Intake of antioxidant vitamins and risk of death from stroke in postmenopausal women[1–3]

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ABSTRACT

Background: Antioxidant vitamins may play a role in the prevention of stroke because they scavenge free radicals and prevent LDL oxidation. Epidemiologic studies that have examined this relation produced conflicting results.

Objective: We examined the association between antioxidant vitamin intakes and death from stroke.

Design: This was a prospective cohort study of 34 492 postmenopausal women.

Results: During follow-up, 215 deaths from stroke were documented. Total vitamin A, carotenoid, and vitamin E intakes were not associated with death from stroke after multivariate adjustment. Relative risks (RRs) and 95% CIs of the highest compared with the lowest category were 0.79 (0.45, 1.38; *P* for trend = 0.33) for vitamin A, 0.80 (0.45, 1.40; *P* for trend = 0.40) for carotenoids, and 0.91 (0.55, 1.52; *P* for trend = 0.86) for vitamin E. The test for trend for total vitamin C intake was significant, although the association appeared somewhat U-shaped, not monotonic. An inverse association was seen between death from stroke and vitamin E intake from food. RRs (and 95% CIs) of death from stroke from the lowest to highest intake categories were 1.0, 0.80 (0.51, 1.26), 0.93 (0.58, 1.49), 0.67 (0.39, 1.14), 0.40 (0.20, 0.80); *P* for trend = 0.008. The results suggest inverse associations between death from stroke and intakes of the most concentrated vitamin E food sources consumed by this cohort: mayonnaise, nuts, and margarine.

Conclusions: Our results suggest a protective effect of vitamin E from foods on death from stroke but do not support a protective role for supplemental vitamin E or other antioxidant vitamins. However, given the number of deaths from stroke in the present cohort, a small-to-moderate association could not be ruled out. *Am J Clin Nutr* 2000;72:476–83.

KEY WORDS Antioxidant vitamins, stroke, diet, postmenopausal women, food-frequency questionnaire, prospective cohort study, cardiovascular disease, Iowa Women's Health Study

INTRODUCTION

Consumption of fruit and vegetables is associated with a lower risk of cardiovascular disease (CVD) and stroke (1–4). The potential protective effects of these foods may be due to their antioxidant vitamin content. β-Carotene, vitamin C, and vitamin E are free radical scavengers and have been shown to squelch singlet oxygen

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(5, 6), superoxide (7, 8), the hydroxyl radical (8), and peroxyradicals (6). In addition, vitamin C may protect membranes from peroxidation by regenerating their α-tocopherol component (7, 9).

Free radical oxidation of LDLs is thought to be an important contributor to the development of atherosclerosis (10, 11). Oxidized LDL is taken up more readily by macrophages, resulting in the formation of foam cells and atherosclerotic plaque (10, 12). Thus, antioxidants may slow or prevent this process and decrease the risk of stroke.

Epidemiologic studies that examined the relation between antioxidant vitamins and stroke incidence or mortality produced conflicting results. Observational studies showed a decreased risk of stroke with increased antioxidant intake (13–15), a decreased risk with some but not all antioxidant vitamins (16, 17), and a decreased risk with high plasma antioxidant concentrations (18). However, 2 randomized trials showed no association between supplementation with β-carotene (19) and other antioxidant vitamins (20) and a reduced risk of stroke. Because the evidence regarding antioxidant vitamin intakes and risk of stroke remains equivocal, we examined this association further in postmenopausal women.

SUBJECTS AND METHODS

Study population

The Iowa Women's Health Study is a prospective investigation of 41 836 women who responded to a baseline questionnaire mailed in 1986. The participants were recruited from a random sample of 99 826 women aged 55–69 y at baseline and who had valid Iowa drivers' licenses. The 16-page questionnaire included questions related to demographic characteristics, medical history, health habits, and reproductive history. A semiquantitative food-frequency questionnaire was used to assess diet.

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Information on several CVD risk factors was collected at baseline. Participants reported a history of high blood pressure, heart attack, angina or other heart disease, and diabetes; they were not asked about history of stroke. Smoking habits (current, past, or never), physical activity (number of times per week that the subject participated in moderate and vigorous physical activity), medication use, menopausal status, and hormone replacement status were also reported. Additional information on weight history, age, current height and weight, education, and marital status was collected. Body mass index (BMI; in kg/m^2) was calculated on the basis of height and weight. Participants were asked to measure their waist and hip circumferences with the tape measure included with the initial questionnaire; the waist-to-hip ratio was calculated from these values (21).

Women were excluded from the analysis if they had not reached menopause at the time the questionnaire was completed (n = 569); if they reported that a physician had told them they had angina, had heart disease, or had had a heart attack (n = 3713); if they had implausible energy intakes (<2.5 or >20.9 MJ/d) (n = 313); or if they skipped >30 items on the food-frequency questionnaire (n = 2749). After these exclusions, data from 34492 women were available for analysis. The study was conducted according to the ethical guidelines of the University of Minnesota Institutional Review Board.

