Vitamin D supplementation improves anxiety but not depression symptoms in patients with vitamin D deficiency

Cuizhen Zhu¹,²,³ | Yu Zhang¹,²,³ | Ting Wang¹,²,³ | Yezhe Lin⁴ | Jiakuai Yu¹,²,³ | Qingrong Xia¹,²,³ | Peng Zhu⁵ | Dao-min Zhu¹,²,³

Abstract
Objective: Epidemiological evidence indicated a relationship between vitamin D (VD) and depression with anxiety, but their therapeutic relationship has not been fully elucidated. This study aimed to examine whether VD supplementation would relieve symptoms in patients with depression and anxiety with low serum 25-hydroxy VD [25(OH) D] levels.
Method: Participants with low 25(OH)D levels were randomized to control or daily VD group and were followed up for 6 months. Serum concentrations of 25(OH) D were measured using commercial kits. Psychological symptoms were evaluated with the Hamilton Depression Rating Scale-17 (HAMD-17), Revised Social Anhedonia Scale (RSAS), Revised Physical Anhedonia scale (RPAS), and Hamilton Anxiety Rating Scale-14 (HAMA-14). The trial was listed in the trial registration (http://www.medremsan.org.cn/uc/index.aspx; NTR number: ChiCTR2000030130).
Results: In this clinical population, no significant difference in depression symptoms was detected between VD group and control group at both baseline and at the endpoint of our study. The HAMD-17, RSAS, and RPAS scores did not change significantly between VD and control groups from baseline to endpoint (all p > .05). However, there was a significant difference in time effect of the total HAMA-14 scores between the two groups ($\beta$ [95% CI] = $-2.235 [-3.818, -0.653], p = .006).
Conclusions: Vitamin D supplementation could improve the anxiety symptoms but not depressive symptoms in depressive patients with low VD level after the 6-month intervention.

KEYWORDS
anxiety, depression, vitamin D deficiency, vitamin D supplementation
1 | INTRODUCTION

Depression and anxiety are two of the most common debilitating illnesses among all mental disorders. Approximately 322 million people suffered from depression worldwide, leading depression to the major cause of disability over the globe (7.5% of all years lived with disability [YLDs]) (Amos et al., 2018; Li et al., 2019). As evidenced by epidemiological and clinical studies, in developed countries, 35.5%–50.3% of patients with serious mood disorders did not receive appropriate treatment and the rate rocketed to 76.3%–85.4% in less developed countries (Dean & Keshavan, 2017). Multiple hypotheses regarding possible pathophysiological mechanisms of these mood disorders included altered neurotransmission, chemical imbalance in the brain, inflammation, reduced neuroplasticity, chronic stress, and nutrient deficiency (Berridge, 2017; Maletic et al., 2007; Pertile, Cui, Hammond, & Eyles, 2018). Extensive research over the past decades has shown a critical role of malnutrition in depression and anxiety disorder (Kuygun Karci & Gul Celik, 2020; Milaneshi et al., 2019; Sanchez-Villegas et al., 2009). Moreover, this body of research has supported a complex involvement of vitamin D (VD) deficiency in mood disorders (Ju, Lee, & Jeong, 2013); however, the relationship between the two was not fully elucidated. While some studies addressed the benefits of VD supplementation on depressive and anxiety symptoms, recent randomized trials presented mixed results (Jorde & Grimmes, 2019; Landsdowne & Provost 1998; Vieth, Kimball, Hu, & Walfish, 2004).

To understand the pathophysiology relationship between mood disorders and VD, it is necessary to explore how VD functions. The active form of VD is 1,25-dihydroxy vitamin D3 [1,25(OH)2D3], which is formed by a series of reactions that take place in a number of different tissues. The VD3 enters the blood and is transferred to the liver where a hydroxyl group is added to the C-25 position by a vitamin D 25-hydroxylase to form 25-hydroxyvitamin D3 [25(OH)D3] that is the immediate precursor for active vitamin D. 25-hydroxy vitamin D [25(OH)D] is the main circulating metabolite of vitamin D, and the serum 25(OH)D level is the most reliable marker of vitamin D status (Almeida, Hankey, Yeap, Golledge, & Flicker, 2015; Jamilian, Bagherzadeh, Nazeri, & Hassaniijidehi, 2013). Rodent experiments have demonstrated that active VD enhanced glutamate and glucose metabolism in neurons, and therefore participated in behavioral changes and neurotransmitter-level alteration (Harms et al., 2012; Michael et al., 2007). Several studies also indicated that VD may be relevant to the gene expression of neurotrophic factors, which consequently stimulated neurogenesis and promoted antioxidation in neurons that protected them from oxidative degenerative processes (Czaja & Montano-Loza, 2019; Gezen-Ak, Dursun, & Yilmazer, 2013; Jeon & Shin, 2018; Khairy & Attia, 2019). Furthermore, studies have demonstrated VD as an essential coenzyme in the synthesis of monoamines such as norepinephrine and dopamine (Chester et al., 2015; Cui, Pertile, Liu, & Eyles, 2015; Pertile, Cui, & Eyles, 2016; Pertile et al., 2018). Those pieces of evidence above indicate the role of VD as a critical neurosteroid hormone involved in numerous brain processes, including brain neuroplasticity, neuroimmunomodulation, and brain development which could have an indirect impact on mood regulation.

