Caloric Intake and the Risk of Alzheimer Disease

Jose A. Luchsinger, MD; Ming-Xing Tang, PhD; Steven Shea, MD; Richard Mayeux, MD

Background: Diet may play a role in Alzheimer disease (AD).

Objective: To examine the association between caloric intake and AD.

Methods: Elderly individuals free of dementia at baseline (N=980) were followed for a mean of 4 years. Daily intake of calories, carbohydrates, fats, and protein were recalled using a semiquantitative food frequency questionnaire administered between the baseline and first follow-up visits. Proportional hazards models were used to examine the associations of quartiles of intake and incident AD, adjusting for confounders.

Results: There were 242 incident cases of AD during 4023 years of follow-up (6 cases per 100 person-years). Compared with individuals in the lowest quartile of caloric intake, those in the highest quartile had an increased risk of AD (hazard ratio, 1.5; 95% confidence interval [CI], 1.0-2.2). Among individuals with the apolipoprotein E ε4 allele, the hazard ratios of AD for the highest quartiles of calorie and fat intake were 2.3 (95% CI, 1.1-4.7) and 2.3 (95% CI, 1.1-4.9), respectively, compared with the lowest quartiles. The hazard ratios of AD for the highest quartiles of calorie and fat intake compared with the lowest quartiles in individuals without the apolipoprotein E ε4 allele were close to 1 and were not statistically significant (P=.83 and P=.61, respectively).

Conclusion: Higher intake of calories and fats may be associated with higher risk of AD in individuals carrying the apolipoprotein E ε4 allele.

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Caloric intake has been shown to affect aging in animals and possibly in humans.1 Caloric restriction in mice and rats increases average and maximum life span,2 presumably through decreased oxidative damage.3 The balance of macronutrients in the diet may also affect oxidative stress unrelated to total caloric intake,4 which in turn may be involved in the pathogenesis of Alzheimer disease (AD).5 The generation of reactive oxygen species increases the damage related to deposition of amyloid β in the brain through at least 3 potential mechanisms: protein oxidation, DNA oxidation, and lipid peroxidation.5 It is, therefore, possible that dietary factors that decrease oxidative stress would lower AD risk.

Studies examining the association between caloric intake and cognition in animals have conflicting findings. Patients with dementia increase their caloric intake and change their food choice,8,9 eating less protein and more sweets than individuals without dementia.8,9 The relation between caloric intake and AD could have important public health implications. Our objective was to examine the association between total calorie and macronutrient intake in relation to the risk of AD.

RESULTS

The mean age of the sample was 75.3±5.8 years, and 67% were women, 25% were white, 43% were Hispanic, and 32% were black. The median number of years of education was 9. Twenty-eight percent of the cohort were homozygous or heterozygous for the APOE ε4 allele, 16% were current smokers, and 33% were former smokers. There were 242 cases of incident AD during 4023 person-years of observation (6 cases per 100 person-years). The mean duration of observation was 4.0±1.5 years.

The mean reported intake of total calories was 1267±453 kcal/d (1186±437 kcal/d in women and 1316±469 kcal/d in men; P<.001). The mean daily intake of fats was 38±19 g; protein, 60±22 g; and carbohydrates, 176±67 g. There were more
PARTICIPANTS AND METHODS

STUDY PARTICIPANTS

Participants were enrolled in the Washington Heights–Inwood Columbia Aging Project cohort by random sampling of healthy Medicare beneficiaries 65 years or older residing in a geographically defined area of northern Manhattan, NY.1 At entry, each individual underwent a structured in-person interview, including an assessment of health and function, a standard medical history, physical and neurological examinations, and a neuropsychological battery.12 Participants were recruited between 1991 and 1996 and were followed annually, with the baseline examination repeated at each follow-up. Individuals who completed at least 1 year of follow-up were included in the analysis. A food frequency questionnaire was completed by 1422 individuals between the baseline and first follow-up examinations. Of these 1422 individuals, 230 were excluded owing to prevalent dementia, 210 owing to loss to follow-up, and 2 because of missing data for macronutrient intake. Thus, the analytic sample comprised 980 individuals. This study was approved by the institutional review board of Columbia-Presbyterian Medical Center, New York.

