ORIGINAL CONTRIBUTION

Dietary Fats and the Risk of Incident Alzheimer Disease

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Background: Few studies have investigated the effects of dietary fats on the development of Alzheimer disease. We examined the associations between intake of specific types of fat and incident Alzheimer disease in a biracial community study.

Methods: We performed clinical evaluations on a stratified random sample of 815 community residents aged 65 years and older who were unaffected by Alzheimer disease at baseline and who completed a food-frequency questionnaire a mean of 2.3 years before clinical evaluation.

Results: After a mean follow-up of 3.9 years, 131 persons developed Alzheimer disease. Intakes of saturated fat and *trans*-unsaturated fat were positively associated with risk of Alzheimer disease, whereas intakes of ω-6 polyunsaturated fat and monounsaturated fat were inversely associated. Persons in the upper fifth of saturated-fat intake had 2.2 times the risk of incident Alzheimer disease compared with persons in the lowest fifth in a multivariable model adjusted for age, sex, race, education, and apolipoprotein E ϵ4 allele status (95% confidence interval, 1.1-4.7). Risk also increased with consumption of *trans*-unsaturated fats, beginning with the second fifth of intake (relative risk, 2.4 compared with the lowest fifth; 95% confidence interval, 1.1-5.3). We observed linear inverse associations between Alzheimer disease and vegetable fat ($P=.002$), and, after further adjustment for other types of fat, marginally significant associations with intake of ω-6 polyunsaturated fat ($P=.10$ for trend) and monounsaturated fat ($P=.10$ for trend). Intakes of total fat, animal fat, and dietary cholesterol were not associated with Alzheimer disease.

Conclusion: High intake of unsaturated, unhydrogenated fats may be protective against Alzheimer disease, whereas intake of saturated or *trans*-unsaturated (hydrogenated) fats may increase risk.

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FEW STUDIES have investigated the effects of dietary fats on neurodegenerative diseases related to aging. Most animal studies have focused on dietary deficiencies in the essential fatty acids, linoleic acid ($C_{18:2\ \omega-6}$) and linolenic acid ($C_{18:3\ \omega-3}$), and cognition during prenatal and postnatal development.[1] A limited number of animal models were designed to test the association between dietary fat composition and cognitive performance in later adult years, and these studies found superior cognitive performance with diets that were higher in monounsaturated and polyunsaturated fats and lower in saturated fat.[2-4] Data from an epidemiologic study suggested that high intake of total fat, saturated fat, and dietary cholesterol may increase the risk of dementia.[5] In the present study, we examined the association of Alzheimer disease with different types of fat, including saturated fat, *trans*-unsaturated fat, ω-6 polyunsaturated fat, monounsaturated fat, and dietary cholesterol, in a biracial community study of older Chicago, Ill, residents.

METHODS

POPULATION

Participants are from the Chicago Health and Aging Project, a longitudinal community study of risk factors for the development of Alzheimer disease. From 1993 through 1997, we conducted a census in a geographically defined area on the south side of Chicago to identify persons aged 65 years and older (N=8501). Age-eligible residents were asked to participate in home interviews that included questions on health and lifestyle and the administration of cognitive tests, and 6158 (78.8%) of 7813 surviving residents complied. Clinical evaluations were performed on a stratified random sample of 729 participants (75.9% of the residents selected) for the diagnosis of prevalent Alzheimer disease. This phase of the study iden-

tified a cohort of 3838 persons free of Alzheimer disease, either by good cognitive performance at the baseline population interview (3369 persons) or direct clinical evaluation (469 persons). Approximately 3 years from the baseline interview, all participants were contacted for follow-up interviews, with 4320 participating (86.7% of the surviving residents). Subsequent to the follow-up interviews, a second stratified random sample of 1249 persons was selected from the disease-free cohort for clinical evaluation of incident disease. Sample participants were randomly selected within strata defined by age, sex, race, and decline in cognitive performance (stable or no decline, small decline, or large decline), and 842 persons participated (75.6% of the surviving residents). Dietary assessments occurred a mean of 2.3 years before the clinical evaluation (1.7 years after baseline). Analyses were restricted to 815 persons with complete data on disease diagnosis and dietary intake. The sample was 52% black and 61% female with a median education of 12 years. Participants ranged in age from 65 to 94 years. The Institutional Review Board of Rush-Presbyterian/St Luke's Medical Center, Chicago, approved the study, and all participants (or their legal guardian) gave written consent. More detailed descriptions of the population interviews[6] and clinical evaluations[7] were published previously.