The relationship between depression and VD has been reported in some population-based studies; however, some other studies revealed contradicted results (Bolland, Grey, Gamble, & Reid, 2011; de Koning et al., 2019). Especially, after regressing for confounding factors, including geography, body mass index, physical activity, and smoking, the relationship between VD and depression did not pass the significance in some studies. Notwithstanding, in cross-sectional and randomized placebo-controlled studies, some have shown a significant effect of VD supplementation on depressive symptoms, whereas others found no such associations (Jorde & Kubiak, 2018). In addition, depression with higher severity often tied with more anxiety symptoms, although the risk factors for the two conditions overlapped upon each other, they are still distinct entity (Shen et al., 2008). Studies exploring the association of VD levels and anxiety are still scarce and underinvestigated, as VD deficiency is potentially preventable for depression with anxiety symptoms, more studies are needed to explore the causal relationship between VD status and symptoms of depression and anxiety.

To the best of our knowledge, it is still unclear whether a decreased serum VD level is associated with anxiety independently from depression. Therefore, we performed a longitudinal study hypothesizing that the more severe depressive and anxiety symptoms would be related to lower VD serum and vice versa. In this study, we included a sample of participants with depression with anxiety; to investigate the VD supplements can effectively improve the symptoms of depression with anxiety patients.

2 | METHODS AND MATERIALS

2.1 | Design

The project is a clinical trial to study the effects of VD supplementation on depression with tied anxiety symptoms. This study was approved by the Medical Ethics Committee of Anhui mental health center (AMHC). All participants were provided written informed consent under the tenets of the Declaration of Helsinki.

Patients were recruited through advertisements from AMHC in China from November 2015 to March 2019. All patients were assessed by the Mini-International Neuropsychiatric Interview (MINI) 6.0.0 (Kadri et al., 2005; Sheehan et al., 1997) to confirm the diagnosis of major depressive disorders (MDD) (Sheehan, Harnett-Sheehan, Spann, Thompson, & Prakash, 2011). Sociodemographic data form, Hamilton Depression Rating Scale-17 (HAM-D-17), Revised Social Anhedonia Scale (RSAS), Revised Physical Anhedonia scale (RPAS), and Hamilton Anxiety Rating Scale-14 (HAMA-14), was applied to all participants. In our study, HAMD-17 was used to determine the severity of depressive symptoms. RSAS and RPAS were recommended optionally to determine the level of depression in the presence of social withdrawal and somatization symptoms.
The inclusion criteria for depressive patients were as follows: (a) diagnosis of MDD according to Diagnosis and Statistical Manual—5th edition (DSM-V); (b) age 18–60 years; (c) Han Chinese ethnicity; and (d) serum 25(OH) D levels ≤75 nmol/L before the entry of our study. The exclusion criteria were as follows: other concurrent psychiatric disorders defined in the DSM-V such as schizophrenia, and substance use disorders; and current severe physical conditions (e.g., neurological diseases, malignancy, cardiovascular diseases, respiratory diseases, severe trauma, state of pregnancy or breastfeeding).

After the strict clinical screening, a sample of 248 subjects entered the criteria of our study, among whom 158 people agreed to participate in this experiment with written informed consent. At the baseline of our study, subjects with serum 25(OH) D levels ≤75 nmol/L were randomly assigned to the intervention group (n = 79) and control group (n = 79). All participants were followed up in the 3rd and 6th months. 17 patients in the intervention group and 35 in the control group dropped out. At the endpoint (the 6th month), 62 participants in the intervention group and 44 in the control group completed the study (Figure 1).

2.2 Clinical assessments

2.2.1 Mini-international neuropsychiatric interview (MINI) 6.0.0

To be enrolled, participants in both the intervention group and the control group were screened by experienced psychiatrists. The initial clinical diagnoses were subsequently validated by the Mini-International Neuropsychiatric Interview (MINI) (Kadri et al., 2005; Sheehan et al., 1997). MINI was applied to all our subjects to confirm the clinical diagnosis of major depressive disorder. MINI contained the diagnosis of both current and past mood episodes.

2.2.2 Hamilton Depression Rating Scale (HAMD)-17

HAMD-17 was developed in 1960 to assess the severity of depressive symptoms. Most of the HAMD-17 items were scored on a scale of 0–4 (Park et al., 2014). Cronbach’s $\alpha$ score of HAMD-17 was 0.714, and the $\kappa$ score was 0.91 (Zhang et al., 2019). We evaluated our patients with HAMD-17 at baseline, the third month, and the 6th month. Score higher than 7 in HAMD-17 indicates the presence of depressive symptoms.

2.2.3 Hamilton Anxiety Rating Scale (HAMA)-14

The HAMA-14 is one of the most commonly used clinician-rated measurements of anxiety in studies of depression. HAMA-14 is rated from 0 to 4 with general guidelines provided for distinguishing the stage-wise anxiety severity. It is a reliable and valid measure of the severity of anxiety in depressed patients and has become the standard in this field. Score higher than 7 indicates the presence of anxiety symptoms (Wolfgang Maier, Philipp, & Heuser, 1988; Zimmerman et al., 2017).

