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IMPACT OF VITAMIN B12 STATUS ON DEPRESSIVE SYMPTOMS: A NARRATIVE REVIEW

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ABSTRACT

BACKGROUND

Depression is a prevalent and disabling mental health disorder associated with substantial individual and societal burden. Emerging evidence suggests that nutritional factors may contribute to its pathophysiology. Vitamin B12 plays a crucial role in one-carbon metabolism, methylation processes, and the synthesis of monoamine neurotransmitters, which are implicated in mood regulation. Deficiency of vitamin B12 has been linked to neuropsychiatric manifestations, including depressive symptoms.

OBJECTIVE

This review aimed to evaluate serum vitamin B12 levels in individuals with depressive disorders and to assess the association between vitamin B12 deficiency and the risk or severity of depression. Additionally, the potential impact of vitamin B12 supplementation on depressive symptoms was examined.

METHODS

A narrative review of the literature was conducted using PubMed, Scopus, Web of Science, and Google Scholar. Randomized controlled trials, meta-analyses, cohort studies, clinical guidelines, and position statements published in

English were included. Studies were selected based on relevance and methodological quality.

RESULTS

Most analyzed studies demonstrated an association between lower serum vitamin B12 levels and the presence or greater severity of depressive symptoms. Elevated homocysteine concentrations accompanied vitamin B12 deficiency. Evidence suggests that persistently low vitamin B12 status may increase the risk of developing depression, particularly in older adults.

CONCLUSIONS

Vitamin B12 deficiency appears to be associated with depressive symptoms and may contribute to underlying neurobiological mechanisms. Low serum concentrations may increase the risk of depression, particularly in older adults. However, supplementation does not consistently improve established symptoms, suggesting a greater preventive than therapeutic role. Further research is warranted.

Keywords: Vitamin B12; depressive disorder; depression; homocysteine; supplementation; neuropsychiatry

INTRODUCTION

Vitamin B12 is an essential nutrient involved in protein metabolism, purine and pyrimidine synthesis, hematopoiesis, and myelin formation [1]. Cobalamin deficiency impairs hematopoiesis, leading to megaloblastic anemia [2] through defective erythroblast production, premature destruction in the bone marrow, and shortened survival in peripheral blood. Deficient myelin metabolism, along with consequent muscle fiber atrophy, can result in neurological symptoms.

Cobalamin absorption begins in the stomach, where it binds to haptocorrin, which is subsequently degraded in the duodenum. Released vitamin B12 then binds to the gastric glycoprotein known as intrinsic factor (historically known as Castle factor) and is absorbed in the ileum via endocytosis [3]. In the bloodstream, most vitamin B12 is bound to transcobalamin I, while 20-30% is bound to transcobalamin II, the bioavailable protein that transports vitamin B12 to the liver for storage [3].

The recommended daily intake of vitamin B12 for adults is 2.4 µg/day (National Institutes of Health)[4], increasing to 2.6 µg/day during pregnancy and 2.8 µg/day during lactation. Dietary sources are exclusively animal-based, including meat, fish, dairy, and eggs, with bioavailability ranging from 20% to 90%. Examples of foods rich in vitamin B12 include clams (3 oz, 84 µg), fortified cereals (1 serving, 6 µg), trout (3 oz, 5.4 µg), salmon (3 oz, 4.9 µg), and canned tuna (3 oz, 2.5 µg), among others. Healthy adults have approximately 3-5 mg of vitamin B12 stored in the body, sufficient for roughly four years without dietary intake [5].

Neurological and psychiatric manifestations are prominent in severe vitamin B12 deficiency, occurring in over 75% of patients. These disorders are linked to the accumulation of neurotoxins such as homocysteine [6], which induces oxidative stress, inflammation, and vascular dysfunction [7,8]. Neurological symptoms include peripheral neuropathy, paresthesia, gait instability, and decreased muscle tone [9,10]. Psychiatric symptoms may involve cognitive impairment, reduced concentration, low mood, depressive symptoms, or exacerbation of existing psychiatric conditions, as well as progression of neurodegenerative diseases such as Alzheimer's and Parkinson's. [11-20]

Common causes of vitamin B12 deficiency include vegan or vegetarian diets, malnutrition, alcoholism, malabsorption (e.g., metformin use [21,22], acid-suppressing drugs, Addison's disease, Biermer's anemia, post-gastrectomy or bariatric surgery, ileal resection, Crohn's disease [23], small intestinal bacterial overgrowth) [24], and congenital conditions (intrinsic factor deficiency, transcobalamin deficiency, Imerslund-Gräsbeck syndrome).

