

The Consequences of B Vitamins on Mental Health and Cognitive Function: A Literature Review Study

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ABSTRACT

Vitamin B's play an important role in health, especially mental health, and their deficiency may be linked to symptoms of psychiatric disorders. Studies have shown that the roles of B vitamins in mental health are not clear. This literature review objective was to investigate the role of vitamin Bs on mental health.

Methods: To obtain studies addressing the vitamin B's group effects on cognition and mental health, researchers used a computerized literature search (Google Scholar, PubMed, ScienceDirect, SpringerLink, ResearchGate, Semantic Scholar, and HINARI).

Results: The majority of studies on the influence of B-vitamins on cognitive function and mental health come up with similar results. There is still no conclusive evidence as to how vitamins work and what role they play in mental health. However, some studies revealed a good improvement while other no significant enhancement, as well as others, showed a slight improvement in cognitive function after replacement therapy (B vitamins supplementation).

Conclusion: Results are still under debate about the effect of vitamin B's (B2, B6, B9, and B 12) on mental health. Some evidence indicates that there is a positive relationship between the B vitamins group and improvement of cognitive function and mental health, whereas others showed no relation. More research and studies are needed to investigate the function of the B vitamins group in mental health.

KEYWORDS: Mental health; B Vitamins; Cognitive function; Supplements; Palestine

ABBREVIATIONS: MCG: Microgram; MMSE: Mini-Mental State Examination; MVM: Multi-Vitamin and Mineral; RCTs: Randomized Controlled trials; RDA: Recommended Dietary Allowance

BACKGROUND

Vitamins are an important substance that humans' bodies need to function, grow, and develop normally Baigent [1]. Vitamin A, vitamin C, vitamin D, vitamin E, and vitamin K, as well as choline and vitamin B's (thiamin, riboflavin, niacin, pantothenic acid, biotin, vitamin B6, vitamin B12, and folate/folic acid), are among them Pike, [2].

However, vitamin Bs are an important group of eight nutrients that have their function on a variety of organs and bodily systems.

Each one of them has its function, but they depend on each other for the best health benefits and proper absorption Berry [3]. These benefits include an explicit impact on body energy levels, brain function, and cell metabolism Cronkleton [4].

Furthermore, emerging research findings show that B12, B1 (thiamin), B2 (riboflavin), B3 (niacin), B6, and B9 (Folic Acid) also play an essential function in preserve optimal mental health Berry [3]. These vitamins are important parts of a healthy diet and may help relieve symptoms of alcohol abuse, depression, schizophrenia,

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and cognitive declines in some cases Lake [5]. Not only have these vitamins been shown to relieve psychiatric symptoms, but they have also been shown to decrease the time of disease. Vitamin B9, also known as folate or folic acid, has also been linked to mental health issues Leahy [6].

Norepinephrine, serotonin, and dopamine are all produced with the help of vitamins B12 and folate. These two vitamins play a key role in maintaining and controlling a balanced central nervous system, low folate, and vitamin B12 levels have been linked to depression Nutrition [7].

On the other hand, vitamin B12 and folate, have daily consumption recommendations of 2.4-2.8 micrograms and 400-600 micrograms, respectively Berry [3]. The Recommended Dietary Allowance (RDA) is the daily nutrient intake that is adequate to meet the needs of 97-98 percent of healthy people Nutrition [7].

However, nutrition is crucial for a person's brain mental wellbeing to remain optimal throughout his or her life. The prevalence of psychological conditions associated with cognitive impairment is on the rise Rathod [8]. The current incidence of mental health issues in Western societies is about 20%, and it is estimated that half of all adult mental health conditions start in adolescence Herbison et al. [9]. Nonetheless, it is a concerning rate that accounts for a large portion of the global disease burden Rathod [8]. Evidence-based practice studies showed a large ratio of the population in developed countries has insufficiencies or inadequacies in only one or more of the vitamin B's Kennedy [10]. Therefore, from this point of view, in recent years, studies exploring the connection between diet and mental health have gotten a lot of attention Rathod [7]. Furthermore, B vitamins play a role in brain chemistry, specifically related to mood Young [11], since they are necessary cofactors in the neurotransmitter's composition like serotonin and dopamine Herbison et al. [9]. These neurotransmitters are both key components in regulating mood and cognitive function Kennedy [10]. Moreover, supplementation with B vitamins has a good safety profile and may have a low risk of side effects Kennedy [10].

Accordingly, malnutrition (Nutritional deficiency) can affect all areas of the nervous system and impair the absorption of essential vitamins. And nutritional neuropathies appear either acutely, sub acutely, or chronically and affect cognitive and mental health Hammond [12]. And that, in the malnutrition, a fair approach to maintaining brain health would be to administer the entire B-vitamin community, rather than a small subset, at doses well above current government guidelines Kennedy [10]. B vitamin deficiencies can be treated and prevented by dietary consumption of high-vitamin foods or taking vitamin supplements Berry [3].

METHODOLOGY

Literature Search: In March 2021, a computerized literature search through Google Scholar, PubMed, ScienceDirect, SpringerLink, ResearchGate, Semantic Scholar, and HINARI was used to collect studies addressing the effect of B vitamins on mental health and cognition. The following search terms were used: effects B vitamins mental, B vitamins cognitive, "B2 AND mental health," "B2 AND cognitive," "Vitamin B AND cognitive," "vitamin B6 AND cognitive," "B6 AND cognitive," "B9 AND cognitive," "Folic acid AND mental," "Folic acid AND mental," "B12 AND cognitive," and " B12 AND mental." By using this search method, the number of founded articles reviewed. A review of reference lists of published papers yielded additional papers that did not appear explicitly in the

electronic database scan. 17 studies remained after examination of articles to meet the included criteria and removing excluded, irrelevant, and duplicated articles. Relevant empirical studies are summarized and presented hither.