CLINICAL EVALUATION FOR ALZHEIMER DISEASE

Clinical evaluations were conducted in participants' homes by a team consisting of a neurologist, a nurse practitioner, a neuropsychological technician, and a phlebotomist. The 2½-hour examinations included a structured neurologic examination, medical history, medication use, laboratory testing, informant interviews for cognitively impaired participants, and neuropsychological testing. Cognitive tests included those used by the Consortium Established for Research on Alzheimer's Disease[8] and others.[9-16] Diagnostic use of magnetic resonance imaging was restricted to persons with evidence of dementia and uncertainty as to whether a stroke had occurred or was related to the dementia. A board-certified neurologist, blinded to participants' dietary information, reexamined each patient and reviewed all clinical data. A diagnosis of probable Alzheimer disease was made based on criteria of the National Institute of Neurological Communicative Disorders and Stroke and the Alzheimer Disease and Associated Disorders Association[17] with the exception that we included all cases of Alzheimer disease whether or not another dementing disease was present (14 cases had a coexisting dementing disease). Persons with dementia but without Alzheimer disease (n=11) were analyzed as noncases. Genotyping for apolipoprotein E (*APOE*) was performed according to the methods of Hixson and Vernier[18] and the primers as described by Wenham et al.[19]

DIETARY ASSESSMENT

We assessed dietary intake using a revised Harvard self-administered food-frequency questionnaire (FFQ).[20,21] The FFQ was either mailed or hand-delivered to study participants along with a self-addressed envelope for its return, although a few participants requested to be interviewed. The 154-item questionnaire included more than 139 foods and the use of vitamin supplements. Completed FFQs were optically scanned and processed for nutrient intake at the Harvard University (Cambridge, Mass) Department of Nutrition, using their continually updated nutritional database derived from the US Department of Agriculture[22] and other sources.[23,24] The nutrient content of food items was modified based on questions about the fat content of dairy products consumed, removal of fat or poultry skin, and specified brand-name products for cereals, margarines, oils, and multivitamins. Nutrient intake was computed by multiplying the nutrient content of individual foods by the frequency of consumption and summing over all food items. The ω-6 polyunsaturated fats for which data are reported included linoleic acid ($C_{18:2\ \omega\text{-}6}$) and arachidonic acid ($C_{20:4\ \omega\text{-}6}$). The *trans*-unsaturated fats included all *trans* isomers of 18-C unsaturated fatty acids. For analysis, all dietary components were calorie-adjusted separately for men and women according to the regression-residual method.[25] We conducted a study of the reproducibility and validity of the FFQ in a random sample of the Chicago Health and Aging Project study population. Intraclass correlation coefficients for reproducibility of fat intake based on two FFQs completed approximately 12 months apart for 192 participants were 0.59 for total fat, 0.60 for saturated fat, 0.61 for monounsaturated fat, 0.54 for polyunsaturated fat, and 0.57 for dietary cholesterol.

Pearson correlations for calorie-adjusted fat intake measured by the FFQ and the mean of from one to six 24-hour dietary recall interviews among 232 participants were 0.45 for saturated fat, 0.39 for monounsaturated fat, 0.36 for polyunsaturated fat, and 0.41 for dietary cholesterol. All correlations were significant with P values $<.001$.

COVARIATES

Age was computed from self-reported birth date and date of determination of disease-free status (baseline clinical evaluation or population interview). Race was determined using questions and categories from the 1990 US Census. Information about other nondietary variables, except clinical stroke, was obtained at the baseline population interview. Information on medication use was obtained from interviewer inspection of all medications taken within the previous 2 weeks. The number of years of education was based on self-reported highest grade completed or years of formal education. History of hypertension was defined as antihypertensive medication use or participant report of high blood pressure. 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 standardized questionnaire.[26] History of stroke was defined as probable or possible stroke as diagnosed at the clinical evaluation by a neurologist on the basis of a uniform structured examination, medical history, and magnetic resonance imaging diagnostic testing.