2.2.4 Revised Social Anhedonia Scale (RSAS)

Social anhedonia is defined as impaired ability to feel pleasure in the interpersonal domain, which is comprised of two factors—social apathy/aversion, and social withdrawal. The Chinese version of the
Revised Social Anhedonia Scale is a 40-binary item self-rated questionnaire. Higher scores indicate more severe social anhedonia. A series of studies revealed its excellent coefficients exceeding 0.80 (Harvey, Pruessner, Czechowska, & Lepage, 2007; Hu et al., 2018; Rizvi, Pizzagalli, Sproule, & Kennedy, 2016).

2.2.5 | Revised Physical Anhedonia scale (RPAS)

Revised Physical Anhedonia scale is developed by the Chapman LJ in 1978 and measures a specific marker of certain endogenous depressions. It is a 61-binary item self-rated questionnaire and estimates participants’ inability to experience physical gratification from typically enjoyable stimuli, such as food and situations. This psychometric instrument offers a reliable and valid measure in depressed patients (Kollias et al., 2008). According to many results show that the RPAS had a good positive predictive value for depression and the cutoff of RPAS score was 18 points (Kollias et al., 2008).

2.3 | Laboratory evaluation

After an overnight fasting period, peripheral venous blood samples (2 ml) were collected from all patients in the morning, samples were sent to the Department of Clinical Laboratory immediately for centrifugation and serum was separated. Serum concentrations of 25-hydroxyvitamin D (25(OH)D) were measured by radioimmunoassay kits (Immunodiagnostic Systems; Roche).

2.4 | VD supplementation methods

The subjects with serum 25(OH)D levels ≤75 nmol/L at baseline were randomly divided into an intervention group and control group, patients remained on their current intake (including fish oil) were continued, and the intervention group were given VD 1,600 mg daily supplementation (Qingdao Double Whale Pharmaceutical Co, Ltd.) throughout the 6-month intervention period (Gowda, Mutowo, Smith, Wluka, & Renzaho, 2015).

2.5 | Statistical analyses

The t tests and chi-squared test were performed to compare the differences in either continuous or categorical parameters between the two groups. Time differences were explored by repeated-measure ANOVA and the Tukey post hoc analyses. Then, in order to eliminate the effect of possible confounding variables, linear mixed model analyses and unstructured covariance structure were used to control confounding factors at 6th months. Statistical significance was set when P values < 0.05, two-sided. All statistical analyses were run on SPSS 22.0 for Windows (IBM Corp).

3 | RESULTS

3.1 | Description of sample

The baseline characteristics of participants are shown in Table 1. 158 participants were included in the final analyses. The levels of VD were not different between control (39.1 ± 10.5 nmol/L) and intervention groups (2.1 ± 12.6 nmol/L). No significant differences were observed in age, BMI index, sex and years of education, household income, drinking, smoking, residential city, daytime outdoor time <2 hr, physical activity, sitting time <2 hr, and antipsychotic use between the two groups (all p values >.05). Similarly, the HAMD-17, HAMA-14, RSAS, and RPAS scores at baseline did not differ between groups (p > .05).

3.2 | Comparison of psychological scales between the two groups at baseline, 3rd month, and 6th month

In the whole cohort, total scores of HAMD-17 did not differ at baseline, 3rd month, and 6th month in the two groups (Figure 2a, p > .05). Additionally, the total scores of RPAS (Figure 2b, p > .05) and the total scores of RSAS (Figure 2c, p > .05) remained unchanged between the two groups throughout time. There was a significant reduction in the total scores of HAMA-14 at 6th month between the two groups (intervention group: 8.502 ± 0.483, versus control group: 7.245 ± 0.402, p = .041, Figure 2d).

3.3 | The effect of VD supplementation on the scores of major scales after 6 months

Linear mixed model analyses and unstructured covariance structure were used to control confounding factors after half a year, and all results are presented in Table 2. Linear mixed model analysis results showed the difference in total scores of HAMA-14 (Model 1: β = −2.235, 95% CI = [−3.818, −0.653], p = .006) and no difference in total scores of HAMA-17 (Model 1: β = −3.450, 95% CI = [−5.807, −1.093], p = .093) in the crude model. Moreover, we found the subitems of HAMA, including BMI (Model 1: β = −0.143, 95% CI = [−0.243, −0.042], p = .042), sense of despair (Model 1: β = −0.675, 95% CI = [−4.546, −3.473], p = .016), and physical anxiety (Model 1: β = −0.843, 95% CI = [−1.627 −0.063], p = .045), are significantly different between the two groups after 6 months. In order to avoid the confounding factors, we use unstructured covariance structure to control confounding factors (gender, age, education level, marital status, survey season, smoking, drinking, physical activity time, sitting or lying time, BMI) in the adjusted model. The results shown the differences in total scores of HAMA (Model 2: β = −2.414, 95% CI = [−4.455, −0.373], p = .021). The results also demonstrated differences in subitems of HAMA, including BMI.
DISCUSSION

In this clinical intervention cohort study, we examined the effects of oral 25(OH)D (1,600 IU daily) supplementation for 6 months on depressive patients with VD deficiency (25(OH)D < 75 nmol). VD supplementation had no significant impact on depressive symptoms after the 6-month intervention in the overall cohort. However, there was a significant improvement in anxiety symptoms for patients in the VD supplementation group compared with the control group after adjusting for covariates known to affect VD status. Despite our modest sample size, the findings suggested that high levels of VD may contribute to reduced anxiety symptoms on depressive patients with VD deficiency. Different options for VD deficiency supplementation were available and recommended as augmentation in the treatment of psychiatric disorders.