Inclusion and Exclusion Criteria: The following requirements were used to determine whether a study was suitable for inclusion: (1) Reviewed B vitamins and both mental health and cognitive function (2) Reviewed the impact of B vitamins on mental health and cognitive function (3) Reviewed vitamins B2, B6, B9 (Folic Acid), and B12 effects on/and mental health and cognition.

All articles that discussed other B vitamins were excluded.

Quality Assessment: Each research was evaluated using a checklist to determine its consistency. The checklist includes items such as clear study objectives, a representative sample, a response rate with losses reported, an appropriate elaboration of results, clear exclusion and inclusion criteria, a reliable and valid measure of mental health, and proper statistical analysis. The principal investigator (IS) investigated the content of the articles and their quality and fixed any contradictions.

RESULTS

Since many patients use vitamins as a supplement to improve their energy, reduce fatigue, or just feel better, it is critical to clarify the relationship between B vitamins and psychiatric symptoms (mental health and cognition); Leahy [6].

The study in which they examined the connection between nutrient intake of six vitamin Bs in middle age and cognitive impairment in old age, among the Chinese population in Singapore. The number of the participants engaged in this study was 16,948 participants (45-74 years old), the study population collected from the Singapore Chinese Health Survey, a prospective cohort study was conducted between 1993 and 1998. A frequency food questionnaire which consisted of 165 validated items was used to test vitamin B's. The average years of follow-up were 20, both cognitive ability and cognitive impairment were evaluated by using the Mini-Mental State Examination scale of Singapore-edited version of in 2014 to 2016 and education-specific severance, respectively. To assess the connection between vitamin B's and the impairment in cognitions the researchers applied a logistic regression model. Depending on the study results, 2443 of the participants were classified with cognitive impairment. Also, depending on the dose, both vitamin B2 and vitamin B9 were significantly and independently associated with cognitive impairment Sheng et al. [13].

Furthermore, for non-demented elderly patients who complain of diminished cognitive impairments, the use of vitamin B12 is recommended Lake [5]. In a pilot study, 18 elderly patients with abnormal low B12 serum levels and cognitive impairment were treated with B12 vitamin supplement (one microgram per day intramuscularly) for 1 week, followed by weekly one mg injections for one month, then one mg injections for six months monthly. The findings of this study revealed that there was a substantial improvement in patients with cognitive impairment for less than one year, while those who were with cognitive impairment more than one year deteriorated. Suggesting that administering supplementation in the early stages of cognitive impairment may relieve symptoms associated with B12 deficiency Lake [5].

Additionally, published cross-sectional research was conducted to determine the effects of vitamin B12 replacement therapy affects vitamin B12-deficient patients with remarkable cognitive

impairment. B12 Vitamin and homocysteine levels were measured among patients with minimal cognitive impairment (MCI) in a multicenter study. The Mini-Mental State Examination (MMSE) and a review of cognitive impairment symptoms were used to evaluate 202 participants with vitamin B12 deficiency after three months of replacement therapy. According to the study's results, 84% of participants indicated significant symptomatic improvement after taking vitamin B12, and 78% of patients' MMSE scores improved. In addition, 44 patients recorded no symptomatic progress, but 26 patients had improved MMSE scores, while 18 patients had not improved MMSE scores; Jatoi et al. [14].

However, a cross-sectional study published in 2012, this study was carried out to investigate the connection between B-group vitamins and adolescent mental health and behavior. A food frequency questionnaire was collected as part of the 17-year follow-up, enabling B-vitamin intake to be calculated. The Youth Self Report (YSR), which tests overall, internalizing (withdrawn/depressed), and externalizing (aggressive/delinquent) behavior scores, was used to assess mental health. Multiple linear regression with correction for relevant confounders was used to investigate the relationship between B-vitamins and mental health (n=709). The findings of this study showed that a lower B vitamin intake was associated with higher externalizing behavior scores ($p=0.05$). Lower vitamin B6 and folate consumption were associated with higher internalizing behavior scores ($p=0.05$). According to this study, poor nutrition can play a role in the pathogenesis of mental health problems in adolescents, and the role of B-vitamins needs to be studied further in randomized controlled trials. Furthermore, the researchers found that a higher B-vitamin intake was protective against adolescent behavioral problems and that B-vitamins have a role in preventing mental health changes in adolescents Herbison et al. [9].

Another randomized, double-blind, placebo-controlled study involving 59 participants (from 18 to 65 years old) aimed to enhance perceived stress by using a specific amino acid structure of micronutrients in the under-investigation group (verum) compared to the placebo group. PSQ30 (Perceived Stress Questionnaire), amino acid profile, anthropometric, clinical, blood, urine parameters, and dietary intake were assessed. The results have shown that after 12 weeks, the verum group achieved significantly higher enhancements in the total score of PSQ30 contrasted with the placebo group Armbrorst et al. [15].