STATISTICAL ANALYSIS

We used logistic regression models in SAS statistical software, version 8 (SAS Institute Inc, Cary, NC) to estimate the relative risks of incident Alzheimer disease for upper quintiles of fat intake compared with the lowest quintile. All models and reported statistics were estimated by using data weighted by the inverse of the stratified random-sampling probability. Variance estimations for the relative risks were based on jackknife repeated replication.[27,28] Multivariable models were adjusted for age (years), sex, race (black/white), education (years), *APOE* ε4 status (any ε4 allele vs none), the interaction between race and *APOE* ε4 status, and the period of observation. All dietary components that were considered to be potential confounders were modeled as log-transformed continuous variables instead of quintile categories. Effect modification was examined in multivariable models that were also adjusted for all dietary fats by adding a multiplicative term between the potential effect modifier and the dietary fat (modeled as a log-transformed continuous variable).

RESULTS

There were 131 cases of incident Alzheimer disease among 815 participants after a mean follow-up of 3.9 years. In-

Table 1. Pearson Correlations Between Intake of Specific Dietary Fats*

	Dietary Fat				
Dietary Fat	Saturated	ω-6 Polyunsaturated	*trans*-Unsaturated	Monounsaturated	ω-3 Polyunsaturated
Saturated	1.00				
ω-6 Polyunsaturated	0.37	1.00			
trans-Unsaturated	0.50	0.47	1.00		
Monounsaturated	0.82	0.70	0.70	1.00	
ω-3 Polyunsaturated	0.31	0.86	0.37	0.60	1.00

*Correlations are weighted for the stratified random sampling design. All correlations are significant at $P<.001$.

Table 2. Baseline Characteristics by Intake of Saturated Fat and ω-6 Polyunsaturated Fat Among 815 Participants Aged 65 Years and Older, Chicago Health and Aging Project, 1993-1997*

	Quintile of Intake				
Characteristic	1	2	3	4	5
Saturated Fat					
Median intake, g/d	13.0	16.1	18.5	21.0	26.0
Age, mean, y	72.1	73.0	73.5	73.3	73.5
Female sex, %	78.9	71.5	60.3	51.7	40.2
Black race, %	58.8	58.8	51.6	47.3	41.7
Education, mean, y	12.3	12.5	12.5	13.1	12.5
APOE ε4 allele, % at least 1	41.2	33.1	33.6	34.5	32.5
Total fat, median, g/d	41.1	51.6	57.7	62.3	70.5
Polyunsaturated-saturated fat ratio	0.8	0.7	0.7	0.6	0.5
Animal fat, median, g/d	17.9	24.2	27.9	31.9	40.8
Vegetable fat, median, g/d	23.2	27.4	29.9	30.3	29.7
Dietary cholesterol, median, mg/d	164	200	219	238	267
Vitamin E from foods, median, U/d	8.6	8.8	9.4	8.8	9.6
Total vitamin C, median, mg/d	405	279	180	221	216
Total beta carotene, median, U/d	4379	3696	3287	3247	3987
ω-6 Polyunsaturated Fat					
Median intake, g/d	7.4	9.6	11.0	12.4	15.1
Age, mean, y	72.8	73.2	73.0	73.2	73.1
Female sex, %	82.6	67.7	58.8	53.2	45.4
Black race, %	48.9	44.7	48.6	59.0	55.2
Education, mean, y	12.5	12.6	12.7	12.5	13.1
APOE ε4 allele, % at least 1	30.8	37.3	38.5	37.3	32.7
Total fat, median, g/d	43.8	51.5	57.2	62.2	66.0
Polyunsaturated-saturated ratio	0.5	0.61	0.6	0.6	0.8
Animal fat, median, g/d	24.2	27.0	29.4	31.1	29.0
Vegetable fat, median, g/d	19.6	24.4	27.8	31.0	37.1
Dietary cholesterol, median, mg/d	175	208	218	242	235
Vitamin E from foods, median, U/d	7.4	8.4	9.3	9.0	10.8
Total vitamin C, median, mg/d	402	298	247	194	193
Total beta carotene, median, U/d	4218	4225	3120	3063	4009

*All variables but age are age-standardized to the total sample using 5-year age groups (65-74 years, 75-79 years, 80-84 years, and ≥85 years). Means and percentages are weighted for the stratified sampling design.

take of the specific types of dietary fats were positively correlated, and the highest correlations occurred between the ω-6 and ω-3 polyunsaturated fats and between monounsaturated fat and each of saturated and *trans*-unsaturated fats (**Table 1**). Women and users of vitamin C supplements were more represented in the lowest quintiles of intake of both saturated fat and ω-6 polyunsaturated fat (**Table 2**). Blacks were somewhat more likely to be in the lowest fifth of saturated fat intake and in the highest fifth of ω-6 polyunsaturated fat intake, and persons with an *APOE* ε4 allele were somewhat more likely to be in the lowest fifth of saturated fat intake.

