

Longitudinal association of vitamin B-6, folate, and vitamin B-12 with depressive symptoms among older adults over time¹⁻³

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ABSTRACT

Background: B-vitamin deficiencies have been associated with depression; however, there is very little prospective evidence from population-based studies of older adults.

Objective: We examined whether dietary intakes of vitamins B-6, folate, or vitamin B-12 were predictive of depressive symptoms over an average of 7.2 y in a community-based population of older adults.

Design: The study sample consisted of 3503 adults from the Chicago Health and Aging project, an ongoing, population-based, biracial (59% African American) study in adults aged ≥ 65 y. Dietary assessment was made by food-frequency questionnaire. Incident depression was measured by the presence of ≥ 4 depressive symptoms from the 10-item version of the Center for Epidemiologic Studies Depression scale.

Results: The logistic regression models, which used generalized estimating equations, showed that higher total intakes, which included supplementation, of vitamins B-6 and B-12 were associated with a decreased likelihood of incident depression for up to 12 y of follow-up, after adjustment for age, sex, race, education, income, and antidepressant medication use. For example, each 10 additional milligrams of vitamin B-6 and 10 additional micrograms of vitamin B-12 were associated with 2% lower odds of depressive symptoms per year. There was no association between depressive symptoms and food intakes of these vitamins or folate. These associations remained after adjustment for smoking, alcohol use, widowhood, caregiving status, cognitive function, physical disability, and medical conditions.

Conclusion: Our results support the hypotheses that high total intakes of vitamins B-6 and B-12 are protective of depressive symptoms over time in community-residing older adults. *Am J Clin Nutr* 2010;92:330-5.

INTRODUCTION

Depression is the most prevalent mental disorder in the US population (1), and associated costs have been estimated at \$44 billion per year (2). Depression is also quite common in later life; reports estimate the community prevalence of clinically relevant depression in older age to range from a low of 7% to 49% (3). Furthermore, depression is a key risk factor for numerous other health outcomes, which include mortality (4-9), and research has shown that regardless of chronic morbidity, elderly depressed patients have approximately 50% higher total health care costs than their nondepressed peers (10).

There is a prevailing hypothesis that insufficient concentrations of B vitamins are associated with depression. The vast majority of studies that have tested this hypothesis are cross-sectional (11-19); there are few prospective investigations, particularly in the United States. However, clinical observations have supported a vitamin B-12 deficiency-neuropsychiatric syndrome association (20, 21). Furthermore, we know that vitamin B-12 deficiency is common in the general population. Recent data have shown vitamin B-12 deficiency among 6% of older adults, and 20% of older adults have marginal depletion (22). Biochemically, vitamin B-6, folate, and vitamin B-12 are involved in the metabolism of homocysteine, S-adenosyl methionine, and methionine, an essential amino acid. The latter 2 compounds are critical to the production of neurotransmitters and methylation in the brain. Although the exact mechanism is unknown, the prevailing homocysteine hypothesis of depression suggests that deficiencies in vitamin B-6, folate, and vitamin B-12 can lead to elevated homocysteine concentrations, which have been associated with depression (23-27).

Of the few prospective studies, a Finnish study (28) and a Korean study (29) showed associations between deficiencies in these B vitamins and depression; however, we cannot necessarily assume that these results will transfer to all populations, because of the differences in nutrient intakes. For example, intakes of total folate are much higher in the United States because of folate fortification of the grain supply, mandated since 1998. Therefore, in our study, we followed 3503 community-based adults (59% African American) aged ≥ 65 y who lived in a large US urban area over an average of 7.2 y to examine the longitudinal associations of vitamin B-6, folate, and vitamin B-12 with depressive symptoms.

