

Dietary Intake of Antioxidant Nutrients and the Risk of Incident Alzheimer Disease in a Biracial Community Study

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A GROWING BODY OF EVIDENCE suggests that oxidative processes may be involved in the etiology of Alzheimer disease (AD).¹ Accumulated damage to lipid membranes and DNA by oxygen free radicals and reactive oxygen species is thought to disrupt normal cell functioning and lead to neuronal death.² Antioxidant nutrients, including vitamin E, vitamin C, and beta carotene, are among the body's natural defense mechanisms against oxidative stress. The antioxidant nutrients have been shown through animal and laboratory studies of brain tissue to decrease lipid peroxidation³⁻¹¹ and the oxidation of proteins,^{12,13} inhibit the production of reactive oxygen species,^{6,14,15} prevent mitochondrial dysfunction^{12,16} and DNA fragmentation,^{6,17} and reduce neurotoxicity,^{18,19} apoptosis,^{15,19-21} and neuronal death.^{18,22} Few studies have examined the relation between dietary intake of antioxidant nutrients and the development of AD. Two prospective

See also pp 3223 and 3261.

Context Oxidative processes have been suggested as elements in the development of Alzheimer disease (AD), but whether dietary intake of vitamin E and other antioxidant nutrients prevents its development is unknown.

Objective To examine whether intake of antioxidant nutrients, vitamin E, vitamin C, and beta carotene is associated with incident AD.

Design, Setting, and Participants Prospective study, conducted from 1993 to 2000, of individuals selected in a stratified random sample of community-dwelling residents. The 815 residents 65 years and older were free of AD at baseline and were followed up for a mean of 3.9 years. They completed food frequency questionnaires an average of 1.7 years after baseline.

Main Outcome Measure Incident AD diagnosed in clinical evaluations with standardized criteria.

Results Increasing vitamin E intake from foods was associated with decreased risk of developing AD after adjustment for age, education, sex, race, *APOE* ϵ 4, and length of follow-up. Relative risks (95% confidence intervals [CIs]) from lowest to highest quintiles of intake were 1.00, 0.71 (0.24-2.07), 0.62 (0.26-1.45), 0.71 (0.27-1.88), and 0.30 (0.10-0.92) (*P* for trend = .05). The protective association of vitamin E was observed only among persons who were *APOE* ϵ 4 negative. Adjustment for other dietary factors reduced the protective association. After adjustment for baseline memory score, the risk was 0.36 (95% CI, 0.11-1.17). Intake of vitamin C, beta carotene, and vitamin E from supplements was not significantly associated with risk of AD.

Conclusion This study suggests that vitamin E from food, but not other antioxidants, may be associated with a reduced risk of AD. Unexpectedly, this association was observed only among individuals without the *APOE* ϵ 4 allele.

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studies^{23,24} that reported on the association of vitamin E and vitamin C supplement use and AD yielded conflicting results, but both had limited power to test the hypothesis, and neither had dietary information. We re-

port on the association between incident AD and intake of antioxidant nutrients from foods and supplements in a large community study, the Chicago Health and Aging Project (CHAP).

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METHODS

Population

CHAP participants are from a geographically defined population of 3 contiguous neighborhoods on the south side of Chicago. A complete census of the community from 1993 to 1997 identified 8501 persons aged 65 years and older, of whom 249 moved and 439 died before participation could be obtained. Of the remaining 7813 persons, 6158 (78.8%) participated in 90-minute interviews that included questions about health and lifestyle and the administration of 4 cognitive tests.²⁵⁻²⁸ Following the interview, 1056 were selected in a stratified random sample, and 729 underwent a full clinical evaluation for prevalent AD. This phase of the study identified a disease-free cohort of 3838 persons by either direct clinical evaluation (n=469) or good performance on the cognitive tests²⁵⁻²⁷ at the baseline population interview (n=3369).

An average 3.2 years after baseline, 4983 of the entire cohort had survived, and follow-up interviews were conducted with 4320 study participants, or 86.7%. A second stratified random sample was then selected from the disease-free cohort for clinical evaluation of incident AD. Participants were randomly sampled with different probabilities of selection (range, 0.05-1.00) from within 94 strata defined by age, sex, race, and change in performance on the cognitive tests from baseline to follow-up interviews (no decline, moderate decline, and substantial decline). The sample design allowed for efficient identification of AD cases and a representative sample of the disease-free cohort (TABLE 1). Of 1249 persons selected, 109 died before the clinical evaluation could be secured, and 298 refused; 842 were clinically evaluated for incident AD (73.9% of survivors). Of these, 815 sample participants had complete data for these analyses. The institutional review board of Rush-Presbyterian-St Luke's Medical Center approved the study, and all participants (or legal guardians) gave written consent. More detailed descriptions of

the population interviews²⁹ and clinical evaluations³⁰ have been published.

