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Serum levels of folate, vitamin B6, and vitamin B12 are associated with cognitive impairments in depression patients

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Original Article

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Abstract

Introduction: Depression is a common mental disorder that endangers physical and mental health. In our study, we aimed to explore whether B vitamins are associated with depression and cognitive dysfunction. *Methods:* We enrolled a total of 220 patients with depression and selected 100 controls at the same time. We determined depression and cognitive impairment by assessments. We recorded the basic parameters of the participants and collected blood samples. In addition, we measured serum levels of B vitamins and brain-derived neurotrophic factor (BDNF). *Results:* We found significant differences in the duration of depression, education, and Hamilton Depression Rating Scale scores between the D-NCI and D-CI groups. We also identified the independent risk factors for patients with depression and cognitive dysfunction. Compared with the healthy controls, serum folate, vitamin B6, and vitamin B12 positively correlated with cognitive dysfunction. The patients with depression and cognitive dysfunction had the lowest levels of B vitamins compared with the other two groups. Our results also showed that the levels of serum folate, vitamin B6, and vitamin B12 in the patients with depression had a positive correlation with each other. *Conclusion:* Our results indicate that vitamin B is associated with depression and cognitive dysfunction and is positively associated with cognitive dysfunction.

Significant outcomes

- The independent risk factors for patients with depression and cognitive dysfunction were identified.
- Compared with the healthy controls, serum folate, vitamin B6, and vitamin B12 were positively correlated with cognitive dysfunction.
- The patients with depression and cognitive dysfunction showed the lowest levels of B vitamins compared with the other two groups.

Limitations

- A larger number of samples should be analyzed to confirm the current results.
- The diagnosis of depression was based solely on the assessment using HAMD, and the diagnosis of cognitive dysfunction relied on MoCA.

Introduction

Depression is a prevalent mental disorder that poses risks to both our physical and mental well-being. Unlike typical mood fluctuations and temporary emotional reactions in everyday life, depression is characterised clinically by a persistent low mood that is disproportionate to the circumstances. Individuals with moderate or severe depression may experience feelings of pessimism and may even exhibit suicidal tendencies or behaviours. In extreme cases, depression can result in fatalities. The incidence of depression is on the rise, driven by the fast-paced nature of modern life. Approximately 280 million people, accounting for about 3.8% of the global population, are estimated to be affected by depression.

The pathogenesis of depression remains unclear. However, various biological, psychological, and social environmental factors are known to be involved in its development. Cognitive function, which encompasses learning and work abilities, is significantly affected in more than 10% of patients with depression (Zhang *et al.*, 2018). Cognitive impairment has been identified as a core symptom in depressed patients, potentially arising from dysfunction in brain-related regions (Srisurapanont *et al.*, 2018).

B vitamins, including folate, vitamin B6, and vitamin B12, are essential nutrients in the diet. They serve as coenzymes in one-carbon metabolism, which is involved in DNA methylation. Deficiency in B vitamins can lead to cognitive impairment through elevated levels of homocysteine (Hcy) and subsequent oxidative damage (Selhub, 2002; Lyon *et al.*, 2020). Previous research has suggested a link between low vitamin B12 levels and an increased risk of Alzheimer's disease (Clarke *et al.*, 2003; Clarke *et al.*, 2004). Inadequate dietary intake of vitamin B12 has also been associated with accelerated cognitive decline (An *et al.*, 2019). Conversely, individuals with sufficient intake of folate, vitamin B6, and vitamin B12 tend to have better cognitive reserve (An *et al.*, 2019). Furthermore, higher plasma folate levels have been proposed as potentially beneficial in preventing cognitive impairment (Chen *et al.*, 2022). In our study, we aimed to investigate the association between B vitamins and depression combined with cognitive dysfunction.

Materials and methods

Participants

In our study, a total of 220 patients with depression were enrolled, and 100 controls who came to the hospital for health check-ups during the same period were selected. All participants willingly agreed to participate after being informed about the research details and providing signed informed consent. Our study adhered to the ethical principles outlined in the Declaration of Helsinki for Medical Research Involving Human Subjects and received full approval from the Ethics Committee of Qingdao Mental Health Center.