The age-adjusted risk of Alzheimer disease for persons in the top fifth of saturated fat intake was 70% higher than for persons in the lowest fifth, but the relative risk was not significant (**Table 3**). With adjustment for confounders in the multivariable model, this risk increased to 2.2 times that of persons in the lowest fifth and was statistically significant ($P=.03$; 95% confidence interval [CI], 1.1-4.7). Further adjustment for other types of dietary fat increased the relative risk to 3.6, although the estimate was less precise as indicated by the wide confidence interval (95% CI, 0.7-18.6). For persons with *trans*-unsaturated fat intake in the second through fifth

Table 3. Relative Risk (RR) for Incident Alzheimer Disease (AD) by Quintile of Intake of Specific Types of Dietary Fats Among 815 Persons After 3.9 Years of Follow-up, Chicago Health and Aging Project, 1993-2000

Variable	Quintiles of Intake					*P* Value Trend*
	1	2	3	4	5	
Saturated fat						
Median, g/d	13.0	16.1	18.5	20.7	25.1	. . .
AD, No. (%) of incident cases	24 (7.8)	25 (12.4)	30 (10.7)	22 (9.0)	30 (14.5)	. . .
RR (95% CI)						
Age-adjusted†	1.0 (Referent)	1.4 (0.6-3.5)	1.1 (0.5-2.4)	1.0 (0.4-2.5)	1.7 (0.8-3.3)	.29
Multivariable‡	1.0 (Referent)	1.8 (0.7-4.3)	1.1 (0.5-2.8)	1.4 (0.5-3.6)	2.2 (1.1-4.7)	.09
Multivariable adjusted for other fats‡	1.0 (Referent)	2.4 (0.8-7.2)	1.8 (0.5-6.6)	2.1 (0.5-10.1)	3.6 (0.7-18.6)	.21
trans-Unsaturated fat						
Median, g/d	1.8	2.3	3.0	3.7	4.8	. . .
AD, No. (%) of incident cases	22 (6.0)	29 (11.0)	28 (15.1)	25 (9.7)	27 (12.6)	. . .
RR (95% CI)						
Age-adjusted†	1.0 (Referent)	2.2 (1.0-4.7)	2.5 (1.0-6.1)	1.6 (0.7-3.4)	2.0 (0.8-4.9)	.41
Multivariable‡	1.0 (Referent)	2.4 (1.1-5.3)	2.9 (1.2-7.2)	1.8 (0.8-4.2)	2.5 (1.0-6.2)	.21
Multivariable adjusted for other fats‡	1.0 (Referent)	3.4 (1.3-8.8)	4.2 (1.4-12.2)	3.1 (0.9-10.5)	5.2 (1.5-18.5)	.09
ω-6 Polyunsaturated fat						
Median, g/d	7.4	9.6	11.0	12.3	14.5	. . .
AD, No. (%) of incident cases	31 (14.0)	25 (11.7)	32 (12.5)	24 (9.8)	19 (5.8)	. . .
RR (95% CI)						
Age-adjusted†	1.0 (Referent)	0.7 (0.4-1.5)	0.8 (0.3-1.9)	0.6 (0.2-1.4)	0.3 (0.1-0.9)	.03
Multivariable‡	1.0 (Referent)	0.8 (0.4-1.6)	0.9 (0.4-2.2)	0.6 (0.2-1.6)	0.3 (0.1-0.8)	.02
Multivariable adjusted for other fats‡	1.0 (Referent)	0.8 (0.3-2.0)	0.8 (0.2-3.1)	0.6 (0.1-2.4)	0.3 (0.1-1.5)	.10
Monounsaturated fat						
Median, g/d	15.2	18.7	21.7	23.9	27.7	. . .
AD, No. (%) of incident cases	31 (12.8)	31 (12.0)	22 (11.5)	22 (6.8)	25 (10.4)	. . .
RR (95% CI)						
Age-adjusted†	1.0 (Referent)	0.9 (0.4-2.1)	0.7 (0.3-1.9)	0.4 (0.2-1.0)	0.7 (0.3-1.6)	.21
Multivariable‡	1.0 (Referent)	1.0 (0.4-2.3)	0.8 (0.3-2.2)	0.5 (0.2-1.2)	0.8 (0.4-1.8)	.32
