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Natural Food Folate and Late-Life Depression

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Abstract

Low folate status has been linked to depression but findings have been inconsistent. The authors sought to examine the association between folate intake and late-life depression. This cross-sectional study included individuals age 60 and over (n=111 depression, n=136 comparison). Depression participants received psychiatric care. Folate and kilocalorie intakes were assessed with a Block 1998 food frequency questionnaire. Naturally occurring food folate was inversely associated with depression after controlling for age, sex, race, education, and total energy (p=0·0047). All other folate variables including total dietary folate and folic acid were non-significant for depression. These findings may indicate that the naturally occurring form of folate is uniquely protective for depression and perhaps brain health. Alternatively, natural folate may be a surrogate for other nutrients or overall dietary quality.

Keywords

folate; folic acid; older adults; depression; nutrition

INTRODUCTION

Major depression is a common mental disorder and the leading cause of disability worldwide (1). Late-life depression has a prevalence between 2 7 and 12 percent in the community-living population but is significantly higher among the seriously ill and nursing home residents (2, 3). Depressed individuals have poorer compliance and worse outcomes for treatment of comorbid medical conditions, including higher mortality, as compared with

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those who are not depressed (4, 5). This may partly explain why late-life depression doubles the cost of medical care, an increase not explained by psychiatric care (6). The frequency and burden of major depression in older adults underscores the need for research into its etiology.

Late-life depression has a multi-factorial etiology. Risk is determined by both stable factors, such as sex and other genetic traits, and alterable features, including cerebrovascular disease and other medical conditions, stress, and diet (7–9). Individuals with comorbid vascular disease are at increased risk of depression and vice versa (10–12). The influence of lifestyle factors such as diet on depression risk offers an opportunity for prevention (13, 14). Folate, a B vitamin, is one possible etiological determinant. Folate may influence depression via brain mechanisms because of its role in neurotransmitter and myelin synthesis, or through vascular pathways by influencing homocysteine metabolism (15). Depressed individuals have been found to exhibit poorer folate status (plasma levels) than non-depressed individuals in some clinical and epidemiological studies (16–19) while several epidemiological studies have failed to demonstrate any relationship between folate status and late-life depression (20–24). These conflicting results may be due to differences in the assessments of folate status and/or depression, as well as to genetic differences in the populations studied. Longitudinal studies to examine this question found that low dietary folate intake was associated with incident depression in middle-aged men (14), and low serum folate was associated with incident depression in elderly individuals (25). An examination of dietary folate among older adults with depression is needed because prior studies of older adults have measured folate levels only, while dietary folate studies have not included older adults. In addition, given that grains in the United States are fortified with folic acid as well as the popularity of dietary supplement use, studies should examine the role of different sources and forms of folate consumed.

We conducted this study in a group of currently and recently depressed older adults, and comparison elderly individuals, to determine whether dietary folate was associated with late-life depression. We hypothesized that reported intakes of folate would be lower in the depression group. In addition, we sought to examine the importance of difference forms of folate (folate versus folic acid), and sources of folate (natural in foods, fortified foods, dietary supplements).

METHODS

Design

This cross-sectional project occurred within a larger longitudinal clinical study of depression in older adults (Conte Center for the Neuroscience of Depression and the NeuroCognitive Outcomes of Depression in the Elderly [NCODE]) which began in 1994 (26). Nutrition assessments were added in March 1999, after which time all comparison subjects and depression subjects who were deemed clinically suitable, based upon acceptable depression management and cognitive functioning (see specific criteria under **Sample**), received a nutrition questionnaire. Going forward from March 1999, those in the comparison group received a nutrition assessment at study baseline, and depression subjects received the assessment when deemed clinically suitable. The nutrition assessments, therefore, did not correspond to a particular time point in the depression study. Nutritional data reported here were collected between 1999 and 2006, after folic acid fortification began in the United States.