All participants were over 18 years old. Patients with depression were diagnosed using the diagnostic criteria for depression in the International Classification of Diseases, 10th revision (ICD-10) (World Health Organization. 1992). The patients with depression had not taken any antidepressants within six weeks prior to enrolment. The healthy controls had no history of mental or physical illness, nor did they have any relatives with a history of mental illness. The levels of depression for all participants were assessed using the Hamilton Depression Rating Scale (HAMD) before enrolment. The HAMD evaluation criteria were as follows: scores less than 7 indicated no depression, scores from 7 to 17 suggested mild depression, scores from 17 to 24 indicated possible moderate depression, and scores above 24 were considered severe depression (Hamilton, 1960; Muller and Dragicevic, 2003). The control group should have HAMD scores below 7, while patients with depression should have scores above 17.

The exclusion criteria for all participants were as follows: 1. History of manic episodes, cranial injury, or neurological disorders; 2. History of psychoactive drug abuse; 3. Organic psychiatric disorders; 4. Severe liver, kidney, or gastrointestinal disorders; 5. Metabolic system disorders; 6. Breastfeeding or pregnant women.

Cognitive assessment

The patients with depression underwent the Montreal Cognitive Assessment (MoCA) to evaluate their cognitive function level (Nasreddine *et al.*, 2005). The MoCA consists of a total score of 30 points across various cognitive domains, including attention and concentration, memory, executive function, visual-spatial skills, language, abstract thinking, calculation, and orientation. A score below 26 indicated cognitive impairment. Moreover, for ischaemic stroke patients with less than 12 years of education, one additional point was added to their total MoCA score (if below 30 points).

Measurement

The basic parameters of the participants were recorded, including age, body mass index (BMI), and gender. In addition, overnight fasting venous blood samples were obtained for biochemical parameters. All the blood samples were collected by venipuncture into ethylene diamine tetraacetic acid vacutainer (BD Vacutainer, USA) and centrifuged as soon as possible. Serum samples were obtained after centrifugation at 500 *g* for 15 min and stored as aliquots at minus 80°C until use. Serum levels of B vitamins were measured by chemiluminescence microparticle immunoassay using an Abbott Architect i2000 SR immunoassay analyser. The concentration of serum brain-derived neurotrophic factor (BDNF) was measured by an enzyme-linked immunosorbent assay kit purchased from (the R&D system, USA).

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) Version 23.0 software (SPSS Inc., Chicago, IL) was used for data analysis and calculations. All data were presented as mean ± standard deviation (SD) based on at least three independent repeated tests. The predictive value was assessed using non-parametric receiver operating characteristic (ROC) analyses. The area under the curve (AUC) was used to determine diagnostic accuracy. A p value less than 0.05 was considered statistically significant.

Results

Basic characteristics

After the MoCA test, 220 patients with depression were divided into two groups: the depression without cognitive impairments (D-NCI) group ($n = 133$) and the depression with cognitive impairments (D-CI) group ($n = 87$). The characteristics of the depression patients are detailed in Table 1. Significant differences were observed in age, duration of depression, smoking status, education level, HAMD scores, and serum levels of BDNF, vitamin B6, B12, and folate between the D-NCI group and D-CI group. Additionally, the mean age of the healthy controls was 43.72 ± 10.88, with a male-to-female ratio of 52:48.

Independent risk factors for patients with depression and cognitive dysfunction

The risk factors for patients with depression and cognitive dysfunction were analysed using multifactorial logistic regression (Table 2). Cognitive dysfunction (0 = no, 1 = yes) was considered as the dependent variable, while age, gender, duration of depression, BMI, levels of depression, family history of depression, smoking, diabetes and hypertension status, education status, HAMD scores, and serum levels of BDNF, vitamin B6, vitamin 12, and folate were considered as independent variables. The stepwise elimination method was used to exclude irrelevant items ($p > 0.05$). It was found that a depression duration of more than 4.5 years, education level at or below junior high school, HAMD score higher than 28, serum BDNF levels below 59.64 ng/mL, serum folate levels below 20.92 nmol/L, serum vitamin B6 levels below 23.05 nmol/L, and serum vitamin B12 levels below 158.52 pg/mL were identified as independent risk factors for patients with depression and cognitive dysfunction (odds ratio >1, $p < 0.05$).

