Dietary niacin and the risk of incident Alzheimer’s disease and of cognitive decline

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Background: Dementia can be caused by severe niacin insufficiency, but it is unknown whether variation in intake of niacin in the usual diet is linked to neurodegenerative decline. We examined whether dietary intake of niacin was associated with incident Alzheimer’s disease (AD) and cognitive decline in a large, prospective study.

Methods: This study was conducted in 1993–2002 in a geographically defined Chicago community of 6158 residents aged 65 years and older. Nutrient intake was determined by food frequency questionnaire. Four cognitive tests were administered to all study participants at 3 year intervals in a 6 year follow up. A total of 3718 participants had dietary data and at least two cognitive assessments for analyses of cognitive change over a median 5.5 years. Clinical evaluations were performed on a stratified random sample of 815 participants initially unaffected by AD, and 131 participants were diagnosed with 4 year incident AD by standardised criteria.

Results: Energy adjusted niacin intake had a protective effect on development of AD and cognitive decline. In a logistic regression model, relative risks (95% confidence intervals) for incident AD from lowest to highest quintiles of total niacin intake were: 1.0 (referent) 0.3 (0.1 to 0.6), 0.3 (0.1 to 0.7), 0.6 (0.3 to 1.3), and 0.3 (0.1 to 0.7) adjusted for age, sex, race, education, and ApoE e4 status. Niacin intake from foods was also inversely associated with AD (p for linear trend = 0.002 in the adjusted model). In an adjusted random effects model, higher food intake of niacin was associated with a slower annual rate of cognitive decline, by 0.019 standardised units (SU) per natural log increase in intake (mg) (p = 0.05).

Stronger associations were observed in analyses that excluded participants with a history of cardiovascular disease (β = 0.028 SU/year; p = 0.008), those with low baseline cognitive scores (β = 0.023 SU/year; p = 0.02), or those with fewer than 12 years’ education (β = 0.035 SU/year; p = 0.002)

Conclusion: Dietary niacin may protect against AD and age related cognitive decline.
Diet was assessed using a modified 152 item Harvard self-administered food frequency questionnaire (FFQ), on average (SD) 1.7 (0.9) years after the baseline in the clinically evaluated sample, and 1.1 (0.9) years after the initial cognitive test for the analyses of change in cognitive function. The FFQ was distributed to participants along with a self-addressed envelope for its return, although some participants were interviewed at their request. The FFQ included questions about usual intake of 139 food items and individual vitamin supplements. Nutrient intake was obtained by multiplying the nutrient content of individual food items by the frequency of consumption and then summing over all items. Nutrient content of individual food items was based on the Harvard University Nutrient Database, which is continually updated using data from the US Department of Agriculture, and from selected individual publications.

Participants were prompted for specific brand names of multivitamins, cereals, and margarines, type of cooking oil, and fat preferences for milk and meat products, and this information was used in the computation of nutrient intake. The computation of total niacin equivalents was based on the sum of niacin intake from foods and supplements, plus the tryptophan contribution (1 mg niacin per 60 mg of tryptophan intake). FFQs were considered potentially invalid (n = 147) and eliminated from the analyses if entire food sections or more than half the items were left blank, total energy intake (kcal) was <500 or >3800 for females or <700 or >4000 for males, or the baseline Mini Mental State Examination (MMSE) score was <10 (out of a possible score of 30). For analysis, dietary intake levels were adjusted for total energy intake using the regression residual method separately for men and women.

The CHAP FFQ has been shown to be a valid and reliable measure of dietary intake in the CHAP population. Pearson’s correlation for niacin intake levels measured by the FFQ and repeated 24 hour dietary recall interviews were 0.52 for total niacin and 0.47 for niacin excluding supplements. Intra-class correlations for reproducibility of intake levels from two FFQs 1 year apart were 0.62 for both total niacin and for niacin excluding supplements.