Sample

All participants who completed a nutrition questionnaire were included in the current study. This sample included 111 patients of the Duke University Psychiatric Service with a primary diagnosis of major depression at study baseline, and 136 comparison participants recruited from the community and the Aging Center Subject Registry at Duke University. Enrollment was restricted to those 60 years or older, and those who could speak and write English. Exclusion criteria included a concurrent diagnosis of a major psychiatric or neurological illness, significant cognitive impairment (as indicated by a Mini-Mental State Examination score of less than 24 out of 30), and metal in body (contraindicated for magnetic resonance imaging, an integral component of the parent study). In addition, participants with severe depression symptomatology were excluded because of concerns about subject burden given the length of the nutrition questionnaire (8 pages). This criterion did not require a specific depression rating cutoff but was instead determined by the treating psychiatrist clinically on a case-by-case basis. Comparison participants were required to have a non-focal neurological examination, no self-report of neurological or depressive illness, and no evidence of a depression diagnosis based on the Diagnostic Interview Schedule portion of the Duke Depression Evaluation Schedule. After complete description of the study to the participants, written informed consent was obtained. This research protocol has been reviewed and approved by the Duke University Medical Center Institutional Review Board.

Treatment

Depression patients received individualized treatment from a psychiatrist, who followed them throughout the study. Most depressed participants received antidepressant medication; some received electroconvulsive treatment (ECT) or psychotherapy.

Measures

Assessments for the overall project included psychiatric, nutrition, medical, imaging, psychosocial, neuropsychological, genetic, and personality measures. At baseline and yearly thereafter a trained interviewer administered the Duke Depression Evaluation Schedule (DDES) in-person to each subject, both depression and comparison individuals. The DDES, a composite diagnostic interview instrument, includes sections of the NIMH (National Institute of Mental Health) Diagnostic Interview Schedule which assesses depression, as well as items on self-reported physical health. Four conditions were included in the vascular comorbidity score: diabetes mellitus, hypertension, arteriosclerosis, and heart trouble. Each condition was assigned a score of 1 if the condition was not reported, and 2-4 indicating the condition was reported as present and interfered not at all (code 2), interfered a little (code 3), or interfered a lot (code 4) with their activities. The comorbidity score thus had a possible range from 4 to 16. Non-vascular conditions such as asthma and cancer were not considered.

Dietary Assessment—The nutrition assessment has been described previously (27). The 1998 Block Food Frequency Questionnaire (FFQ), which estimates the components of a person's total dietary intake over the preceding year, was used for nutrition assessment. It has been validated against and shows moderate correlation with other nutrition assessment instruments, including the Willett FFQ (28). The Block FFQ is a semi-quantitative assessment in that the respondent is asked to estimate both the frequency of consumption of listed food items and the typical serving size of each food. The 1998 Block questionnaire (Block Dietary Data Systems; Berkeley, CA) is a revision that includes standardized portion sizes, a wider variety of low-fat foods, questions on dietary supplements, and an updated database to reflect folic acid fortification in the food supply. Food items chosen for the questionnaire were based upon the third National Health and Nutrition Examination Survey

(NHANES III), and were foods contributing to the top 90% of population nutrient intake. Three categories of supplements were used in calculating supplemental folic acid, namely, regular multivitamin, B-complex multivitamin, and folic acid supplement.

Returned questionnaires were checked for completeness and rejected if more than 15 food items were skipped. Intake estimates included total energy and folate, and were calculated by Block Dietary Data Systems. Folate estimates included dietary folate equivalents (DFEs) for natural food folate, folic acid from fortified foods, and folic acid from supplements. DFEs are used instead of μg to account for increased bioavailability of the folic acid form [DFE = folate (μg) + [1·7 * folic acid (μg)] (15).

Analyses

All statistical analyses were run using SAS software (Cary, NC). General descriptive statistics were calculated to examine the characteristics of the sample by group (depression vs. comparison). Bivariate comparisons between group and covariates were conducted using (a) chi-squared test if the covariates were categorical (sex, race, and education), and (b) t-test if the variables were continuous (age, kilocalories, and comorbidity score).

To describe the depression and comparison groups in terms of each of 5 folate intake variables (natural food folate, folic acid from foods, total food folate, supplemental folic acid, and total dietary folate), t-tests were performed.

Logistic regression was performed to determine the effect of these same folate variables upon depression while controlling for potential confounders. Separate models were evaluated because of concerns about multicollinearity. Covariates in the 5 logistic models included age, sex, race (Caucasian/non-Caucasian), education (high school completion yes/no), and energy intake. Since 5 folate variables were examined, a Bonferroni correction level of 0·01 was used for declaring significant differences in depression likelihood. Lastly, for any significant folate variables, the comorbidity score was added to the model to determine if vascular disease may explain any relationship of folate with depression.