DIAGNOSIS OF DEMENTIA AND COGNITIVE IMPAIRMENT

A group of neurologists, psychiatrists, and neuropsychologists reviewed data gathered at the initial and follow-up visits. By consensus, diagnosis of dementia was made based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria13 and required evidence of cognitive decline on the neuropsychological test battery and evidence of impairment in social or occupational function (Clinical Dementia Rating ≥0.5).14 This excluded individuals who might have had prevalent dementia at baseline that was mild enough not to be detected, possibly biasing the results of the study. Diagnosis of AD was based on the National Institute of Neurological and Cognitive Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association criteria.15 These criteria and diagnostic methods have been used extensively in the analysis of data in this cohort.16,17

DIETARY DATA

Dietary data were obtained using a 61-item version of the semiquantitative food frequency questionnaire (Channing Laboratory, Cambridge, Mass) of Willett et al.18 The semiquantitative food frequency questionnaire was administered by telephone between the baseline and first follow-up examinations by trained interviewers in English or Spanish. Total caloric intake was measured in kilocalories per day. Intakes of macronutrients—carbohydrates, fats, and protein—were measured in grams per day and were adjusted for total caloric intake as recommended by Willett19 by calculating the residuals from linear regression models (nutrient intake regressed on total caloric intake using transformed values for nutrients and calories) and adding a constant (mean nutrient intake). Square root transformation was used for total calories, carbohydrates, fats, and protein. Semiquantitative food frequency questionnaires have been used and validated for the determination of nutrient intake in the elderly.20-28 The validity of the questionnaire used in this study was assessed in a subsample of 78 individuals using two 7-day food records as the criterion. The intraclass correlations for energy-adjusted nutrients were 0.30 for total calories, 0.28 for carbohydrates, 0.41 for fats, and 0.33 for protein, based on energy-adjusted nutrient intakes (Maliha Siddiqui, MS, MPH, written communication, December 7, 2000).

DEFINITIONS OF COVARIATES

Ethnic group was based on self-report using the format of the 1990 census.29 Individuals were also asked whether they were of Hispanic origin. Participants were then assigned to 1 of 3 groups: black (non-Hispanic), Hispanic, or white (non-Hispanic). Data on years of education were obtained by self-report. Apolipoprotein E (APOE) genotyping was obtained by amplification of genomic DNA with polymerase chain reaction subjected to CfoI restriction analysis using APOE primers and conditions similar to those described by Hixson and Vernier.30 Participants were classified as positive for the APOE ε4 allele genotype if they had 1 or 2 ε4 alleles.

DATA ANALYSIS

Participants were grouped by the 2 highest vs 2 lowest quartiles of caloric and macronutrient intake and were compared with respect to sex and APOE ε4 status using χ² tests. T tests (2 sample) were used to compare mean age and number of years of education. Proportional hazards regression was used for multivariate analyses, with the time-to-event variable in the models specified as the time from baseline examination to onset of AD. In light of the association reported between education and macronutrient intake,31 the final model was stratified by number of years of education. Calorie and macronutrient intakes were categorized as quartiles and were included in the multivariate models as dummy variables, using the lowest quartile of intake as the reference. Dietary intakes and other covariates were treated as baseline time constant covariates. Trend tests were conducted using Cox proportional hazards regression, with each dietary intake variable categorized into quartiles of intake; the P value for the coefficient of the dietary intake variable was used as the P value for the trend test.32 We also conducted additional analyses stratifying by the presence of the APOE ε4 allele. Statistical software (SAS Version 7 for Windows; SAS Institute Inc, Cary, NC) was used for all analyses. Data are given as mean ± SD.

women in the 2 lowest quartiles of caloric intake. Individuals in the 2 highest quartiles of caloric intake were older and had more years of education than those in the 2 lowest quartiles (Table 1).

Compared with the lowest quartile, the hazard ratio (HR) of AD for the highest quartile of caloric intake was 1.5 (95% confidence interval [CI], 1.0-2.2; P = .06 for trend) (Table 2). Compared with the lowest quartile, the HR of AD was 1.4 (95% CI, 0.9-2.1) for the highest quartile of calorie-adjusted fat intake, and the trend was not significant (Table 3). The HR of AD for the highest quartile of intake of carbohydrates was 0.8 (95% CI, 0.5-
Our analyses of 242 cases of incident AD in 4023 person-years of observation with 4 years of follow-up (6 cases per 100 person-years) revealed that the risk of AD is associated with higher total calorie intake and fat intake in individuals homozygous or heterozygous for the APOE ε4 allele. In individuals without the APOE ε4 allele, calorie and fat intake were not associated with risk of AD.

Rodents under caloric restriction perform better in tests of cognitive performance compared with rats fed ad libitum. Moreover, caloric restriction is related to neuronal protection in rat models of AD. Rats with increased saturated fatty acid intake have impairment on tests of cognitive performance compared with rats with low intakes, presumably because of a deleterious effect of saturated fatty acids on the metabolism of amyloid β. The main effect of caloric restriction on aging may be a decrease in oxidative damage. Experimental evidence suggests that accumulation of amyloid β protein generates reactive oxygen species that are toxic to neurons. Oxidative stress has also been shown to promote the intracellular accumulation of amyloid β protein by enhancement of the amyloidogenic pathway. The relation between total calorie intake and intake of specific macronutrients and AD could be mediated through oxidative stress and its effect on amyloid β deposition. Diets higher in carbohydrates, particularly complex carbohydrates, fruits, and vegetables and lower in saturated fats exert a lower oxidative burden on the organism than high-calorie, high-fat diets. Calorie restriction may also decrease neuronal death and increase expression of neurotrophic factors in the brain. Reduced caloric intake can increase the brain’s capacity for plasticity and repair in neurodegenerative disorders, including AD.