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Table 1. Characteristics of depression patients with and without cognitive impairments (CI) and healthy controls (HC)

Characteristics	HC ($n = 100$)	D-NCI ($n = 133$)	D-CI ($n = 87$)	p value (between D-NCI and D-CI)
Age (years)	43.72 ± 10.88	41.84 ± 10.15	46.87 ± 10.37	<0.001
Body mass index (kg/m^2)	22.69 ± 4.75	23.18 ± 4.11	23.52 ± 4.37	0.169
Course of depression (year)	–	2.96 ± 1.78	4.25 ± 2.22	<0.001
Gender				
Male	52 (52 %)	74 (55.6 %)	46 (52.9 %)	0.782
Female	48 (48 %)	59 (44.4 %)	41 (47.1 %)	
Severity of depression				
Mild	–	53 (39.8 %)	29 (33.3 %)	0.127
Moderate		48 (36.1 %)	26 (29.9 %)	
Severe		32 (24.1 %)	32 (36.8 %)	
Family history of depression				
Yes	–	49 (36.8 %)	28 (32.2 %)	0.563
No		84 (63.2 %)	59 (67.8 %)	
Smoke history				
Yes	28 (28 %)	57 (42.9 %)	51 (58.6 %)	0.027
No	72 (72 %)	76 (57.1 %)	36 (41.4 %)	
Diabetes mellitus				
Yes	9 (9 %)	18 (13.5 %)	19 (21.8 %)	0.139
No	91 (91 %)	115 (86.5 %)	68 (78.2 %)	
Hypertension				
Yes	11 (11 %)	14 (10.5 %)	12 (13.8 %)	0.524
No	89 (89 %)	119 (89.5 %)	75 (86.2 %)	
Education				
Junior high school and below	27 (27 %)	30 (22.6 %)	32 (36.8 %)	0.031
High school and above	73 (73 %)	103 (77.4 %)	55 (63.2 %)	
HAMD-17 score	3.21 ± 0.84	26.59 ± 4.78	28.37 ± 5.13	0.007
Serum folate (nmol/L)	24.98 ± 7.29	20.52 ± 8.25	12.74 ± 6.73	<0.001
Serum vitamin B6 (nmol/L)	42.85 ± 14.36	32.21 ± 13.67	21.84 ± 11.92	<0.001
Serum vitamin B12 (pg/mL)	194.88 ± 50.89	160.82 ± 58.61	119.93 ± 50.87	<0.001
Serum BDNF (ng/mL)	91.16 ± 20.54	84.31 ± 27.23	41.22 ± 18.29	<0.001

The data presented are mean ± SD or n (percentage). The comparisons of data were done by Mann–Whitney U-test or Fisher's exact test or chi-square test. D-NCI: depression without cognitive impairments, D-CI: depression with cognitive impairments, HAMD: Hamilton Depression Rating Scale, BDNF: brain-derived neurotrophic factor.

Table 2. Multivariate logistic analysis for cognitive impairments in depression patients

	OR	95% CI	p value
Course of depression more than 4.5 years	1.216	1.063 to 1.369	0.003
Junior high school and below	1.154	1.032 to 1.276	0.015
HAMD-17 score more than 28	1.195	1.041 to 1.349	0.009
Serum BDNF less than 59.64 ng/mL	1.636	1.395 to 1.877	<0.001
Serum folate less than 20.92 nmol/L	1.328	1.194 to 1.462	<0.001
Serum vitamin B6 less than 23.05 nmol/L	1.407	1.225 to 1.589	<0.001
Serum vitamin B12 less than 158.52 pg/mL	1.269	1.098 to 1.440	0.002

OR: Odds Ratio, CI: confidence interval.