Dietary Assessments

Study participants completed a self-administered food frequency questionnaire a mean of 1.7 years from the baseline, or a mean of 2.3 years (SD, 2.0; range, 0-5.7 years) before the clinical evaluations for incident disease. The CHAP food frequency questionnaire, a modified version of the Harvard food frequency questionnaire,^{31,32} was used to measure usual intake of 139 food items throughout the previous year, as well as the use of vitamin supplements. Nutrient intakes were computed by multiplying the nutrient contents of food items by frequency of consumption and summing across all items. Nutrient levels were adjusted for total energy intake separately for men and women by using the regression residual method.³³ In a validation study of 232 randomly selected CHAP participants, correlations between total intake of the antioxidant nutrients as assessed by the food frequency questionnaire and repeated 24-hour dietary recalls collected throughout 1 year

were 0.67 for vitamin E (0.41 excluding supplements) and 0.60 for vitamin C (0.46 excluding supplements). In linear regression models adjusted for age, sex, race, total energy intake, and total plasma cholesterol and triglyceride levels for 56 of these participants, the partial correlation between plasma beta carotene and intake was 0.43; that between plasma α -tocopherol and total vitamin E intake, 0.63.

Clinical Evaluation for Diagnosis of AD

The 2½-hour clinical evaluations were conducted in participants' homes by a team consisting of a neurologist, nurse practitioner, and neuropsychological technician. The evaluations included a medical history, a structured neurological examination, neuropsychological testing (using the tests of Consortium Established for Research on Alzheimer's Disease, CERAD³⁴), informant interviews, and laboratory testing. Magnetic resonance imaging (MRI) was performed when dementia was evident and stroke occurrence was clinically uncertain (9 persons). A board-certified neurologist blinded to the dietary as-

Table 1. Baseline Characteristics of the Analyzed Sample and the Referent Disease-Free Population

Characteristic	Analyzed Sample	Disease-Free Cohort*	
		All	Surviving Participants
No.	815	3838	2948
Age, mean (SD), y	73.3 (9.7)	73.6 (6.1)	73.1 (5.8)
Female, %	62.0	59.6	61.0
Black, %	51.4	51.3	52.2
Education, mean (SD), y	12.6 (6.2)	12.9 (3.4)	12.9 (3.4)
Vitamin E†			
Median intake from food sources, IU/d	8.5	8.6	8.6
No. (%) taking supplements	138 (17.3)	624 (18.5)	546 (18.5)
Vitamin C†			
Median intake from food sources, IU/d	124.7	121.5	122.4
No. (%) taking supplements	141 (16.1)‡	634 (18.8)	547 (18.6)
Beta carotene			
Median intake from food sources, IU/d	2680	2759	2279
No. (%) taking supplements	30 (4.3)‡	128 (3.8)	114 (3.9)

*Data on the disease-free cohort are provided for all persons identified as free of Alzheimer disease at the baseline phase of the study (n = 3838) and for the subset of persons in this group (n = 2948) who were alive at follow-up and participated in the follow-up interview (the sampling frame). Of the 890 persons who were not included in the sampling frame, 407 died, 91 moved, and 392 did not participate.

†Dietary information was available for 3382 of the 3838 persons identified as disease free at baseline and for 2887 of the 2948 persons eligible for sampling for clinical evaluation.

‡Represents the crude number (unweighted) for the stratified sampling design; all percentages and means are weighted.

assessment data reviewed all clinical evaluation data before making clinical diagnoses of neurological diseases. Diagnoses of AD were made according to criteria of the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Dementia Association (NINCDS-ADRDA),³⁵ except that we did not exclude as cases persons who met the criteria but had another coexisting condition that was thought to contribute to dementia. Eleven persons with incident dementia caused by a condition other than AD were analyzed as non-cases.