Dietary assessment

Usual dietary intake was assessed by using a 127-item semiquantitative food-frequency questionnaire nearly identical to that used in the Nurses' Health Study (22). Current intake of vitamin and mineral supplements was also assessed. The brand of multivitamin used and the frequency and dose of specific vitamins were recorded. No data were collected on the duration of use. The questionnaire also contained questions about the specific brand of oil used in cooking, the type of breakfast cereal typically eaten, and the brand of multivitamin used. Nutrient values were based primarily on data from the US Department of Agriculture (23).

The ability of the questionnaire to estimate vitamin intakes was assessed by comparing mean intakes from five 24-h dietary recalls with responses from the food-frequency questionnaire in a subgroup of 44 women (24). The correlation coefficients for the comparison of the 2 methods of diet assessment for intakes of vitamins A, E, and C were r = 0.14, 0.79, and 0.53, respectively, for food only and r = 0.56, 0.55, and 0.76, respectively, for total intake from both food and supplements.

Deaths were identified annually through the State Health Registry of Iowa, which collects information on deaths in Iowa, and through the National Death Index (25). Underlying cause of death was assigned by state vital registries with use of the *Manual of International Classification of Diseases, 9th revision* (ICD-9) (26). Death was considered to be due to stroke if one of codes 430 through 438 was assigned as an underlying cause. Ischemic and hemorrhagic strokes were not analyzed separately because the validity of the ICD-9 codes for stroke subtypes on death certificates is generally believed to be low.

Statistical analysis

For each woman, length of follow-up was calculated as the number of days from completion of the baseline questionnaire to the date of death or 31 December 1997. During this time, 215 deaths from stroke were documented. The association between antioxidant vitamins and death from stroke was examined. Components of vitamin A (retinol and provitamin A carotenoids) were evaluated separately because provitamin A carotenoids have antioxidant properties and retinol does not. The association was examined in several ways. First, intake of total antioxidant vitamins was divided into quintiles. The risk of death from stroke in the higher quintiles of intake compared with the lowest was then examined by using proportional hazards regression analysis. Next, the association of death from stroke with specific antioxidant vitamins from food sources was examined. Finally, intake of antioxidant vitamins derived exclusively from supplements was considered in relation to death from stroke. Each of the proportional hazards analyses was first adjusted for age and energy intake. Additional nondietary confounders were then added to the model, including BMI, waist-to-hip ratio, smoking status, diabetes mellitus, hypertension, physical activity, use of estrogen replacement therapy, alcohol intake, marital status, and education level. These analyses were subsequently adjusted for intakes of cholesterol, saturated fat, fish, dietary fiber, whole grains, and other antioxidants. Finally, we examined the risk of death from stroke on the basis of foods that were concentrated sources of vitamin E. The analysis was conducted by using SAS (version 6.12; SAS Institute Inc, Cary, NC).

RESULTS

For the 34492 women aged 55–69 y, median daily vitamin intakes from both food and supplements were as follows: 190.5 mg vitamin C, 9.7 mg vitamin E, 2053 μg retinol equivalents (RE), 678 μg RE carotenoids, and 1178 μg RE retinol. The distribution of CVD risk factors by baseline intake of vitamins A, C, and E from food and supplements is shown in **Table 1**. Women in each category of vitamin E and C intakes contributed a similar number of person-years. Person-years (from the lowest to highest category of intake) were 78482, 78450, 78214, 78567, and 78522 for vitamin E and 78404, 78766, 78562, 78438, and 78065 for vitamin C. Individuals with higher intakes of vitamin E from both food and supplements had lower BMIs and waist-to-hip ratios and higher levels of physical activity than did those with lower intakes. Women with higher vitamin E intakes were also more likely to be receiving estrogen replacement therapy, to be nonsmokers, and not to have diabetes or hypertension. The distribution of CVD risk factors according to category of vitamin E intake from food only followed a similar pattern, although the distribution of BMI was relatively consistent across quintiles.

The overall distribution of CVD risk factors according to category of vitamin C, vitamin A, and carotenoid intakes was comparable with that for vitamin E. The only exceptions were that the prevalence of diabetes was not related to intake of vitamin A or carotenoids and that the prevalence of hypertension was not related to intake of carotenoids.