Depression, one of the most prevalent psychiatric disorders, may be associated with deficiencies in vitamin B12 and folate. Dietary insufficiencies of these micronutrients have been linked to increased severity of depressive symptoms and may influence the effectiveness of pharmacological treatments [25]. These deficiencies are particularly common in older adults, a population at higher risk for depressive episodes [26]. Furthermore, the multifactorial etiology of depression complicates establishing a direct causal link with a single nutrient, though the prevalence of depression is higher in groups prone to vitamin B12 deficiency, such as patients with Crohn's disease [27].

Despite the growing recognition of nutritional psychiatry, the precise role of vitamin B12 in the pathophysiology and management of depression remains inadequately integrated into routine clinical practice. Given that vitamin B12 deficiency is a highly modifiable risk factor, understanding its impact offers a low-cost and accessible avenue for preventive and adjunctive strategies. This narrative review provides an updated synthesis of recent evidence, encompassing diverse methodologies such as longitudinal cohorts, clinical trials, and Mendelian randomization studies, to evaluate both the risk of depression incidence and the severity of existing symptoms. However, a significant knowledge gap persists regarding whether vitamin B12 supplementation is primarily effective as a

preventive measure against mood decline in vulnerable populations or as a direct therapeutic intervention for established depressive episodes - a discrepancy this review aims to systematically address.

AIM OF THE STUDY

This review synthesizes existing evidence regarding serum vitamin B12 concentrations in individuals diagnosed with depressive disorders, as well as the potential association between vitamin B12 deficiency and the subsequent development of depression. Particular attention is given to studies comparing vitamin B12 levels in patients with clinically diagnosed depression and in non-depressed control populations.

The majority of included studies focused on adults aged 18-65 years; however, evidence derived from older populations (≥65 years) was also considered, given the increased prevalence of both vitamin B12 deficiency and depressive symptoms in this age group.

Additionally, the potential role of vitamin B12 supplementation in modulating current depressive symptoms and in reducing the risk of incident depressive episodes was examined.

RESEARCH OBJECTIVES

To achieve the primary aim, the following research objectives were formulated:

1. To evaluate and compare serum vitamin B12 concentrations between individuals with clinically diagnosed depressive disorders and non-depressed control groups.
2. To determine the association between the degree of vitamin B12 deficiency and the severity of depressive symptoms across different adult populations.
3. To analyze the longitudinal risk of developing incident depression in relation to baseline vitamin B12 status, with a particular focus on the elderly.
4. To assess the efficacy of vitamin B12 supplementation in modulating depressive symptoms and reducing elevated homocysteine levels.
5. To identify potential neurobiological mechanisms, such as one-carbon metabolism and monoamine synthesis, through which vitamin B12 influences mood regulation.

MATERIAL AND METHODS

A narrative review of the literature was conducted to synthesize current evidence on the association between vitamin B12 status and depressive symptoms. The review encompassed randomized controlled trials, meta-analyses, cohort studies, cross sectional studies, as well as selected clinical guidelines and position statements where relevant.

A comprehensive search of the electronic databases PubMed, Scopus, Web of Science, and Google Scholar was performed to identify relevant publications. The search covered studies published up to December 2025 and was restricted to full text articles published in peer reviewed journals and written in English. Language filters were applied at the database level where available.

The search strategy incorporated combinations of predefined keywords and Medical Subject Headings, where applicable. The following terms were used: "vitamin B12 level," "cobalamin," "depressive disorder," "depression," "vitamin B12 supplementation in depression," "folate and vitamin B12," and "symptoms of depression." These terms were combined using the Boolean operators AND and OR. Searches were performed in titles and abstracts where database functionality allowed. The search was adapted to the syntax of each database.

Studies were selected based on predefined inclusion and exclusion criteria. Inclusion criteria comprised peer reviewed full text studies involving human participants that reported data on serum vitamin B12 status in relation to depressive symptoms, risk of depression, severity of symptoms, homocysteine concentrations, or the effects of vitamin B12 supplementation. Eligible study designs included randomized controlled trials, meta-analyses, cohort studies, cross sectional studies, and relevant clinical guidelines. The review primarily focused on adult populations, including studies involving older adults.

Exclusion criteria included publications not available in full text, articles not published in English, studies not involving human participants, conference abstracts without sufficient data, and reports lacking relevant biochemical or clinical outcome measures related to vitamin B12 and depression. Studies focusing exclusively on unrelated neurological or metabolic outcomes without assessment of depressive symptoms were also excluded.

