Dietary Folate and Vitamin B₁₂ Intake and Cognitive Decline Among Community-Dwelling Older Persons

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Background: Deficiencies in folate and vitamin B₁₂ have been associated with neurodegenerative disease.

Objective: To examine the association between rates of age-related cognitive change and dietary intakes of folate and vitamin B₁₂.

Design: Prospective study performed from 1993 to 2002.

Setting: Geographically defined biracial community in Chicago, Ill.

Participants: A total of 3718 residents, 65 years and older, who completed 2 to 3 cognitive assessments and a food frequency questionnaire.

Main Outcome Measure: Change in cognitive function measured at baseline and 3-year and 6-year follow-ups, using the average z-score of 4 tests: the East Boston Tests of immediate and delayed recall, the Mini-Mental State Examination, and the Symbol Digit Modalities Test.

Results: High folate intake was associated with a faster rate of cognitive decline in mixed models adjusted for multiple risk factors. The rate of cognitive decline among persons in the top fifth of total folate intake (median, 742 µg/d) was more than twice that of those in the lowest fifth of intake (median, 186 µg/d), a statistically significant difference of 0.02 standardized unit per year (P = .002). A faster rate of cognitive decline was also associated with high folate intake from food (P for trend = .04) and with folate vitamin supplementation of more than 400 µg/d compared with nonusers (β = −.03, P < .001). High total B₁₂ intake was associated with slower cognitive decline only among the oldest participants.

Conclusions: High intake of folate may be associated with cognitive decline in older persons. These unexpected findings call for further study of the cognitive implications of high levels of dietary folate in older populations.

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Vitamin B₁₂ and Folate have long been studied in relation to neurologic function. In addition to the well-established importance of vitamin B₁₂ deficiency to neurologic disease, a number of cross-sectional studies observed lower cognition among persons with insufficient serum or plasma levels of vitamin B₁₂ and folate. Furthermore, inadequate levels of either vitamin can lead to elevated plasma homocysteine levels, which may be independently associated with Alzheimer disease, thus raising interest in these vitamins as a means of prevention. As of January 1998, the US Food and Drug Administration required the fortification of grain products with folic acid to prevent neural tube defects. The long-term effects of the program on other health outcomes or in special populations are not yet known. We examined the associations of dietary folate and vitamin B₁₂ with 6-year cognitive change in a 1993 to 2002 study in Chicago, Ill.

METHODS

Subjects

Subjects were participants of the Chicago Health and Aging Project (CHAP), an ongoing study of residents 65 years and older from a geographically defined biracial population. A census identified 7813 age-eligible residents of whom 6158 participated in home interviews that included 4 cognitive tests. Of 4930 surviving participants, 4390 (89%) completed the food frequency questionnaire (FFQ) and at least 1 of the 3- and 6-year follow-up interviews. We eliminated 217 persons because of potentially invalid FFQ data and 460 persons whose FFQ was completed more than 2.5 years after baseline, leaving 3718 persons for analysis of cognitive change with a median follow-up of 5.5 years. Three cognitive as-
Dietary assessments were obtained for 1946 persons with a median follow-up of 6.3 years. Dietary assessments occurred a median of 1.2 years after baseline, most (86%) before the January 1998 folate fortification. Ninety-one percent had at least 1 follow-up cognitive assessment after this date. The institutional review board of Rush University Medical Center, Chicago, approved the study, and all participants gave written informed consent.

DIETARY ASSESSMENTS

Diet was assessed using a modified Harvard FFQ13 that inquired about usual intake during the past year of 139 food items and vitamin supplements. Post-1997 estimates of folate intake were multiplied by frequency of intake and summed over all food items to estimate daily nutrient intake. All nutrients were energy adjusted using the regression residual method.14 In a validation study of 232 randomly selected CHAP participants using repeated 24-hour dietary recalls as a comparison, correlations were 0.70 and 0.50 for total folate reproducibility and validity, respectively, and 0.50 and 0.38 for total vitamin B12.15

COGNITIVE ASSESSMENT

The 4 cognitive tests included the East Boston Tests of immediate and delayed recall (0 to 12 ideas recalled),16 the Mini-Mental State Examination (0 to 30 correct items),17 and the Symbol Digit Modalities Test18 of perceptual speed and attention (0 to 96 correct items). We computed z scores for the 4 tests and averaged the scores for a global measure of cognitive function.