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SUBJECTS AND METHODS

Study population

The Chicago Health and Aging Project (CHAP) is an ongoing, longitudinal, population-based study of risk factors for incident Alzheimer disease and other age-related chronic conditions among community-dwelling residents who were aged ≥ 65 y at baseline. The biracial cohort was drawn from a complete census of 3 contiguous neighborhoods on the south side of Chicago. A total of 6158 residents (response rate of 78.9%) participated in the baseline survey (65% black) during the period of 1993 to 1996. Details of the study procedure have been provided elsewhere (30, 31), but essentially, assessments are conducted at ≈ 3 -y intervals. Thus, 4 follow-up interviews were conducted between 1997 and 2000 ($n = 4320$), 2000 and 2003 ($n = 2943$), 2003 and 2006 ($n = 2351$), and 2006 and 2009 ($n = 1566$). All data were collected by trained interviewers in the participants' homes. The interviews included structured questions about sociodemographic characteristics, health, and lifestyle, as well as performance-based tests of physical and cognitive function. The Institutional Review Board of Rush University Medical Center approved the study, and all participants provided written informed consent.

Measures

Dietary assessment

The CHAP study participants completed a semiquantitative, self-report food-frequency questionnaire (FFQ) based on a modified version of the Harvard FFQ (32) that ascertains usual frequency of intake over the past year of 139 different foods, vitamin supplements, and dietary behaviors. Post-1997 estimates of folate intake reflect the folate fortification. In a validation study of the FFQ in the CHAP study population, Pearson's correlations between nutrient intakes measured by multiple 24-h dietary recall interviews and the FFQ were 0.50 for total folate, 0.51 for total vitamin B-6, and 0.38 for total vitamin B-12. The validation correlations were comparable for persons of different ages, with different levels of cognitive ability, of different educational levels, and of black or white race (33).

Nutrient intake was computed by the multiplication of the nutrient content of specified foods by the frequency of consumption and summing over all food items. All nutrients were energy adjusted separately for males and females with the use of the residual regression method (34). In these analyses, we considered both total nutrient intake (ie, with supplementation) and food nutrient intake only (ie, without supplementation).

Depressive symptoms

Assessment of depressive symptoms was based on the 10-item version of the Center for Epidemiologic Studies Depression scale (CES-D) (35). This abbreviated CES-D is derived from the original 20-item version (36) and has been shown to have acceptable reliability compared with the original version and a similar factor structure (35). Item responses are coded in a yes-no format and yield a summary measure (CES-D) with a range from 0 to 10 after summation across the individual items. Six of the 10 items had to be nonmissing for the summary score to be nonmissing. Because the distribution of CES-D scores is highly,

positively skewed (mean \pm SD: 0.84 ± 0.99 ; skewness: 0.91), we computed a dichotomous CES-D variable to represent participants with an elevated level of depressive symptoms. We split the CES-D variable into 2 categories: scores of ≤ 3 and scores of ≥ 4 . A score of ≥ 4 on this version of the CES-D is the standard cut point and has shown reasonable specificity and sensitivity in the identification of older adults with major depression (37).

Sociodemographic variables

The sociodemographic variables considered in these primary analyses included age (in y), sex, race (non-Hispanic black compared with non-Hispanic white), education (in years of schooling completed), and income. Income was assessed through the respondents' selection of 1 of 10 categories that represented a range of personal income during the past month or year. Responses were recoded to a rank-order variable that ranged from 1 to 10; the lowest category represented an income $< \$5000$ /y and the highest category represented an income $> \$75,000$ /y. For the purpose of the analysis, the age and education variables were centered at their approximate median values—that is, age 75 y and 12 y of education. Furthermore, for subsequent analyses we included participants who became widowed over the observation period. In addition, at the baseline interview and for 2 subsequent follow-up interviews, participants were asked if they had provided basic care to anyone; thus, caregiving status was also included as a binary variable in the analyses.