Study selection was performed in two stages, initial screening of titles and abstracts followed by full text assessment.

Studies that met the eligibility criteria were included in the qualitative synthesis. Data extraction included study design, population characteristics, diagnostic criteria for depression, methods of vitamin B12 assessment, and key outcomes related to depressive symptoms and biochemical markers.

Due to the narrative design of the review, studies were evaluated descriptively with attention to methodological transparency, internal consistency of reported outcomes, and comparability across study designs. The synthesis was conducted through thematic grouping of studies according to study design and primary outcomes.

RESULTS

According to the latest 2025 data from the World Health Organization (WHO), depression is among the most prevalent mental disorders worldwide, affecting approximately 332 million people, or 5.7% of the adult population (4.6% of men and 6.9% of women). Depression represents a major global health burden and a leading cause of disability, with its impact increasing with age and in populations underserved by healthcare systems [28]. Emerging evidence suggests a link between vitamin B12 deficiency and the development of depression, and supplementation may potentially improve treatment outcomes. Dietary habits also play a critical role in mental well-being, with numerous studies confirming the influence of nutrition on nervous system function [29].

ADDITIONAL FACTOR - ALCOHOL

The relationship between depression and the risk of developing addictions, including alcohol use disorder, should also be considered. This association is bidirectional, as up to 80% of individuals with alcohol dependence may experience mood disorders or other psychiatric symptoms during their lifetime [30]. One study [31] involving 188 participants undergoing detoxification, with 156 followed for six months, found a significant link between depression and the level of alcohol dependence. At admission, 120 participants exhibited depressive symptoms, which decreased to 47 participants after six months of detoxification, indicating an improvement in mood following addiction rehabilitation. The association between depression and alcohol dependence was statistically significant (p value = 0.002). Moreover, individuals who continued to experience depressive symptoms after six months reported stronger alcohol cravings (p value= 0.03). Alcohol also negatively affects cobalamin absorption and is a major contributor to vitamin B12 deficiency, as discussed in the Introduction.

DIETARY PATTERNS AND BIOCHEMICAL MARKERS

Khosravi et al. [32] conducted a cross-sectional study examining the relationship between dietary patterns, serum biochemical markers, and depression. The study included 260 adults aged 18-65, recently diagnosed with depression (within the past three months), along with healthy controls. Among women, 87 were depressed and 173 were healthy, while among men, 22 were depressed and 48 were healthy. Exclusion criteria included cognitive impairment, severe psychotic disorders, hormonal disorders (e.g., hyperthyroidism or hypothyroidism), viral infections (including HIV), recent pneumonia, adherence to special diets in the past two months, and vitamin B12 supplementation.

Serum levels of folate, vitamin B12, tryptophan, and homocysteine were compared between depressed patients and controls, and the relationship between dietary patterns and depression was analyzed. The detailed comparison of these biochemical markers and their statistical significance is presented in Table 1.

Table 1. Main findings regarding serum biochemical markers in depressed patients versus healthy controls (data adapted from Khosravi et al. [32])

Biochemical Marker	Case (Mean ± SE)	Control (Mean ± SE)	P-value (t-test)	P-value (adjusted)*	OR (95% CI)
Folate (ng/ml)	5.8 ± 0.3	7.7 ± 0.28	<0.001	<0.001	0.54 (0.38-0.75)
Vitamin B12 (pg/ml)	550.9 ± 55.1	954.9 ± 57.7	<0.001	<0.001	0.996 (0.993-0.998)
Homocysteine (µmol/l)	11.2 ± 1.1	11.9 ± 0.9	0.2	0.5	0.97 (0.9-1.05)

Tryptophan (µmol/l)	70.3 ± 2.9	75.3 ± 3.9	0.3	0.1	0.97 (0.94-1.01)
Tryptophan/CAA ratio	0.113 ± 0.003	0.104 ± 0.002	0.02	0.5	1.46 (0.45-4.76)

*Study Characteristics: Cross-sectional study design; Total participants: N = 260 adults (aged 18-65). Group Definitions: Case group refers to participants recently diagnosed with depression (within the past three months); Control group refers to healthy participants without a diagnosis of depression. Statistical Indicators & Abbreviations: SE = Standard Error (a measure of the statistical accuracy of an estimate); OR = Odds Ratio (represents the odds that an outcome will occur given a particular exposure); CI = Confidence Interval (a range of values likely to include a population value with a certain degree of confidence); CAA = Competing Amino Acids (the ratio of tryptophan to other large neutral amino acids, which influences its transport into the brain). *P-values from multiple logistic regression adjusted for demographics, lifestyle, depression history, energy intake, physical activity, and dietary patterns.*