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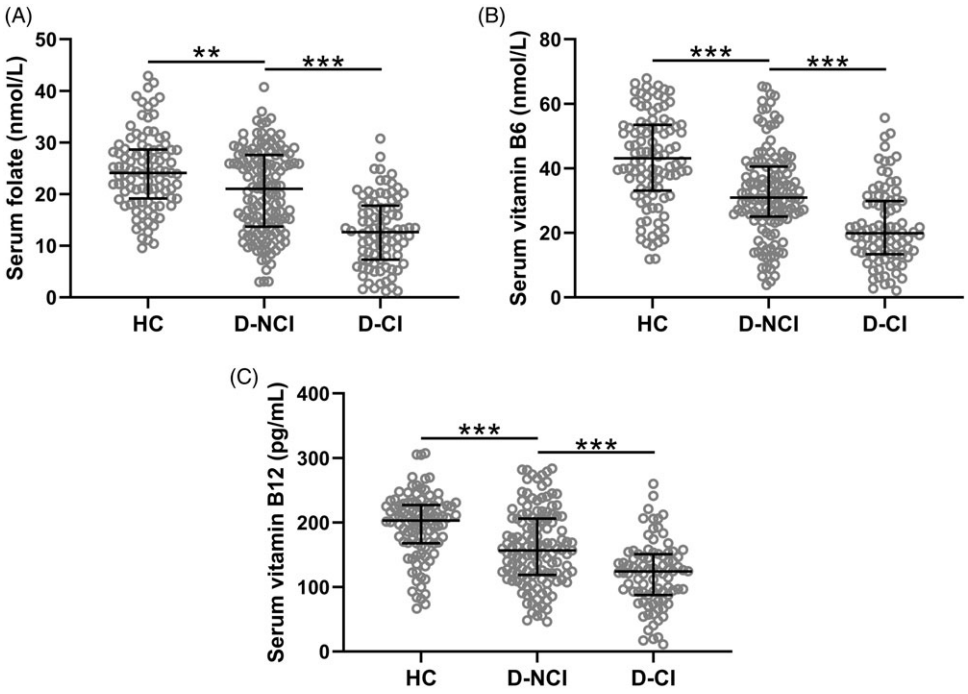

Figure 1. Comparisons of serum folate (A), vitamin B6 (B) and vitamin B12 (C) among healthy controls (HC, $n = 100$), depression patients without cognitive impairments (D-NCI, $n = 133$), and depression patients with cognitive impairments (D-CI, $n = 87$). Data were presented as median (interquartile range). $^{**}p < 0.01$, $^{***}p < 0.001$. Kruskal–Wallis test followed Dunn's multiple comparison test.

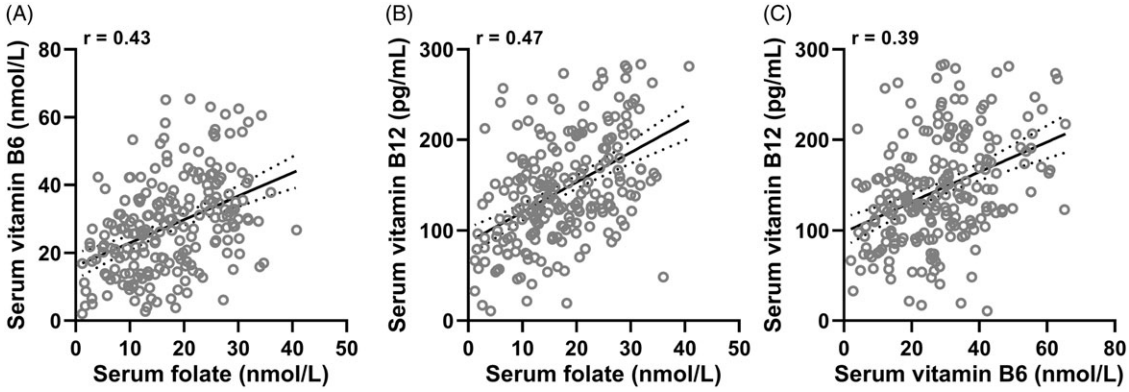

Figure 2. Spearman's correlation coefficient analysis of serum folate with vitamin B6 (A), serum folate with vitamin B12 (B), and serum vitamin B6 with vitamin B12 (C) in depression patients. $n = 220$.

Vitamin B6, B12, and folate were correlated with depression

The differences in serum folate, vitamin B6, and vitamin B12 levels were compared among the healthy controls, D-NCI group, and D-CI group (Fig. 1A–C). The results showed that patients with depression had lower serum folate, vitamin B6, and vitamin B12 levels compared to healthy controls. Furthermore, patients with depression and cognitive dysfunction exhibited the lowest levels of serum folate, vitamin B6, and vitamin B12.