Health status

In our analyses, we also controlled for antidepressant use (yes or no), smoking (never smoked, former smoker, current smoker), alcohol use, cognitive function, physical disability, and medical conditions. Alcohol use was measured with the use of a Lifetime Daily Alcohol Intake index based on the following primary question: "In your entire life, when you drank the most, about how often did you drink any type of alcoholic beverage, including beer, wine, and liquor?" Responses ranged from 0 to 6, where, for example, 0 = no history of alcohol intake or < 1 drink/mo in any 1 y of your entire life, 0.4 = 2–4 drinks/wk, 2.5 = 2–3 drinks/d, and 6 = ≥ 6 drinks/d. Cognitive function was assessed based on 4 brief tests: 2 measures of episodic memory, immediate and delayed recall of 12 ideas contained in the brief, orally presented East Boston Story (38); one test of perceptual speed via a modified form of the oral version of the Symbol Digit Modalities Test (39), a procedure in which participants are given 90 s to identify as many digit-symbol matches as possible; and the Mini-Mental State Examination (40), a widely used 30-item screening test to measure global cognitive functioning in older adults. A summary measure of cognitive function was created by the conversion of the scores on each of the 4 tests to z scores with the use of the baseline mean and SD of each test, which were then averaged to yield a single measure scaled in standard units; higher scores indicated higher cognitive performance (41). Physical disability was assessed with the 6 self-reported activities of daily living questions based on the work of Katz et al (42), which emphasize the ability to perform basic self-care functions (eg, eating, bathing, dressing). The activities of daily living were rated on a 3-point scale, where 1 = no help required, 2 = help required, and 3 = unable to do, and the composite is the

total count of items with answer choices of 2 or 3; higher scores indicate greater physical disability. Self-reported history of 9 medical conditions, which included myocardial infarction, stroke, cancer, diabetes, high blood pressure, Parkinson disease, shingles, thyroid disease, and hip fracture, were summarized into a continuous measure of number of chronic medical conditions.

Analyzed sample

Of the 6158 CHAP participants at baseline, we excluded data from participants whose CES-D baseline scores were ≥ 4 ($n = 991$), which left us with 5167 observations. Then we excluded data from participants who died ($n = 918$) before their first follow-up, which resulted in 4249 observations. Next, we excluded data from participants with invalid baseline CES-D data ($n = 67$), no food-frequency data ($n = 164$), and invalid food-frequency data ($n = 258$), which resulted in 3760 observations. Then we excluded participants with missing race-ethnicity ($n = 33$), and finally we excluded data for participants with < 2 CES-D values ($n = 224$). Thus, the final analytic sample consisted of 3503 participants, which included 11,266 observations over the 4 observation cycles, and an average of 7.2 ± 2.7 y of follow-up per study participant. Fifty percent of the participants completed all 4 interview cycles, 22% completed 3 cycles, and 28% completed 2 cycles.

Analysis

For the multivariable analyses, we used logistic regression with the generalized estimating equation (GEE) function to model the likelihood over time of a participant becoming "depressed," defined by a CES-D score ≥ 4 . The dichotomous CES-D variable was modeled with the use of GEE with a logit link function and binomial error structure, with the category of

≤ 3 symptoms as the referent category (37). GEE is particularly suitable for the analysis of these data, because it offers a choice of link functions to model the outcome variable and accounts for the within-person correlation across repeated measurements (43). The "working" within-person correlation was assumed to be identical for each pair of times of observation (exchangeable error structure); the estimates from GEE models are robust to the choice of working correlation matrix.

We tested our primary hypotheses that vitamin B-6, folate, and vitamin B-12 intakes were predictive of a participant becoming depressed in separate models adjusted for multiple covariates, time lag (ie, years since baseline), and interaction terms for each covariate and time lag. As a test of sensitivity, we also excluded participant data with the lowest 10% cognitive function scores. In preliminary analyses, widowhood status, caregiving status, and number of chronic medical conditions did not change the primary estimates of interest and thus they were removed from subsequent analyses. Model assumptions were examined graphically and analytically and shown to be adequately met. All longitudinal analyses were performed with the use of the GENMOD Procedure of SAS, version 9.2 (SAS Institute Inc, Cary, NC) (44).

RESULTS

The average age of the sample ($n = 3503$) was 73.5 ± 6.1 y, 41.0% were male, 59.3% were African American, and the average level of education was 12.3 ± 3.6 y. The average annual income level was \$20,000–\$24,999. Slightly more than one-third (36.8%) of the sample reported being widowed, and 17.7% of participants reported being a caregiver. A total of 471 participants (13.7%) reported ≥ 4 depressive symptoms at interview cycle 2, 256 (10.7%) at cycle 3, and 260 (13.4%) at cycle 4 (data not shown).