Covariates

Sex and race were reported as part of the census and verified at the population interview. Race questions and categories were those used by the 1990 US census. Age was computed from self-reported birth date and date of the population interview. All nondietary variables except clinical stroke were obtained at the baseline population interview that included interviewer inspection of all medications taken within the previous 2 weeks. Level of education was computed from self-reported highest grade or years of formal education. Current smoking was based on the question, "Do you smoke cigarettes now?" History of diabetes was defined as use of antidiabetic medication or participant report of clinically diagnosed diabetes, sugar in the urine, or high blood glucose level. 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 according to participant responses to a standardized questionnaire.³⁶ 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, a medical history, and MRI diagnostic testing. Apolipoprotein E (APOE) genotype was determined from blood samples according to a process developed by Hixson and Vernier.³⁷

Table 2. Age-Adjusted Baseline Characteristics by Quintile of Intake of Vitamin E, Vitamin C, and Beta Carotene Among 815 Persons Free of Alzheimer Disease (Chicago Health and Aging Project, 1993-1997)

	Quintile of Vitamin Intake				
	1	2	3	4	5
Vitamin E					
From food and supplements					
Free of Alzheimer disease, No.	163	162	164	163	163
Range, IU/d	<7.9	7.9-9.7	9.7-17.4	17.4-50.6	51.0-1660
Age, mean, y	73.6	73.0	73.0	73.2	72.4
Female, No. (%)*	103 (67.8)	88 (49.9)	90 (56.2)	107 (68.7)	99 (65.0)
Black, No. (%)*	77 (62.1)	80 (53.8)	95 (58.7)	56 (44.3)	55 (36.3)
Education, mean, y	11.6	12.0	12.2	14.0	13.5
APOE ε4, No. (%)*	540 (40.8)	47 (34.7)	54 (32.9)	52 (34.2)	43 (30.1)
Current smokers, No. (%)*	24 (17.5)	23 (19.1)	18 (11.9)	13 (0.9)	18 (15.6)
Mean dietary intake†					
Total fat, g/d	52.6	58.1	60.0	57.0	53.3
Vitamin C, mg/d	161	142	155	258	621
Beta carotene, IU/d	2420	3267	3374	4221	5509
From foods only					
Free of Alzheimer disease, No.	162	163	165	161	164
Range, IU/d	<7.0	7.0-8.1	8.1-9.1	9.1-10.4	10.4-43.0
Age, mean, y	72.8	73.5	72.3	73.6	73.2
Female, No. (%)*	118 (75.0)	95 (60.7)	100 (61.4)	92 (56.1)	82 (48.8)
Black, No. (%)*	61 (47.4)	65 (45.1)	80 (59.4)	67 (45.6)	90 (56.0)
Education, mean, y	12.6	13.0	12.4	12.3	13.0
APOE ε4, No. (%)*	56 (36.8)	46 (32.2)	57 (42.8)	39 (25.3)	52 (32.7)
Current smokers, No. (%)*	22 (18.5)	15 (10.9)	28 (24.3)	16 (11.2)	15 (5.5)
Mean dietary intake†					
Total fat, g/d	48.9	55.5	58.2	57.9	61.6
Vitamin C, mg/d	317	260	264	276	213
Beta carotene, IU/d	3368	3142	3437	4379	4564
Vitamin C					
From food and supplements					
Free of Alzheimer disease, No.	163	163	163	163	163
Range, mg/d	<93	93-134	135-185	185-308	310-2530
Age, mean, y	73.5	73.0	73.5	72.3	73.2
Female, No. (%)*	98 (57.4)	80 (51.1)	104 (59.9)	101 (67.0)	104 (73.6)
Black, No. (%)*	90 (63.8)	72 (50.9)	66 (47.2)	76 (53.2)	59 (40.6)
Education, mean, y	11.5	12.8	12.9	12.9	13.0
APOE ε4, No. (%)*	55 (40.1)	50 (36.0)	47 (32.7)	54 (31.8)	44 (34.0)
Current smokers, No. (%)*	23 (16.4)	21 (15.6)	15 (15.5)	19 (12.5)	18 (16.7)
Mean dietary intake†					
Total fat, g/d	60.6	60.4	57.9	52.9	48.8
Vitamin E, IU/d	24	55	50	48	287
Beta carotene, IU/d	2499	3328	3940	4102	4878
From foods only					
Free of Alzheimer disease, No.	163	163	163	163	163
Range, mg/d	<72	72-106	106-135	136-173	173-417
Age, mean, y	73.6	72.8	73.1	73.0	72.9
Female, No. (%)*	100 (55.3)	100 (63.0)	84 (56.4)	102 (65.0)	101 (68.6)
Black, No. (%)*	78 (55.6)	80 (53.6)	84 (41.3)	102 (48.3)	101 (56.4)
Education, mean, y	11.9	13.0	13.1	12.9	12.3
APOE ε4, No. (%)*	49 (34.1)	49 (35.1)	55 (37.0)	47 (35.5)	50 (31.4)
Current smokers, No. (%)*	22 (17.0)	20 (12.2)	17 (15.1)	14 (3.3)	23 (18.6)