Multivariable adjusted for other fats	1.0 (Referent)	0.6 (0.2-1.7)	0.3 (0.1-1.4)	0.2 (0.03-1.0)	0.2 (0.02-1.5)	.10
Total fat						
Median, g/d	40.6	50.2	56.6	62.7	71.0	. . .
AD, No. (%) of incident cases	32 (12.3)	28 (11.9)	23 (11.4)	25 (8.1)	23 (10.0)	. . .
RR (95% CI)						
Age-adjusted†	1.0 (Referent)	0.9 (0.4-2.3)	0.7 (0.3-1.9)	0.5 (0.2-1.2)	0.7 (0.4-1.5)	.14
Multivariable‡	1.0 (Referent)	1.1 (0.4-2.7)	0.9 (0.3-2.3)	0.7 (0.3-1.6)	0.9 (0.4-1.8)	.41
Dietary cholesterol						
Median, g/d	124.5	176.5	203.1	242.7	317.5	. . .
AD, No. (%) of incident cases	25 (8.8)	29 (14.2)	30 (13.9)	24 (9.4)	23 (8.3)	. . .
RR (95% CI)						
Age-adjusted†	1.0 (Referent)	1.5 (0.6-3.9)	1.6 (0.7-4.0)	1.0 (0.6-1.9)	1.0 (0.4-2.9)	.65
Multivariable‡	1.0 (Referent)	1.5 (0.6-3.9)	1.5 (0.6-3.8)	1.0 (0.5-1.8)	0.9 (0.4-2.1)	.33
Multivariable adjusted for other fats‡	1.0 (Referent)	1.5 (0.5-4.1)	1.5 (0.6-3.9)	1.0 (0.5-2.1)	0.9 (0.4-2.4)	.39
Animal fat						
Median, g/d	17.7	23.3	27.7	31.4	39.0	. . .
AD, No. (%) of incident cases	25 (10.8)	24 (9.5)	31 (11.2)	24 (9.9)	27 (12.3)	. . .
RR (95% CI)						
Age-adjusted†	1.0 (Referent)	0.7 (0.3-1.6)	0.9 (0.4-2.0)	0.8 (0.3-1.8)	1.0 (0.5-2.1)	.80
Multivariable‡	1.0 (Referent)	0.7 (0.3-1.8)	0.8 (0.4-2.0)	0.8 (0.3-1.9)	1.1 (0.6-2.4)	.60
Multivariable adjusted for vegetable and *trans* fats	1.0 (Referent)	0.6 (0.2-1.7)	0.7 (0.3-1.7)	0.6 (0.2-1.7)	0.7 (0.3-1.6)	.53
Vegetable fat						
Median, g/d	18.6	24.0	28.0	32.1	38.6	. . .
AD, No. (%) of incident cases	28 (11.4)	36 (16.8)	21 (7.5)	28 (9.9)	18 (8.6)	. . .
RR (95% CI)						
Age-adjusted†	1.0 (Referent)	1.3 (0.5-3.0)	0.5 (0.2-1.3)	0.8 (0.3-1.9)	0.5 (0.2-1.6)	.10
Multivariable‡	1.0 (Referent)	1.4 (0.6-3.0)	0.5 (0.2-1.3)	1.0 (0.4-2.4)	0.7 (0.2-2.0)	.24
Multivariable adjusted for animal and *trans* fats	1.0 (Referent)	0.9 (0.4-2.0)	0.3 (0.1-0.8)	0.4 (0.2-1.3)	0.2 (0.1-0.7)	.002

Abbreviation: CI, confidence interval.

**P* value for linear trend is based on logistic regression models with the nutrient variable modeled as a continuous variable with persons in each quintile assigned the median value for that quintile. Ellipses indicate not applicable.

†Age-adjusted models include terms for age (years), time period of observation (years), and indicator variables for quintiles of nutrient intake.

‡Multivariable RRs are based on logistic regression models with terms from the age-adjusted model plus sex, race (black/white), education (years), *APOE* genotype (any ϵ4 allele vs none), and the interaction between race and *APOE* ϵ4. Multivariable models with additional adjustment for dietary fats also include log-transformed continuous variables for saturated fat, *trans*-unsaturated fat, ω-6 polyunsaturated fat, ω-3 polyunsaturated fat, and monounsaturated fat.