There is growing evidence showing that VD supplementation may improve the severity of the psychopathology through several potential mechanisms (Gezen-Ak et al., 2013; Kalueff, Lou, Laaksi, & Tuohimaa, 2004; Yang, Wei, Ju, & Chen, 2019). For example, VD is used to maintain Ca²⁺ homeostasis and this feature is a link between VD deficiency and depression. Another important function of VD interferes with the synthesis of serotonin by the expression of serotonin-synthesizing gene tryptophan hydroxylase 1 and tryptophan hydroxylase 2, and VD may thus prevent depression by maintaining normal serotonin levels (Berridge, 2017). VD is an important regulator of gene expression in a wide range of cellular functions, and VD receptors were found to mediate several biological pathways including insulin and serotonin, which were
associated with depression, anxiety, and other moods (Bertone-Johnson, 2009; Kelley, Sanders, & Beaton, 2016). These epigenetic alterations that lead to a decline in the expression of key signaling proteins are a feature of many neural diseases including depression. Also, remarkable VD deficiency was shown to be associated with severe more depressive symptoms (Anglin, Samaan, Walter, & McDonald, 2013; Parker & Brotchie, 2011). However, different VD supplementation doses and duration, and levels of serum 25-hydroxyvitamin (OH)-D at baseline led to divergent results concerning the effects of psychiatric symptoms. It is worth noting that VD supplementation was more effective in specific populations, such as pregnant women, the elderly, or people living in places with long winters; however, no convincing evidence has yet been found in the causal relationship between VD and depressive symptoms (de Koning et al., 2017; Ju et al., 2013). Moreover, many studies did not adjust or measure for multiple confounders, such as the presence of somatic diseases, physical activity, or psychopharmaceutical state (Jorde & Grimnes, 2019). Furthermore, many studies applied cutoff points on self-reported psychiatric rating scales as inclusion criterion rather than a clinician-administered standardized psychiatric interview and therefore endorsed multiple potential biases. Our research found that VD supplementation did not show superiority in the treatment of depression. This result is consistent with the study by Libuda L et al, which is the largest study published so far on VD intervention in depression, and they included 113,769 cases and 208,811 controls and presented a strong but not conclusive argument against a causal relationship between the VD and depression status (Jorde & Kubiak, 2018; Libuda et al., 2019). Studies have also evidenced that there is a minority of depressive patients showing an extreme degree of anhedonia. Anhedonia is a key symptom of MDD and is defined as a reduced capacity to experience pleasurable situations (Treadway & Zald, 2011). RPAS and RSAS were used to evaluate the association between physical anhedonia and social anhedonia with depression in this study, and we did not find any significant difference between hedonic and anhedonic with depressive patients compared to control group in the VD supplementation dose of consumed at 6-month endpoints, which was in accordance with the previous studies (Kollias et al., 2008).

To the best of our knowledge, many studies focused on the association between serum 25(OH) D levels and depressive symptoms. However, only a few studies examined the relationship between 25(OH) D levels and anxiety symptoms. Animal research showed that the genetic ablation of VD receptors in mice may be
associated with altered emotional behaviors and increased anxiety-like behaviors (Kalueff et al., 2004). In human studies, Armstrong et al demonstrated that fibromyalgia patients accompanied by low levels of VD had higher levels of anxiety and depression symptoms (Armstrong et al., 2007). Similarly, Chao et al reported serum 25(OH) D deficiency showed more symptoms of anxiety and depression on health-related quality-of-life instrument, and Elisa J. de Koning et al found that lower serum 25(OH) D levels were associated with more anxiety symptoms at baseline in older persons. However, after they adjusted it with multiple confounders, this relationship was no longer significant. Moreover, longitudinal studies showed that there was no significant correlation between serum 25(OH) D and anxiety symptoms after three years of follow-up (de Koning et al., 2017). Notably, our results confirmed that 25(OH) D deficiencies were significantly associated with anxiety symptoms at 6-month endpoint. The discrepancy among these results gave rise to the need for more research on VD deficiency and anxiety symptoms.

Evidence from experimental and clinical studies had explored the relationship between anxiety symptoms and VD. Dana L. et al found males with anxiety showed a greater trend toward overweight in comparison with controls (Rofey et al., 2009). Dressler et al confirmed that overweight BMI and limited exposure to sun were associated with an increased risk of VD deficiency (Dressler et al., 2016; Pourshahidi, 2014). Our results suggest that BMI is more likely to associate with reduced 25(OH) D concentrations with anxiety symptoms, whatever in the crude model or adjusted model. These findings indicate that BMI is an important factor that should be closely monitored. The feeling of despair may be expressed as hatred and low self-esteem, and people suffer from a great feeling of despair that can affect their psychological well-being and lead to outcomes such as depression and anxiety (Thasuk Junprasert, Piasai, & Chaiakkarakan, 2016). In our study also shown was a clear correlation between feelings of despair and VD deficiency, while VD supplementation may help prevent such anxiety symptoms. Given the complexity of depression, it has been shown to be related to multiple neurotransmitter imbalance and declined physical functions and mental capability, and such dysfunctions are the main factors leading to anxiety throughout the course and vice versa (de Koning et al., 2019). Tout results suggest that VD intervention can effectively relieve the physical anxiety of patients, indicating its beneficiary in such patients.