As shown in Table 1, depressed individuals exhibited significantly lower mean levels of folate (5.8 vs. 7.7 ng/ml) and vitamin B12 (550.9 vs. 954.9 pg/ml) compared to the control group ($p < 0.001$). These results demonstrate that dietary patterns influence depression risk indirectly through these biochemical markers. A healthy diet, associated with higher vitamin B12 and folate concentrations, was linked to a lower risk of depression, while decreased levels of these vitamins were associated with an increased likelihood of depressive symptoms.

LONGITUDINAL RISK ASSESSMENT OF VITAMIN B12 AND DEPRESSION

Laird et al. [33] analyzed data from the Irish Longitudinal Study on Aging (TILDA), which included **3,849 community-dwelling adults aged ≥50 years**, to examine the relationship between serum vitamin B12 and folate levels and the development of depressive symptoms over a four-year period. Participants underwent serum measurements of vitamin B12 and folate and were screened for depressive symptoms using the **20-item Center for Epidemiological Studies Depression Scale (CES-D-20)**, with scores above 16 indicating clinically significant depression. Individuals with depression at baseline or lacking four-year follow-up data were excluded.

The study found that participants with low or deficient vitamin B12 levels had a significantly higher likelihood of developing depressive symptoms ($p = 0.021$); this association remained significant after adjusting for age, gender, and education ($p = 0.043$). Higher serum vitamin B12 levels were associated with a lower risk of depression ($p = 0.045$), whereas folate levels did not show a significant correlation. Overall, individuals with low or deficient vitamin B12 were 51% more likely to develop depressive symptoms over the four-year follow-up period.

INSIGHTS FROM MENDELIAN RANDOMIZATION

Hu et al. [34] conducted a two-sample Mendelian randomization study to investigate the causal relationship between B-vitamin and homocysteine levels and five common mental disorders. The study included 44,147 European participants from the UK Biobank with measured vitamin B12 and homocysteine levels. Data on mental disorders were obtained from the FinnGen database, comprising 47,696 cases and 359,290 controls. The disorders analyzed were depression, anxiety disorders, bipolar disorder, obsessive-compulsive disorder (OCD), and schizophrenia.

Results indicated that serum vitamin B12 levels were associated with anxiety disorders (p value = 0.046), but no causal relationship was observed between vitamin B12 levels and depression (p value = 0.415), OCD, or schizophrenia. Similarly, homocysteine levels showed no significant association with depression. These findings suggest that while vitamin B12 may influence the risk of anxiety disorders, it does not appear to have a direct causal effect on depression.

SEVERITY CORRELATIONS AND CLINICAL THRESHOLDS

Harikaran et al. [35] investigated the role of vitamin B12 in neurotransmission and its association with depression severity. The study included 59 adults aged 18-65 (31 women and 28 men) with newly diagnosed depression based on ICD-10 criteria. Depression severity was assessed using the Hamilton Depression Rating Scale (HAM-D), and serum vitamin B12 and homocysteine levels were measured. Exclusion criteria included other psychiatric disorders and the use of vitamin B12 supplements.

Participants were categorized by depression severity: mild (n = 3), moderate (n = 22), severe (n = 24), and very severe (n = 10). All patients exhibited reduced vitamin B12 levels, ranging from 107.6 to 234.3 pg/ml (median 164.2 pg/ml; reference range 200-900 pg/ml), and elevated homocysteine levels, consistent with B12 deficiency. Vitamin

B12 concentrations were significantly lower in patients with severe and very severe depression (p value = 0.031). Mean corpuscular volume (MCV) was higher in the very severe group compared to moderate depression, though this difference was not statistically significant. Nineteen participants were diagnosed with anemia, including 16 women. Additionally, median vitamin B12 levels were significantly higher in participants who consumed meat compared to those with less healthy diets (p value = 0.031).

The study concluded that all depressed patients exhibited low vitamin B12 levels, which correlated with symptom severity, suggesting that these individuals may benefit from vitamin B12 supplementation.

THE NUANCES OF SUPPLEMENTATION IN THE ELDERLY

Kwok et al. [36] conducted a randomized study in adults over 65 years with mild cognitive impairment and elevated homocysteine levels. Participants were randomized to receive either 500 µg of methylcobalamin plus 400 µg of folic acid daily (n = 138) or a placebo (n = 141) for 24 months, with assessments at 12-month intervals. A total of 118 participants in the supplementation group and 120 in the placebo group completed the study.

