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**Narrative Review of the Relationship between Depression and Low Blood
Folate and Vitamin B12 Levels**

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Abstract

Depression is a common psychological mood disorder that impacts more than 16 million adults in the United States. It can impact several areas of a person's life including physical activity, diet and daily activities. The role of nutrition in depression therapy has been researched for several years, with folate and vitamin B12 being the main highlights. Folate and vitamin B12 play a vital role in the development of the central nervous system and conversion of homocysteine to methionine. Past research has found inconsistent findings regarding the relationship between folate, vitamin B12 and their role in depression. This article dives into the existing research to evaluate why there is an inconsistency. A total of 13 studies met the criteria and were included in the review. The findings from these studies show the inconsistency of the research, with some studies finding a relationship and others finding no relationship. Several studies imply that depression can increase the chance of individuals developing vitamin deficiencies, which can increase the severity of depression symptoms. However, there are studies that have found no relationship between folate, vitamin B12 and depression. Several limitations need to be addressed and continued research needs to be done before a conclusive answer be provided.

Keywords: Depression, Serum Folate, Serum Vitamin B12

Introduction

Depression is a very common psychological mood disorder that can interfere with different areas of a person's life. This disorder can impact how a person feels, thinks and acts. Untreated depression can turn into a serious health condition and impact the ability to undergo activities of daily living, such as appetite, physical activity and concentration.¹ According to the Anxiety and Depression Association of America, major depressive disorder impacts more than 16 million adults in the United States and is the leading cause of disability between the ages of 15 and 44 years. Mental health conditions are seen in one out of every five American people and the number of cases increased in the past year by 1.5 million.³ While there are several effective treatments for mental disorders and depression, more than 75% of individuals in low-income countries get no treatment for their disorder.¹

Folate and vitamin B12 play a large role in the development of the central nervous system with their part in the homocysteine conversion to methionine.⁵ Vitamin B12 aids in the maintenance of myelin sheaths that protect and cover the nerves. The synthesis of methionine occurs with the help of Vitamin B12. This combination is crucial because methionine helps produce myelin which is needed for neurological development, maintenance and functions. A vitamin B12 deficiency may lead to neurological and psychiatric problems such as delusions and depression. The cause of these problems are due to high levels of homocysteine and methylmalonic acid. An additional cause to this problem is due to the deranged production of neurotransmitters.⁶ Without vitamin B12, homocysteine does not get converted to methionine, which increases the neurological problem.⁶ Folate is also important in the homocysteine to methionine conversion. Folate functions as a coenzyme for single-carbon transfers and amino acid metabolism. Folate deficiency can impact the metabolism of homocysteine and lead to

psychiatric problems, such as depression.⁷ Some possible mechanisms for low folate status and its relationship to depression include folate's role in methylation reactions in the brain, neurotransmitter synthesis and homocysteine metabolism. Folate is a limiting factor in the methylation cycle and if intake is not optimal, neural development may be impacted. Folate is also necessary for proper biosynthesis of monoamine neurotransmitters such as serotonin, epinephrine and dopamine. Some secondary factors can also be linked to depression and low folate levels, such as unhealthy eating patterns and alcohol use disorder.⁷

Studies have been done on folate deficiency with depression since the mid-1960s with low serum folate levels resulting in higher incidence of mental symptoms in epileptic patients.⁹ A 1967 Carney study showed the first incidence of folate deficiency in 29-30% of patients with depression.⁹ This first study paved the way for continued research in the relationship between serum folate levels and depression.

Low serum folate and low serum vitamin B12 have been linked to depression in some studies, whereas others have found no relationship. Due to this inconsistency in the research, major depression treatment is still focused on antidepressant medications.⁷ The purpose of this review is to review the current research to evaluate the inconsistent results of serum folate and serum vitamin B12 on depression and discover what needs to be implemented to pinpoint the inconsistency.