It is worth being noted the several strengths of our study: Most of our patients were in severe depression; the diagnoses were based on semi-structured interview kit. This paper also examined three dimensions of depressive symptoms—HADM-17, RSAS, and RPAS, and thus, it provides the comprehensive assessment of the relationship between depression symptoms and VD supplementation conducted to date. On the other hand, there are also several limitations in this

| Scale score | Model 1 |  | Model 2 |  |
|------------|---------|---|---------|---|
|            | \(\beta\) | 95% CI | \(P\) | \(\beta\) | 95% CI | \(P\) |
| HAMA       | -2.235  | -3.818,-0.653 | 0.006 | -2.414  | -4.455,-0.373 | 0.021 |
| Somatization of anxiety | -0.952 | -1.694,-0.209 | -0.209 | -0.701  | -1.602,0.200  | 0.125 |
| Body mass index(BMI) | -0.143 | -0.243,-0.042 | -0.042 | -0.149  | -0.268,-0.030 | 0.015 |
| Cognitive impairment | -0.693 | -1.133,-0.252 | -0.252 | -0.182  | -0.509,0.146  | 0.273 |
| Day and night | -0.065 | -0.281,0.15 | 0.018 | 0.103  | -0.201,0.407  | 0.499 |
| Slow to respond | -0.801 | -1.427,-0.174 | -0.174 | -0.399  | -1.100,0.301  | 0.259 |
| Sleep disorder | -0.588 | -1.061,-0.115 | -0.015 | -0.355  | -0.963,0.227  | 0.228 |
| Sense of despair | -0.675 | -4.546,-3.473 | -0.016 | -0.546  | -1.051,-0.041 | 0.034 |
| Physical anxiety | -0.843 | -1.627,-0.06 | -0.045 | -1.04  | -2.061,-0.019 | 0.046 |
| Mental anxiety | -0.952 | -1.694,-0.209 | -0.209 | -0.701  | -1.602,0.200  | 0.125 |
| HAMD | -3.450 | -5.807,-1.093 | -1.093 | -1.908  | -4.549,0.734  | 0.154 |
| RPAS | 0.892 | -3.739,5.524 | 5.524 | 0.834  | -12.491,4.961 | 0.789 |
| RSAS | 0.250 | -2.523,3.023 | 3.023 | -0.414  | -4.027,3.198  | 0.82 |

Note: Using linear mixed model analyses and unstructured covariance structure to control confounding factors (baseline outcome indicators, gender, age, education level, marital status, survey season, smoking, drinking, physical activity time, sitting or lying time, BMI) at the endpoint of six months of vitamin D intervention.

Abbreviations: HAMA-14, Hamilton Anxiety Rating Scale-14; HAMD-17, Hamilton Depression Rating Scale-17; RPAS, Revised Physical Anhedonia scale; RSAS, Revised Social Anhedonia Scale.
study that worth further investigation. First, our study only followed up patients for 6 months, whether the effect of VD could last longer remained unclear. Second, the sample size in this clinical research is relatively smaller; thus, future studies should target on larger-sized cohorts of depressive patients with VD deficiency. Third, we only implemented one dosage of VD for supplementation, so an ideal or the least effective dosage could not be established through our conclusion. However, indications from our study could provide further optimization of VD supplementation therapy.

In conclusion, we have shown there is no significant correlation between depressive symptoms and VD supplementation, and a clear relationship between low VD levels and high levels of anxiety. Although whether VD deficiency contributes to low mood is still had confusion, further studies should warrant to address this issue on validation.

ACKNOWLEDGMENTS

The work was supported by the key research and development projects in Anhui Province of China (grant numbers: 201904a07020015), the in-hospital project of Hefei Fourth People's Hospital (grant numbers: 2019010 and 2019023), Joint Laboratory Project of University of Science and Technology of China and the Fourth People's Hospital of Hefei (grant numbers: 2019LH02) and Fund Project of Anhui Medical University (grant numbers: 2019kxj206), and the Municipal Health Planning Commission Applied Medical Research project of Anhui Hefei (hwk2018yb001).

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Zhu Dao-min and PengZhu were responsible for study design and manuscript editing. Cuizhen Zhu and Yeze Lin were responsible for literature searches, statistical analyses, and manuscript writing. Yu Zhang and TingWang were responsible for clinical-scale assessment data collection. Jiakui Yu and Qingrong Xia were responsible for clinical blood data collection. All authors have contributed to and have approved the final manuscript.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/brb3.1760.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in the Chinese Clinical Trial Registry (http://www.medresman.org.cn/uc/index.aspx, Reference Number: ChiCTR2000030130). We originally included other variables and hypotheses but did not present them in this paper due to space restrictions.