RESULTS

This sample of older adults included a total of 111 depression and 136 comparison participants. Demographic and medical comorbidity variables for the two groups are shown in Table 1. The comparison group had more years of education ($\chi 2=15{\cdot}1557$, df=1, p=0·000099) and a lower comorbidity score (t=−4·36, df=241, p=0·000019) than the depression group. Dietary characteristics for the groups are shown in Table 2. The depression group exhibited a lower but non-significant (at $p < 0{\cdot}01$) intake of natural food folate (t=2·21, df=245, p=0·0277). No other differences were found.

Five logistic regression models (one for each of the 5 folate variables) were analyzed for this study. Natural folate had a significant effect on depression at the Bonferroni correction level of 0 01 (estimate= −0·00676 ± 0·00239, Wald $\chi 2=7.9731$, p=0·0047). The estimate indicates that depression decreases as natural folate increases. All other folate variables including total dietary folate were non-significant for depression. Energy intake was positively associated with depression in the natural folate model (p=0·0388). Education level was significant for depression in all models. Age, sex, and race did not have a significant effect in any of the 5 models.

The natural folate model was re-analyzed adding the comorbidity score to determine if vascular disease may have moderated the folate/depression relationship. Natural folate

continued to have a significant effect on depression (estimate= −0·00663 ± 0·00256, Wald $\chi 2$=6·6866, p=0·0097).

DISCUSSION

The major finding of this study is that elderly depression participants consumed less natural folate than elderly comparison participants. This relationship remained after controlling for age, sex, race, education, and energy intake. Intakes of folic acid from fortified foods and dietary supplements, as well as total dietary folate (natural folate plus folic acid from foods and supplements) were not significantly related to depression. These results suggest that forms of dietary folate may have differential effects on depression and brain health. Naturally occurring folate in foods may be more beneficial than folic acid from grain fortification and dietary supplements.

Our finding of an inverse association between natural folate intake and depression is consistent with previous dietary studies (14, 29). These studies were conducted in countries without folic acid fortification and among participants who rarely or never consumed folic acid-containing dietary supplements. Therefore, almost 100% of the folate consumed was naturally occurring. A Finnish study of 2,313 middle aged men found that participants who consumed less than the median folate intake at baseline had a three times greater risk of being hospitalized for depression during follow-up (14). Similarly, a Japanese study of 309 men and 208 women between 21 and 67 years of age showed that men in the upper quartile of folate intake were half as likely to exhibit depressive symptoms as those in the bottom quartile (29). Women did not show this effect, perhaps due to their higher folate intakes.

Potential mechanisms to explain a protective association between natural folate and depression include the role of folate in serotonin synthesis and release, membrane health, and the formation of S-adenosyl methionine (SAM) - the sole methyl donor in the nervous system (30). In addition to these direct nervous system functions, folate is necessary for converting homocysteine to methionine (30). This reduction in homocysteine may promote vascular as well as neuronal health, both of which may reduce risk of depression (30). It appears unlikely that the folate and depression relationship found in this study is due solely to vascular effects since controlling for vascular diseases did not attenuate these findings. Lastly, it is possible that the natural folate and depression association is due not to folate but rather to other dietary factors that vary with folate intake, such as fruits, vegetables, and certain antioxidants. Regression models did include total energy so as to control for changes in appetite that often accompany depression.

The absence of associations between folic acid and total folate with depression may be explained by differences in vitamin form. Folate is a general term used to describe multiple forms of the water-soluble vitamin B_9, including naturally occurring food folate or pteroylpolyglutamate, and folic acid or pteroylmonoglutamic acid. The forms differ in the number of glutamate residues, with folic acid having only one while natural folates have between one and six (15). In addition, natural folate is in a reduced form, while folic acid is in the most oxidized and stable form (15). Because of this difference, folic acid must go through an additional reduction reaction before entering into the cytoplasmic methylation and folate cycles (31). Recently questions have arisen about the level of folic acid fortification in the United States. Folic acid fortification has resulted in a mean increase in folic acid intake that is approximately twice as large as previously projected (32) and intakes are also significant from dietary supplements. Unmetabolized folic acid has been detected in 78% of postmenopausal women, an anomaly which has been linked to reduced natural killer cell cytotoxicity (33) and may impair the normal functioning of natural folate. In terms of

brain health, folic acid may interfere with transport of folate across the blood brain barrier by blocking receptors (31).