OTHER COVARIATES

Nondietary variables were collected at participants’ baseline interview and included the following: age (in years), sex, race (black or white), education (in years), cigarette smoking (ever or never), smoking pack-years, number of depressive symptoms,19 heart disease (self-reported history of myocardial infarction, digitalis use, or angina pectoris20), hypertension (self-reported history or measured blood pressure ≥160 mm Hg systolic or ≥95 mm Hg diastolic or use of antihypertensive medications), stroke history (self-report), and diabetes mellitus (self-report or antidiabetic medication use). Information on medications was based on interviewer inspection.

STATISTICAL ANALYSIS

We used mixed-effects21 models in SAS statistical software22 to estimate effects of vitamin B12 and folate on the annual rate of change in cognitive score. The model explicitly accounts for individual differences in initial level of cognition and its correlation with rate of change. Energy-adjusted folate and vitamin B12 intakes were modeled in quintiles. Other energy-adjusted nutrients were modeled as continuous log-transformed variables. Model coefficients (β) represent the difference in slopes (rates of cognitive change per year) for an upper quintile of intake compared with the referent lowest quintile. Effect modification was examined by including terms in the model for all 2-way and 3-way interaction terms among the covariate, intake of folate or vitamin B12, and time.

RESULTS

Multivitamins were consumed by 33% of the analyzed cohort of 3718 persons. Folic acid (folate) and cobalamin (vitamin B12) supplementation were mostly through multivitamins (99% and 97%, respectively), with use of an individual folic acid vitamin indicated in 10 persons and cobalamin in 42 persons.

Persons with high intake of total folate (from food and supplements) tended to have a more favorable risk profile for cognitive change than persons with low intake, with more years of education, higher baseline cognitive scores, and greater consumption of vitamin E and vitamin C (Table 1). They were also less likely to have a history of heart disease or hypertension. The mean cognitive score at baseline for the cohort was 0.18 (range, −3.5 to 1.6), with an overall decline in score of 0.04 standardized unit per year.

Persons with higher intake of total folate had a marginally significantly faster rate of cognitive decline in the age-adjusted model (Table 2). With further adjustment for demographic factors, education, and intakes of

Table 1 presents the baseline characteristics of 3718 participants of the Chicago Health and Aging Project, 1993-2002.*
vitamin E in food and total vitamin C, the rate differences for persons in the fourth and fifth quintiles compared with the first quintile were increased and statistically significant (Table 2). The estimates changed little with additional adjustment for cardiovascular factors, including history of stroke, heart disease, hypertension, diabetes, smoking, alcohol use, and depressive symptoms ($\beta = -0.01, P = 0.09$ for the fourth quintile; and $\beta = -0.02, P = 0.005$ for the fifth quintile). The estimates also did not change when we added control for total intakes of vitamin B$_6$, thiamin, and riboflavin in separate multiple-adjusted models.

Food intake of folate was not associated with cognitive change in the age-adjusted model, but with multiple adjustment, higher intake was associated with faster cognitive decline (Table 2). The rate difference for persons in the fifth quintile (median intake, 382 µg/d) compared with the first quintile (median intake, 175 µg/d) was statistically significant (Table 2). When we further adjusted for the cardiovascular factors, the difference in rates for persons in the fifth quintile compared with the first quintile was reduced to $-0.01$ ($P = 0.07$).

In an analysis restricted to 2546 persons who did not take a multivitamin, the multiple-adjusted effect estimate for the fifth quintile for food intake of folate was $\beta = -0.02$ ($P = 0.06$). In further analyses of the folic acid dose from vitamin supplements, persons who consumed in excess of 400 µg/d had a significantly faster rate of cognitive decline than supplement nonusers (Table 3).