Furthermore, 138 participants (aged from twenty to fifty years old) were given a multivitamin including vitamin B's contra a placebo for 16 weeks, in a double-blind placebo-controlled trial. Salivary cortisol levels were assessed at baseline, eight weeks, and sixteen weeks, as well as at waking, fifteen minutes, thirty minutes, and bedtime. At baseline, 8 weeks, and 16 weeks, the participants' perceived stress (PSS), levels of B6 and B12 in the blood, homocysteine (HCy), and red cell folate (B9) were all measured. The Cortisol Awakening Response showed a major interaction between the treatment group and the study visit, according to the findings (CAR). When compared to placebo, supplementation of a multivitamin was found to be correlated with a slight increased tendency toward increased CAR after 16 weeks. Furthermore, there were no substantial differences in PSS between classes, and both groups' PSS increased during the analysis Camfield et al. [16].

Additionally, a randomized, double-blind, placebo-controlled trial was conducted among 139 healthy, elderly volunteers (60±83 years), to define the relationship between vitamin condition

and cognitive function and mood, as well as the influence of multivitamin supplementation, especially vitamins B2, B6, and B12, on these measures. Blood vitamin levels, cognitive functioning, and mood were measured at baseline and after that every twelve weeks. The findings revealed numerous associations between vitamin levels and cognitive functioning at baseline, but multivitamin administration had very little impact on success, despite increasing blood vitamin levels. The researchers concluded that short-term multivitamin administration in healthy, elderly patients had an unmarkable impact on cognitive ability or mood Cockle et al. [17]. Another randomized pilot study published in 2017 evaluated the relationship between the intake of vitamin B and cognitive function among 155 participants aged between 60 to 88 years old. The Mini-Mental State Examination (MMSE) was used. The mean cognitive scores of MMSE had decreased from 29.1 +/- 1.3 at baseline to 27.5 +/- 2.4 ($p=0.001$) after follow-up evaluation for four-year, but 27 percent of participants displayed a faster rate of cognitive decline than predicted. After adjusting for age and baseline MMSE score, lower vitamin B6 status was linked to a 3.5-fold increased risk of instant cognitive drop. Similarly, a lower intake of vitamin B6 (0.9–1.4 mg per day) was also correlated with a higher rate of cognitive drop. No markable relationships of the status of a biomarker or dietary intake with cognitive impairments were detected for the other vitamin B's Hughes et al. [18].

However, a double-blind, placebo-controlled multicenter trial published study aimed to examine the biochemical and clinical effects of B vitamin supplementation in adults with longstanding coeliac disease. A sample consists of 65 coeliac patients (61% women) aged from 45 to 64 years who had been on a tough gluten-free diet for several years were randomly assigned to receive either a regular dose of 0.8mg folic acid, 0.5mg cyanocobalamin, and 3mg pyridoxine or placebo for six months. Psychological general well-being (PGWB) and plasma total homocysteine (tHcy), a marker of B vitamin status, were used to assess the outcomes. The experiment was completed by 88 percent of the participants, according to the findings. The baseline median tHcy level was 11.7 micromole/L (7.4-23.0), which was slightly greater than matched population controls [10.2 micromole/L (6.7-22.6) ($P=0.01$). Following vitamin administration, tHcy decreased by 34% ($P=0.001$), which was followed by a substantial increase in well-being ($P=0.01$), especially Anxiety ($P=0.05$) and Depressed Mood ($P=0.05$) for patients with poor well-being Hallert et al. [19].

In addition, a cohort study was conducted in 2020 among 2991 Korean participants aged 76.4 3.9 years old to evaluate cognitive ability, using a short form of the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K). The Mini-Mental State Examination (MMSE-KC) was included in the Korean edition of the CERAD evaluation packet, and a linear regression analysis was used to measure the coloration between cognitive function and B12 levels. According to the findings, 13.8 percent of those tested were B12 deficient, while 86.2 percent were B12 appropriate Soh [20].

Furthermore, a pilot study conducted from June 2001 to June 2004 aimed to investigate whether taking vitamins B12, B6, and folate (B9) were linked to less severe depressive symptoms and a lower 2-year frequency of clinically significant depression. A total of 299 men aged 75 and up were included in the study, all of whom were free of clinically significant depression (a Beck Depression Inventory (BDI) score of less than 18). They were given either 400 micrograms of B12, 2 micrograms of folic acid, and 25 micrograms of B6 per day (N= 150) or a placebo (N=149). The study's primary

outcome factor was the BDI. Six, twelve, eighteen, and twenty-four months after the baseline, follow-up tests were conducted. According to the findings, 84.3% of men given vitamins and 79.1% of men given a placebo stayed free of clinically relevant depressive symptoms. To demonstrate benefit, a total of 21 people had to be treated Ford et al. [21].

Moreover, a double-blind, randomized study was conducted to determine the impact of four-week Multi-Vitamin and Mineral (MVM) administration on mood and neurocognitive function among 58 healthy adults. Participants' ages ranged from 18 to 40 years. After four weeks of administration at baseline, participants'

mood and blood biomarkers were measured. Both of them were tested at baseline and after four weeks of supplementation. MVM administration was correlated with slightly lower homocysteine and increased B-vitamins levels in the blood ($p=0.01$) as compared to placebo, according to the findings. MVM therapy was also associated with a significant improvement in mood, as measured by lower scores on the Profile of Mood States' "depression-dejection" subscale ($p=0.018$). The researchers concluded that four weeks of MVM supplementation may improve mood in healthy young adults, owing to higher B-vitamin levels and lower homocysteine levels White et al. [22]; (Table 1,2).