Methods

A literature search was conducted between October 1, 2020 and April 1, 2021, using PubMed MeSH terms *Folate* and *Vitamin B12* and *Depression* and *Serum Folate* and *Serum Vitamin B12* and *Blood Folate Levels*. The search was limited to peer-reviewed articles that were published in the English language within the last 22 years. Articles were excluded if folate and

vitamin B12 status were not based on serum levels, depression was not assessed, or the article was non-peer reviewed.

Results

Using the search terms listed above, 394 papers were identified. Thirteen papers met the criteria and were included in this review. The remaining 381 papers were excluded as the results were not based on serum levels of folate and vitamin B12, depression was not assessed or the papers were review papers. Of the thirteen papers reviewed, four reported no relationship between depression, folate and vitamin B12 and nine found a relationship between depression, folate and vitamin B12 levels. Table 1 below presents a summary of the literature studies that show a positive relationship for serum levels of folate and vitamin B12 to depression. Table 2 below presents a summary of the literature studies that show no relationship for serum levels of folate and vitamin B12 to depression.

Table 1. Studies that show a positive relationship for serum levels of folate and Vitamin B12 to depression.

References	Participants	Design	Measurement Tools	Primary Outcome	Results/Conclusions	Limitations
Beydou n et al. (2010) ¹	2524	Cross-Sectional	Patient Health Questionnaire	Serum folate concentrations, serum vitamin B12 concentrations, tHcy concentrations	Depressive symptoms may be associated with low serum folate status	Cross-sectional design, lack of control for several potential cofounders, measurement error

Bjelland et al. (2015)	5948	Cross-Sectional	Hospital Anxiety and Depression Scale Questionnaire; blood levels, logistic regression model	Plasma total homocysteine level, plasma folate, plasma vitamin B12	Positive association between tHcy levels and depression, folate levels and depression and vitamin B12 levels and depression	Selection bias possibility
Hintikka et al. (2003)	115	Naturalistic Prospective Follow-Up Study	17-item Hamilton Depression Rating Scale; chi-squared test, Pearson's correlation coefficient, student's t-test; ANOVA, univariate and multivariate linear regression analysis	Hematological indices, erythrocyte folate and serum vitamin B12 levels	Higher vitamin B12 levels significantly associated with better outcome for depression treatment; association between folate level and treatment outcome weak; no relationship between haematological indices and 6-month outcome	More women than men were included, only 1 subject was above the age of 65
Huang et al. (2018)	2791	Cross-Sectional Analysis	National Health and Nutrition Examination Survey, High Performance Liquid Chromatography, standardized liquid chromatography-tandem mass spectrometry, 9-item Patient Health Questionnaire; binary logistic	Serum vitamin concentrations, serum folate, serum Vitamin B12; depression level	Folate and trans-beta-carotene concentrations were inversely correlated with depression; vitamin B12 and Vitamin A concentrations were positively related to depression in whole populations; folate and vitamin B12 concentrations	Study only analyzed the relationship between current serum concentrations and depression; dietary factors ignored

			regression model		were correlated with depression in females	
Kaner et al. (2015)	59	Randomized Control Study	Diagnostic and Statistical Manual of Mental Disorders; 24-hour dietary recall; anthropometric measurements; biochemical analysis; Shapiro-Wilk test, Chi-square analysis	Serum fasting blood glucose, triglyceride, total cholesterol, vitamin B12 concentrations, folic acid concentrations	Intake of vitamins A, thiamine, riboflavin, B6, folate, C, Na, Mg, Ca, P, Fe, Zn, and fiber were lower in depression group; median levels of body weight, waist circumference, hip circumference, waist-to-hip ratio were significantly higher in depression group; fasting blood glucose, serum vitamin B12 and serum folic acid in depression group were lower than controls; serum insulin and HOMA levels of two groups were similar	Small sample size; self-reported dietary intake data likely inaccurate
Khosravi et al. (2020)	330	Case-Control Study	Semi-quantitative food frequency questionnaire; Diagnostic and Statistical Manual of Mental Disorders	Serum folate, serum vitamin B12, tHcy, Trp and Trp/CAA ratio	Healthy dietary pattern was associated with reduced risk of depression via increased serum levels of folate and vitamin B12; unhealthy	Biochemical measurements were not conducted for all participants