Next, Spearman's correlation analysis was performed to measure the correlation between serum folate, vitamin B6, and vitamin B12 levels in all patients with depression (Fig. 2A–C). The analysis revealed a positive correlation among the levels of serum folate, vitamin B6, and vitamin B12 in patients with depression.

Vitamin B6, B12, and folate were predictors of depression with cognitive impairment

The predictive value of serum folate, vitamin B6, and vitamin B12 was determined by ROC analysis (Fig. 3A–C). The levels of serum folate, vitamin B6, and vitamin B12 yielded area under the curves (AUC) of 0.76, 0.72, and 0.69, respectively ($p < 0.001$). The results indicated that serum folate, vitamin B6, and vitamin B12 had predictive value for cognitive impairments in patients with depression. The correlation between HAMD scores and serum folate, vitamin B6, and B12 was examined in all patients with depression. HAMD scores exhibited negative correlations with serum folate, vitamin B6, and vitamin B12 (Fig. 4A–C). Furthermore, it indicated that serum folate, vitamin B6, and vitamin B12 were negatively correlated with the severity of depression. More severe depression was associated with lower levels of serum folate, vitamin B6, and vitamin B12.

Finally, Fig. 5A–C depicts the correlation of serum folate, vitamin B6, and vitamin B12 with the severity of cognitive impairment in depressed patients. First, the correlation analysis between B vitamins and MoCA scores revealed that higher MoCA scores were associated with higher levels of serum folate, vitamin B6, and vitamin B12. Subsequently, the correlation analysis between levels of B vitamins and BDNF showed that the levels of

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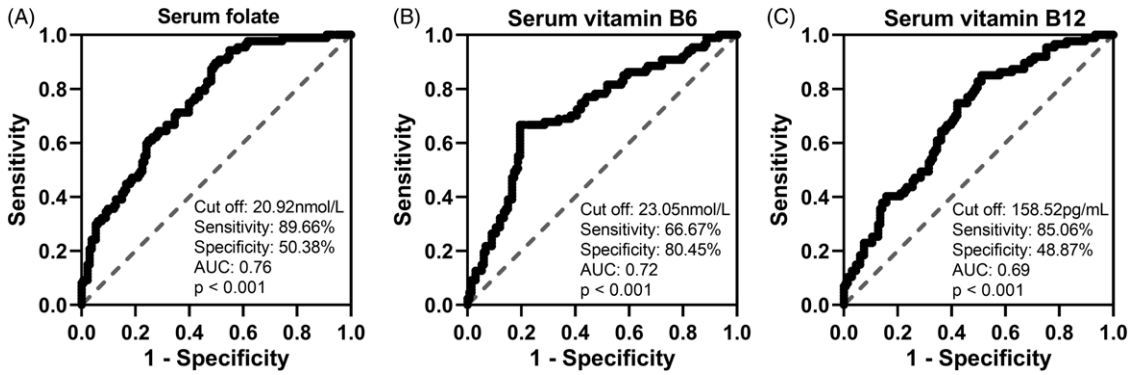

Figure 3. ROC analysis of serum folate (A), vitamin B6 (B), and vitamin B12 (C) for the prediction of cognitive impairments in depression patients.