Table 1:

Database/Search Engine	Key words/ search terms	Number Hits	Number of Related Articles
Google Scholar	B2 AND mental health	1	0
	B2 AND cognitive	2	1
	Vitamin B AND cognitive	6	2
	Vitamin B6 AND cognitive	10	3
	B6 AND cognitive	12	1
	B9 AND cognitive	1	1
PubMed	Folic acid AND mental health	10	0
	Folic acid AND cognitive	12	4
Research Gate	B12 AND cognitive	93	4
	B12 AND mental	1	0

Table 2:

No.	Study Title and Author Name	Aim	Method	Result
1	Impact of a Specific Amino Acid Composition with Micronutrients on Well-Being in Subjects with Chronic Psychological Stress and Exhaustion Conditions Armbrorst D, Metzner C, Altheheld B, Bitterlich N, Rösler D, Siener R 2018	Aim of the study was to improve perceived stress by a specific amino acid composition with micronutrients in the verum versus placebo group.	A total of 59 participants (18-65 years) with self-reported perceived chronic stress and exhaustion conditions participated in this randomized, double-blind, placebo-controlled study. The Perceived Stress Questionnaire (PSQ30), amino acid profile, anthropometric, clinical, blood, urine parameters, and dietary intake were assessed	After 12 weeks, the verum group achieved significantly greater improvements in the total PSQ30 score compared with the placebo group. In the verum group, serum taurine concentration, folic acid concentration, urinary magnesium excretion, and the ratio of l-tryptophan to the sum of competing amino acids rose significantly. In the placebo group, serum concentrations of serotonin, protein, and magnesium decreased significantly, whereas the cardiometabolic risk parameters body weight, body mass index, waist circumference, and waist-to-height ratio increased significantly. Compared with placebo, the verum supplementation resulted in a higher improvement in perceived stress. Beneficial effects on the serotonergic system and preventive effects on magnesium homeostasis and some cardiometabolic risk factors were supposed. Additional effects might be caused by the optimized food intake
2	The Effects of Multivitamin Supplementation on Diurnal Cortisol Secretion and Perceived Stress. Camfield D, Wetherell M, Scholey A, Cox K, Fogg E, White D 2013	Given the effects of stress on a range of biological mechanisms including the endocrine system, it could be reasonably expected that multivitamin supplementation may also affect markers of these mechanisms such as diurnal cortisol secretion.	In the current double-blind placebo-controlled study 138 adults (aged 20 to 50 years) were administered a multivitamin containing B-vitamins versus placebo over a 16-week period. Salivary cortisol measurements were taken at waking, 15-min, 30-min and at bedtime, at baseline, 8-weeks and 16-weeks. Perceived Stress (PSS) was measured at baseline, 8-weeks and 16-weeks, while blood serum measures of B6, B12 and homocysteine (HCy) as well as red cell folate (B9) were also collected at these time points.	A significant interaction was found between treatment group and study visit for the Cortisol Awakening Response (CAR). Compared to placebo, at 16-weeks multivitamin supplementation was found to be associated with a near-significant trend towards an increased CAR. No significant differences in PSS were found between groups, with PSS increasing in both groups across the course of the study. Red cell folate was found to be significantly correlated with the CAR response at 16-weeks while HCy levels were not found to be associated with the CAR response, although HCy significantly correlated with waking cortisol levels at 8-weeks. A possible interpretation of the elevation in CAR associated with multivitamin supplementation is that this represents an adaptive response to everyday demands in healthy participants.