The relative risks (RRs) of death from stroke by category of vitamin intake from both food and supplements are shown in **Table 2**. After adjustment for age and energy intake, there was no association between vitamin A intake and risk of death from stroke. Although the RRs in the 3 highest quintiles compared with the lowest quintile were below 1, all CIs were broad and included 1.0. After multivariate adjustment, the RR in the highest quintile of antioxidant intake was 0.79 for vitamin A. There was no relation between death from stroke and intake of retinol or vitamin E from food and supplements after multivariate adjustment. There was a suggestion of a decreased risk of death

TABLE 1
Association of various cardiovascular disease risk factors according to total intakes of vitamins E, C, and A and carotenoids in 34 492 postmenopausal women, 1986

	Quintile of total antioxidant intake						
	1 (Lowest)	2	3	4	5 (Highest)	*P* for trend	SD
Vitamin E (food and supplements)							
Median vitamin E intake (mg/d)	4.9	7.0	9.7	22.1	238.4	—	148.04
Age (y)	61.4	61.4	61.5	61.6	61.6	0.008	4.18
BMI (kg/m^2)	27.2	27.1	27.1	26.6	26.6	<0.0001	5.07
Waist-to-hip ratio	0.843	0.837	0.836	0.835	0.831	<0.0001	0.086
Current smoker (%)	18.9	14.9	13.7	14.5	14.0	<0.001	—
Diabetes mellitus (%)	7.0	5.5	5.6	5.5	5.2	<0.001	—
Hypertension (%)	39.1	37.0	35.9	35.3	33.8	<0.001	—
High level of physical activity (%)	18.9	22.4	25.8	27.5	30.1	<0.001	—
Current estrogen replacement therapy (%)	33.6	36.1	35.8	39.8	45.2	<0.001	—
Vitamin C (food and supplements)							
Median vitamin C intake (mg/d)	82.4	138.3	190.6	280.9	678.7	—	300.4
Age (y)	61.1	61.6	61.6	61.7	61.6	<0.0001	4.18
BMI (kg/m^2)	26.9	27.1	27.1	26.6	26.6	<0.0001	5.07
Waist-to-hip ratio	0.841	0.838	0.837	0.836	0.829	<0.0001	0.086
Current smoker (%)	22.1	14.2	12.9	12.0	14.8	0.001	—
Diabetes mellitus (%)	4.8	6.3	6.3	6.2	5.3	0.001	—
Hypertension (%)	33.8	36.6	38.0	37.7	35.0	0.001	—
High level of physical activity (%)	16.8	21.9	26.3	28.6	31.1	0.001	—
Current estrogen replacement therapy (%)	34.4	35.9	36.3	38.8	45.1	0.001	—
Vitamin A (food and supplements)							
Median vitamin A intake (retinol equivalent/d)	783	1442	2053	2787	4381	—	1441
Age (y)	61.5	61.4	61.5	61.7	61.7	<0.0001	4.18
BMI (kg/m^2)	27.0	26.9	27.0	27.0	26.8	0.048	5.07
Waist-to-hip ratio	0.842	0.839	0.836	0.835	0.830	<0.0001	0.086
Current smoker (%)	19.7	21.7	14.7	13.1	11.2	0.001	—
Diabetes mellitus (%)	5.6	5.9	5.8	5.8	5.8	0.946	—
Hypertension (%)	37.4	36.3	36.8	35.8	34.8	0.025	—
High level of physical activity (%)	17.1	21.7	14.7	13.1	11.2	0.001	—
Current estrogen replacement therapy (%)	35.8	36.6	38.4	39.4	40.4	0.001	—
Carotenoids (food and supplements)							
Median carotenoid intake (retinol equivalent/d)	325	511	709	1038	1659	—	810.2
Age (y)	61.2	61.3	61.7	61.6	61.8	<0.0001	4.18
BMI (kg/m^2)	27.0	27.0	26.9	26.9	26.8	0.021	5.07
Waist-to-hip ratio	0.843	0.839	0.838	0.834	0.828	<0.0001	0.086
Current smoker (%)	20.7	17.1	15.7	12.2	10.4	0.001	—
Diabetes mellitus (%)	5.6	6.0	5.8	5.4	5.9	0.536	—
Hypertension (%)	36.6	36.5	36.4	36.2	35.3	0.551	—
High level of physical activity (%)	17.1	21.5	24.5	27.3	34.3	0.001	—
Current estrogen replacement therapy (%)	36.4	37.8	38.4	38.8	39.2	0.006	—

from stroke with total intake of carotenoids after adjustment for age and energy; however, this association was attenuated after multivariate adjustment.

The linear test for trend for overall vitamin C intake and death from stroke was significant; after multivariate adjustment, the overall trend remained significant, although the association appeared somewhat U-shaped, not monotonic. The RRs in quintiles 2, 3, and 4 were all <1.0; only the RR for quintile 5 was >1.0 (RR: 1.23; 95% CI: 0.76, 1.23). When a nonlinear term was added to the model, it was not significant. Additionally, an interaction between iron and vitamin C intake was evaluated but was not significant.

No association was seen between death from stroke and intake of vitamin A from food, carotenoids, or retinol after multivariate adjustment (**Table 3**). There was no association between the intake of vitamin C from food and risk of death from stroke. A significant inverse association was seen with intake of vitamin E from food after adjustment for age and energy. This association was strengthened after adjustment for dietary and nondietary variables. RRs (and 95% CIs) in the higher 4 categories of intake compared with the lowest were 0.80 (0.51,1.26), 0.93 (0.58, 1.49), 0.67 (0.39, 1.14), and 0.40 (0.20, 0.80); *P* for trend = 0.008. The RRs of death from stroke by category of antioxidant intake from supplements alone are shown in **Table 4**. Intakes of vitamins A, C, and E from supplements were not associated with death from stroke.