Intake of vitamin B$_{12}$, with or without vitamin supplementation, was not significantly associated with cognitive change in the age- or multiple-adjusted models or with adjustment for folate intake. However, when we examined the possibility of interactive effects, we observed a small, statistically significant interaction between total intake of vitamin B$_{12}$ and older age ($P$ for

### Table 2. Difference in the Estimated Rate of Change in Cognitive Score During 6 Years by Quintile of Folate Intake Among 3718 Participants of the Chicago Health and Aging Project, 1993-2002

<table>
<thead>
<tr>
<th>Model</th>
<th>Quintile of Intake</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>$P$ for Trend</td>
</tr>
<tr>
<td>Total folate intake, µg/d</td>
<td>186</td>
<td>251</td>
<td>311</td>
<td>419</td>
<td>742</td>
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<tr>
<td>Age-adjusted*</td>
<td>$\beta$</td>
<td>$-0.01$</td>
<td>$0.01$</td>
<td>$-0.04$</td>
<td>$-0.01$</td>
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</tr>
<tr>
<td></td>
<td>SE</td>
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</tr>
<tr>
<td></td>
<td>$P$ value</td>
<td>$0.94$</td>
<td>$0.94$</td>
<td>$0.54$</td>
<td>$0.15$</td>
<td>0.08</td>
</tr>
<tr>
<td>Multiple-adjusted†</td>
<td>$\beta$</td>
<td>$-0.01$</td>
<td>$-0.01$</td>
<td>$-0.02$</td>
<td>$-0.02$</td>
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<tr>
<td></td>
<td>SE</td>
<td>$0.01$</td>
<td>$0.01$</td>
<td>$0.01$</td>
<td>$0.01$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$P$ value</td>
<td>$0.41$</td>
<td>$0.38$</td>
<td>$0.04$</td>
<td>$0.002$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Folate from food intake, µg/d</td>
<td>175</td>
<td>227</td>
<td>268</td>
<td>312</td>
<td>382</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted*</td>
<td>$\beta$</td>
<td>$-0.01$</td>
<td>$-0.01$</td>
<td>$-0.01$</td>
<td>$-0.004$</td>
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<tr>
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<tr>
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<td>$P$ value</td>
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<td>$0.23$</td>
<td>$0.35$</td>
<td>$0.51$</td>
<td>0.73</td>
</tr>
</tbody>
</table>

*Age-adjusted model includes age, quintiles of folate intake, time, and time interactions with age and quintiles of folate intake.

†Multiple-adjusted model includes terms from the age-adjusted model plus sex, education, race, vitamin E intake from food, total vitamin C intake, and time interactions with all covariates. The model for folate intake from food sources also includes terms for multivitamin use (yes or no).

### Table 3. Differences in the Rate of Cognitive Change ($\beta$) During 6 Years by Dose Level of Folate Vitamin Supplementation, Chicago Health and Aging Project, 1993-2002

| Folate Supplement Dose, µg/d | No. of Patients | Age-Adjusted Model* | | | Multiple-Adjusted Model* | | |
|-------------------------------|-----------------|---------------------|---|---|---------------------|---|
|                               |                 | $\beta$ (SE) | $P$ Value | $\beta$ (SE) | $P$ Value |
| Nonusers                      | 2541            | Referent          | | | Referent          | | |
| 1-200                         | 224             | $-0.01$ (.01)     | .39 | | $-0.01$ (.01)     | .25 |
| 201-399                       | 303             | $-0.01$ (.01)     | .39 | | $-0.01$ (.01)     | .18 |
| 400                           | 380             | $-0.004$ (.01)    | .61 | | $-0.01$ (.01)     | .22 |
| 401-1200                      | 270             | $-0.002$ (.01)    | .01 | | $-0.03$ (.01)     | .001 |

*Age- and multiple-adjusted models are described in the footnote to Table 2.
interaction = .009). In the multiple-adjusted model that included folate intake, the rate of decline for an average 80-year-old who consumed a supplemental dose of 20 µg/d of vitamin B₁₂ was 25% slower than the rate of a similar person who consumed the recommended dietary allowance of 2.4 µg/d. By contrast, the estimated rates of decline for an average 70-year-old did not differ by vitamin B₁₂ intake.