Clinical evaluation for incident AD
AD was diagnosed based on structured clinical evaluations that were conducted in participants’ homes. A board certified neurologist, who was blinded to participant information on dietary intake, examined every participant. The evaluations included neuropsychological testing (using tests of Consortium Established for Research on Alzheimer’s Disease), a complete medical history, medication use, laboratory testing, neurologic examination, and informant interviews for cognitively impaired participants. The diagnosis of probable AD was based on criteria of the National Institute of Neurological Communicative Disorders and Stroke, and the AD and Associated Disorders Association, with the exception that the definition of AD included all cases that met the criteria, thereby including 14 participants with a co-existing dementing condition. Demented participants without AD (n = 11) were analysed as non-cases. MRI was performed when dementia was evident and clinical stroke was uncertain.

Change in cognitive function
Cognitive function was assessed on the entire study population during in-home interviews at baseline and 3 year and 6 year follow ups using four cognitive tests: the East Boston Tests of Immediate and Delayed Recall, the MMSE, and the Symbol Digit Modalities test. Raw scores on each test were converted to z scores, using the baseline mean and standard deviation of the study population, and averaged to form a composite measure.

Covariates
Information for all non-dietary variables except clinical stroke and ApoE e4 was obtained at participants’ baseline population interview. Alcohol consumption (g/day) was based on three separate FFQ questions about usual consumption of beer, wine, and spirits. Education (years) was

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Table 1: Baseline characteristics by quintiles of total niacin intake including supplements, and niacin from food among 815 randomly selected participants of the Chicago Health and Aging Project

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Quintile</th>
<th>Total niacin</th>
<th>Niacin from foods only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>Intake range (mg/day)</td>
<td></td>
<td>7-15 16-18 18-22 22-36 36-71</td>
<td>71-14 14-16 16-18 18-20 20-48</td>
</tr>
<tr>
<td>Age (median years)</td>
<td></td>
<td>72.9 73.2 72.2</td>
<td>71.0 72.2 72.2 71.5 73.1</td>
</tr>
<tr>
<td>Female (%)</td>
<td></td>
<td>69.4 66.1 49.3</td>
<td>63.4 62.1 79.9 68.8 58.8</td>
</tr>
<tr>
<td>Blacks (%)</td>
<td></td>
<td>62.2 55.1 56.8</td>
<td>47.5 33.1 59.8 50.3 52.2</td>
</tr>
<tr>
<td>Education (median years)</td>
<td></td>
<td>11.4 12.2 12.6</td>
<td>12.7 13.0 11.9 12.6 12.5</td>
</tr>
<tr>
<td>ApoE e4 [% with at least 1 allele]</td>
<td></td>
<td>3.2 3.3 12.4</td>
<td>94.9 42.5 35.8 34.3 30.2</td>
</tr>
<tr>
<td>Multivitamin Use [%]</td>
<td></td>
<td>17.7 21.5 14.7</td>
<td>17.6 21.8 21.8 12.5 20.3</td>
</tr>
<tr>
<td>Vitamin E in food (median IU/day)</td>
<td></td>
<td>50.8 63.8 51.5</td>
<td>59.1 64.7 67.8 62.5 48.3</td>
</tr>
<tr>
<td>Clinical stroke</td>
<td></td>
<td>10.2 16.1 24.5</td>
<td>19.8 16.8 11.0 13.6 18.4</td>
</tr>
</tbody>
</table>

All percentages and medians are weighted for the stratified random sample design. All variables (except age and niacin intake) are age standardized to the age distribution of the disease-free cohort at baseline.
Niacin intake and incident Alzheimer’s disease

Relative risks (95% confidence intervals) of incident AD by quintile of intake of niacin, tryptophan, and niacin equivalents among 815 participants initially free of AD and followed a median 3.8 years, Chicago Health and Aging Project, 1993–2000

<table>
<thead>
<tr>
<th>Quintile of intake</th>
<th>Niacin equivalents</th>
<th>Niacin from foods</th>
<th>Tryptophan</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>2</td>
<td>0.9</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>3</td>
<td>0.8</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>4</td>
<td>0.7</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>5</td>
<td>0.6</td>
<td>0.4</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Table 2

Statistical methods

We used logistic regression analysis programmed in SAS to generate OR as estimates of the relative risk of incident AD weighted for the stratified random sample design. Variance estimation was computed by jackknife repeated replication. We used random effects models to estimate the effect of niacin intake on intra-person rate of change in cognitive score while controlling for initial cognitive score and other covariates. Before examination of associations between the outcomes and niacin, we first determined the best basic models of the most important confounders, including non-linear and interactive associations. The basic model for incident AD was based on a previous report of the CHAP study. For the analysis of cognitive function, we considered higher order terms of age and education because of earlier studies indicating non-linear associations with cognitive function and exponential associations with AD. We also examined interactions among the demographic variables in baseline cognitive score to ensure optimal adjustment of initial score level when modelling change (all terms were statistically significant at \( p<0.05 \) in a model of the total study population).