					<p>dietary pattern associated with increased risk of depression</p> <p>vita decreased serum levels of folate and vitamin B12</p>	
Kim et al. (2008)	732	Cross-Sectional Study	Geriatric Mental State schedule; blood samples; logistic regression model	Serum folate, serum vitamin B12, plasma homocysteine levels	<p>Lower levels of folate and vitamin B12 and higher homocysteine levels at baseline were associated with a higher risk of depression at follow-up; incident depression was associated with a decline in vitamin B12 and an increase in homocysteine levels over the follow-up period.</p>	Study may have been incomplete ; obscured by dietary habits
Papakostas et al. (2005)	110	Cross-Sectional	17-item Hamilton Depression Rating Scale; blood samples; t-tests	Folate blood levels, vitamin B12 blood levels, homocysteine blood levels	<p>Low serum folate levels were found to be associated with a delayed onset of clinical improvement with fluoxetine</p>	<p>Follow-up visits were performed every other week instead of every week; treatment was open, without blinding of the subjects or evaluators, no placebo</p>

Seppala et al. (2013)	2806	Population-Based Cross-Sectional Study	Beck Depression Inventory; Chi-Squared Test, t-test, regression analysis and models; blood samples	Serum vitamin B12 levels	The mean Vitamin B12 level was 331±176 pmol/L in those without depressive symptoms while the subjects with non-melancholic depressive symptoms had a mean vitamin B12 level of 324±135 pmol/L and those with melancholic depressive symptoms had the lowest mean vitamin B12 level of 292±112 pmol/L	group was included Causality due to cross-sectional study design; unable to present sensitivity analysis
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Table 2. Studies that show no difference in serum folate and serum vitamin B12 to depression.

References	Participants	Design	Measurement Tools	Primary Outcome	Results/Conclusions	Limitations
Gilbody et al. (2007)	15315	Meta-Analysis	Summary odd ratios, group mean folate levels, Egger's regression test	Plasma folate, red cell folate	Low folate status is associated with depression, though difficult to establish whether relationship is causal	Heterogeneity

Kendrick et al. (2015)	7210	Longitudinal Follow-Up Study	General Health Questionnaire	Red cell folate levels	Lower blood folate levels at baseline were significantly associated with symptoms of anxiety and depression; No relationship was found between red cell folate levels and incident depressive symptoms over 2 years.	Cases of anxiety and depression were identified based on screening instrument and not diagnosis.
Noronha et al. (2015)	84	Cross-Sectional Study	Mini-Nutritional Assessment; 20-item version of the Center for Epidemiologic Studies Depression Scale	Serum folic acid, serum vitamin B12	53 adults were at depression risk; 34% of those were at risk of undernutrition; 42.9% had low plasma levels of Vitamin B12 and 5.9% had low levels of folic acid; no significant differences concerning the existence of depressive symptoms were found.	Does not call the establishment of causal relationship between nutritional status and depression risk
Pourghassemi et al. (2012)	70	Cross-Sectional - Descriptive	Fasting blood samples, 17-item Hamilton	Plasma folate, plasma vitamin B-12	97.1% of patients had less folate than RDA, 95.7% of	Cross-sectional, descriptive study; only one form of

			Depression Rating Scale		patients had less B12 than RDA; mean for plasma folate was 5.18±6.11; mean for plasma vitamin B12 was 389.05±346.9; Low plasma folate and vitamin B12 was observed in 51.4% and 50% of patients. No significant relationship between blood folate and B12 levels with depression severity.	questionnaire was used for definition of major depression; possible selective bias in sampling; only done on depressive patients
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Studies Investigating Serum Folate on Depression