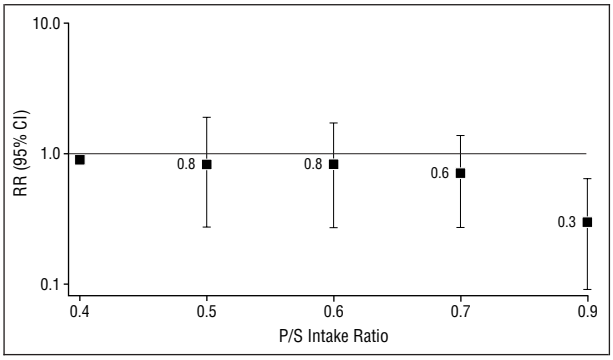

Figure 1. Relative risks (RRs) (95% confidence intervals [CIs]) for Alzheimer disease by quintile of polyunsaturated fat (P)–saturated fat (S) intake ratio based on a multivariable logistic model adjusted for time on study, age (years), sex, race, education (years), *APOE ϵ4*, and the interaction between race and *APOE ϵ4*.

quintiles, the age-adjusted risk of Alzheimer disease was approximately 2 times higher than for persons in the first quintile and was statistically significant in the second and third quintiles only. The relative risks were slightly increased in the multivariable model, but with additional adjustment for other types of fat they increased substantially, ranging from 3.1 to 5.2; all relative risks but that for the fourth quintile of intake were statistically significant.

Dietary intake of ω-6 polyunsaturated fats was significantly and inversely associated with Alzheimer disease (Table 3). The relative risks did not differ appreciably in age-adjusted and multivariable-adjusted models. In both models, persons in the top fifth of intake had a statistically significant 70% reduction in risk compared with persons in the lowest fifth of intake. When we adjusted for other types of fat, the relative risk estimate did not change but was no longer statistically significant. The relative risks for upper quintiles of monounsaturated fat intake were inverse compared with those of the lowest quintile of intake but were not statistically significant in either the age- or multivariable-adjusted models. When intakes of other types of fats were also considered, the relative risks for monounsaturated fat intake became more strongly protective, such that persons in the fourth and fifth quintiles of intake had an 80% lower risk of disease than did persons in the lowest quintile (although only the fourth quintile was statistically significant). The total amount of fat in the diet was not associated with incident Alzheimer disease, nor was intake of dietary cholesterol (Table 3).

Intake of animal fat had no association with Alzheimer disease whether we adjusted for important confounders or for intake of vegetable and *trans*-unsaturated fats. In contrast, intake of vegetable fat was strongly protective against Alzheimer disease after adjustment for animal and *trans*-unsaturated fats in the multivariable model ($P=.002$ for trend). In this model, persons in the highest fifth of intake had a statistically significant 80% reduction in risk relative to those in the lowest fifth of intake (95% CI, 0.1-0.7). The ratio of polyunsaturated fat intake to saturated fat intake was also inversely associated with the development of Alzheimer disease. There was a statistically significant 70% reduction in risk of Alzheimer disease among persons in the highest fifth (median ratio, 0.9) vs the lowest fifth (median ratio, 0.4) of intake in the multivariable model (**Figure 1**).

Because of the strong confounding by related fats, we conducted all further analyses using multivariable models that also adjusted for fat intake (saturated, *trans*, monounsaturated, ω-6 polyunsaturated, and ω-3 polyunsaturated). First, we examined whether control for intake of antioxidant nutrients (vitamin E from food, total vitamin C, and beta carotene) could account for the observed results, but the relative risks were not appreciably different. The relative risks for quintiles 2 to 5 of *trans*-unsaturated fat intake (the fat with the most substantial change in relative risks) were 3.5 (95% CI, 1.4-9.0), 4.4 (95% CI, 1.5-12.6), 3.2 (95% CI, 1.0-10.6), and 5.8 (95% CI, 1.7-20.5). Next, we repeated the analysis with adjustment for cardiovascular-related conditions (stroke, heart disease, hypertension, and diabetes mellitus). Again, *trans*-unsaturated fat was the only fat for which there were any material differences in the relative risks (for quintiles 2 to 5 the relative risks were 3.5 [95% CI, 1.3-9.1], 3.7 [95% CI, 1.2-11.3], 2.6 [95% CI, 0.7-9.6], and 4.7 [95% CI, 1.3-17.1]). Analyses that controlled for current smoking and alcohol consumption had little effect on the relative risk estimates, as did control for statin drugs.