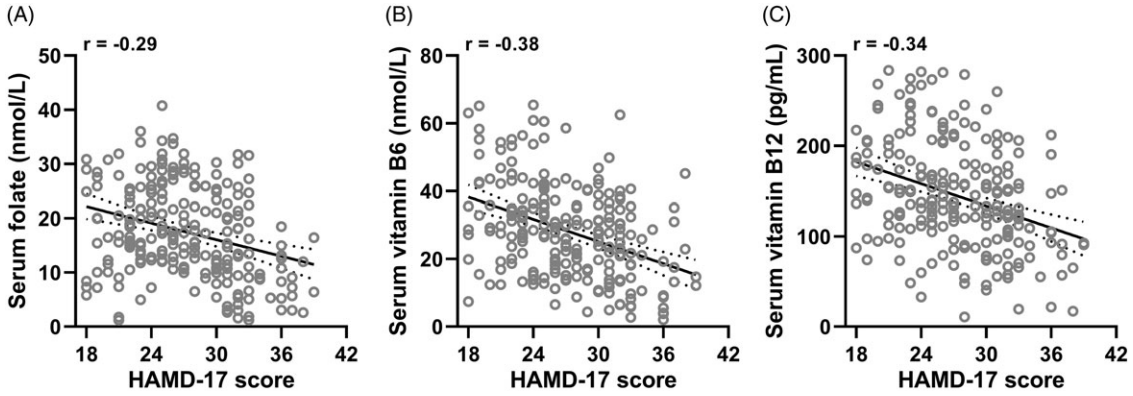

Figure 4. Spearman's correlation coefficient analysis of HAMD-17 score with serum folate (A), vitamin B6 (B), and vitamin B12 (C) in depression patients. $n = 220$.

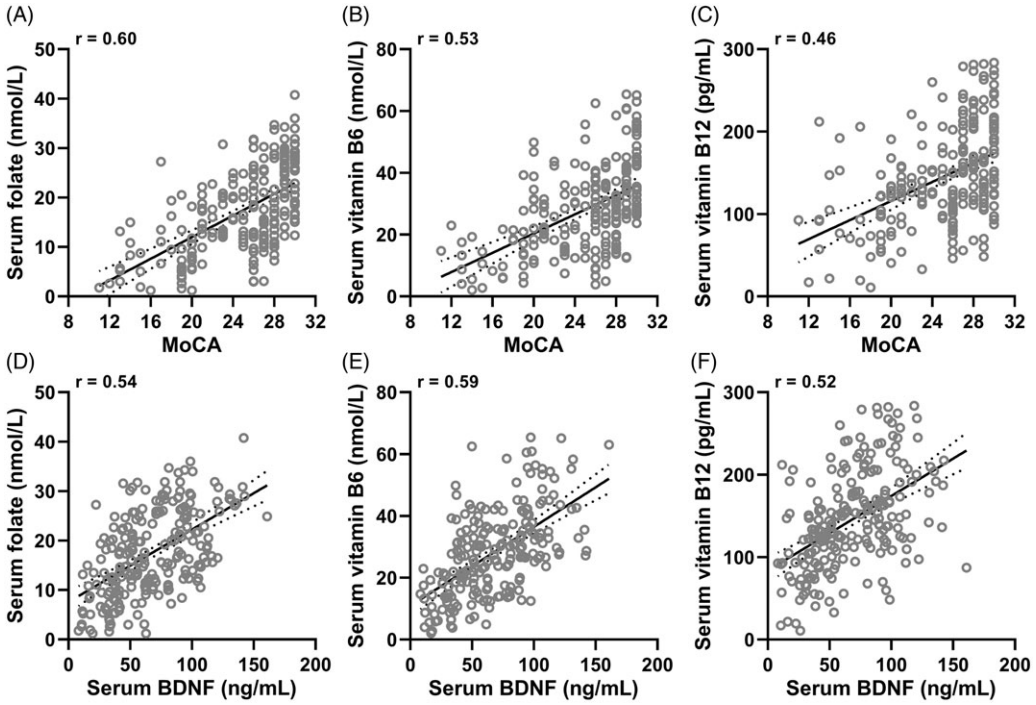

Figure 5. Spearman's correlation coefficient analysis of MoCA score with serum folate (A), vitamin B6 (B), and vitamin B12 (C) in depression patients. $n = 220$. Spearman's correlation coefficient analysis of serum BDNF level with serum folate (D), vitamin B6 (E), and vitamin B12 (F) in depression patients. $n = 220$.

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serum BDNF had a positive correlation with the levels of serum folate, vitamin B6, and vitamin B12 (Fig. 5D–E). Therefore, the results further support the notion that serum folate, vitamin B6, and vitamin B12 in patients with depression are correlated with combined cognitive dysfunction.

