthier and positive coping style, learn to reduce loneliness, and reduce the occurrence of IA among adolescents.

### Limitations

First, this study investigated only six schools in one province, which somewhat reduces the generalizability of the conclusions. A study with a nationally representative sample and a multicenter design is needed. Second, this study used self-report data, which may have some problems, such as recall bias. Although no common method bias was found in this study, more objective assessments should also be considered in subsequent studies. Finally, this study had a cross-sectional design, and further longitudinal studies are needed to investigate causality.

### CONCLUSION

This study constructed a chain mediation model from the perspective of adolescents to explore the process and mechanisms by which childhood trauma influences IA. Childhood trauma had a positive predictive effect on adolescent IA, and loneliness and negative coping styles had a chain mediating role in the influence of childhood on IA among adolescents. The path of childhood trauma<sup>®</sup> loneliness<sup>®</sup> negative coping styles<sup>®</sup> IA in adolescents was confirmed. This study provides empirical support and guidance for research and interventions for adolescent IA. In addition, it provides important insights into the mental health of middle school and the development of harmonious school life.

### **ARTICLE HIGHLIGHTS**

### Research background

Internet addiction (IA) refers to a compulsive or excessive use of the internet that interferes with daily life activities, relationships, and overall well-being. It is characterized by an individual's inability to control or limit their online behavior, leading to negative consequences.

### Research motivation

This study aimed to explore the effect of childhood trauma on adolescent IA and to consider the roles of loneliness and negative coping styles.

#### **Research objectives**

The study hypothesized that childhood trauma would be positively associated with adolescent IA, and this relationship would be partially mediated by loneliness and negative coping styles. Negative coping styles refer to maladaptive strategies used to deal with stress, such as avoidance, substance use, and self-blame.

#### Research methods

This study constructed a chain mediation model from the perspective of adolescents to explore the process and mechanisms by which childhood trauma influences IA. Childhood trauma had a positive predictive effect on adolescent IA, and loneliness and negative coping styles had a chain mediating role in the influence of childhood on IA among adolescents.

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### Research results

The results showed that childhood trauma was positively associated with both loneliness and negative coping styles. Moreover, loneliness and negative coping styles were found to mediate the relationship between childhood trauma and adolescent IA. The findings suggest the importance of addressing childhood trauma and its subsequent impact on mental health and addictive behaviors.

### Research conclusions

This study provides empirical support and guidance for research and interventions for adolescent IA, and it also provides important insights into the mental health of middle school and the development of harmonious school life.

#### Research perspectives

This study used self-report data, which may have some problems, such as recall bias. Although no common method bias was found in this study, more objective assessments should also be considered in subsequent studies.

### FOOTNOTES

Co-first authors: Wang-Lin Dong and Yuan-Yuan Li.

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