To investigate the possibility that high folate intake might be a marker of poor health, we first restricted the analyses to 2706 persons who reported good or excellent health at baseline, but there were no appreciable differences in the estimated effects (multiple-adjusted $\beta = -0.02$, $P = .007$ for fifth quintile of folate intake). Next, we reanalyzed the data after excluding persons from the entire cohort whose baseline cognitive scores were in the bottom 15% of the distribution, and again, there were no material changes in the effect estimates (fifth quintile $\beta = -0.02$, $P = .005$).

In this large population-based study of older persons, we observed slower decline in cognitive function among persons with higher intake of vitamin B₁₂, but only among the oldest participants. Unexpectedly, persons with high intake of folate had faster rate of decline.

Vitamin B₁₂ plays an important role in the maintenance of neuronal cell function, and deficiency in this nutrient can result in neurologic damage characterized in part by memory loss and confusion. Vitamin B₁₂ deficiency is particularly a problem in older populations because of decreased dietary absorption. Except for some malabsorption syndromes, serum vitamin B₁₂ is positively associated with intake, particularly when the intake is from multivitamins or fortified food. These well-established relations are supportive of our finding of slower cognitive decline with high intake of vitamin B₁₂ among the oldest participants.

The observed association between high folate intake and cognitive change was opposite to our hypothesized direction. We expected a slower rate of decline because low folate status is a cause of elevated homocysteine levels, which some but not all studies have found to be associated with increased risk of Alzheimer disease, the primary reason for cognitive decline. Consistent with the folate-homocysteine relationship, deficient folate intake levels would be the relevant range for cognitive decline, but this is likely a rare occurrence in the United States since the folate acid fortification program.

Previous studies on this topic are not comparable to the present study in 2 important ways. First, most studies measured cognition only at one point and cannot distinguish between lifetime differences in cognitive ability and decline related to aging. Second, none of these studies measured the association with cognition after the folate acid fortification program, whereas 91% of the analyzed CHAP participants had follow-up cognitive assessments during this period.

The CHAP study has a number of strengths that lend confidence to the validity of the observed associations. The large number of participants and the longitudinal analytic design allowed for the detection of small within-person cognitive change and the ability to separate baseline cognitive level from age-related decline. The observed associations did not appear to be due to differences in health or poor recall of diet. Notably, the known confounders were each associated with higher folate intake and slower cognitive decline; thus, the potential for residual confounding is in the opposite direction of the folate association. The validity of the findings is further supported by the specificity of the associations with vitamin B₁₂ and folate and not with other B vitamins, even though they commonly occur together in food and supplements.

A limitation of the study is the reliance on the FFQ as the sole measure of intake, with no corresponding measure of tissue concentrations of these micronutrients, which prevents examination of whether vitamin deficiencies can account for the results. In addition, due to the potential for spurious associations in an observational study design, we must caution against a causal interpretation of the findings.

The mechanism by which high folate intake may increase cognitive decline is not clear. One possibility is that high intake may be masking unrecognized vitamin B₁₂ deficiency. This complication was previously suggested as a potential pitfall of folic acid supplementation in food and multivitamins. There was also the unresolved question of whether folic acid may exacerbate the neurologic syndrome associated with vitamin B₁₂ deficiency. Such concerns were instrumental in the recommended upper limit for folate intake of 1000 µg/d. With widespread multivitamin use and folic acid fortification, it is likely that a significant percentage of the population is consuming more than the upper limit and well above the dietary reference intake of 400 µg/d. The possibility that high intake of folic acid through multivitamins and fortified food may have deleterious effects on the health of the older population warrants further study.

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