The RR of death from stroke by category of food intake containing high amounts of vitamin E is presented in **Table 5**. There was a suggestion of an inverse association with intake of margarine and nuts and seeds and risk of death from stroke. Each category of intake compared with the lowest was <1.0, although most 95% CIs included 1.0. The overall trend after multivariate adjustment was not significant for the intake of either margarine or nuts and seeds. There was a suggestion of a monotonic, inverse association between consumption of mayonnaise and

TABLE 2
Relative risk of death from stroke according to quintile of antioxidant intake from food and supplements in 34 492 postmenopausal women, 1986–1995

	Quintile of total antioxidant intake					
	1 (Lowest)	2	3	4	5 (Highest)	*P* for trend
Vitamin A						
No. of deaths from stroke	42	48	41	41	43	—
Median vitamin A intake (μg retinol equivalent/d)	783	1442	2053	2787	4381	—
Relative risk (95% CI)						
Age and energy adjusted	1.0	1.06 (0.70, 1.60)	0.87 (0.56, 1.36)	0.82 (0.53, 1.28)	0.83 (0.53, 1.31)	0.30
Adjusted for nondietary variables[1]	1.0	1.04 (0.67, 1.61)	0.95 (0.61, 1.50)	0.91 (0.57, 1.46)	0.94 (0.57, 1.53)	0.72
Multivariate adjusted[2]	1.0	1.01 (0.64, 1.58)	0.90 (0.57, 1.44)	0.84 (0.51, 1.36)	0.79 (0.45, 1.38)	0.33
Retinol						
No. of deaths from stroke	39	49	34	44	49	—
Median retinol intake (μg retinol equivalent/d)	286	602	1178	1755	3133	—
Relative risk (95% CI)						
Age and energy adjusted	1.0	1.14 (0.74, 1.75)	0.81 (0.51, 1.29)	1.03 (0.66, 1.61)	1.12 (0.72, 1.73)	0.62
Adjusted for nondietary variables[1]	1.0	1.11 (0.71, 1.73)	0.79 (0.49, 1.30)	0.95 (0.59, 1.52)	1.07 (0.67, 1.69)	0.78
Multivariate adjusted[2]	1.0	1.09 (0.70, 1.70)	0.75 (0.46, 1.22)	0.87 (0.54, 1.40)	0.85 (0.52, 1.40)	0.45
Carotenoids						
No. of deaths from stroke	44	44	41	49	37	—
Median carotenoid intake (μg retinol equivalent/d)	325	511	709	1038	1659	—
Relative risk (95% CI)						
Age and energy adjusted	1.0	0.95 (0.62, 1.45)	0.81 (0.52, 1.24)	0.96 (0.63, 1.45)	0.67 (0.42, 1.06)	0.09
Adjusted for nondietary variables[1]	1.0	0.95 (0.61, 1.48)	0.91 (0.58, 1.44)	1.07 (0.68, 1.67)	0.81 (0.49, 1.33)	0.37
Multivariate adjusted[2]	1.0	0.95 (0.60, 1.49)	0.90 (0.57, 1.44)	1.07 (0.67, 1.72)	0.80 (0.45, 1.40)	0.40
Vitamin C						
No. of deaths from stroke	45	33	41	36	60	—
Median vitamin C intake (mg/d)	82.4	138.3	190.6	280.9	678.7	—
Relative risk (95% CI)						
Age and energy adjusted	1.0	0.66 (0.42, 1.03)	0.79 (0.51, 1.22)	0.68 (0.43, 1.08)	1.18 (0.79, 1.75)	0.024
Adjusted for nondietary variables[1]	1.0	0.69 (0.43, 1.10)	0.77 (0.48, 1.21)	0.70 (0.42, 1.13)	1.24 (0.81, 1.89)	0.018
Multivariate adjusted[3]	1.0	0.70 (0.43, 1.11)	0.78 (0.49, 1.26)	0.72 (0.43, 1.18)	1.23 (0.76, 1.23)	0.050
Vitamin E						
No. of deaths from stroke	47	53	34	31	50	—
Median vitamin E intake (mg/d)	4.9	7.0	9.7	22.1	238.4	—
Relative risk (95% CI)						
Age and energy adjusted	1.0	1.00 (0.67, 1.51)	0.57 (0.35, 0.93)	0.52 (0.32, 0.86)	0.88 (0.57, 1.34)	0.41
Adjusted for nondietary variables[1]	1.0	1.20 (0.78, 1.84)	0.75 (0.45, 1.24)	0.60 (0.35, 1.02)	1.08 (0.68, 1.71)	0.25
Multivariate adjusted[4]	1.0	1.21 (0.78, 1.86)	0.76 (0.45, 1.27)	0.58 (0.34, 0.99)	0.91 (0.55, 1.52)	0.86

[1] Adjusted for age, total energy intake, BMI, waist-to-hip ratio, high blood pressure (yes or no), diabetes (yes or no), use of estrogen replacement therapy (current, former, or never), alcohol intake (none, < 4 g/d, 4 to ≤ 10 g/d, or >10 g per day), education (no high-school diploma, high-school diploma, college or vocational school but no degree, or college degree), marital status (currently married, never married, separated or divorced, or widowed), pack-years of smoking (0, 1–19, 20–39, or ≥ 40), and physical activity level (low, moderate, or high).