ORCID

Cuizhen Zhu https://orcid.org/0000-0002-1779-9547
Dao-min Zhu https://orcid.org/0000-0001-7160-2592

REFERENCES

Almeida, O. P., Hankey, G. J., Yeap, B. B., Gollek, J., & Flicker, L. (2015). Vitamin D concentration and its association with past, current and future depression in older men: The Health In Men Study. *Maturitas*, 81(1), 36–41. https://doi.org/10.1016/j.maturitas.2015.01.016

Amos, T. B., Tandon, N., Lefebvre, P., Pilon, D., Kamstra, R. L., Pivneva, I., & Greenberg, P. E. (2018). Direct and indirect cost burden and change of employment status in treatment-resistant depression. *The Journal of Clinical Psychiatry*, 79(2), 24–32. https://doi.org/10.4088/JCP.17m11725

Anglin, R. E., Samaan, Z., Walter, S. D., & McDonald, S. D. (2013). Vitamin D deficiency and depression in adults: Systematic review and meta-analysis. *British Journal of Psychiatry*, 202, 100–107. https://doi.org/10.1192/bjp.bp.111.106666

Armstrong, D. J., Meenan, G. K., Bickle, I., Lee, A. S., Curran, E. S., & Finch, M. B. (2007). Vitamin D deficiency is associated with anxiety and depression in fibromyalgia. *Clinical Rheumatology*, 26(4), 551–554. https://doi.org/10.1007/s10067-006-0348-5

Berridge, M. J. (2017). Vitamin D and depression: Cellular and regulatory mechanisms. *Pharmacological Reviews*, 69(2), 80–92. https://doi.org/10.1124/pr.116.013227

Bertone-Johnson, E. R. (2009). Vitamin D and the occurrence of depression: Causal association or circumstantial evidence? *Nutrition Reviews*, 67(8), 481–492. https://doi.org/10.1111/j.1753-4887.2009.00220.x

Bolland, M. J., Grey, A., Gamble, G. D., & Reid, I. R. (2011). Calcium and vitamin D supplements and health outcomes: A reanalysis of the Women's Health Initiative (WHI) limited-access data set. *The American Journal of Clinical Nutrition*, 94(4), 1144–1149. https://doi.org/10.1093/ajcn/nqz141

Chester, D. S., DeWall, C. N., Derefenko, K. J., Estus, S., Peters, J. R., Lynam, D. R., & Jiang, Y. (2015). Monoamine oxidase A (MAOA) genotype predicts greater aggression through impulsive reactivity to negative affect. *Behavioral Brain Research*, 283, 97–101. https://doi.org/10.1016/j.bbr.2015.01.034

Cui, X., Pertile, R., Liu, P., & Eyles, D. W. (2015). Vitamin D regulates tyrosine hydroxylase expression: N-cadherin a possible mediator. *Neuroscience*, 304, 90–100. https://doi.org/10.1016/j.neuroscience.2015.07.048

Czaja, A. J., & Montano-Loza, A. J. (2019). Evolving role of vitamin D in immune-mediated disease and its implications in autoimmune hepatitis. *Digestive Diseases and Sciences*, 64(2), 324–344. https://doi.org/10.1007/s10620-018-5251-6

de Koning, E. J., Lips, P., Penninx, B. W. J. H., Elders, P. J. M., Heijboer, A. C., den Heijer, M., … van Schoor, N. M. (2019). Vitamin D supplementation for the prevention of depression and poor physical function in older persons: The D-Vitaal study, a randomized clinical trial. *American Journal of Clinical Nutrition*, 110(5), 1119–1130. https://doi.org/10.1093/ajcn/nqz141

de Koning, E. J., Verweij, L., Lips, P., Beekman, A. T. F., Comijs, H. C., & van Schoor, N. M. (2017). The relationship between serum 25(OH)D levels and anxiety symptoms in older persons: Results from the Longitudinal Aging Study Amsterdam. *Journal of Psychosomatic Research*, 97, 90–95. https://doi.org/10.1016/j.jpsychores.2017.04.005

Dean, J., & Keshavan, M. (2017). The neurobiology of depression: An integrated view. *Asian Journal of Psychiatry*, 27, 101–111. https://doi.org/10.1016/j.ajp.2017.01.025

Dressler, N., Chandra, A., Aguirre Davila, L., Spinelli, L. M., Schippert, C., & von Versen-Hoyneck, F. (2016). BMI and season are associated with vitamin D deficiency in women with impaired fertility: A two-centre analysis. *Archives of Gynecology and Obstetrics*, 293(4), 907–914. https://doi.org/10.1007/s00404-015-3950-4

Gezen-Ak, D., Dursun, E., & Yilmazer, S. (2013). Vitamin D inquiry in hippocampal neurons: Consequences of vitamin D-VDR pathway disruption on calcium channel and the vitamin D requirement. *Neurological Sciences*, 34(8), 1453–1458. https://doi.org/10.1007/s10072-012-1268-6
Gowda, U., Mutowo, M. P., Smith, B. J., Wluka, A. E., & Renzaho, A. M. N. (2015). Vitamin D supplementation to reduce depression in adults: Meta-analysis of randomized controlled trials. *Nutrition, 31*(3), 421-429. https://doi.org/10.1016/j.nut.2014.06.017