TABLE 1

Characteristics of the study sample by energy-adjusted, total (food and supplement) nutrient intake tertiles at baseline (1993–1996): the Chicago Health and Aging Project ($n = 3503$)

	Total nutrient tertile range ¹								
	Vitamin B-6 (mg)			Folate (μg)			Vitamin B-12 (μg)		
	0.6–1.6	1.6–2.4	2.4–207.0	63–263	263–397	397–1731	0.3–5.4	5.4–10.9	10.9–265.8
Sociodemographic characteristics									
Age (y)	73.7 ± 6.4^2	73.7 ± 6.1	73.2 ± 6.0	73.4 ± 6.2	73.9 ± 6.1	73.3 ± 6.0	73.6 ± 6.0	73.6 ± 6.2	73.5 ± 6.3
Male sex (%)	41.1	46.3	35.5	41.7	43.6	37.7	42.0	43.3	37.7
Black race (%)	73.0	59.3	45.9	71.0	58.0	48.9	64.6	60.2	53.1
Education (y)	11.5 ± 3.5	12.4 ± 3.6	13.2 ± 3.6	11.6 ± 3.6	12.4 ± 3.5	13.1 ± 3.6	12.0 ± 3.6	12.3 ± 3.5	12.6 ± 3.7
Income ³	4.4 ± 2.3	5.0 ± 2.4	5.4 ± 2.5	4.5 ± 2.3	5.0 ± 2.4	5.3 ± 2.5	4.8 ± 2.4	4.9 ± 2.5	5.1 ± 2.5
Widowed (%)	39.7	37.3	38.9	38.2	38.3	39.3	37.5	39.4	38.9
Caregiving (%)	17.7	16.9	18.8	17.5	18.0	17.9	19.1	16.7	17.5
Health status									
Antidepressant use (%)	1.0	1.4	1.6	1.2	1.6	1.1	1.3	1.0	1.6
Cognitive function (z score) ⁴	0.1 ± 0.7	0.2 ± 0.7	0.4 ± 0.6	0.1 ± 0.7	0.2 ± 0.7	0.3 ± 0.7	0.2 ± 0.7	0.2 ± 0.7	0.3 ± 0.6
Physical disability (range: 0 to 6)	0.2 ± 0.7	0.2 ± 0.7	0.1 ± 0.6	0.2 ± 0.7	0.2 ± 0.7	0.1 ± 0.6	0.2 ± 0.7	0.2 ± 0.7	0.1 ± 0.6
Medical conditions (range: 0 to 9)	1.2 ± 1.0	1.3 ± 1.0	1.2 ± 1.0	1.2 ± 1.0	1.3 ± 1.0	1.2 ± 1.0	1.2 ± 1.0	1.2 ± 1.0	1.2 ± 1.0
Outcome: depressive symptoms	0.9 ± 1.0	0.8 ± 1.0	0.8 ± 1.0	0.9 ± 1.0	0.8 ± 1.0	0.8 ± 1.0	0.9 ± 1.0	0.8 ± 1.0	0.9 ± 1.0

¹ Tertile ranges overlap because of rounding.

² Mean \pm SD (all such values).

³ Range: 1 ($<$ \$5000) to 10 ($>$ \$75,000). A score of 4 represents an annual income of \$15,000–\$19,999, and a score of 5 represents an annual income of \$20,000–\$24,999.

⁴ Actual range = -3.08 to $+1.42$.

TABLE 2
Logistic regression models for longitudinal associations between total intakes (with supplementation) and food intakes (without supplementation) of B vitamins and depressive symptoms (*n* = 3503)¹