The associations between dietary fats and Alzheimer disease did not differ significantly by presence or absence of the *APOE ϵ4* allele or by educational level. Significant interactions were observed between race and saturated fat intake and between sex and ω-6 polyunsaturated fat intake (*P* values for the interactions were .05 and .03, respectively) in multivariable models that also adjusted for intake of other types of fat. In these models, the positive association between Alzheimer disease and intake of saturated fat was restricted to black participants, and the protective association with high intake of ω-6 polyunsaturated fat was restricted to women. Examination of the data for interactive effects among the different types of fat in the multivariable model revealed a statistically significant interaction between intakes of *trans*-unsaturated and total (ω-6 and ω-3) polyunsaturated fats. The deleterious effect of increased *trans*-unsaturated fat intake on the risk of developing Alzheimer disease was substantially greater among persons with low polyunsaturated fat intake, whereas the effects were minimized among persons with high polyunsaturated fat intake ($P=.04$ for interactive term) (**Figure 2**).

The results did not change when we controlled for the timing of dietary assessments in the multivariable model adjusted for intake of other fats or when we repeated the analyses after deleting persons who had poor memory performance at baseline (n=50).

COMMENT

We found increased risk of incident Alzheimer disease among persons with high intakes of saturated and *trans*-unsaturated fats and marginally significant decreased risk with high intakes of ω-6 polyunsaturated and monounsaturated fats. Consumption of vegetable fat and a high ratio of polyunsaturated to saturated fats were also pro-

tective, whereas total fat, animal fat, and dietary cholesterol had no association with Alzheimer disease.

The observed associations were strong in magnitude for the different types of fat and not likely due to confounding by other factors. The associations remained after adjustment for a number of potential confounders, including dietary intake of antioxidant nutrients, other dietary fats, and cardiovascular-related conditions. The study used structured clinical evaluations for the identification of Alzheimer disease cases in a random sample from the community, thus minimizing biases that can occur when case identification relies on a clinic population or medical records. This is especially problematic for the study of Alzheimer disease, in which only a small and highly select group from the general population is likely to come to the attention of the medical care system. Disease diagnosis was made by the examining neurologist using standardized criteria and blinded to participant responses to the FFQ. A limitation of the study is that the dietary assessments were not obtained at baseline for a number of participants, and this could have affected the study results if persons experiencing cognitive decline altered their diets or had inaccurate reporting. However, the overall results remained even after adjustment for the timing of participants' dietary assessments or the deletion of data from persons with low cognitive scores at baseline. Inadequate measurement of fat intake is not a likely explanation for the findings because this would tend to result in random error, and thus null results, rather than the observed pattern of associations with different types of fat.

The study from Rotterdam, the Netherlands,[5] is the only other epidemiologic study to report on the association between dietary fats and Alzheimer disease. In that study, high intake of total fat was significantly associated with increased risk of incident dementia, whereas high intakes of saturated fat and dietary cholesterol were marginally associated with increased risk and linoleic acid, a type of ω-6 polyunsaturated fat, was inversely but not significantly associated with Alzheimer disease. Kalmijn et al[5] also reported stronger associations for intakes of total and saturated fats among demented persons with cerebrovascular disease than for Alzheimer disease alone, although the number of cases was too small for meaningful interpretation.

An underlying biological mechanism for the observed associations between dietary fat composition and Alzheimer disease is currently unknown. Substitution of caloric energy from saturated fat with polyunsaturated and monounsaturated fats has been shown to lower low-density lipoprotein cholesterol levels and increase high-density lipoprotein cholesterol levels.[3] *Trans*-unsaturated fats decrease cholesterol levels of high-density lipoprotein and increase levels of low-density lipoprotein.[29] We did not observe an association between dietary cholesterol intake and risk of Alzheimer disease; however, metabolic studies have shown that dietary cholesterol has substantially less effect on serum cholesterol levels than does saturated fat intake.[30] Two epidemiologic studies found a decreased risk of Alzheimer disease among patients taking cholesterol-lowering drugs (statins).[31,32] Other studies have found that high-fat/high-cholesterol diets increased[33] and cholesterol-lowering drugs decreased[34-36] amyloid-β peptide deposition and Alzheimer disease–related abnormalities. Another mechanism may be the activation of protein kinase C and phosphorylation of protein F_1 by highly unsaturated fatty acids, resulting in greater synaptic plasticity for the storage of memory.[2] Rodents fed a highly unsaturated diet of polyunsaturated and monounsaturated fats had superior learning and memory as well as greater activation of protein kinase C than did rodents fed a diet high in saturated fat.[2]