[2] Adjusted for the covariates listed in footnote 1 and intakes of cholesterol, saturated fat, fish, vitamin E, vitamin C, dietary fiber, and whole grains.

[3] Adjusted for the covariates listed in footnote 1 and intakes of cholesterol, saturated fat, fish, vitamin E, carotenoids, dietary fiber, and whole grains.

[4] Adjusted for the covariates listed in footnote 1 and intakes of cholesterol, saturated fat, fish, vitamin C, carotenoids, dietary fiber, and whole grains.

creamy salad dressing and risk of death from stroke after adjustment for age and energy, although this association was attenuated after multivariate adjustment. RRs (95% CIs) in the higher quintiles compared with the lowest were 0.78 (0.53, 1.12), 0.67 (0.42, 1.07), and 0.56 (0.29, 1.11).

DISCUSSION

Our results suggest that intake of vitamin E from food was associated with a decreased risk of death from stroke in this cohort of postmenopausal women. Death from stroke in the highest quintile of vitamin E intake was 60% lower than that in the lowest quintile, with a trend that was significant. There was a suggestion of an inverse association between specific foods rich in vitamin E and death from stroke. However, our results did not suggest a potential protective effect of vitamin E consumption from supplements. Although the linear test for trend for vitamin C was significant, the association appeared somewhat U-shaped. No association was seen for intake of carotenoids or vitamin A.

Prospective studies that examined the association between vitamin E intake and death from stroke have produced conflicting results. In 2 prospective studies, serum concentrations of vitamin E were measured and no association with death from stroke was found (17, 18). In a large cohort study of US nurses, a nonsignificantly decreased incidence of stroke was found in the highest quintile of vitamin E intake compared with the lowest

TABLE 3
Relative risk of death from stroke according to quintile of antioxidant intake from food in 34 492 postmenopausal women, 1986–1995

	Quintile of total antioxidant intake					
	1 (Lowest)	2	3	4	5 (Highest)	*P* for trend
Vitamin A						
No. of deaths from stroke	47	45	48	38	37	—
Median vitamin A intake (retinol equivalent/d)	695	1120	1622	2145	3049	—
Relative risk (95% CI)						
Age and energy adjusted	1.0	1.04 (0.68, 1.59)	0.88 (0.57, 1.37)	0.86 (0.55, 1.34)	0.89 (0.56, 1.42)	0.54
Adjusted for nondietary variables[1]	1.0	1.13 (0.71, 1.74)	0.90 (0.56, 1.44)	1.01 (0.63, 1.64)	1.06 (0.64, 1.75)	0.87
Multivariate adjusted[2]	1.0	1.12 (0.72, 1.76)	0.91 (0.56, 1.47)	1.04 (0.63, 1.71)	1.09 (0.62, 1.92)	0.80
Retinol						
No. of deaths from stroke	46	42	39	41	47	—
Median retinol intake (retinol equivalent/d)	237	434	696	1207	1739	—
Relative risk (95% CI)						
Age and energy adjusted	1.0	0.70 (0.50, 1.10)	0.92 (0.60, 1.41)	0.76 (0.49, 1.18)	0.92 (0.59, 1.43)	0.84
Adjusted for nondietary variables[1]	1.0	0.85 (0.54, 1.35)	0.99 (0.62, 1.57)	0.83 (0.52, 1.33)	0.91 (0.56, 1.47)	0.72
Multivariate adjusted[2]	1.0	0.86 (0.54, 1.37)	0.99 (0.63, 1.55)	0.82 (0.51, 1.31)	0.86 (0.52, 1.41)	0.52
Carotenoids						
No. of deaths from stroke	44	37	50	45	39	—
Median carotenoid intake (retinol equivalent/d)	311	491	677	1079	1731	—
Relative risk (95% CI)						
Age and energy adjusted	1.0	0.80 (0.51, 1.24)	0.99 (0.66, 1.50)	0.88 (0.58, 1.36)	0.71 (0.44, 1.12)	0.18
Adjusted for nondietary variables[1]	1.0	0.75 (0.47, 1.21)	1.07 (0.70, 1.66)	0.98 (0.62, 1.54)	0.85 (0.52, 1.38)	0.71
Multivariate adjusted[2]	1.0	0.76 (0.47, 1.22)	1.08 (0.69, 1.68)	1.01 (0.62, 1.62)	0.88 (0.50, 1.54)	0.88
Vitamin C						
No. of deaths from stroke	46	39	36	44	50	—
Median vitamin C intake (mg/d)	67.2	110.0	142.2	178.5	247.9	—
Relative risk (95% CI)						
Age and energy adjusted	1.0	0.77 (0.50, 1.19)	0.69 (0.44, 1.07)	0.81 (0.53, 1.25)	0.89 (0.57, 1.39)	0.92
Adjusted for nondietary variables[1]	1.0	0.83 (0.53, 1.31)	0.75 (0.47, 1.20)	0.87 (0.55, 1.39)	0.94 (0.58, 1.52)	0.98
Multivariate adjusted[3]	1.0	0.84 (0.53, 1.33)	0.76 (0.47, 1.23)	0.91 (0.56, 1.48)	0.99 (0.58, 1.72)	0.80
Vitamin E						
No. of deaths from stroke	47	45	48	38	37	—
Median vitamin E intake (mg/d)	4.4	6.0	7.4	9.0	12.3	—
Relative risk (95% CI)						
Age and energy adjusted	1.0	0.78 (0.52, 1.19)	0.79 (0.51, 1.22)	0.54 (0.33, 0.88)	0.41 (0.23, 0.75)	0.01
Adjusted for nondietary variables[1]	1.0	0.80 (0.51, 1.26)	0.94 (0.60, 1.49)	0.67 (0.40, 1.12)	0.40 (0.21, 0.78)	0.006
Multivariate adjusted[4]	1.0	0.80 (0.51, 1.26)	0.93 (0.58, 1.49)	0.67 (0.39, 1.14)	0.40 (0.20, 0.80)	0.008