Limitations of this study include the modest sample size. In addition, given its cross-sectional nature, this study cannot confirm an etiological effect of dietary folate on depression, especially since the nutrition assessment was administered after depression diagnosis. Individuals with severe, unremitting depression were not given a nutrition assessment which may have introduced a systematic bias. However, if the more severely depressed individuals had the lowest folate as in prior studies (16), their omission would have served to bias the results towards the null. This project did not incorporate measurement of plasma folate levels or metabolism, homocysteine or other biomarkers, so we cannot conclude that dietary folate was related to depression because of any specific mechanism. The nature of depression course combined with the nutrition assessment period of one year make interpretation difficult. Individuals differed in how much of the year (covered by the nutrition assessment) they were depressed. Self-report of diet has obvious limitations including recall bias, which may differ between depression and comparison participants. In addition, estimation of fortified foods from a food frequency questionnaire is difficult because of the lack of precision about food items. It should also be noted that depression itself as well as antidepressants and other medications may affect appetite and dietary intake. However, we did control for energy intake which should partially account for appetite changes secondary to depression or medication use. Finally, these results may be generalizable only to older individuals with depression who have received psychiatric treatment.

In conclusion, natural folate was found to be inversely associated with depression in this sample of elderly depression and comparison participants, while folic acid and total folate were not associated. These results may indicate that vitamin form is critical to the role of folate in depression and nervous system functioning. Future studies are needed to confirm these findings, to establish an etiological relationship, and to clarify the mechanisms by which folate may influence depression and brain health.

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TAKE AWAY POINTS

- Natural folate intake may be lower in older adults with depression than in comparison individuals, while intake of folic acid may not differ between the two groups.
- Natural folate may be uniquely beneficial for depression or it may be a surrogate marker for other beneficial dietary components.
- Longitudinal studies are needed to confirm this association and to determine if differences in folate intake commence prior to or during a depressive episode.

Table 1

Sample Characteristics

	Total (n=247)	Depression (n= 111)	Comparison (n= 136)	p value*
Mean Age (SD)	70·7 (6·1)	70·0 (6·3)	71·2 (5·9)	0·1265
Female sex, N (%)	158 (64%)	65 (59%)	93 (68%)	0·1097
Caucasian race, N (%)	214 (87%)	98 (88%)	116 (85%)	0·4914
Education, N (%)†	229 (93%)	95 (86%)	134 (99%)	0·000099
Mean comorbidity score (SD)‡	4·8 (1·2)	5·2 (1·4)	4·5 (0·9)	0·000019

*p value for difference between groups (chi-squared test used to compare proportions; t-test used to compare means).

†Education ≥ 12 years (yes/no)

‡Comorbid conditions include diabetes, hypertension, arteriosclerosis, and heart disease (score of 1–4 for each condition to yield total score of 4–16)

Table 2

Folate Intake by Source, and Kilocalories*

	Total (n=247)	Depression (n= 111)	Comparison (n= 136)	p value†
Energy (kcals)	1727·9 (698·4)	1750·6 (761·5)	1709·4 (644·6)	0 6453
FOLATE (DFEs)‡				
Food (natural)	229·6 (92·9)	215·2 (84·4)	241·3 (98·0)	0·0277
Food (fortification)	243·5 (156·1)	239·1 (157·1)	247·1 (155·8)	0·689
Food (total)	473·1 (214·2)	454·3 (208·1)	488·4 (218·6)	0·2137
Supplements	437·0 (432·8)	459·5 (454·1)	418·6 (415·4)	0·4613
Total	910·0 (486·5)	913·7 (511·7)	907·0 (466·8)	0·1209

*Mean (standard deviation)

†p value for difference between groups (t-test)

‡DFEs (dietary folate equivalents) = folate (μg) + [1·7*folic acid(μg)] 15)