Of the 13 articles reviewed, 12 investigated serum folate and depression. When looking at the nutritional status of Iranian major depressive disorder patients, Pourghassem et al. found that the average level of plasma folate was 5.18 ± 6.11 ng/ml in 70 patients with major depressive disorder and that 51.4% had low plasma folate levels of ≤ 3 ng/ml. The average serum folate level in the United States at that time had been reported to be 10.4 ng/ml, which was higher than what was found in the study.⁹ Low levels of serum folate were also found in the depression group versus the control group in the Kaner et al. study. Another relationship between low folate levels and depression was found in a study done on young women in Southampton.¹³

The study found that lower blood folate levels at baseline were found to be significantly associated with symptoms of depression using the GHQ-12 Scale as measurement. Even after adjusting for socio-economic and lifestyle factors, the relationship between low blood folate and depression held.¹³ A 2007 meta-analysis found a significant relationship between folate status and depression with a moderate level of between-study statistical heterogeneity, however, it is difficult to figure out if the relationship is causal.¹² After two years of follow-up in the Kendrick et al. study, no relationship between baseline folate levels and incident symptoms of depression were found. This indicated a possibility that low blood folate is more of a consequence of depression rather than a cause for depression.¹³ Another study that looked into serum folate levels for depression at baseline found no significant association, however, incident depression was associated with lower baseline levels of folate.¹¹ This study found that folate deficiency was not associated with depression in cross-sectional analysis, but lower levels of folate were associated with an increased chance of incident depression two years later.¹¹

An inverse association was found between serum folate and depressive symptoms both among women and in the total population of the Beydoun et al. study. Within the total population, the odds of elevated depressive symptoms in the upper tertile of serum folate was almost half of that in the lowest tertile. Among women in that study, being in the upper tertile of folate status was associated with a one-third reduced chance of elevated depressive symptoms versus the lowest tertile.¹⁴ The results suggest that serum folate may be an important factor in the prevention of elevated depressive symptoms.¹⁴ A weak negative relationship between folate and depression was found after generalized additive logistic regression of the Bjelland study. A 2003 Hintikka study found that baseline folate levels and a decline in 17-item Hamilton Depression Rating Scale score had a weak association in univariate linear regression analysis, but the

association was not any more significant when adjustments were made. Low folate levels were found in 18% of patients with major depressive disorder, which went along with previous research.¹⁷ Also observed, was a weak indication that low erythrocyte folate level may be associated with poor treatment outcome.¹⁷ Folate concentrations showed an inverse association with depression and the same folate concentration with depression was found in females after adjustments.¹⁸ A more recent study by Khosravi et al. found that increasing the serum level of folate decreased depression risk and decreased serum levels of folate increased the risk of depression.

Serum folate levels may also play a role in length of clinical improvement when it comes to major depressive disorder. A 2005 study found that presence of low folate levels significantly predicted a later time to improve symptoms of major depressive disorder with fluoxetine.¹⁵ The average time it took major depressive disorder patients with low folate levels to improve was 5.0 ± 1.8 weeks versus 3.5 ± 1.9 weeks for patients with normal folate levels to improve.¹⁵

Studies Investigating Serum B12 on Depression

Of the 13 articles reviewed, 11 investigated serum B12 on depression. The Huang study that looked into the correlations between vitamin concentrations and depression found a positive association among vitamin B12 concentrations and depression adjusted by gender, BMI, family income to poverty ration, race/ethnicity, education, marital status, smoking history, age, and examination time from NHANES websites, demographics, examinations, laboratories and questionnaire data parts. In regards to gender, this study found differences when it came to vitamin B12 and depression. Vitamin B12 concentration was positively correlated to depression in females, whereas, males saw no significant association. When looking at depression at baseline in the Kim et al. study, depression was associated with a lower level of vitamin B12

along with higher levels of homocysteine. Incident depression was associated with lower baseline levels of vitamin B12 and higher baseline levels of homocysteine. The study also found that incident depression was found more in people with a decline in vitamin B12 levels. The strong relationship between vitamin B12 level decline and incident depression remained strong following adjustments for other covariates.¹¹ The relationship increased in strength after an adjustment was done for vitamin supplementation at follow-up and decreased in strength after a change in homocysteine.¹¹ The Kim et al. study saw findings where incident depression was predicted by low vitamin B12 levels along with low folate levels. Also, a decline in vitamin B12 levels was found.