[1] Adjusted for age, total energy intake, BMI, waist-to-hip ratio, high blood pressure (yes or no), diabetes (yes or no), use of estrogen replacement therapy (current, former, or never), alcohol intake (none, < 4 g/d, 4 to ≤ 10 g/d, or >10 g per day), education (no high-school diploma, high-school diploma, college or vocational school but no degree, or college degree), marital status (currently married, never married, separated or divorced, or widowed), pack-years of smoking (0, 1–19, 20–39, or ≥ 40), and physical activity level (low, moderate, or high).
[2] Adjusted for the covariates listed in footnote 1 and intakes of cholesterol, saturated fat, fish, vitamin E, vitamin C, dietary fiber, and whole grains.
[3] Adjusted for the covariates listed in footnote 1 and intakes of cholesterol, saturated fat, fish, vitamin E, carotenoids, dietary fiber, and whole grains.
[4] Adjusted for the covariates listed in footnote 1 and intakes of cholesterol, saturated fat, fish, vitamin C, carotenoids, dietary fiber, and whole grains.

(RR: 0.76; 95% CI: 0.49, 1.20) (14). A prospective study conducted in the Netherlands showed a nonsignificant positive association of stroke incidence with higher intakes of vitamin E (RR: 1.64; 95% CI: 0.54, 4.97) (16). The estimates in this study were based on only 42 stroke endpoints and had wide 95% CIs. Although our results suggest an inverse association between death from stroke and intake of vitamin E from foods, this association was not observed consistently in the literature.

It is unclear why we found an association between death from stroke and intake of vitamin E from foods, but not between death from stroke and vitamin E intake from supplements. A large randomized trial conducted in China showed a nonsignificant, 10% reduction in cerebrovascular death (95% CI: −24%, 0.7%) with a daily combination of vitamin E (30 mg), selenium (50 μg), and β-carotene (15 mg) supplements (20). The Nurses' Health Study showed a nonsignificantly reduced risk of incident stroke with intake of vitamin E from both food and supplements (14). Although it is possible that other components of vitamin E–containing foods may have been responsible for our observed association, we were unable to identify any. Our results were not appreciably modified after adjustment for intakes of other antioxidant vitamins, fiber, whole grains, potassium, and magnesium ($P = 0.007$).

One possible reason for the observed association between risk of death from stroke and vitamin E intake from foods but not from supplements is that we did not collect information on

TABLE 4
Relative risk of death from stroke according to quintile of antioxidant intake from supplements in 34 492 postmenopausal women, 1986–1995