3	The influence of multivitamins on cognitive function and mood in the elderly. Cockle S, Haller J, Kimber S, Dawe R, Hindmarch I 2000	The objectives of the study were to examine the relationship between vitamin status and cognitive functioning and mood in healthy, elderly volunteers and to assess the subsequent impact of multivitamin supplementation on these measures.	A double-blind, placebo-controlled, parallel group study was carried out with 139 healthy, elderly volunteers (60-83 years) being randomly allocated to daily treatment with multivitamins or placebo for up to 24 weeks. Assessments of blood vitamin levels, cognitive functioning and mood were performed at baseline and at 12-weekly intervals thereafter.	This population was deficient in various vitamins, particularly vitamins B-2, B-6 and B-12. Various correlations between vitamin levels and cognitive functioning were observed at baseline, but although multivitamin supplementation increased blood vitamin levels, it had very little effect on performance. Short-term multivitamin supplementation in healthy, elderly volunteers had little effect on cognitive function or mood. However, vitamin status correlated with certain measures at baseline, and therefore it is possible that supplementation over longer periods of time and/or in volunteers with poorer nutritional status may prove beneficial.
4	B-Vitamin Intake and Biomarker Status in Relation to Cognitive Decline in Healthy Older A Hughes C, Ward M, Tracey F, Hoey L, Molloy A, Pentieva K, McNulty H 2017	The hypothesis addressed in this study was that lower dietary intake or biomarker status of folate and/or the metabolically related B-vitamins would be associated with a greater than expected rate of cognitive decline over a 4-year follow-up period in healthy older adults.	Participants (aged 60-88 years; n = 155) who had been previously screened for cognitive function were reassessed four years after initial investigation using the Mini-Mental State Examination (MMSE).	At the 4-year follow-up assessment when participants were aged 73.4 ± 7.1 years, mean cognitive MMSE scores had declined from 29.1 ± 1.3 at baseline to 27.5 ± 2.4 ($p < 0.001$), but some 27% of participants showed a greater than expected rate of cognitive decline (i.e., decrease in MMSE > 0.56 points per year). Lower vitamin B6 status, as measured using pyridoxal-5-phosphate (PLP; <43 nmol/L) was associated with a 3.5 times higher risk of accelerated cognitive decline, after adjustment for age and baseline MMSE score (OR, 3.48; 95% CI, 1.58 to 7.63; $p < 0.05$). Correspondingly, lower dietary intake (0.9-1.4 mg/day) of vitamin B6 was also associated with a greater rate of cognitive decline (OR, 4.22; 95% CI, 1.28-13.90; $p < 0.05$). No significant relationships of dietary intake or biomarker status with cognitive decline were observed for the other B-vitamins. In conclusion, lower dietary and biomarker status of vitamin B6 at baseline predicted a greater than expected rate of cognitive decline over a 4-year period in healthy older adults. Vitamin B6 may be an important protective factor in helping maintain cognitive health in ageing
5	Clinical trial: B vitamins improve health in patients with coeliac disease living on a gluten-free diet. Alimentary Pharmacology & Therapeutics Hallert C, Svensson M, Tholstrup J, Hultberg B 2009	To study the biochemical and clinical effects of B vitamin supplementation in adults with longstanding coeliac disease.	In a double blind placebo controlled multicenter trial, 65 coeliac patients (61% women) aged 45-64 years on a strict gluten-free diet for several years were randomized to a daily dose of 0.8 mg folic acid, 0.5 mg cyanocobalamin and 3 mg pyridoxine or placebo for 6 months. The outcome measures were psychological general well-being (PGWB) and the plasma total homocysteine (tHcy) level, marker of B vitamin status.	Fifty-seven patients (88%) completed the trial. The tHcy level was baseline median 11.7 micromol/L (7.4-23.0), significantly higher than in matched population controls [10.2 micromol/L (6.7-22.6) ($P < 0.01$)]. Following vitamin supplementation, tHcy dropped a median of 34% ($P < 0.001$), accompanied by significant improvement in well-being ($P < 0.01$), notably Anxiety ($P < 0.05$) and Depressed Mood ($P < 0.05$) for patients with poor well-being.
6	Association between Vitamin B12 levels and cognitive function in the elderly Korean population. Soh Y, Lee D, Won C 2020	To assess cognitive function, a short form of the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K) was used.	Of the CERAD-K tests, we included the Mini-Mental State Examination in the Korean version of the CERAD assessment packet (MMSE-KC), the word list: memory/recall/recognition, digit span (forward, backward), trail making test-A, and the frontal assessment battery. B12 concentrations were classified into clinically relevant categories, insufficient (<350 pg/mL) and sufficient (≥ 350 pg/mL). A linear regression analysis was used to evaluate the relationship between cognitive function and B12 levels.	The mean age of the 2991 participants was 76.4 ± 3.9 years old. Overall, 414 (13.8%) were classified as B12 insufficient, and 2577 (86.2%) as B12 sufficient. The sufficient B12 group performed better in the MMSE-KC, Wordlist: memory, Wordlist: recognition, TMT-A test, digit span, and FAB tests. This was statistically significant ($P < .05$). However, in the multivariable linear regression analysis, after adjusting for age, sex, education period, marriage, smoking and drinking habits, and comorbidities, the association between the B12 group and cognitive function was not statistically significant. Although our study does not show that B12 insufficiency is a direct risk factor to cognitive decline, B12 levels could be a contributing factor to cognitive function. Our results suggest that cognition was affected by the B12 levels, along with demographic and sociological variables.