Model ²	Vitamin B-6 × time lag			Folate × time lag			Vitamin B-12 × time lag					
	Total intake		Food intake	Total intake		Food intake	Total intake		Food intake			
	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>		
1	0.998 (0.997, 1.000)	0.05	1.012 (0.979, 1.047)	0.49	1.000 (0.999, 1.000)	0.89	1.000 (0.999, 1.000)	0.70	0.998 (0.997, 0.999)	0.01	0.997 (0.994, 1.000)	0.08
2	0.998 (0.997, 0.999)	0.04	1.010 (0.976, 1.045)	0.56	1.000 (0.999, 1.000)	0.91	1.000 (0.999, 1.000)	0.76	0.998 (0.997, 0.999)	0.01	0.997 (0.994, 1.000)	0.07
3	0.999 (0.997, 1.000)	0.07	1.017 (0.983, 1.052)	0.34	1.000 (0.999, 1.000)	0.91	1.000 (0.999, 1.000)	0.52	0.998 (0.997, 0.999)	0.01	0.997 (0.994, 1.000)	0.07
4	0.999 (0.997, 1.000)	0.05	1.003 (0.968, 1.039)	0.88	1.000 (0.999, 1.000)	0.61	1.000 (0.999, 1.000)	0.87	0.998 (0.997, 0.999)	0.01	0.998 (0.994, 1.001)	0.14

¹ Values were derived by using a generalized estimating equation function with a logit link function and binomial error structure; 12 models were analyzed on the basis of an average of 10,773 observations. Time lag, years since baseline; OR, odds ratio.

² Model 1: adjusted for age, sex, race, education, income, antidepressant use, (nutrition variable), time lag, and each variable's interaction with time lag. Model 2: model 1 + alcohol, smoking, and both variables' interactions with time lag. Model 3: model 1 + cognitive function, physical disability, and both variables' interactions with time lag. Model 4: model 1, excluding participant data with the lowest 10% cognitive function scores (*n* = 3153).

The characteristics of the study sample at baseline by total (ie, food and supplementation) nutrient intakes in tertiles are shown in **Table 1**. Note that whereas the Recommended Daily Allowance for folate (400 μg) is represented in the top tertile, the Recommended Daily Allowances for vitamin B-6 (1.5 mg) and vitamin B-12 (2.4 μg) are represented in the lowest tertiles, likely because of folate fortification. Generally, there were few substantive differences in demographic variables across tertiles for each of the 3 nutrients. African Americans were disproportionately represented in the lowest tertile of total intake of each of the nutrients. There were distinct trends of participants with more education and higher income, as well as participants with higher cognitive function, having higher intakes of each of the nutrients.

The odds ratios and 95% CIs from the logistic regression models for the associations between total intakes of vitamin B-6, folate, and vitamin B-12 and depression, followed by those of food intakes of the vitamins and depression, are shown in **Table 2**. The modeling results for total intakes show that both vitamin B-6 and vitamin B-12 were inversely associated with depressive symptoms; that is, higher intakes of both nutrients were predictive of decreased depressive symptoms over time (*P* values ranged from 0.01 to 0.07). However, folate was not prospectively associated with depressive symptoms (*P* values ranged from 0.61 to 0.91). Compared with the basic model, which controlled for age, sex, race, education, income, antidepressant use, time lag, and all the covariates' interactions with time lag, the odds ratios for both vitamin B-6 and B-12 intakes remained virtually unchanged after adjustment for additional covariates such as alcohol intake, smoking status, cognitive function, and physical disability. There were no significant interactions on depression risk between any of the B vitamins and age, sex, race, education, or income. Food intakes of vitamin B-12 were marginally significant (*P* values were 0.07 and 0.08) and inversely associated with depression in models 1–3, such that high intakes of vitamin B-12 in food were marginally associated with decreased depressive symptoms.

DISCUSSION

In this large, US population-based study of older adults, higher total intakes of both vitamin B-6 and vitamin B-12 were associated with a decreased likelihood of the development of depressive symptoms over an average of 7.2 y. For example, each additional 10 mg of vitamin B-6 and 10 μg of vitamin B-12 via total intake from food and supplements were associated with 2% lower odds of development of depressive symptoms per year. Of note, the Food and Nutrition Board has set the recommended upper limit for vitamin B-6 at 100 mg/d (45). Food intake of vitamin B-12 was marginally associated with depression, which likely represents the poor bioavailability and absorption of vitamin B-12 from food sources, especially in older age (46, 47). Food intake of vitamin B-6 was not significantly associated with depression; thus, it is possible that the association with total intake is due to partial confounding by vitamin B-12 contained in multivitamin supplements. Folate intake was not associated with depression.

