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

M C Morris, D A Evans, J L Bienias, P A Scherr, C C Tangney, L E Hebert, D A Bennett, R S Wilson, N Aggarwal

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.

Subjects and Methods

Population
Participants are from the Chicago Health and Aging Project (CHAP), a biracial study of three geographically defined contiguous neighbourhoods on the south side of Chicago. A census identified 8501 residents aged 65 years and older, of whom 439 had died and 249 had moved before participation could be secured. In total, 6158 participated (79% participation overall; 81% among blacks, 75% among whites). The study population was 62% black, 38% white, and 39% male, 61% female, with a mean educational level of 11.8 years. Data were collected from 1993–2002 in cycles of approximately 3 years, each consisting of at home interviews of all participants (including the administration of four cognitive tests), and clinical neurological evaluation on a stratified random sample.

Baseline data provided risk factor information on the entire population, identified prevalent cases of AD in a sample of 729 people, and identified a cohort of 3838 unaffected participants to follow for incident disease. The disease free cohort consisted of 3369 people who had good performance on two14-15 of the baseline cognitive tests, and 469 whose cognitive performance was intermediate or poor, but were unaffected by AD at the baseline clinical evaluation. Subsequent to the 3 year population interview, a second stratified random sample of 1249 participants was drawn from the disease free cohort, and 842 of these (73.9% of survivors) were clinically evaluated for incident AD. Sample participants were randomly selected within strata defined by age, sex, race, and change in cognitive performance from baseline to the 3 year follow up (stable or improved, small decline, and large decline).

Abbreviations: AD, Alzheimer’s disease; CHAP, Chicago Health and Aging Project; FFQ, food frequency questionnaire; MMSE, Mini Mental State Examination; RDA, recommended dietary allowance/ recommended daily amount
Evaluations have been published previously. The study examination (MMSE) score was.

or energy intake (kcal) was (n = 147) and eliminated from the analyses if entire food sum of niacin intake from foods and supplements, plus the The computation of total niacin equivalents was based on the information was used in the computation of nutrient intake.

and fat preferences for milk and meat products, and this multivitamins, cereals, and margarines, type of cooking oil, Participants were prompted for specific brand names of 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 >8000 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 neuropsychologist, 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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<th>Quintile</th>
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<th>Niacin from foods only</th>
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<td>Intake range (mg/day)</td>
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<td>Female (%)</td>
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<td>Blacks (%)</td>
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<td>Education (median years)</td>
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RESULTS

A total of 815 people, all of whom were initially free of AD at baseline, were included in the analyses. We used logistic regression analysis programmes in SAS, incorporating multiple adjustments for demographic factors and confounders, including non-linear and interactive associations between the outcomes and niacin, we first determined the best basic models of the most important associations with AD. 18 41 We also examined interactions among the demographic variables in baseline cognitive score and other covariates. Before examination of associations with cognitive function, we considered higher order terms of age to estimate the effect of niacin in each individual. AD was defined as self-reported diagnosis of dementia, based on a uniform, structured examination, medical history, and MRI diagnostic testing if requested by the examining neurologist. AD was defined as clinically diagnosed if a participant was diagnosed with dementia by a clinician who was aware of the participant’s dietary history. AD was defined as clinically diagnosed if a participant was diagnosed with dementia by a clinician who was aware of the participant’s dietary history. AD was defined as clinically diagnosed if a participant was diagnosed with dementia by a clinician who was aware of the participant’s dietary history. AD was defined as clinically diagnosed if a participant was diagnosed with dementia by a clinician who was aware of the participant’s dietary history.
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 ε4 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 ε4, 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, betacarotene, or vitamin E from food sources) that were found in previous reports9–11 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 = 0.05) (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 to 1.6), 0.8 (0.3 to 2.1), 0.5 (0.2 to 1.5), and 0.6 (0.2 to 1.4), respectively.

The recommended dietary allowance (recommended daily amount; RDA) for niacin is described in terms of niacin equivalents, which includes intake from both pre-formed niacin and tryptophan. The basic adjusted relative risks for intake of niacin equivalents were of the same magnitude as for total niacin intake and all but the fourth quintile were statistically significant (table 2).

Because some studies34–36 suggest that dietary intakes of folate and other B vitamins (vitamins B6, B12, B1, and B2) may be involved in the development of AD, and dietary intakes of the B vitamins are inter-correlated, we adjusted for these individually in separate basic adjusted models, but there were no material changes in the relative risks for niacin (total and from foods) or for tryptophan. Because cardiovascular related conditions may be associated with the development of AD, we investigated whether the observed associations for niacin and tryptophan could be attributed to the presence of clinical stroke, heart disease, hypertension, or diabetes. There were no appreciable differences in any of the relative risks when we simultaneously adjusted for these conditions in the basic adjusted models. We also found no evidence of confounding in separate basic adjusted models that controlled for alcohol consumption and pack years of smoking. In a previous report, we found evidence that different types of fat were associated with the incidence of AD.37 Therefore we examined whether additional control for intake of saturated, trans, monounsaturated, n-6 polyunsaturated, and n-3 polyunsaturated fats could have biased the observed associations, but there were no material changes in the relative risks.

We found no statistically significant modifications in the protective niacin effect by age or within categories of ApoE ε4 status, race, education, sex, heart disease or clinical stroke. There was no appreciable change in the protective relative risks when we controlled for the time between the dietary assessment and the clinical evaluation for incident AD. We also re-analysed the data after excluding participants (n = 51) who had poor cognitive performance at baseline but there was little change in the multivariable relative risks (for quintiles 2–5 of niacin food intake: 0.2, 0.4, 0.3, and 0.2, respectively; p for trend = 0.02). When we restricted the analysis to participants with good cognitive performance at baseline, the multivariable relative risks were virtually unchanged and remained statistically significant.

**Niacin intake and cognitive change in the entire study population**

We also examined whether dietary intake of niacin was associated with 6 year cognitive change among 3718 people in the larger study population. Although this type of analysis is not specific to AD, it provides an objective and sensitive measure of gradual decline, the central characteristic of this disease. Much of the cognitive decline in the population is probably due to disease processes associated with AD, which is the leading cause of dementia, followed by vascular dementia.46

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 384 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...
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 foods 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 multi-vitamins 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.\textsuperscript{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 recognized 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 kcal\textsuperscript{36}) 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.\textsuperscript{10}

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 administered to older people to prevent confusional states, and there have been several published clinical trials of medications for this indication.\textsuperscript{21} In this prospective study, we observed a protective association of niacin against the development of AD and cognitive decline within normal levels of dietary intake, which could have substantial public health implications for disease prevention if confirmed by further research.

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REFERENCES


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