Individuals with dementia increase their caloric intake and change their food choices, eating less protein and more sweets than controls without dementia. A 1-year follow-up study found a significantly higher energy intake in patients with AD compared with con-

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<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Calories</th>
<th>Carbohydrates</th>
<th>Fats</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lowest Quartiles</td>
<td>Highest Quartiles</td>
<td>Lowest Quartiles</td>
<td>Highest Quartiles</td>
</tr>
<tr>
<td>Age, mean, y</td>
<td>74.5</td>
<td>75.2</td>
<td>74.3</td>
<td>75.3</td>
</tr>
<tr>
<td>Women, %</td>
<td>72.5</td>
<td>61.9</td>
<td>73.9</td>
<td>60.5</td>
</tr>
<tr>
<td>Education, mean, y</td>
<td>9</td>
<td>10</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>White, %</td>
<td>23.5</td>
<td>25.9</td>
<td>23.0</td>
<td>26.3</td>
</tr>
<tr>
<td>Black, %</td>
<td>34.5</td>
<td>30.4</td>
<td>35.9</td>
<td>28.9</td>
</tr>
<tr>
<td>Hispanic, %</td>
<td>42.0</td>
<td>43.8</td>
<td>41.1</td>
<td>44.7</td>
</tr>
<tr>
<td>Presence of apolipoprotein ε4, %</td>
<td>28.5</td>
<td>28.3</td>
<td>26.7</td>
<td>30.0</td>
</tr>
</tbody>
</table>

*P < .001. †P < .05.

Table 2. Hazards Ratios of Alzheimer Disease for Individuals in Each Quartile of Total Daily Calorie Intake Using the Lowest Quartile as a Reference

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Calorie Intake, Mean, kcal</th>
<th>Hazard Ratio (95% CI) Adjusted for Age and Sex</th>
<th>Full Model†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>758</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>1078</td>
<td>1.02 (0.69-1.48)</td>
<td>1.21 (0.81-1.81)</td>
</tr>
<tr>
<td>3</td>
<td>1363</td>
<td>1.08 (0.75-1.56)</td>
<td>1.20 (0.81-1.78)</td>
</tr>
<tr>
<td>4</td>
<td>1870</td>
<td>1.38 (0.97-1.97)</td>
<td>1.48 (1.00-2.19)</td>
</tr>
</tbody>
</table>

P value for trend . . . .09 .06.

*CI indicates confidence interval.
†The full model is adjusted for age, sex, presence of the apolipoprotein ε4 allele, years of education, and ethnic group.
controls. Higher intake of complex carbohydrates, fruits, and vegetables and lower intake of saturated fat were associated with better cognition, as measured by the Mini-Mental State Examination.8 However, another study13 reported that macronutrient intake is of little importance in the worsening cognition related to aging. Kalmijn et al44 reported a higher risk of incident AD with higher intake of saturated fats and calories confined to APOE ε4 allele, and it is possible that the presence of the APOE ε4 allele modifies the effect of high calorie and fat intake on amyloid β metabolism, consistent with our observation of an increased risk of AD with higher intake of fats and calories confined to APOE ε4 carriers. It seems reasonable to assume that the deleterious effects of high calorie and fat intake (or the protective effects of low calorie and fat intake) would be more prominent in individuals most susceptible to developing AD. The mechanisms underlying this interaction need further investigation.

Individuals with the highest intake of calories and fats may have been in the preclinical stage of dementia at baseline. Increased energy intake has been reported in individuals with AD, making this explanation possible.36,37 However, all individuals with cognitive impairments and even mild impairment of function were excluded, making it unlikely. The mean time from beginning of observation to diagnosis of dementia was 3.4 ± 1.4 years (interquartile range, 2.1-4.9 years). In our cohort, a prodromal change in dietary habits would have had to precede the diagnosis of AD by 2 years in most cases to bias our findings.