Energy adjusted niacin and tryptophan intakes were each modelled as continuous log transformed variables and also in quintiles with the lowest quintile as the reference category. Dietary covariates were energy adjusted and modelled as continuous log transformed variables. Effect modification was examined in separate multiple adjusted models that included terms for nutrient intake (as continuous variables), the potential effect modifier (age, sex, race, education, ApoE e4), and interaction terms between these variables.

RESULTS

A total of 815 people, all of whom were initially free of AD at baseline, were clinically evaluated on average 3.9 years later, and 131 were diagnosed with incident AD. The annual incidence rate was 2.6% after appropriate weighting for the stratified random sampling design. Non-dietary niacin supplementation was through multivitamins, including B complex vitamins, as opposed to use of individual supplements. Only 9 of the 815 participants were taking a prescribed form of niacin at baseline. The lowest quintile groups of total niacin intake and niacin food intake had higher percentages of females, blacks, people with clinical stroke, and people with low food intake of vitamin E than did

computed from self reported highest grade or years of formal education, and pack years (packs per day multiplied by number of years ever smoked). History of diabetes was defined as use of anti-diabetic medication or participant report of clinically diagnosed diabetes. Hypertension was defined as participant report of high blood pressure, anti-hypertensive medication use, or measured systolic pressure \( >160 \text{ mmHg} \) or diastolic pressure \( >95 \text{ mmHg} \). Heart disease was defined as self reported history of myocardial infarction, use of digitalis, or evidence of angina pectoris based on participant responses to a standardised questionnaire. Medication information was obtained through interviewer inspection of all medications taken within the 2 week period prior to the baseline. For the analyses of AD, clinical stroke was defined as probable or possible stroke as diagnosed by the examining neurologist based on a uniform, structured examination, medical history, and MRI diagnostic testing if indicated. ApoE genotyping was conducted on blood samples collected at the clinical evaluations using methods of Hixson and Vernier, and the primers described by Wenham et al. ApoE genotype was not obtained on the total study population and therefore not available for the analyses of cognitive change.
higher quintile groups (table 1). Participants in the lowest quintile of total niacin intake, but not of food intake, were more likely to have an ApoE e4 allele than were those in the highest quintile. There was a higher prevalence of diabetes among participants in the highest quintiles of both total and food intake of niacin.

Total niacin intake, including intake from food and supplements, was inversely associated with incident AD after adjustment for age, sex, race, education, ApoE e4, and time period of observation in both continuous and categorical models. Compared with the risk of disease among participants in the lowest fifth of intake (median of 14.1 mg/day), those in the second, third, and fifth quintiles had significantly lower risk by 70% (table 2). Participants in the fourth quintile of intake had a 40% non-significant reduction in risk compared with the lowest quintile group. The protective association with higher niacin intake became stronger (p for trend = 0.04) after further adjustment for multivitamin use and intake of the antioxidant nutrients (vitamin C, beta-carotene, or vitamin E from food sources) that were found in previous reports to be possibly protective against AD.

Intake of niacin from foods had an inverse association with AD in the basic adjusted model (p for trend = 0.002) (table 2). Participants in intake quintiles 2–4 had 70% reductions in risk compared with those in the lowest quintile (median intake 12.6 mg/day), whereas participants in the highest fifth of intake (median 22.4 mg/day) had an 80% reduction in risk; all were statistically significant. The relative risks were only slightly less protective in the multiple adjusted model and remained statistically significant.

We considered that the observed protective association of niacin could be entirely due to greater risk of AD among participants in the lowest quintile of niacin intake. When we excluded these from the analyses, we observed a statistically significant inverse log linear association among participants in the upper quintiles of intake (>14 mg/day) with niacin intake from food measured as a continuous log transformed variable. The basic adjusted relative risk was 0.4 (p = 0.04) per 7.2 mg/day increase in dietary niacin, which represents the difference in median intakes for the second and fifth quintiles.