7	Vitamins B12, B6, and Folic Acid for Onset of Depressive Symptoms in Older Men Ford A, Flicker L, Thomas J, Norman P, Jamrozik K, Almeida O	To examine whether use of vitamins B(12), B(6), and folate was associated with reduced severity of depressive symptoms and 2-year incidence of clinically significant depression.	The investigators recruited 299 men aged 75 years and older free of clinically significant depression (Beck Depression Inventory [BDI] score < 18). They were randomly assigned to treatment with 400 microg B(12) + 2 mg folic acid + 25 mg B(6) per day (N = 150) or placebo (N = 149). The BDI was the primary outcome measure of the study. Follow-up assessments took place 6, 12, 18, and 24 months after baseline. Analyses were intention-to-treat. The study was conducted from June 2001 to June 2004.	118 and 123 men treated with vitamins and placebo, respectively, completed this 2-year trial (19.4% dropout rate). Analysis of variance for repeated measures showed that there was no difference between the groups ($F = 0.76$, $df = 1$, $p = .384$) nor was there a significant change of BDI scores over time ($F = 1.26$, $df = 4$, $p = .284$). Cox regression revealed that participants treated with vitamins were 24% more likely to remain free of depression during the trial, although the difference between groups was not significant (95% CI = 0.68 to 2.28). At the end of the study, 84.3% of men treated with vitamins and 79.1% of those treated with placebo remained free of clinically significant depressive symptoms. The number of people needed to treat to show benefit was 21.
8	Effects of Four-Week Supplementation with a Multi-Vitamin/Mineral Preparation on Mood and Blood Biomarkers in Young Adults: A Randomised, Double-Blind, Placebo-Controlled Trial White D, Cox K, Peters R, Pipingas A, Scholey A 2015	This study explored the effects of four-week multi-vitamin and mineral (MVM) supplementation on mood and neurocognitive function in healthy, young adults.	Fifty-eight healthy adults, 18–40 years of age ($M = 25.82$ years, $SD = 4.87$) participated in this randomised, double-blind, placebo-controlled trial, in which mood and blood biomarkers were assessed at baseline and after four weeks of supplementation.	Compared to placebo, MVM supplementation was associated with significantly lowered homocysteine and increased blood B-vitamin levels ($p < 0.01$). MVM treatment was also associated with significantly improved mood, as measured by reduced scores on the “depression-dejection” subscale of the Profile of Mood States ($p = 0.018$). These findings suggest that the four weeks of MVM supplementation may have beneficial effects on mood, underpinned by elevated B-vitamins and lowered homocysteine in healthy young adults.
9	No effect of vitamin B-12 treatment on cognitive function and depression: a randomized placebo-controlled study White D, Cox K, Peters R, Pipingas A, Scholey A 2015	The main outcome measure was change in cognitive function and depression score from baseline to follow-up 3 months later.	A randomized placebo controlled study including 140 individuals with an increased plasma methylmalonic acid (0.40–2.00 micromol/l) not previously treated with vitamin B-12. Cognitive function was assessed by the Cambridge Cognitive Examination (CAMCOG), Mini-Mental State Examination (MMSE), and a 12-words learning test. Symptoms of depression were evaluated by the Major Depression Inventory.	At baseline 78 (56%) individuals had cognitive impairment judged from the CAMCOG score and 40 (29%) according to the MMSE; 18 (13%) individuals had symptoms of depression. No improvement was found in cognitive function comparing the treatment and placebo group (total CAMCOG score: $P = 0.43$), nor among individuals with only slightly impaired cognitive function ($n = 44$, total CAMCOG score: $P = 0.42$). The treatment group did not improve in depression score as compared to the placebo group ($P = 0.18$).
10	The possible beneficial effects of higher vitamin B6 intake from diet on cognitive function of patients with neuromyelitis optica spectrum disorder. Rezaeimanesh N, Saeedi R, Sahraian M, Razeghi Jahromi S, Naser Moghadasi A 2020	To evaluate the correlation between dietary vitamin B6 intake and cognitive function among NMOSD patients.	A cross-sectional study was designed on 24 definite NMOSD patients in Sina hospital, Tehran, Iran. A validated 168-item food frequency questionnaire was used to obtain the participants' routine dietary habits. For the cognitive function assessment, Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) battery was administered. Vitamin B6 intake per day was calculated, and the correlation between vitamin B6 and the results of MACFIMS subtests was examined.	The results revealed a positive correlation between dietary vitamin B6 intake and cognitive function in all subtests of MACFIMS. This direct correlation was significant in case of verbal and learning memory according to CVLT-II subtest (p -value:0.02; r :0.45) as well as speed of information processing and working memory according to SDMT subtest (p -value:0.04; r :0.43). The results from linear regression analysis adjusted for carbohydrate intake and disease duration indicated a significant ascending trend for the score of CVLT-II, SDMT, CVLT-II-delayed recall, and Brief Visuospatial Memory Test-Revised (BVM-T-R) subtests through the quartiles of vitamin B6 intakes.

11	Effect of vitamin B12 supplementation on neurologic and cognitive functions in older people-A review Rao GM, Kamath S2020	Researchers investigated whether vitamin B-12 supplementation benefits neurologic and cognitive function in moderately vitamin B-12-deficient older people.	a double-blind, randomized, placebo-controlled trial in 7 general practices in South East England, United Kingdom. Study participants were aged ≥ 75 y and had moderate vitamin B-12 deficiency (serum vitamin B-12 concentrations: 107-210 pmol/L) in the absence of anemia and received 1 mg crystalline vitamin B-12 or a matching placebo as a daily oral tablet for 12 mo. Peripheral motor and sensory nerve conduction, central motor conduction, a clinical neurologic examination, and cognitive function were assessed before and after treatment.	A total of 201 participants were enrolled in the trial, and 191 subjects provided outcome data. Compared with baseline, allocation to vitamin B-12 was associated with a 177% increase in serum concentration of vitamin B-12 (641 compared with 231 pmol/L), a 331% increase in serum holotranscobalamin (240 compared with 56 pmol/L), and 17% lower serum homocysteine (14.2 compared with 17.1 $\mu\text{mol/L}$). In intention-to-treat analysis of covariance models, with adjustment for baseline neurologic function, there was no evidence of an effect of supplementation on the primary outcome of the posterior tibial compound muscle action potential amplitude at 12 mo (mean difference: -0.2 mV; 95% CI: -0.8, 0.3 mV). There was also no evidence of an effect on any secondary peripheral nerve or central motor function outcome, or on cognitive function or clinical examination.
12	Association Between Dietary Intakes of B Vitamins in Midlife and Cognitive Impairment in Late-Life: The Singapore Chinese Health Study. The Journals of Gerontology Sheng, L., Jiang Y, Pan X, Feng L, Yuan J, Pan A, Koh W 2019	This study evaluated the relationships of dietary intakes of six B vitamins in midlife with cognitive impairment in old age in a Chinese population living in Singapore.	This study included 16,948 participants from the Singapore Chinese Health Study, a population-based prospective cohort. Baseline dietary intakes of B vitamins were assessed using a validated 165-item food frequency questionnaire when the participants were aged 45–74 years (1993–1998). After an average follow-up of 20 years, cognitive function was examined using a Singapore-modified version of Mini-Mental State Examination scale in 2014–2016, and cognitive impairment was defined using education-specific cutoffs. Logistic regression models were applied to estimate the association between B vitamins and cognitive impairment. All the six B vitamins were mutually adjusted in the final model.	In the 2014–2016 interview, 2,443 participants were defined as cognitive impairment. Riboflavin and folate were significantly and independently associated with cognitive impairment in a dose-dependent manner: the odds ratio (95% confidence interval) comparing the highest with the lowest quartile was 0.82 (0.69, 0.97) for riboflavin and 0.83 (0.70, 0.98) for folate (both p-trend <.05). Dietary intakes of thiamine, niacin, vitamin B-6, and B-12 were not significantly associated with risk of cognitive impairment.
13	B Vitamins Play Important Roles in Mental Health Care	V In a pilot study (N = 22), 18 elderly patients with abnormal low serum B12 levels and cognitive impairment were treated with B12 (1 mg per day intramuscularly) for 1 week, followed by weekly 1-mg injections for 1 month, then monthly 1-mg injections for 6 months.	A pilot study (N = 22), 18 elderly patients with abnormal low serum B12 levels and cognitive impairment were treated with B12 (1 mg per day intramuscularly) for 1 week, followed by weekly 1-mg injections for 1 month, then monthly 1-mg injections for 6 months.	Patients who had been cognitively impaired for less than 1-year experienced significant improvement, whereas patients who had been impaired for longer than 1 year became worse, suggesting that supplementation may ameliorate symptoms related to B12 deficiency only in the early stages of cognitive impairment.