(continued)

Table 2. Age-Adjusted Baseline Characteristics by Quintile of Intake of Vitamin E, Vitamin C, and Beta Carotene Among 815 Persons Free of Alzheimer Disease (Chicago Health and Aging Project, 1993-1997) (cont)

	Quintile of Vitamin Intake				
	1	2	3	4	5
Vitamin C (cont)					
From foods only (cont)					
Mean dietary intake†					
Total fat, g/d	59.6	59.0	57.2	55.6	48.7
Vitamin E, IU/d	92.8	87.8	127.4	101.6	65.0
Beta carotene, IU/d	3479	3784	3875	3640	3935
Beta Carotene					
From food and supplements					
Free of Alzheimer disease, No.	163	163	163	163	163
Range, IU/d	<1903	1906-2678	2679-3611	3615-5113	5127-28788
Age, mean, y	73.0	73.3	72.5	72.5	74.0
Female, No. (%) [*]	87 (57.3)	88 (52.0)	112 (70.8)	89 (55.9)	111 (71.6)
Black, No. (%) [*]	93 (64.2)	73 (55.0)	83 (51.4)	57 (40.5)	57 (40.8)
Education, mean, y	11.6	12.1	12.7	13.7	13.0
APOE ε4, No. (%) [*]	65 (48.1)	51 (36.3)	37 (21.1)	50 (33.4)	47 (34.8)
Current smokers, No. (%) [*]	28 (17.5)	20 (16.6)	24 (15.4)	10 (10.2)	14 (15.7)
Mean dietary intake†					
Total fat, g/d	57.6	59.5	56.6	54.2	53.0
Vitamin C, mg/d	191	220	243	311	400
Vitamin E, IU/d	60.8	86.4	61.2	86.2	173.1
From foods only					
Free of Alzheimer disease, No.	163	163	163	163	163
Range, IU/d	<1788	1796-2438	2438-3162	3162-4310	4311-18521
Age, mean, y	72.7	73.4	73.0	72.7	73.6
Female, No. (%) [*]	85 (59.3)	102 (57.7)	97 (59.6)	106 (70.4)	97 (63.1)
Black, No. (%) [*]	85 (58.9)	71 (51.7)	74 (51.3)	70 (45.4)	63 (45.2)
Education, mean, y	12.1	12.3	12.6	13.3	12.9
APOE ε4, No. (%) [*]	66 (50.9)	49 (29.5)	32 (20.4)	54 (36.6)	49 (31.6)
Current smokers, No. (%) [*]	26 (17.6)	19 (18.0)	19 (13.2)	21 (14.9)	11 (12.0)
Mean dietary intake†					
Total fat, g/d	58.0	58.8	57.8	53.1	52.8
Vitamin E, IU/d	79.3	112.7	65.9	100.1	110.5
Vitamin C, mg/d	214	261	255	283	357

*No. indicates the crude number (unweighted) for the stratified sampling design; all percentages and means are weighted.
†Mean intake of vitamin E, vitamin C, and beta carotene is based on intake from food and supplements.

Statistical Analysis

We examined whether intake of the antioxidant nutrients was associated with incident AD in SAS logistic regression models (version 8; SAS Institute Inc, Cary, NC) that generated odds ratios as estimates of relative risks (RRs). Estimation of all model parameters and other statistics (eg, means and percentages) were based on data weighted by the inverse of the sampling probability to adjust for the stratified random sample design. Variance estimates for model parameters from this complex design were computed by jackknife re-

peated replication.^{38,39} Intakes of antioxidant nutrients were modeled in quintiles. We first analyzed the associations in models adjusted for age and then for other important risk factors in a multivariable model that included terms for age (years), sex, race, education (years), APOE ε4 status (at least 1 allele vs none), and period of observation (number of years from determination of disease-free status to clinical evaluation for incident disease). We examined other potential confounders in separate multivariable models that simultaneously controlled for intake of