	Quintile of antioxidant intake					
	1 (Lowest)	2	3	4	5 (Highest)	*P* for trend
Vitamin A						
No. of deaths from stroke	143	42	14	12	—	—
Median vitamin A intake (μg retinol equivalent/d)	0	1650	2640	4950	—	—
Relative risk (95% CI)						
Age and energy adjusted	1.0	1.16 (0.76, 1.76)	1.07 (0.55, 2.06)	1.17 (0.51, 2.69)	—	0.29
Adjusted for nondietary variables[1]	1.0	1.08 (0.70, 1.67)	1.09 (0.57, 2.11)	1.10 (0.44, 2.71)	—	0.41
Multivariate adjusted[2]	1.0	1.08 (0.70, 1.68)	1.11 (0.57, 2.14)	1.10 (0.45, 2.75)	—	0.72
Vitamin C						
No. of deaths from stroke	114	44	22	29	6	—
Median vitamin C intake (mg/d)	0	60	310	560	1120	—
Relative risk (95% CI)						
Age and energy adjusted	1.0	0.79 (0.56, 1.12)	1.23 (0.78, 1.94)	1.93 (1.28, 2.90)	0.89 (0.39, 2.02)	0.80
Adjusted for nondietary variables[1]	1.0	0.80 (0.55, 1.16)	1.31 (0.81, 2.11)	1.93 (1.23, 3.02)	1.00 (0.44, 2.28)	0.62
Multivariate adjusted[3]	1.0	0.79 (0.54, 1.15)	1.27 (0.77, 2.09)	1.82 (1.12, 2.98)	0.90 (0.36, 2.19)	0.82
Vitamin E						
No. of deaths from stroke	135	29	18	12	21	—
Median vitamin E intake (mg/d)	0	1–25	26–100	101–250	>250	—
Relative risk (95% CI)						
Age and energy adjusted	1.0	0.66 (0.35, 1.24)	1.56 (0.93, 2.61)	1.17 (0.43, 3.19)	0.83 (0.45, 1.56)	0.25
Adjusted for nondietary variables[1]	1.0	0.75 (0.47, 1.22)	1.29 (0.82, 2.02)	1.20 (0.53, 2.72)	0.67 (0.38, 1.18)	0.30
Multivariate adjusted[4]	1.0	0.76 (0.47, 1.22)	1.28 (0.82, 2.01)	1.21 (0.53, 2.75)	1.21 (0.38, 1.19)	0.31

[1] Adjusted for age, total energy intake, BMI, waist-to-hip ratio, high blood pressure (yes or no), diabetes (yes or no), use of estrogen replacement therapy (current, former, or never), alcohol intake (none, <4 g/d, 4 to ≤10 g/d, or >10 per day), education (no high-school diploma, high-school diploma, college or vocational school but no degree, or college degree), marital status (currently married, never married, separated or divorced, or widowed), pack-years of smoking (0, 1–19, 20–39, or ≥40), and physical activity level (low, moderate, or high).

[2] Adjusted for the covariates listed in footnote 1 and intakes of cholesterol, saturated fat, fish, vitamin E, vitamin C, dietary fiber, and whole grains.

[3] Adjusted for the covariates listed in footnote 1 and intakes of cholesterol, saturated fat, fish, vitamin E, carotenoids, dietary fiber, and whole grains.

[4] Adjusted for the covariates listed in footnote 1 and intakes of cholesterol, saturated fat, fish, vitamin C, carotenoids, dietary fiber, and whole grains.

duration of supplement use. Although no other studies of stroke occurrence evaluated the influence of the duration of supplement use, studies that observed an inverse association between vitamin E and CVD did so after 2 y of supplemental vitamin E use. Note that in this same cohort of Iowa women, vitamin E intake from foods but not from supplements was also inversely associated with coronary heart disease (27).

Although we observed a nonsignificant inverse association between risk of death from stroke and intake of margarine and nuts and seeds, the result of the overall test for trend for these foods was not significant. We also observed a borderline significant association between risk of death from stroke and intake of mayonnaise and creamy salad dressing, foods that are also rich in vitamin E. This relation was attenuated after multivariate adjustment. It is possible that these individual foods were measured with less precision, making it more difficult to detect a significant association.

Our findings do not support a protective effect of vitamin C. The overall linear test for trend for total vitamin C intake was significant, although the association was somewhat U-shaped. Only the highest category of vitamin C intake was >1.0 (RR: 1.23), with the 95% CI being relatively broad and including 1.0 (95% CI: 0.76, 1.23). Addition of a nonlinear term did not improve the fit of the model.

The Basel Prospective Study reported a nonsignificant, negative association between death from stroke and high serum vitamin C concentrations (RR: 0.78; 95% CI: 0.24, 2.50) (18). Other prospective studies found both a nonsignificant increase (16) and a nonsignificant decrease (14) in stroke incidence with higher vitamin C intakes. A nonsignificant decrease in both fatal and nonfatal strokes with greater vitamin C intakes was observed by Daviglus et al (15). One supplementation trial found no effect of vitamin C on death from stroke (RR: 1.04; 95% CI: 0.88, 1.24) (20). Thus, the role of vitamin C in the prevention of stroke incidence and mortality remains unclear in the epidemiologic literature; our results suggest a U-shaped association.

Inconsistencies in the literature may be due, in part, to the prooxidant properties of vitamin C (28). Vitamin C is not exclusively an antioxidant and has been shown to be a prooxidant in some circumstances (29). For example, supplementation with 500 mg vitamin C/d significantly increased DNA damage in volunteers (28).

Other observational studies showed nonsignificant inverse associations between β-carotene intake and risk of stroke incidence. For example, Daviglus et al (15) found an RR of 0.84 (95% CI: 0.57, 1.24) for fatal and nonfatal stroke in relation to high compared with low intakes of β-carotene. Randomized trials found no effect (RR: 0.96, 95% CI: 0.83, 1.11) (19) or a slight protective effect (20) of β-carotene supplementation on stroke prevention.