14	<p>Low Vitamin B12 Levels: An Underestimated Cause of Minimal Cognitive Impairment and Dementia Jatoi, S., Hafeez, D., Riaz, S., Ali, A., Ghauri, M., & Zehra, M. 2020</p>	<p>To determine the effect of vitamin B12 replacement therapy on vitamin B12-deficient patients with noted cognitive impairment.</p>	<p>A cross-sectional, multicenter study of patients with minimal cognitive impairment (MCI) to assess for Vitamin B12 and homocysteine levels. All patients found to be deficient in vitamin B12 underwent replacement therapy and were assessed again after three months via the Mini-Mental State Examination (MMSE) and a review of symptoms.</p>	<p>A total of 202 patients were included in the study. Of those, 171 (84%) patients reported marked symptomatic improvement after vitamin B12 replacement while MMSE scores improved in 158 (78%) patients. Of the remaining 44 patients who reported no symptomatic improvement, MMSE scores improved in 26 while 18 patients showed no MMSE score improvements.</p>
15	<p>B Vitamins and the Brain: Mechanisms, Dose and Efficacy: A Review</p>	<p>The following review will therefore describe some of the closely inter-related cellular functions of the entire group of B vitamins in catabolic and anabolic metabolism; examine evidence from human studies suggesting widespread sub-optimal consumption of a number of these vitamins in developed societies, and the related case for consumption of these vitamins well in excess of governmental minimum recommendations</p>	<p>A review study</p>	<p>evidence from the largely equivocal human literature describing intervention with a small sub-set of B vitamins, and the more promising literature describing the effects of "multi-vitamin" treatments. Taken together, these strands of evidence suggest that supplementation with the entire B group of vitamins is a more rational approach than selecting one, two or three compounds from this sub-group of vitamins.</p>
16	<p>Low intake of B-vitamins is associated with poor adolescent mental health and behaviour Herbison C, Hickling S, Allen K, O'Sullivan T, Robinson M, Bremner, A 2012</p>	<p>To examine the relationship between B-group vitamins and adolescent mental health and behaviour.</p>	<p>This is a cross-sectional analysis of the West Australian Pregnancy Cohort (Raine) Study. The 17-year follow-up included collection of a food frequency questionnaire allowing B-vitamin intake calculation. Mental health was assessed using the Youth Self Report (YSR) which measures total, internalising (withdrawn/depressed) and externalising (aggressive/delinquent) behaviour scores. Multiple linear regression was used to analyse associations between B-vitamins and mental health with adjustment for relevant confounders (n = 709).</p>	<p>Lower intake of vitamins B1, B2, B3, B5, B6, and folate was associated with higher externalising behaviour scores ($p \leq 0.05$). Reduced intake of vitamin B6 and folate was associated with higher internalizing behavioural scores ($p \leq 0.05$).</p>
17	<p>Novel insights into the effect of vitamin B12 and omega-3 fatty acids on brain function Rathod R, Kale A, Joshi S 2016</p>	<p>An overview of vitamin B12 and omega-3 fatty acids, the possible mechanisms and the evidences through which vitamin B12 and omega-3 fatty acids modulate mental health and cognition.</p>	<p>Systematic review</p>	<p>Studies indicate a need for supplementation of vitamin B12 and omega-3 fatty acids to reduce the risk of cognitive decline, although the results of intervention trials using these nutrients in isolation are inconclusive. In the present article, we provide an overview of vitamin B12 and omega-3 fatty acids, the possible mechanisms and the evidences through which vitamin B12 and omega-3 fatty acids modulate mental health and cognition. Understanding the role of vitamin B12 and omega-3 fatty acids on brain functioning may provide important clues to prevent early cognitive deficits and later neurobehavioral disorders.</p>

A published, 140 patients with elevated plasma methylmalonic acid (0.40–2.00 mol/l) who had not previously been treated with vitamin B-12 participated in a randomized, placebo-controlled study. In this study, the Cambridge Cognitive Examination (CAMCOG), Mini-Mental State Examination (MMSE), and a 12-words learning test were used to assess cognitive function, while the Major Depression Inventory was used to assess depression symptoms. Results showed that 56 percent of individuals had cognitive disability based on the CAMCOG scores, 29 percent had cognitive impairment according to the MMSE, and 13 percent had depression symptoms. There was no difference in cognitive function between the treatment and placebo groups (total CAMCOG score: $P=0.43$, nor among individuals with only slightly impaired cognitive function ($n=44$, total CAMCOG score: $P=0.42$). The treatment group did not improve in depression score as compared to the placebo group ($P=0.18$); Hvas [23].