The study evaluated the effects of supplementation and homocysteine reduction on cognitive function. Over the follow-up period, homocysteine levels decreased in the supplementation group but remained unchanged in the placebo group. While a modest improvement in cognitive function was observed at 12 months in the treatment group, this effect was not sustained at 24 months. The supplementation group also reported a reduction in depressive symptoms at 12 months, despite the exclusion of participants with clinical depression at baseline. Overall, the study highlights that the impact of vitamin B12 and folate supplementation on depressive symptoms in older adults remains inconclusive.

OBSERVATIONAL STUDY ON VITAMIN B12 DEFICIENCY AND DEPRESSION

Rastogi et al. [37] analyzed the prevalence of depressive symptoms in adults aged 18-60 years with low vitamin B12 levels. The study included 400 participants, of whom 68.5% were women and 31.5% were men. Depressive symptom severity was assessed using the Beck Depression Inventory II (BDI-II), a 21-item self-administered questionnaire. Participants were categorized into two groups based on serum vitamin B12 levels:

- B12 ≤ 150 pg/mL (deficient)
- B12 151-200 pg/mL (insufficient)

Exclusion criteria included pregnancy and breastfeeding in women, chronic diseases such as tuberculosis, pneumonia, hepatitis, HIV infection, active cancer, vitamin B12 supplementation, and age outside the study range.

The study found that 16% of participants had vitamin B12 deficiency (≤150 pg/mL), while 84% had insufficient levels (151-200 pg/mL). Significant associations were observed between vitamin B12 levels and age (p = 0.001), dietary habits (p = 0.0007), gender (p = 0.003), and place of residence (rural vs. urban, p = 0.048).

Depressive symptoms were identified in 8.5% of participants with BDI scores >20, of whom 47.1% belonged to the deficient group and 52.9% to the insufficient group. Overall, the study demonstrated a significant association between low vitamin B12 levels and the presence of depressive symptoms (p < 0.05). The authors highlighted that early vitamin B12 supplementation may be a promising strategy to prevent early-onset depression, although further research is warranted to confirm these findings.

The characteristics and key findings of this study, along with other analyzed research investigating the link between vitamin B12 status and depressive symptoms, are synthesized and compared in Table 2.

Table 2. Summary of included studies investigating the association between vitamin B12 status and depressive symptoms

Study & Design	Population (N, Age)	Diagnostic Criteria / Scales Used	B12 Measurement / Intervention	Key Quantitative Outcomes & Main Findings
Khosravi et al. [32] Cross-sectional	N = 260 18-65 years	Clinical diagnosis of depression (diagnosed within the past	Serum measurement	Mean B12 levels were significantly lower in depressed individuals compared to healthy controls

		3 months)		(550.9 vs. 954.9 pg/ml, p<0.001). Healthy diet correlated with higher B12 and lower depression risk.
Laird et al. [33] Longitudinal cohort (TILDA)	N = 3,849 ≥50 years	CES-D-20 scale (score >16 indicating clinical depression)	Serum measurement	Participants with low/deficient B12 levels had a 51% higher likelihood of developing depressive symptoms over a 4-year period (p=0.043, adjusted for covariates).
Hu et al. [34] Mendelian Randomization	N = 44,147 Adults	Clinical records (FinnGen database)	Genetically predicted serum B12 levels	B12 was associated with anxiety disorders (p=0.046), but no causal relationship was observed between B12 levels and depression (p=0.415) or between homocysteine and depression.
Harikaran et al. [35] Clinical study	N = 59 18-65 years	ICD-10 criteria, HAM-D scale	Serum measurement	All depressed patients exhibited low B12 (median 164.2 pg/ml). B12 concentrations were significantly lower in patients with severe and very severe depression (p=0.031).
Kwok et al. [36] Randomized Controlled Trial (RCT)	N = 279 ≥65 years	Mild cognitive impairment criteria (clinical depression excluded at baseline)	Intervention: 500 µg methylcobalamin + 400 µg folic acid daily	Supplementation significantly reduced homocysteine levels and led to a temporary reduction in depressive symptoms at 12 months, though the effect on cognition was not maintained at 24 months.
Rastogi et al. [37] Observational	N = 400 18-60 years	BDI-II questionnaire (score >20 indicating depression)	Serum measurement (Deficient: ≤150 pg/mL; Insufficient: 151-200 pg/mL)	8.5% of participants had depressive symptoms. Among them, 47.1% were B12-deficient and 52.9% were insufficient. Significant association between low B12 and

				depression (p<0.05).