Vitamin B-12 deficiency causes a neurologic syndrome that includes cognitive and depressive symptoms (20). In previous studies, we found evidence that probable vitamin B-12 deficiency

defined biochemically (48) and low total dietary intake of vitamin B-12 (49) were both associated with faster rates of cognitive decline. Vitamin B-6 has a strong biologic mechanism that underlies a relation with depression in that its primary biologic form, pyridoxal 5'-phosphate, is a cofactor in the synthesis of neurotransmitters, which include serotonin (50).

Most studies that have examined the relation of B vitamins to depression are cross-sectional in design and thus it is difficult to interpret whether observed nutrient associations are a cause or an effect of the depression. Of the few prospective studies, one Finnish study (28) reported a 3-fold increased risk of depression with low folate intake (mean folate intake was 256 mg/d), and a Korean study (29) showed associations with both low serum folate and low serum vitamin B-12 (mean serum concentrations of folate and vitamin B-12 were 24.4 nmol/L and 385.6 pmol/L, respectively). A possible reason for the discrepant findings among these and the CHAP studies for folate is the low likelihood of folate deficiency in the US population (51–53). National studies have shown that the prevalence of serum folate deficiency has fallen from 16% to <1% since the 1998 US Food and Drug Administration mandate for folic acid fortification of the grain supply (54). Thus, it is possible that folate is associated with the onset of depressive symptoms but only at insufficient concentrations that are below the range of intake that occur in fortified folic acid populations such as the CHAP population.

The primary strength of our study is that the observed associations are based on data from a large, prospective study with up to 5 assessments of depressive symptoms over 12 y and comprehensive dietary assessment with a validated questionnaire. The primary limitation of our study is that the CHAP is an observational study and therefore confounding is always an alternative explanation for the observed findings. For example, although we adjusted for antidepressant use, we did not adjust for other medications that may be associated with depression. However, statistical adjustment for a number of other potential confounders had no effect on the magnitude of the estimated B-vitamin associations with depression. For several reasons we believe that confounding bias is not a likely explanation for the protective associations of vitamin B-6 and vitamin B-12. We were able to adjust statistically for a wide range of potential confounders and the effect estimates for the vitamin nutrients did not change materially in any of these models. In crude analyses we observed that low vitamin intake was associated with several factors (ie, black race, low education, and low income) that are related to increased depression (55). However, these associations were apparent for all 3 B vitamins and not just vitamin B-6 and vitamin B-12, which had protective associations with depressive symptoms. Nevertheless, we urge caution in the interpretation of our results to imply a causal relation between higher intakes of vitamin B-6 and vitamin B-12 and decreased depression, because these nutrition variables may be proxies for other unmeasured factors, such as a healthy overall diet. Additionally, there are the standard limitations of self-report data in general, as well as the known limitations of the FFQ as a means of dietary assessment, specifically that it may not be a good indicator of biochemical vitamin B-12 status because of the absorption issues. Finally, these results may not be generalizable to other race-ethnic subpopulations of older adults because data from the National Health and Nutrition Examination Surveys show lower dietary, serum, and red blood cell folate status concentrations among Mexican

Americans compared with non-Hispanic whites, likely because of differences in dietary patterns and supplement use (52).

In summary, we found that higher intakes of vitamin B-6 and vitamin B-12 were associated with a lower likelihood of depression in older adults. Folate intake was not associated with depression in our study. However, interestingly, there is clinical evidence that the augmentation of antidepressant treatment with folate may improve patients' depression outcomes; further evidence is anticipated from a larger randomized controlled trial in the United Kingdom (56). These associations are supported by underlying biologic mechanisms as well as by clinical observations. In their review of the literature on vitamin B-6 as a treatment of depression, Williams et al (57) found consistent evidence to support the value of vitamin B-6 supplementation for depression among premenopausal women. In the assessment and treatment of depressive symptoms in older adults, clinicians and other health care professionals should be mindful of the patient's nutritional status in general, and whether there are vitamin insufficiencies in these nutrients before treatment.

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