When looking at vitamin B12 and folate levels in the Noronha et al. study, it was found that 42.9% of older adults had low plasma levels of vitamin B12. However, there was no significant difference concerning depressive symptoms. A study assessed in the Kaner et al. paper found that people with vitamin B12 deficiency have a higher risk of depression by 2.05 times, whereas, another study saw no significant difference between depression level and serum vitamin B12 levels. The Kaner et al. study findings saw the depression group to have significantly lower serum vitamin B12 levels than the control group. This finding may be related to the fact that people who are depressed consume a poor quality diet and have a greater chance of vitamin deficiencies. In regards to these findings, it may be important to provide adequate nutrition to people with an increased chance of developing depression. Also, being aware of the probability of individuals with vitamin deficiencies to develop depression. Educating individuals of the importance of adequate nutrient intake is a great step to help reduce the chance of developing depression.

The Hintikka et al. study looked into the relationship between vitamin B12 levels and treatment outcome in patients with major depressive disorder. The research found no correlation between depression severity and vitamin B12 level at baseline, which shows the inconsistency of the research with this topic area.

Discussion

The purpose of this paper was to review the current research on serum folate, serum vitamin B12 and their relationship with depression. After reviewing the research, the main objective was to discover what needs to be implemented to increase the chance for concrete results. Based on the review of the current research, there is inconclusive results regarding the relationship between folate, vitamin B12 and depression. The inconsistent results have to do with the research limitations in each study. Several of the studies had many limitations that impacted the final results, including diagnostic tools and cofounders. In order to determine a conclusive answer, research studies need to incorporate proper depression diagnostic tools to identify patients with depression and have controls for potential cofounders throughout the studies. The limitations of the reviewed articles are included below and provide improvements that future research can benefit from.

Limitations of Research

Limitations of the Pourghassem et al. study include that it was a cross sectional - descriptive study, co-morbid psychiatric diseases were not considered, depressive patients were only utilized and selection bias may have occurred during sampling. Limitations of the Kendrick et al. study were that baseline depression scores were identified on the GHQ-12, which is a screening instrument and not a diagnostic tool. Also, information on incident depression were only symptoms recorded in the GP records during follow-up (Kendrick et al). Limitations of the

Beydoun et al. study include that there was a lack of control for several potential cofounders (family history of depression, social isolation, etc) and depressive symptoms were used as an outcome and was not a clinical diagnosis of depression. The Bjelland study pointed out that people battling with depression may be less likely to participate in the study due to the impact of the mental disorder itself. This creates a limitation for both that specific study and all other studies.

In regards to vitamin B12, the Huang study only analyzed the relationship between current serum concentrations and depression.¹⁸ This could have caused biological flaws and led to wrong conclusions. Dietary factors were also ignored, which have an impact on serum vitamin concentrations.¹⁸ Several studies that have looked into the association between folate, vitamin B12 and depression have a cross-sectional design. This limits the extent to which causal relationships can be clarified. Depressive states can impact nutritional status since changes in appetite and food intake occur with depression. The definition of depression in some studies has also been an area of limitation, as several studies have not been utilizing a proper diagnostic tool to define depression. Several studies were simply using a screening tool and not a diagnostic tool for depression definition. Screening tools only evaluate an individual's risk of developing depression, whereas, diagnostic tests identify a proper diagnosis. To further increase the strength of the research, depression definition should be captured by a widely validated diagnostic tool.