Harms, L. R., Cowin, G., Eyles, D. W., Kurniawan, N. D., McGrath, J. J., & Byrne, T. H. J. (2012). Neuroanatomy and psychomimetic-induced locomotion in C57Bl/6J and 129X1/SvJ mouse exposed to developmental vitamin D deficiency. *Behavioral Brain Research, 230*(1), 125-131. https://doi.org/10.1016/j.bbr.2012.02.007

Harvey, P. O., Pruessner, J., Czechowska, Y., & Lepage, M. (2007). Individual differences in trait anhedonia: A structural and functional magnetic resonance imaging study in non-clinical subjects. *Molecular Psychiatry, 12*(8), 767-775. https://doi.org/10.1038/sj.mp.4002021

Hu, H. X., Chu, M. Y., Yang, Y., Wang, L. L., Zhang, R. T., Lui, S., ... Chan, R. C. K. (2018). Mediation effect of beliefs about pleasure and emotional experience between social anhedonia and prediction of pleasant events. *Psychiatry Research, 264*, 39-45. https://doi.org/10.1016/j.psychres.2018.03.070

Jamilian, H., Bagherzadeh, K., Nazeri, Z., & Hassanijirdehi, M. (2013). Vitamin D, parathyroid hormone, serum calcium and phosphorus in patients with schizophrenia and major depression. *International Journal of Psychiatry in Clinical Practice, 17*(4), 365–370. https://doi.org/10.3109/13651501.2012.667111

Kalueff, A. V., Lou, Y.-R., Laaksi, I., & Tuohimaa, P. (2004). Increased anxiety in mice lacking vitamin D receptor gene. *NeuroReport, 15*(8), 1271–1274. https://doi.org/10.1097/01.wnr.0000129370.02448.92

Kelley, L., Sanders, A. F., & Beaton, E. A. (2016). Vitamin D deficiency, behavioral atypicality, anxiety and depression in children with chromosome 22q11.2 deletion syndrome. *Journal of Developmental Origins of Health and Disease, 7*(6), 616–625. https://doi.org/10.1002/jid.25040

Khairy, E. Y., & Attia, M. M. (2019). Protective effects of vitamin D on neurophysiologic alterations in brain aging: Role of brain-derived neurotrophic factor (BDNF). *Nutritional Neuroscience, 4*, 1-10. https://doi.org/10.1080/1028415X.2019.1665854

Kollias, C. T., Kontakakis, V. P., Havaki-Kontakakis, B. J., Stamoulis, S., Margaritis, M., & Petridou, E. (2008). Association of physical and social anhedonia with depression in the acute phase of schizophrenia. *Psychopathology, 41*(6), 365–370. https://doi.org/10.1159/000152378

Kuygun Karci, C., & Gul Celik, G. (2020). Nutritional and herbal supplements in the treatment of obsessive compulsive disorder. *General Psychiatry, 33*(2), e100159. https://doi.org/10.1136/gpsych-2019-100159

Landsdowne, A. T., & Provost, S. C. (1998). Vitamin D 3 enhances mood in healthy subjects during winter. *Psychopharmacology (Berl), 135*(4), 319–323. https://doi.org/10.1007/s002130050517

Li, G., Fife, D., Wang, G., Sheehan, J. J., Bodén, R., Brandt, L., ... DiBernardo, A. (2019). All-cause mortality in patients with treatment-resistant depression: A cohort study in the US population. *Annals of General Psychiatry, 18*, 23. https://doi.org/10.1186/s12991-019-0248-0

Libuda, L., Laabs, B.-H., Ludwig, C., Bühmeier, J., Antel, J., Hinney, A., ... Peters, T. (2019). Vitamin D and the risk of depression: A causal relationship? Findings from a Mendelian Randomization Study. *Nutrients, 11*(5), 1085. https://doi.org/10.3390/nu11051085

Maletic, V., Robinson, M., Oakes, T., Iyengar, S., Ball, S. G., & Russell, J. (2007). Neurobiology of depression: An integrated view of key findings. *International Journal of Clinical Practice, 61*(12), 2030–2040. https://doi.org/10.1111/j.1742-1241.2007.01602.x

Michael, B., Sanders, K. M., Pasco, J. A., Jacka, F. N., Williams, L. J., Hayes, A. L., & Dodd, S. (2007). Vitamin D deficiency may play a role in depression. *Medical Hypotheses, 69*, 1316–1319. https://doi.org/10.1016/j.mehy.2007.04.001

Milaneschi, Y. P., Nivard, W. J., Mbarek, M. G., Boomsma, H., Penninx, D. I., & Brenda, W. J. H. (2019). A role for vitamin D and omega-3 fatty acids in major depression? An exploration using genomics. *Translational Psychiatry, 9*(1), 219. https://doi.org/10.1038/s41590-018-0005-8

Park, S.-C., Choi, J., Kim, J.-M., Jun, T.-Y., Lee, M.-S., Kim, J.-B., ... Park, Y. C. (2014). Is the Psychotic Depression Assessment Scale a useful diagnostic tool? The CRESCEND study. *Journal of Affective Disorders, 166*, 79–85. https://doi.org/10.1016/j.jad.2014.05.004

Parker, G., & Brotchie, H. (2011). D’ for depression: Any role for vitamin D? ‘Food for Thought’ II. *Acta Psychiatrica Scandinavica, 124*(4), 243–249. https://doi.org/10.1111/j.1600-0447.2011.01705.x