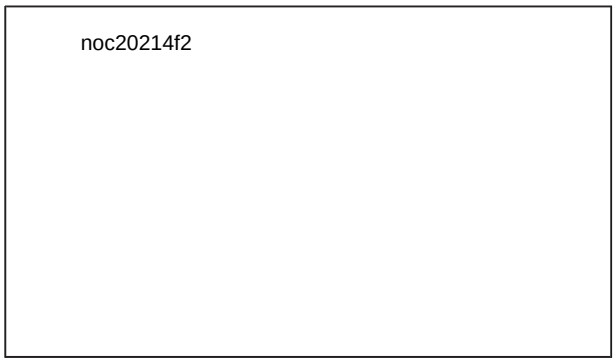

Figure 2. The 1-year risk of incident Alzheimer disease by quintile median levels of *trans*-unsaturated fat and polyunsaturated fat. Data are based on a multivariable logistic model adjusted for age (years), sex, race, education (years), *APOE* ϵ4, time period of observation, *trans*-unsaturated fat (continuous log transformed), polyunsaturated fat (continuous log transformed), and the interactive term for *trans* and polyunsaturated fats (P=.04).

We observed a strong increased risk of Alzheimer disease with consumption of *trans*-unsaturated fat. *Trans*-unsaturated fats occur as a result of partial hydrogenation of vegetable oils to create commercially baked products and hardened margarine. Our finding of an interactive effect between intakes of *trans*-unsaturated and polyunsaturated fats on the risk of Alzheimer disease has also been observed for heart disease.[37] The observed association between Alzheimer disease and intake of saturated fat appeared to be restricted to black participants; however, we had limited data for accurate estimation of risks within subgroups.

These data, along with those of the Rotterdam study[5] and animal models,[2-4] provide promising evidence that diets high in unsaturated, unhydrogenated fats and low in saturated and *trans*-unsaturated fats may protect against dementing disease. Interestingly, a similar pattern of associations has been observed between these dietary fats and coronary heart disease.[37,38] Whether dietary fat composition is related to the development of Alzheimer disease can only be answered definitively through consistent findings from large prospective epidemiologic studies and primary prevention trials.

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son); *statistical expertise* (Drs Morris, Bienias, and Tangney); *obtained funding* (Dr Morris); *administrative, technical, and material support* (Drs Morris, Evans, Bennett, Schneider, and Wilson); *study supervision* (Drs Morris, Evans, and Aggarwal).

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Correction

Error in Figure Key. In the original contribution titled "Dietary Fats and the Risk of Incident Alzheimer Disease," published in the February 2003 issue of the ARCHIVES (2003;60:194-200), the key to **Figure 2** was reversed during processing for production. Figure 2 is reprinted correctly here.

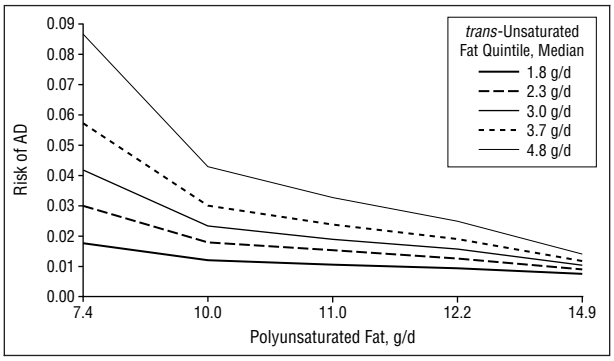

Figure 2. The 1-year risk of incident Alzheimer disease (AD) by quintile median levels of *trans*-unsaturated fat and polyunsaturated fat. Data are based on a multivariable logistic model adjusted for age (years), sex, race, education (years), *APOE* ϵ4, time period of observation, *trans*-unsaturated fat (continuous log transformed), polyunsaturated fat (continuous log transformed), and the interactive term for *trans* and polyunsaturated fats (P=.04).