The Kim et al. study saw limitations in that the data on vitamin supplementation was not available at the baseline evaluation. Also, during the follow-up evaluation, mental health information was restricted to what was available from the previous month.¹¹ A huge limitation from this study and most research is that circulating vitamin B12 is only a proxy marker of

cobalamin deficiency at a cellular level. ¹¹ A more specific marker for functional vitamin B12 status is methylmalonic acid. ¹¹

The Noronha et al. study utilized a cross-sectional design which did not allow the establishment of a causal relationship between depression risk and nutrition status. That study also limited its sample of people to those who volunteered and had no cognitive impairment limits. This created a major limitation for that study. The Beydoun et al. study highlighted limitations in the lack of control for several cofounders. These include family history of depression, social isolation and personality dimensions. The study also highlighted the importance of examining whether folate status and depressive symptoms differ between men, women and different age groups.

Need for Future Research

Key findings from this narrative review show that the research is inconclusive. Findings are still inconsistent and require continued research to come to a concrete conclusion. Further research needs to be done on the relationship between dose, duration and constituents of vitamin supplements for prevention of depression in nutritionally deficient and older populations.¹¹ Several studies have been done that focus on weight changes and body types for nutritional status. This may cause deficiencies and micronutrient levels to go unnoticed. Serum levels are the best way to measure these nutrient levels. Future research also needs to explore the overall nutritional status of individuals with depression. The Bjelland et al. study highlighted the importance to further research a dose-response relationship between B vitamins, metabolic markers and clearly defined subgroups of depression.

Studies need to be done that include both patients with depression, patients without depression and that limit selection bias. Utilizing a consistent diagnostic depression tool would

help determine whether individuals included in the studies are diagnosed properly, as some articles use a screening tool instead of a diagnostic tool. The need for a definitive definition of depression is required so that each study utilizes the same definition for depression. This would increase the strength of the findings and provide more accurate information. Incorporating more randomized, controlled studies in place of descriptive studies would provide more reliable findings.

Clinical Practice for Health Professionals

When evaluating individuals with depression, it is important to look at their overall nutrition status along with their depressive symptoms. It is common for depressed individuals to have poor nutritional intake. Research suggests that a vitamin B12 deficiency can increase the likelihood of developing depression. Improving the diet of an individual with depression could help relieve depressive symptoms. Meeting with individuals who battle depression and providing education on shopping and meal preparation could help lessen the chance of them developing vitamin deficiencies. Also, highlighting the importance of quality nutrition can help lessen the chance of individuals developing depression as well. Finding ways to encourage proper nutrition without adding any more stress to everyday life could help lessen the chance of depression. Encouraging a meal preparation day during the weekend would allow for adequate time to prepare healthy meals that are ready to eat during the busy work week. This could increase the likelihood that meals are getting consumed throughout the week.

When assessing patients with depression, folate and vitamin B12 levels should be included in the physiological assessment process. Being aware of which nutrients are being limited in their diet and finding ways to incorporate more of those missing nutrients could provide some benefits. The main findings of this research is still inconclusive and clinicians need

to be aware of the upcoming research regarding this topic. For now, providing nutrition education and/or nutrition supplements can help increase nutrient intake with patients battling depression. Patients battling depression have increased odds of having a poor diet and could be at risk for developing deficiencies. It is important to encourage these patients to consume a healthy diet to help prevent deficiencies.