As for all epidemiologic studies of diet and disease, our results are limited by probable misclassification of dietary exposures, which can attenuate true associations and make it more difficult to detect an association if one is present (30). In addition, our analyses were based on one assessment of diet made in 1986 and did not consider any changes that could have occurred during the follow-up period. It is possible that women who were at higher risk of stroke changed their diets during this time, affecting our

TABLE 5
Relative risk of death from stroke according to quintile of intake of foods with high amounts of vitamin E in 34 492 postmenopausal women, 1986–1995

	Quintile of food intake				
	1 (Low)	2	3	4	*P* for trend
Margarine					
No. of deaths from stroke	33	39	64	79	—
No. of times eaten/wk	0	0.5–3	4–7	>7	—
Relative risk (95% CI)					
Age and energy adjusted	1.0	0.64 (0.40, 1.02)	0.62 (0.41, 0.95)	0.71 (0.47, 1.07)	0.28
Adjusted for nondietary variables[1]	1.0	0.67 (0.41, 1.10)	0.60 (0.38, 0.95)	0.65 (0.42, 1.00)	0.11
Multivariate adjustment[2]	1.0	0.67 (0.41, 1.09)	0.59 (0.38, 0.93)	0.64 (0.41, 1.00)	0.10
Nuts and seeds					
No. of deaths from stroke	105	65	28	17	—
No. of times eaten/mo	0	1 or 2	3 or 4	>4	—
Relative risk (95% CI)					
Age and energy adjusted	1.0	0.74 (0.54, 1.01)	0.75 (0.49, 1.14)	0.65 (0.39, 1.10)	0.24
Adjusted for nondietary variables[1]	1.0	0.85 (0.61, 1.17)	0.78 (0.50, 1.24)	0.73 (0.41, 1.28)	0.37
Multivariate adjustment[2]	1.0	0.85 (0.61, 1.18)	0.79 (0.50, 1.24)	0.73 (0.41, 1.29)	0.38
Mayonnaise or creamy salad dressing					
No. of deaths from stroke	41	117	44	13	—
No. of times eaten/wk	0	0.5–1	2–3	>3	—
Relative risk (95% CI)					
Age and energy adjusted	1.0	0.72 (0.51, 1.03)	0.65 (0.42, 1.00)	0.53 (0.28, 1.00)	0.097
Adjusted for nondietary variables[1]	1.0	0.79 (0.53, 1.15)	0.67 (0.42, 1.07)	0.55 (0.28, 1.08)	0.13
Multivariate adjusted[2]	1.0	0.78 (0.53, 1.12)	0.67 (0.42, 1.07)	0.56 (0.29, 1.11)	0.14

[1] Adjusted for age, total energy intake, BMI, waist-to-hip ratio, high blood pressure (yes or no), diabetes (yes or no), use of estrogen replacement therapy (current, former, or never), alcohol intake (none, <4 g/d, 4 to ≤10 g/d, or >10 g/d), education (no high-school diploma, high-school diploma, college or vocational school but no degree, or college degree), marital status (currently married, never married, separated or divorced, or widowed), pack-years of smoking (0, 1–19, 20–39, or ≥40), and physical activity level (low, moderate, or high).

[2] Adjusted for the covariates listed in footnote 1 and intakes of cholesterol, saturated fat, fish, vitamin C, carotenoids, dietary fiber, and whole grains.

ability to detect an association. We assessed vitamin use at ages 55–69 y; it is possible that antioxidant intake earlier in life is more protective. Our results are further limited by our lack of information on the history of stroke in the subjects studied. In addition, the analyses were based on death from stroke in the Iowa cohort, not on incidence. The total number of deaths from stroke was modest, resulting in relatively wide 95% CIs.

Overall, our results suggest that higher intakes of vitamin E from foods (compared with the lower intake from foods) may be associated with a lower risk of death from stroke. Evidence for a protective role of vitamin E against death from stroke is supported by a plausible biologic mechanism (5–8, 11, 12) and our observation of a strong, dose-response relation. Vitamin E is a free radical scavenger (6–8) and thus may help prevent the oxidation of LDL, an important step in the atherosclerotic process. However, observational studies have produced conflicting results regarding the role of blood lipids in the development of stroke. Some studies showed a positive association between blood lipid concentrations and stroke, whereas others did not show such an association (31). However, β-hydroxy-β-methylglutaryl coenzyme A reductase drugs, which lower blood lipid concentrations, do seem to prevent stoke (32). Thus, it is unclear whether oxidation of LDL is as important a mechanism in the development of stroke as it is in the development of CVD.

Our results suggest that intake of vitamin E from foods may reduce the risk of death from stroke in older women. Our results do not support a protective role for supplemental vitamin E or for other antioxidant vitamins, but given the number of deaths from stroke, a small-to-moderate association could not be ruled out.

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