It is also possible that known risk factors for dementia were associated with caloric and macronutrient intake in such a way that our results were explained by confounding. Lower education has been reported to be associated with higher caloric intake and a higher intake of saturated fats.35 However, we adjusted all our mod-

### Table 3. Hazard Ratios of Alzheimer Disease for Individuals in Each Quartile of Daily Macronutrient Intake Using the Lowest Quartile as a Reference*

<table>
<thead>
<tr>
<th>Carbohydrates</th>
<th>Fats</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Quartile</strong></td>
<td><strong>Intake, Mean, g</strong></td>
<td><strong>Adjusted for Age and Sex</strong></td>
</tr>
<tr>
<td>1</td>
<td>146.12</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>160.78</td>
<td>0.88 (0.61-1.26)</td>
</tr>
<tr>
<td>3</td>
<td>172.86</td>
<td>0.72 (0.94-1.94)</td>
</tr>
<tr>
<td>4</td>
<td>223.52</td>
<td>0.78 (0.54-1.13)</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval.
†The full model is adjusted for age, sex, presence of apolipoprotein E ε4 allele, years of education, and ethnic group.

### Table 4. Adjusted Hazard Ratios of Alzheimer Disease per Quartile of Daily Calorie Intake and per Quartile of Fat Intake by Apolipoprotein E (APOE) ε4 Status*

<table>
<thead>
<tr>
<th>Total Calories</th>
<th>Fats</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Quartile</strong></td>
<td><strong>Absence of APOE ε4 (n = 667)</strong></td>
</tr>
<tr>
<td>1</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>1.07 (0.65-1.75)</td>
</tr>
<tr>
<td>3</td>
<td>1.12 (0.69-1.83)</td>
</tr>
<tr>
<td>4</td>
<td>1.06 (0.64-1.73)</td>
</tr>
</tbody>
</table>

*Values in parentheses are 95% confidence intervals.©2002 American Medical Association. All rights reserved.
els by years of education and other known risk factors for dementia, and in most cases there was no appreciable change between HRs. The relationship between macronutrients and AD may not be specific and may reflect the association between caloric intake and AD. Intake of carbohydrates was inversely related to fat intake. Because increased fat intake would be expected to be associated with higher caloric intake, the association between fat intake and AD would parallel the association between caloric intake and AD. All measures of macronutrient intake were adjusted for calories and were uncorrelated with total calorie intake. Thus, our findings of relations between macronutrients and AD are intended to be independent of caloric intake, and, if causal, they would reflect the specific effects of each macronutrient. The relationship between macronutrient intake and disease is not well understood, and we must also consider the possibility of unmeasured confounders.

Our study has several strengths. The main purpose of the Washington Heights–Inwood Columbia Aging Project was the longitudinal study of dementia and determination of its risk factors, and all measurements were made prospectively with that intention. The determination of dementia was made in a standardized fashion according to widely accepted criteria. In addition, measures were available for other established risk factors for AD, including education and APOE ε4 status.

The main limitation of our study pertains to the measure of nutrient intake. The food frequency questionnaire is a measure of habitual intake during 1 year and does not account for day-to-day variation or for longer-term periods of intake. The measures obtained from the semiquantitative food frequency questionnaire may not have enough precision to make inferences about absolute levels of nutrient intake as related to the occurrence of disease. The results of this study should be interpreted in terms of the relation between ranks of intake of nutrients (higher or lower) and incident AD rather than in terms of the absolute values in the quartiles of intake we defined. Elderly men and women have been shown to consistently underreport caloric intake, and this may account for the apparently low caloric intakes that we report. However, to the extent that this measurement error is random (ie, not related to AD incidence or to covariates used to adjust the multivariate risk for AD), this would reduce statistical power and bias the magnitude of the observed effects toward the null. However, there may be other reasons for the reported low caloric intakes. Food intake decreases with age for reasons that are unclear. The responsiveness of energy expenditure to negative energy balance is attenuated in old age, suggesting that energy regulation is disregulated in old age, making such low intakes possible. Dietary intake has been reported to decrease 1000 to 1200 kcal in men and 600 to 800 kcal in women, which would make the reported intakes plausible.

Higher intake of total calories and fats in elderly individuals without dementia is associated with higher risk of AD in carriers of the APOE ε4 allele. There is no association between calorie and fat intake and AD in non-carriers of APOE ε4. Our findings indirectly support the theory that caloric restriction modifies aging-related conditions in humans and also suggest the possibility of modifying the risk of AD with caloric restriction and low-fat diets in susceptible individuals.

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Author contributions: Study concept and design (Drs Luchsinger, Shea, and Mayeux); acquisition of data (Drs Tang and Mayeux); analysis and interpretation of data (Drs Luchsinger, Tang, and Mayeux); drafting of the manuscript (Drs Luchsinger and Mayeux); critical revision of the manuscript for important intellectual content (Drs Luchsinger, Tang, Shea, and Mayeux); statistical expertise (Dr Tang); obtained funding (Drs Luchsinger and Mayeux); administrative, technical, and material support (Dr Mayeux); study supervision (Drs Shea and Mayeux).

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