other antioxidant nutrients (total intake of vitamin E, vitamin C, beta carotene, and vitamin A), for different types of fat (polyunsaturated, saturated, and monounsaturated), or for conditions related to cardiovascular disease (smoking, diabetes, hypertension, heart disease, and clinical stroke). Dietary covariates were modeled as continuous log-transformed variables. Examination of confounding with the dietary components modeled in quintiles produced similar results in age-adjusted models. Effect modification by age (<80 years vs ≥80 years), race, sex, education (<12 years vs ≥12 years), and APOE ε4 status (at least 1 allele vs none) was examined in separate age-adjusted models that included terms for quintiles of nutrient intake, the potential effect modifier, and interaction terms between these variables. Effect modification among the antioxidant nutrients was explored in multivariable models, with total intake of the antioxidant nutrients modeled as continuous variables.

RESULTS

A total of 131 persons developed incident AD after a mean follow-up of 3.9 years (SD, 1.7; range, 0.4-6.9), for an overall incidence rate of 2.8% annually after adjustment for the stratified sampling design. Vitamin E supplements were consumed by 17.3% (n=138) of the sample; vitamin C supplements, by 16.1% (n=141); and beta carotene supplements, by 4.3% (n=30) (Table 1). For each of the antioxidant nutrients, persons in the upper quintiles of total intake (foods plus supplements) were more likely to be white, had more years of education on average, and had higher intake of other antioxidant nutrients than persons in the lowest quintiles (TABLE 2). Persons with high food intake of vitamin E tended to be men and to have a higher intake of fat and beta carotene and lower intake of vitamin C, whereas persons with high food intake of vitamin C tended to be women and to have a lower intake of vitamin E and total fat. Persons in the lowest quintile of beta caro-

tene intake were more likely than those in the upper quintiles to be black and have an APOE ε4 allele.

For total vitamin E intake, the age-adjusted RRs for incident AD were inverse for upper quintiles compared with the first quintile, but none was statistically significant, and there was no trend (P=.62) (TABLE 3). Further adjustment for race, sex, APOE ε4 sta-

tus, and education reduced any apparent protective association. Vitamin E intake from foods had a statistically significant dose-response protective effect in the age-adjusted model (P for trend=.04). The risk for persons in the top fifth of intake was lower by 67% compared with that of persons in the lowest fifth of intake. After adjustment for other confounders in the mul-

tivariable model, the RR for the highest quintile was virtually unchanged at 0.30 (95% confidence interval [CI], 0.10-0.92; P=.04), and the test for linear trend across quintiles remained significant (P=.05). After adjustment for use of multivitamins and vitamin E supplements in the multivariable model, the RRs (95% CIs) for the second through fifth quintiles of intake

Table 3. Relative Risks of Incident Alzheimer Disease by Quintile of Intake of Vitamin E, Vitamin C, and Beta Carotene Among 815 Persons 65 Years and Older and a Median Follow-up of 3.9 Years (Chicago Health and Aging Project, 1993-2000)