Abbreviations: CES-D-20 = Center for Epidemiological Studies Depression Scale; ICD-10 = International Classification of Diseases, 10th Revision; HAM-D = Hamilton Depression Rating Scale; BDI-II = Beck Depression Inventory II.

As summarized in Table 2, while the majority of observational and clinical studies indicate a significant correlation between low vitamin B12 levels and increased depressive symptoms, evidence from Mendelian Randomization [34] suggests that this relationship may not be strictly causal, highlighting the complexity of the B12-depression axis.

DISCUSSION

Accumulating evidence indicates that vitamin B12 is not merely an ancillary nutrient, but a fundamental component required for the proper functioning and maintenance of the central nervous system. As a rate-limiting cofactor in one-carbon metabolism, vitamin B12 plays a critical role in the synthesis of S-adenosylmethionine (SAMe), the principal methyl donor involved in numerous methylation reactions, including those necessary for the biosynthesis of monoamine neurotransmitters such as serotonin, dopamine, and norepinephrine.

In addition, cobalamin is essential for the remethylation of homocysteine to methionine, thereby regulating homocysteine concentrations. Vitamin B12 deficiency may lead to elevated homocysteine levels, which have been associated with increased oxidative stress, neurotoxicity, and structural brain changes. These mechanisms provide a biologically plausible link between inadequate vitamin B12 status and neuropsychiatric manifestations, including depressive symptoms.[38,39]

The analyzed studies consistently indicate an association between vitamin B12 status and depressive symptoms. Indirect evidence also suggests that dietary patterns observed in individuals experiencing low mood may be characterized by inadequate intake of essential nutrients, including vitamin B12 and folate. Moreover, several studies reported a correlation between the severity of depressive symptoms and the degree of vitamin B12 deficiency.

Longitudinal data suggest that persistently low vitamin B12 concentrations may be associated with an increased risk of developing depressive disorders, particularly among older adults, a population at heightened risk of both nutritional deficiencies and mood disturbances. Reduced vitamin B12 levels were frequently accompanied by elevated homocysteine concentrations, which were shown to respond to vitamin B12 supplementation.

However, current evidence indicates that correction of vitamin B12 deficiency in individuals with established depressive symptoms does not consistently result in significant clinical improvement [40,41], suggesting that supplementation may have greater relevance in prevention rather than as a standalone therapeutic intervention.

Vitamin B12 supplementation represents a relatively low-cost and accessible intervention for reducing elevated homocysteine concentrations. By normalizing vitamin B12 status, it may contribute to the modulation of oxidative stress-related pathways and support overall neurological function.

Nevertheless, further well-designed studies are required to evaluate the impact of comprehensive dietary patterns, rather than isolated nutrient supplementation, in individuals with established depressive disorders. In particular, future research should assess whether dietary optimization may alleviate symptom severity, enhance treatment response, or serve as an adjunct to standard pharmacological and psychotherapeutic interventions. [42]

CONCLUSIONS

In conclusion, the current body of evidence indicates a significant association between low serum vitamin B12 concentrations and the presence, as well as the severity, of depressive symptoms. This relationship is biologically supported by the role of vitamin B12 in one-carbon metabolism, its regulation of homocysteine levels, and its necessity for monoamine neurotransmitter synthesis.

While persistently low vitamin B12 status appears to increase the longitudinal risk of developing depression - particularly among older adults - the efficacy of vitamin B12 supplementation as a standalone therapeutic intervention for established depressive episodes remains inconclusive. The existing literature suggests that maintaining adequate vitamin B12 levels may hold greater clinical value as a preventive strategy against mood decline rather than a primary curative treatment.

Future research should prioritize well-designed, large-scale randomized controlled trials to clarify the potential of targeted vitamin B12 supplementation and comprehensive dietary optimization as adjunctive therapies in the long-term management of depressive disorders.

DISCLOSURE

AUTHORS' CONTRIBUTIONS

FUNDING

The study did not receive special funding.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

USE OF ARTIFICIAL INTELLIGENCE

The authors used artificial intelligence tools to assist with language editing and structural refinement. All AI-assisted content was reviewed and revised by the authors to ensure that its use did not influence the scientific integrity or substantive content of the work. Artificial intelligence was not used to extract data from primary studies; all information was checked manually.

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