Tryptophan intake from food was also inversely associated with incident AD. The basic adjusted risk decreased with increased level of intake (p for trend = 0.03) (table 2). There was no appreciable change in the relative risks with further adjustment for intake of the antioxidant nutrients and multivitamin use. Because many of the same foods that contain tryptophan also contain niacin we added control for the effect of niacin intake from foods in the multiple adjusted model; the relative risks for tryptophan intake were less protective and no longer statistically significant (for quintiles 2–5, the relative risks (95% confidence interval) were 0.6 (0.2 to1.6), 0.8 (0.3 to2.1), 0.5 (0.2 to1.5), and 0.6 (0.2 to1.4), respectively.

The recommended dietary allowance (recommended daily amount; RDA) for niacin is described in terms of niacin (0.2 to1.6), 0.8 (0.3 to2.1), 0.5 (0.2 to1.5), and 0.6 (0.2 to1.4), respectively.

The mean cognitive score at the initial assessment (average z score of four cognitive tests) was 0.18 (range: −3.50 to 1.58), and the average annual decline was 0.042 standardised units (SU) per year. Food intake of niacin had a linear protective association in both continuous and categorical models. In the continuous model adjusted for demographic confounders, the rate of cognitive decline decreased by 0.019 SU/year (p = 0.05) per ln increase in intake (mg) (table 3). The effect was attenuated slightly (β = 0.017 SU/year; p = 0.12) after additional control for dietary intakes of antioxidant nutrients and folate, multivitamin use, smoking and alcohol use, stroke, heart disease, diabetes, and hypertension. Substitution of each of the other B vitamins for folate produced similar results.

Because of the likelihood of dietary changes among people who experience major cardiovascular events, we next repeated the analyses after excluding the 894 participants who reported a history of stroke or myocardial infarction at the baseline or first follow up interviews. Food intake of niacin had a linear protective association with cognitive decline in the basic adjusted model (β = 0.028 SU/year; p = 0.004). In the categorical model, the rate of cognitive decline was significantly reduced by 44% among participants in the top fifth of niacin food intake (median 22.1 mg/day) compared with those in the lowest fifth (median 12.6 mg/day), a difference of 0.021 SU/year (p = 0.003) (fig 1). Adjustment for other dietary and cardiovascular-related risk
Table 3  Adjusted effects of niacin intake from food (per ln increase in intake (mg)) on the rate of cognitive change over 6 years, among the total cohort of 3718 participants, and among 2824 participants with no history of stroke or myocardial infarction at baseline or first follow up, Chicago Health and Aging Project, 1993-2002

<table>
<thead>
<tr>
<th>Model</th>
<th>Total cohort (n = 3718)</th>
<th>Excluding participants with stroke or myocardial infarction (n = 2824)</th>
<th>Excluding participants with low cognitive scores (n = 3158)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>SE</td>
<td>p</td>
</tr>
<tr>
<td>Basic adjusted†</td>
<td>0.019</td>
<td>0.009</td>
<td>0.05</td>
</tr>
<tr>
<td>Multiple adjusted†</td>
<td>0.017</td>
<td>0.011</td>
<td>0.12</td>
</tr>
</tbody>
</table>

‘Multiple adjusted model does not include terms for stroke or heart disease. †Lowest 15% of scores distribution.
*Includes age (years), age², sex, race, education (years), education² interactions between sex and age, sex and education, and race and education, time, niacin intake from foods (continuous log transformed), and interactions between time and age, education, education squared, and niacin intake.
†Includes terms from the basic-adjusted model plus vitamin E intake from food sources (IU/day), total intakes of vitamins C (mg/day), beta-carotene (IU/day), folate (μg/day), diabetes, hypertension, ever smoked (yes/no), pack years of smoking, alcohol use (g/day), multivitamin use, history of stroke, heart disease, and interactions between time and each of these covariates.

Factors resulted in an even greater reduction in the rate (table 3).