Furthermore, a cross-sectional survey, in 2020, aimed to assess the relationship between dietary intake of vitamin B6 and cognitive function in patients with neuromyelitis optical spectrum disorder (NMOSD). The sample size was 24 patients. A validated 168-item food frequency questionnaire was used to collect information on the participants' daily eating habits. Cognitive function was evaluated by using the MACFIMS (Minimum Assessment of Cognitive Function in Multiple Sclerosis) systems. The relationship between vitamin B6 and MACFIMS subtest results was investigated, and vitamin B6 intake was measured per day. The findings of this study showed a positive relationship between dietary vitamin B6 intake and cognitive function in all MACFIMS subtests. This markable relation was significant in the cases of verbal and learning memory, as well as the speed of information processing and working memory Rezaeimanesh et al. [24].

However, in 2020, A review research was conducted to see what effect vitamin supplementation has on improving cognitive performance. From 2010 to 2019, this review investigated through random controlled trials in healthy elderly populations, including prospective cohort studies, nested case-control studies, and cross-sectional studies that included vitamin B12 supplementation and evaluated serum or plasma. The final proof was scrutinized and described in detail. The results indicate that biomarkers have increased, but cognitive functions have only marginally improved Rao et al. [25].

DISCUSSION

Understanding the connection between vitamin B's and mental health and cognition is critical Leahy [6]. Vitamin B deficiency has been associated with neurological pathology and has been shown to affect mental health and cognitive function in previous research White et al. [22]. There appears to be a relation between dietary vitamin B6 intake and cognitive function, according to some evidence Rezaeimanesh et al. [24]. In addition, B12 levels, as well as demographic and sociological factors, may have influenced cognitive function Soh [20]. According to a study, aging is associated with a drop in vitamin B12 levels and cognitive function Soh [20].

One study on patients with cognitive impairment found that, depending on the dosage, riboflavin and folic acid were substantially and separately associated with cognitive impairment Sheng et al. [13]. Patients with cognitive impairment for less than a year significantly improved, while those who had been impaired for more than a year worsened, according to a supporter report, indicating that supplementation in the early stages of cognitive impairment may alleviate symptoms associated with B12 deficiency

Lake [5]. According to study results published by Jatoi et al., after vitamin B12 supplementation, 84 percent of participants recorded a substantial symptomatic improvement in cognition, 78 percent of patients' Mini-Mental State Examination (MMSE) scores improved, and 44 patients showed no symptomatic improvement in cognitive function Jatoi et al. [14].

According to Cockle et al. [17], there are various associations at baseline between the levels of vitamins and cognitive functioning, but multivitamin supplementation has very little influence on progress, despite raising blood vitamin levels. Administration of short-term multivitamins in healthy, elderly patients had a slight impact on cognitive function or mood, despite increasing vitamin levels in the blood Cockle et al. [17]. For the other B-vitamins, no major relationships between dietary intake and biomarker status and cognitive impairment were found, according to a supporter report Hughes et al. [18].

In contrast, one of the papers' results highlighted a lower vitamin B intake was linked to higher externalizing behavior scores, whereas a lower vitamin B6 and folic acid (vitamin B9) intake were associated with higher internal behavior scores. In addition, an inadequate diet may lead to the pathogenesis of mental health problems in adolescents. Findings show that a higher B-vitamin intake is protective against adolescent behavioral problems and that B-vitamins may help adolescents avoid mental health problems Herbison et al. [9]. Another study backs up the argument, claiming that after taking vitamins, homocysteine (tHcy) levels fell by a median of 34%, accompanied by significant improvement in cognition, notably anxiety and depressed mood for patients with poor well-being Hallert et al. [19]. High vitamin B6 concentrations showed no significant benefit on cognition and dementia risk Lake [5]. Also, studies showed that vitamins B12, B6, and folate may not be modifiable risk factors for slowing cognitive decline among community-dwelling older individuals Camfield et al. [16], while others showed symptomatic improvement after vitamin B12 replacement Jatoi et al. [14] and some studies showed a little effect on cognitive function or mood Cockle et al. [17].

Indeed, according to a study by White et al., four weeks of supplementing with multivitamins and minerals may boost healthy young adults' mood by increasing B-vitamin levels and decreasing homocysteine levels White et al. [22]. In all the Minimum Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) subtests, the research found a positive interaction between cognitive function and vitamin B sex intake, as well as a positive link between nutrient intake of vitamin B6 and cognitive function. In the cases of verbal and learning memory, as well as information processing speed and working memory, this clear association was important Rezaeimanesh et al. [24]. Additionally, biomarkers have improved, but cognitive functions have only marginally improved Rao et al. [25].

The majority of research on the impact of B-vitamins on cognition and mental health comes up with similar results. There is still no conclusive evidence as to how vitamins work and what role they play in mental health. However, some studies showed a major improvement in cognitive function, while others showed only a minor improvement in cognitive function following replacement therapy (B-vitamins supplementation); [26].

CONCLUSION

In conclusion, results are still under debate about the effect of the B vitamin on mental health. And the benefits of B-vitamins

supplementations in enhancing and improving mental health and cognitive function cannot be generalized, which appears from the inconstant of studies (elderly, adults, men, women). For recommendation, more studies need to investigate the effect of vitamins on mental health.

Limitation: The literature review has discussed the role of vitamin B's (B2, B6, B9, and B12) on mental health, not enough studies about B vitamins have existed and their relationship with cognitive and mental health. And the studies were not consistent (children, adults, elderly, lifestyle).

Availability of Data: All data for this evidence synthesis study can be found in primary research studies or from the corresponding author.

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This study is inexpensive to finance, and no funds are needed to carry it out.

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