Discussion

Vitamins are essential dietary components for our well-being, contributing to our overall health and being linked to symptoms of mental disorders. B vitamins, including folate, vitamin B6, and vitamin B12, play crucial roles in brain development, maintenance, and function (Mitchell, *et al.*, 2014). Deficiencies in B vitamins can impact memory function, cognitive impairment, and even lead to dementia (Mikkelsen, *et al.*, 2016). Depression is believed to arise from complex interactions between environmental and genetic factors, often associated with significant complications such as increased negative life experiences and an elevated risk of suicide (Birmaher *et al.*, 2007). Cognitive impairment is a key symptom of depression (Srisurapanont *et al.*, 2018). A prolonged state of insufficient B vitamins is thought to be linked to depressive behaviour (Semmes, 2005). Therefore, our study aims to explore the correlation between B vitamins and depression, as well as their association with cognitive dysfunction.

Firstly, we assessed whether patients with depression had cognitive impairment using the MoCA assessment. We observed significant differences in the serum levels of BDNF, vitamin B6, vitamin B12, and folate between the D-NCI group and the D-CI group. BDNF, a member of the neurotrophin family, plays a vital role in neuronal growth and differentiation (Barua *et al.*, 2018). Therefore, BDNF is considered an adjunct for evaluating depression symptoms in clinical settings (Murawska-Cialowicz *et al.*, 2021). Vitamin B6 is involved in regulating mood and affects neurotransmitters linked to depression and anxiety. Previous studies have found that low levels of serum vitamin B6 are associated with major depression (Hvas *et al.*, 2004). Folate is necessary for the synthesis, methylation, and repair of DNA. Low folate levels have been consistently observed in studies of patients with depression (Gilbody, *et al.*, 2007).

Moreover, postpartum depression can be prevented by moderate consumption of folate-rich foods (Miyake *et al.*, 2006). Vitamin B12 is also known to play a crucial role in the nervous system. Deficiency of vitamin B12 can lead to severe depressive symptoms (Seppala *et al.*, 2013). On the other hand, vitamin B12 supplementation has been shown to improve depressive symptoms in older adults (Walker *et al.*, 2012). Vitamins B6, B12, and folate are essential for neurotransmitter and neuron synthesis. Therefore, low levels of vitamin B6, B12, and folate are associated with depressive symptoms.

The study results revealed significant differences in the duration of depression, education, and HAMD scores between the D-NCI and D-CI groups. It was observed that a depression duration exceeding 4.5 years, education level at or below junior high school, HAMD scores higher than 28, serum BDNF levels below 59.64 ng/mL, serum folate levels below 20.92 nmol/L, serum vitamin B6 levels below 23.05 nmol/L, and serum vitamin B12 levels below 158.52 pg/mL were identified as independent risk factors for patients with depression and cognitive dysfunction. These findings further support the correlation between B vitamins and depression with cognitive dysfunction. Then, we compared serum folate, vitamin B6, and vitamin B12 levels among the healthy controls, the D-NCI, and D-CI groups. Compared with the healthy controls, there was a positive correlation between serum folate, vitamin B6, and vitamin B12 levels and cognitive dysfunction. Conversely, patients with depression and cognitive dysfunction had the lowest levels of B vitamins compared to the other two groups. Additionally, our results revealed a positive correlation among serum folate, vitamin B6, and vitamin B12 levels in patients with depression.

However, it is important to consider the limitations of our study. Firstly, due to financial constraints, we could only recruit participants from one hospital simultaneously, resulting in a small sample size and potential selection bias. Secondly, the diagnosis of depression was based solely on the assessment using HAMD, and the diagnosis of cognitive dysfunction relied on MoCA. These factors may have influenced our results, and it is crucial to address them in future studies.

Conclusion

In conclusion, our results indicated that vitamin B was associated with depression and cognitive dysfunction and was also positively associated with cognitive dysfunction.

Author contribution. All the authors had full access to all the data in the study and took responsibility for the integrity of the data and accuracy of the data analysis. Conceptualisation, L.Z. and X.L.; Validation, L.Z., L.G., J.S., and X.L.; Investigation, L.Z., L.G., J.S., and X.L. Resources, X.L.; Writing-Original Draft, L.Z., L.G., J.S., and X.L.; Writing-Review & Editing, L.Z., L.G., J.S., and X.L.; Project Administration, X.L.; Funding Acquisition, X.L.

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Competing interests. The authors declare that they have no conflict of interest.

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