Perrile, R. A., Cui, X., & Eyles, D. W. (2016). Vitamin D signaling and the differentiation of developing dopamine systems. *Neuroscience, 333*, 193–203. https://doi.org/10.1016/j.neuroscience.2016.07.020

Perrile, R. A. N., Cui, X., Hammond, L., & Eyles, D. W. (2018). Vitamin D regulation of GDNF/Ret signaling in dopaminergic neurons. *The FASEB Journal, 32*(2), 819–828. https://doi.org/10.1096/fj.20170713R

Poursahehdi, L. K. (2014). Vitamin D and obesity: Current perspectives and future directions. *Proceedings of the Nutrition Society, 74*(2), 115–124. https://doi.org/10.1017/s0029665114001578

Rizvi, S. J., Pizzagalli, D. A., Sproule, B. A., & Kennedy, S. H. (2016). Assessing anhedonia in depression: Potentials and pitfalls. *Nutritional Neuroscience & Biobehavioral Reviews, 65*, 21–35. https://doi.org/10.1016/j.neuobiorev.2016.03.004

Rofey, D. L., Kolk, R. P., Iosif, A.-M., Silk, J. S., Bost, J. E., Feng, W., ... Dahl, R. E. (2009). A longitudinal study of childhood depression and anxiety in relation to weight gain. *Child Psychiatry and Human Development, 40*(4), 517–526. https://doi.org/10.1007/s10578-009-0141-1

Sanchez-Villegas, A., Doreste, J., Schatter, J., Pla, J., Bes-Rastrollo, M., & Martinez-Gonzalez, M. A. (2009). Association between folate, vitamin B6 and vitamin B12 intake and depression in the SUN cohort study. *Journal of Human Nutrition & Dietetics, 22*(2), 122–133. https://doi.org/10.1111/j.1365-277X.2008.00931.x

Sheehan, D. V., Harnett-Sheehan, K., Spann, M. E., Thompson, H. F., & Prakash, A. (2011). Assessing remission in major depressive disorder and generalized anxiety disorder clinical trials with the discan metric of the Sheehan disability scale. *International Clinical Psychopharmacology, 26*(2), 75–83. https://doi.org/10.1097/YIC.0b013e328341b5f

Sheehan, D. V., Lecrubier, Y., Harnett Sheehan, K., Janavs, J., Weiller, E., Keskeriner, A., ... Dunbar, G. C. (1997). The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. *European Psychiatry, 12*(5), 232–241. https://doi.org/10.1016/S0924-938X(97)83297-X

Shen, B. J., Avivi, Y. E., Todaro, J. F., Spiro, A. 3rd, Laurenceau, J. P., Ward, K. D., & Niaura, R. (2008). Anxiety characteristics independently and prospectively predict myocardial infarction in men the unique
contribution of anxiety among psychologic factors. *Journal of the American College of Cardiology, 51*(2), 113–119. https://doi.org/10.1016/j.jacc.2007.09.033

Thasuk Junprasert, T. P., Piasai, P., & Chaiakkarakan, N. (2016). Depression and anxiety in the elderly: Formulation and development of preventive model through community participation. *International Journal of Behavioral Science, 11*(2), 77–92. https://doi.org/10.14456/ijbs.2016.13

Treadway, M. T., & Zald, D. H. (2011). Reconsidering anhedonia in depression: Lessons from translational neuroscience. *Neuroscience and Biobehavioral Reviews, 35*(3), 537–555. https://doi.org/10.1016/j.neubiorev.2010.06.006

Vieth, R., Kimball, S., Hu, A., & WalFish, P. G. (2004). Randomized comparison of the effects of the vitamin D3 adequate intake versus 100 mcg (4000 IU) per day on biochemical responses and the wellbeing of patients. *Nutrition Journal, 3*, 8. https://doi.org/10.1186/1475-2891-3-8

Wolfgang Maier, R. B., Philipp, M., & Heuser, I. (1988). The Hamilton Anxiety Scale reliability validity and sensitivity to change in anxiety and depressive disorders. *Journal of Affective Disorders, 14*, 61–68. https://doi.org/10.1016/0165-0327(88)90072-9

Yang, B., Wei, J., Ju, P., & Chen, J. (2019). Effects of regulating intestinal microbiota on anxiety symptoms: A systematic review. *General Psychiatry, 32*(2), e100056. https://doi.org/10.1136/gpsych-2019-100056

Zhang, A., Li, G., Yang, C., Liu, P., Wang, Y., Kang, L., & Zhang, K. (2019). Alterations of amplitude of low-frequency fluctuation in treatment-resistant versus non-treatment-resistant depression patients. *Neuropsychiatric Disease and Treatment, 15*, 2119–2128. https://doi.org/10.2147/NDT.S199456

Zimmerman, M., Martin, J., Clark, H., McGonigal, P., Harris, L., & Holst, C. G. (2017). Measuring anxiety in depressed patients: A comparison of the Hamilton anxiety rating scale and the DSM-5 Anxious Distress Specifier Interview. *Journal of Psychiatric Research, 93*, 59–63. https://doi.org/10.1016/j.jpsychires.2017.05.014