To investigate whether the observed protective association of niacin might be due to unreliable reporting among people with poor cognition, we repeated the analyses after excluding 551 participants from the total cohort who had baseline scores in the lowest 15% of the distribution. In this cognitively restricted group, high intake of dietary niacin was associated with a greater protective effect than that observed for the total cohort in both the basic and multiple adjusted models (table 3). In other analyses, we examined whether low socioeconomic status could account for the findings by excluding participants from the total cohort who had fewer than 12 years of formal schooling. Even among the higher educated (n = 2495), the rate of cognitive decline was significantly reduced with higher food intake of niacin (β = 0.035; p = 0.002 in the basic adjusted model).

Total niacin intake (including intake from vitamin supplements) had no association with cognitive change; the effect estimates fluctuated around 0 in both the basic and multiple adjusted models in the total cohort as well as in the cohort restricted to those with no history of stroke or myocardial infarction.

DISCUSSION

In this prospective population based study, we observed inverse associations between AD and dietary intakes of total niacin (foods and supplements), niacin from foods only, and tryptophan. Although participants in the lowest fifth of intake had the greatest risk of AD, a statistically significant log linear inverse association remained when we restricted the analyses to participants with higher intake levels. Higher intake of niacin from food sources was also linearly associated with lower cognitive decline in the study population.

The protective association of niacin against AD was observed after controlling for the important risk factors for dementia (age, education, race, ApoE e4) as well as many other dietary and non-dietary factors that could potentially account for the results, including cardiovascular conditions, and dietary intake of antioxidant nutrients, fats, folate, and vitamins B6, B12, B1, and B2. It is possible that residual confounding may have influenced the magnitude of the protective effect; however, there is good evidence in support of an association. Firstly, protective associations were observed after adjustment for race and education, and there was no evidence of modification in the effect by these factors. Secondly, the protective association was specific to niacin intake as opposed to other related B vitamins. Finally, we also found a specific protective effect of niacin intake from food against 6 year cognitive decline among 3718 participants in the larger cohort that was only strengthened in sensitivity analyses excluding participants with low initial cognitive scores or with less than a high school education, and with control for dietary and other potential confounders. We did not observe an association between total niacin intake and cognitive change. It is difficult to test for associations with supplemental niacin because it is obtained through multivitamins that contain many other nutrients that may confound observed effects.

A major strength of the study is the unbiased selection of clinically evaluated participants from a random sample from a community population, and unbiased detection of AD cases through uniform, structured neurological examination using standardised criteria. For a number of clinically evaluated participants, the dietary assessments occurred after baseline, and this could have biased the results if dietary behaviours or that responses to the dietary questionnaires were affected by the onset of disease. However, the protective association remained when we controlled for the timing of the dietary assessment, when we eliminated participants with the poorest memory at baseline, and when we further restricted the analyses by also eliminating those with intermediate memory performance. Further, in a validity study of 232 randomly selected CHAP participants, we found no marked
differences in the correlations between nutrient intake on the FFQ and repeated 24 hour recall interviews by cognitive ability, age, race, or educational level.24

Niacin rich foods include meats, legumes, nuts, enriched grains/cereals, coffee, and tea. In addition, niacin is synthesized endogenously through the conversion of tryptophan, an amino acid that constitutes about 1% of the protein in foods. The association with tryptophan was lessened when niacin was included in the model, suggesting the protective benefit may be due to the niacin rather than the tryptophan.

It has been known since the 1930s that pellagra is a result of niacin deficiency and is responsive to synthetic niacin. Confusion and psychosis are well recognised symptoms of pellagra and of the encephalopathy associated with niacin deficiency in severe alcoholism. The level of dietary insufficiency associated with these conditions (8.8 mg niacin equivalents per 2000 kcal25) is lower than the range of intake for the lowest quintile (13.2 to 27 mg per day). The current RDA for niacin equivalents is 16 mg per day for men and 14 mg per day for women.26

Much attention has been focused on the relation between dementia and other B vitamins, particularly vitamin B12, vitamin B6 and folate. There has been little previous examination of dietary niacin and AD, although niacin has been shown to reduce cognitive decline and the risk of incident Alzheimer’s disease in a biracial community study.27

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Competing interests: none declared

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