	Quintile of Intake					P for Trend*
	1	2	3	4	5	
Vitamin E						
Intake from foods and supplements						
Incident Alzheimer disease, %†	15.1	10.6	8.3	10.5	8.8	
Median intake, IU/d	6.8	8.7	11.1	32.4	363.6	
Relative risk (95% CI)						
Age-adjusted‡	1.00	0.73 (0.34-1.55)	0.52 (0.23-1.18)	0.69 (0.29-1.66)	0.64 (0.29-1.43)	.62
Multiple-adjusted§	1.00	0.82 (0.42-1.59)	0.50 (0.21-1.21)	0.84 (0.33-2.09)	0.81 (0.37-1.81)	.92
Intake from foods only						
Incident Alzheimer disease, %†	14.3	11.7	9.1	12.5	5.9	
Median intake, IU/d	6.2	7.7	8.6	9.6	11.4	
Relative risk (95% CI)						
Age-adjusted‡	1.00	0.70 (0.24-2.00)	0.59 (0.25-1.42)	0.71 (0.27-1.84)	0.33 (0.12-0.88)	.04
Multiple-adjusted§	1.00	0.71 (0.24-2.07)	0.62 (0.26-1.45)	0.71 (0.27-1.88)	0.30 (0.10-0.92)	.05
Vitamin C						
Intake from foods and supplements						
Incident Alzheimer disease, %†	13.7	8.6	10.9	11.8	9.3	
Median intake, IU/d	67.1	114.7	156.3	214.4	730.9	
Relative risk (95% CI)						
Age-adjusted‡	1.00	0.61 (0.19-1.90)	0.74 (0.28-1.94)	1.06 (0.37-3.05)	0.67 (0.24-1.91)	.60
Multiple-adjusted§	1.00	0.68 (0.24-1.97)	0.79 (0.34-1.87)	1.11 (0.47-2.65)	0.79 (0.33-1.91)	.79
Intake from foods only						
Incident Alzheimer disease, %†	15.5	8.2	9.6	6.5	14.4	
Median intake, IU/d	50.3	92.3	122.1	149.4	213.6	
Relative risk (95% CI)						
Age-adjusted‡	1.00	0.49 (0.16-1.49)	0.59 (0.19-1.86)	0.37 (0.15-0.90)	1.06 (0.40-2.77)	.84
Multiple-adjusted§	1.00	0.53 (0.17-1.63)	0.62 (0.21-1.87)	0.37 (0.17-0.82)	1.03 (0.41-2.56)	.88
Beta Carotene						
Intake from foods and supplements						
Incident Alzheimer disease, %†	16.5	10.3	8.8	7.1	10.7	
Median intake, IU/d	1453	2215	3137	4240	6730	
Relative risk (95% CI)						
Age-adjusted‡	1.00	0.50 (0.21-1.22)	0.45 (0.15-1.29)	0.38 (0.15-0.96)	0.50 (0.20-1.23)	.21
Multiple-adjusted§	1.00	0.49 (0.19-1.29)	0.46 (0.16-1.36)	0.39 (0.14-1.06)	0.54 (0.21-1.39)	.31
Intake from foods only						
Incident Alzheimer disease, %†	15.9	9.0	7.8	9.1	11.1	
Median intake, IU/d	1372	2092	2775	3668	5197	
Relative risk (95% CI)						
Age-adjusted‡	1.00	0.41 (0.17-1.00)	0.36 (0.14-0.92)	0.48 (0.17-1.35)	0.52 (0.22-1.25)	.32
Multiple-adjusted§	1.00	0.47 (0.19-1.16)	0.38 (0.13-1.15)	0.56 (0.20-1.57)	0.55 (0.22-1.35)	.37

*P value for trend based on modeling vitamin intake as a continuous variable, with persons in each quintile assigned the median value of the quintile. CI indicates confidence interval.
 †Percentage weighted for stratified sampling.
 ‡Age-adjusted models included a term for the period of observation.
 §Multivariable models included terms for age (years), sex, education (years), APOE ε4 status (any allele vs none), race (black or white), an interaction term between race and APOE ε4, and period of observation.

Table 4. Multivariable-Adjusted Relative Risks of Incident Alzheimer Disease by Quintiles of Vitamin E Intake From Foods According to *APOE* ϵ 4 Allele Among 815 Persons 65 Years and Older With a Median Follow-up of 3.9 Years (Chicago Health and Aging Project, 1993-2000)*

<i>APOE</i> ϵ 4 Allele Status	Quintile of Vitamin E Intake From Foods				
	1	2	3	4	5
<i>APOE</i> ϵ 4 allele absent					
No.	106	117	108	122	112
Incident Alzheimer disease, %	16.7	13.1	8.7	6.5	4.2
Relative risk (95% CI)	1.00	0.63 (0.20-2.01)	0.34 (0.13-0.89)	0.23 (0.08-0.67)	0.17 (0.06-0.47)
<i>APOE</i> ϵ 4 allele present					
No.	63	49	61	41	56
Incident Alzheimer disease, %	11.9	9.3	9.0	28.4	9.6
Relative risk (95% CI)	1.00	0.72 (0.18-2.66)	0.97 (0.39-2.52)	2.62 (0.67-6.94)	0.64 (0.15-2.77)

*Relative risks are based on a multivariable logistic regression model, as described in Table 3.

were 0.71 (0.24-2.14), 0.62 (0.27-1.44), 0.71 (0.27-1.90), and 0.31 (0.10-0.93). In that model, vitamin E supplement use was not associated with AD (RR, 1.11; 95% CI, 0.58-2.15). The protective RR for the fifth quintile decreased in magnitude in separate multivariable models that simultaneously adjusted for other antioxidant nutrients (total intake of vitamin C, vitamin A, and beta carotene) (RR, 0.36; 95% CI, 0.11-1.13) and types of fat (polyunsaturated, monounsaturated, and saturated) (RR, 0.49; 95% CI, 0.13-1.76).