References

1. "Depression." *World Health Organization*, World Health Organization, www.who.int/news-room/fact-sheets/detail/depression.
2. "Facts & Statistics." *Anxiety and Depression Association of America, ADAA*, adaa.org/about-adaa/press-room/facts-statistics.
3. "Number of People Reporting Anxiety and Depression Nationwide since Start of Pandemic Hits All-Time High in September, Hitting Young People Hardest." *Mental Health America*, 20 Oct. 2020, www.mhanational.org/number-people-reporting-anxiety-and-depression-nationwide-start-pandemic-hits-all-time-high.
4. Khosravi M, Sotoudeh G, Amini M, Raisi F, Mansoori A, Hosseinzadeh M. The relationship between dietary patterns and depression mediated by serum levels of Folate and vitamin B12. *BMC Psychiatry*. 2020;20(1):63. Published 2020 Feb 13. doi:10.1186/s12888-020-2455-2
5. Reynolds E. Vitamin B12, folic acid, and the nervous system. *The Lancet Neurology*. 2006;5(11):949-960. Published 2006 Nov 1. doi.org/10.1016/S1474-4422(06)70598-1
6. Viatcheslav Wlassoff, PhD. "Vitamin B12 Deficiency and Its Neurological Consequences." *Brain Blogger Vitamin B12 Deficiency and Its Neurological Consequences Comments*, brainblogger.com/2014/07/30/vitamin-b12-deficiency-and-its-neurological-consequences/.
7. "Office of Dietary Supplements - Folate." *NIH Office of Dietary Supplements*, U.S. Department of Health and Human Services, ods.od.nih.gov/factsheets/Folate-HealthProfessional/.
8. Kaner G, Soylu M, Yuksel N, Inanc N, Ongan D, Basmisirli E. Evaluation of Nutritional Status of Patients with Depression. *Biomed Res Int*. 2015;2015:521481.
9. Pourghassem Gargari B, Saboktakin M, Mahboob S, Pourafkari N. Nutritional status in patients with major depressive disorders: a pilot study in tabriz, iran. *Health Promot Perspect*. 2012;2(2):145-152. Published 2012 Dec 28. doi:10.5681/hpp.2012.017
10. Bjelland I, Tell G, Vollset S. Folate, Vitamin B12, Homocysteine, and the MTHFR 677C→T Polymorphism in Anxiety and Depression: The Hordaland Homocysteine Study. *Arch Gen Psychiatry*. 2003;60(6):618-626
11. Kim JM, Stewart R, Kim SW, Yang SJ, Shin IS, Yoon JS. Predictive value of folate, vitamin B12 and homocysteine levels in late-life depression. *The British Journal of Psychiatry*. 2008;192, 268-274.
12. Gilbody S, Lightfoot T, Sheldon T. Is low folate a risk factor for depression? A meta-analysis and exploration of heterogeneity. *J Epidemiol Community Health*. 2007;61(7):631-637. doi:10.1136/jech.2006.050385
13. Kendrick T, Dunn N, Robinson S, et al. A longitudinal study of blood folate levels and depressive symptoms among young women in the Southampton Women's Survey. *J Epidemiol Community Health*. 2008;62(11):966-972. doi:10.1136/jech.2007.069765
14. Beydoun MA, Shroff MR, Beydoun HA, Zonderman AB. Serum folate, vitamin B-12, and homocysteine and their association with depressive symptoms among U.S. adults. *Psychosom Med*.2010;72(9):862-873.

15. Papakostas G, Peterson T, Lebowitz B, Mischoulon D, Ryan J, Nierenberg A, Bottiglieri T, Alpert J, Rosenbaum J, Fava M. The relationship between serum folate, vitamin B12, and homocysteine levels in major depressive disorder and the timing of improvement with fluoxetine. *International Journal of Neuropsychopharmacology*. 2005; 8(4):523-528.
16. Seppala J, Koponen H, Kautiainen H, et al. Association between vitamin B12 levels and melancholic depressive symptoms: a Finnish population-based study. *BMC Psychiatry*. 2013;13:145.
17. Hintikka J, Tolmunen T, Tanskanen A, Viinamaki H; High Vitamin B12 level and good treatment outcome may be associated in major depressive disorder. *BMC Psychiatry*. 2003; 3:17.
18. Huang X, Fan Y, Han X, et al. Association between Serum Vitamin Levels and Depression in U.S. Adults 20 Years or Older Based on National Health and Nutrition Examination Survey 2005-2006. *International Journal of Environmental Research and Public Health*. 2018; 15:6