Total vitamin C intake was not significantly associated with AD in age- or multivariable-adjusted models, and there was no evidence of a trend (Table 3). Vitamin C intake from foods appeared to have an inverse relationship with AD in the age-adjusted and multivariable models but was statistically significant in the fourth quintile only, and no dose-response relationship was seen. The RR in the fourth quintile remained statistically significant after further adjustment for total intake of vitamin E, vitamin A, and beta carotene (RR, 0.40; 95% CI, 0.19-0.85). The RRs for quintiles of vitamin C food intake did not change appreciably with adjustment for use of multivitamins, vitamin C supplements, and vitamin E supplements in the multivariable model. In that model, the RR of AD among persons who were taking a vitamin C supplement was 0.51 (95% CI, 0.23-1.12; $P=.09$). Overall, the findings for vitamin C were not statistically significant but remain suggestive

enough to be of interest for further study.

The RRs for intake of beta carotene (total and from foods only) were inverse but not significantly associated with incident AD in both the age-adjusted and multivariable models (Table 3). The inverse RRs became even less protective with further adjustment for total intake of vitamin E, vitamin C, and vitamin A in the multivariable model (the RRs for quintiles 2 to 5 were 0.59 [95% CI, 0.24-1.45], 0.54 [95% CI, 0.14-1.90], 0.86 [95% CI, 0.29-2.55], and 1.13 [95% CI, 0.34-3.72]).

Adjustment for cardiovascular-related conditions in the multivariable model did not appreciably change any of the RRs for total or food sources of the antioxidant nutrients. Relative risks for quintiles 2 through 5 for vitamin E intake from foods in the cardiovascular-adjusted model were 0.74 (95% CI, 0.25-2.22), 0.63 (95% CI, 0.26-1.50), 0.76 (95% CI, 0.28-2.06), and 0.30 (95% CI, 0.09-1.05), respectively. However, because we had found that participants in the top quintile of food intake for vitamin C were more likely than those in the lowest to report history of stroke (26% vs 8%) and hypertension (24% vs 19%), we considered that this quintile may have included persons who modified their diet to reduce their risk of stroke. Therefore, we repeated the analysis with the multivariable model after excluding persons in the fifth quintile who reported increasing their consumption of fruits and orange juice in the previous 10 years. In this model, the RRs from

lowest to highest quintiles were 1.0, 0.53, 0.67, 0.40, and 0.51 (P for trend=.11). We also analyzed data among nonsmokers only. Among nonsmokers, the multiple-adjusted RRs for incident AD for quintiles 2 through 5 of vitamin E intake from foods were 0.51 (95% CI, 0.17-1.53), 0.49 (95% CI, 0.20-1.19), 0.38 (95% CI, 0.15-0.98), and 0.27 (95% CI, 0.08-0.86), respectively.

When we analyzed the data for modifications in the effects by age, sex, race, education, or *APOE* ϵ 4 status, only that between the vitamin E association and *APOE* ϵ 4 was statistically significant. Among persons who were *APOE* ϵ 4 negative, vitamin E from foods showed a strong linear protective association with AD (TABLE 4). There was no indication of an interaction between vitamin E and vitamin C from either foods or supplements.

The protective association between incident AD and vitamin E intake from foods remained in multivariable analyses that adjusted for the timing of the dietary assessment (RR, 0.32 for the fifth vs first quintiles; 95% CI, 0.11-0.92) and in analyses that excluded 96 persons with dietary assessments completed within the year before the clinical evaluations (RR, 0.33 for the fifth vs first quintiles; 95% CI, 0.11-1.02). In further analyses that controlled for baseline memory score in the multivariable model, the pairwise estimate did not change, but the CI crossed 1.00. The RRs for quintiles 2 to 5 were 0.75 (95% CI, 0.26-2.10), 0.59 (95% CI, 0.24-1.42), 0.75 (95% CI, 0.28-2.05), and 0.36 (95% CI, 0.11-1.17).

COMMENT

In this large biracial community study, intake of vitamin E from food was inversely associated with incident AD. There was no association with vitamin E supplement use. Vitamin C and beta carotene also had no statistically significant association with AD.

The linear protective association of vitamin E was found only among persons who were *APOE* ϵ 4 negative. The mechanisms of this potential interaction are unknown, but vitamin E is highly lipid soluble, and *APOE* is one of the major lipid transport proteins in the brain.⁴⁰ One possible explanation for the interaction is that the protective effect of vitamin E is insufficient to overcome the deleterious effects of *APOE* ϵ 4 on the development of AD. In the CHAP study, presence of the *APOE* ϵ 4 allele was associated with increased risk of AD among white participants but had no effect in blacks, a group that overall had a nonsignificant 80% increased risk of AD compared with whites (D. Evans, written communication, September 2001). The vitamin E association did not explain these differences by race. We found no modifications in the vitamin E association by race, and the racial difference in AD risk remained in models stratified by *APOE* status that included vitamin E intake.

The reduced magnitude of the vitamin E association after dietary fats and other antioxidant nutrients were controlled for suggests that some of the protective effect may be due to these other dietary constituents. Our findings of no association with total vitamin E intake must be interpreted with caution because of secular changes in the use of vitamin E supplements. Only 8.7% of the participants who completed the food frequency questionnaire in 1994 reported taking a vitamin E supplement as compared with 17.4% of those who completed the food frequency questionnaire in 1997. This fact calls into question whether the negative findings may be due to an insufficient period of use for protective benefit or due to persons taking a vitamin E supplement in response to problems with cog-

nitition. The negative findings for high vitamin C intake may have been confounded by dietary changes among persons diagnosed with vascular disease.

Few investigations have examined the association between food intake of antioxidant nutrients and the development of AD, although 2 prospective studies^{23,24} investigated the association with use of vitamin E and vitamin C supplements. In one of the studies,²⁴ use of the vitamin supplements was inversely associated with AD. In the other, vascular dementia was significantly less frequent among the vitamin-supplement users, but there was no association with AD.²³ One clinical trial investigated the effects of 2000 IU of vitamin E daily on the progression of AD.⁴¹ The study found reduced occurrence of the combined outcome of mortality, institutionalization, decline in function, and severe dementia with vitamin E supplementation but was largely inconclusive about whether vitamin E altered the progression of AD. A few secondary prevention trials are in progress to examine the effect of vitamin E in persons with mild cognitive impairment (D. Bennett, oral communication, January 2002).

The finding of an association of vitamin E with reduced risk of AD is strengthened by the ability to control for many dietary and nondietary factors that could explain the association. Identifying study participants from a community population helped to minimize bias that can occur when only a select group of persons affected (or unaffected) by disease is studied. Misclassification of disease status was also minimized by the use of a uniform structured clinical evaluation for the diagnosis of AD. This study has limitations, however. The modest correlations between different dietary assessments of nutrient intake from foods likely reflect imprecise measurement of long-term dietary intake by each of the dietary assessment methods. Unreliable reporting or imprecise measurement, however, would tend to result in random misclassification of the dietary exposure and thus a greater likelihood of null associations as opposed to the observed protective association with vita-

min E. In addition, dietary assessment occurred after baseline, which raises the possibility that the observed findings could be due to unreliable reporting or to poor overall diet or dietary changes among persons who developed AD. However, these alternative explanations appear unlikely for several reasons. First, the protective effect was observed only for dietary vitamin E and not for intake of other so-called healthy dietary components, vitamin C, beta carotene, and vitamin supplements. Further, the estimate of the vitamin E effect changed little after adjustment for baseline memory score (although the association was no longer significant) and timing of the dietary assessments and after exclusion of persons with dietary assessments within 1 year of the clinical evaluations. In addition, all analyses were based on energy-adjusted nutrient levels, so the findings refer to the composition of these nutrients in the diet as opposed to total absolute intake. Finally, we observed a protective association between vitamin E intake (total and from foods alone) and 3-year decline in cognitive function in the entire study community.⁴² Although the findings for cognitive decline are not specific to AD, they reflect protection much earlier in the disease process. Taken together, these reports provide complementary evidence that vitamin E may protect against neurodegenerative decline. The findings are supported by numerous laboratory studies showing that oxidative processes may contribute to the development of AD^{1,2} and that vitamin E helps minimize the damaging effects of oxidative stress in the brain.^{4,7,8,12,15} Evidence from clinical trials would be required for a definitive determination that dietary vitamin E protects against the development of AD.

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