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Original Contribution

The Association of Antioxidants and Cognition in the Nurses' Health Study

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The authors examined long-term antioxidant intake in relation to cognitive decline among older women. Beginning in 1980, Nurses' Health Study (NHS) participants completed dietary assessments every 4 years; in 1995–2001, 16,010 participants aged ≥70 years completed initial cognitive assessments, which were repeated 3 times at 2-year intervals. Long-term antioxidant intake was averaged from 1980 through the time of initial cognitive interviews. Multivariable-adjusted linear regression was used to estimate mean differences in rates of cognitive decline across categories of vitamin E, vitamin C, and carotenoid intake; statistical tests were 2-sided. No associations were evident for vitamin E or total carotenoid intake and cognitive decline (e.g., after multivariable adjustment, *P*-trend = 0.44 and *P*-trend = 0.51, respectively, for a global composite score averaging all 6 cognitive tests), although higher lycopene intake and lower vitamin C intake were related to slower cognitive decline. In alternative analyses of overall cognitive status at older ages (averaging all 4 cognitive assessments), results for vitamins E and C were generally null, but higher carotenoid intake was related to better cognition. Overall, long-term vitamin E and C intakes were not consistently related to cognition, although greater consumption of carotenoids may have cognitive benefits in older adults.

antioxidants; cognition; cohort studies; diet

Abbreviations: CI, confidence interval; NHS, Nurses' Health Study; TICS, Telephone Interview for Cognitive Status.

Experimental data indicate that oxidative stress plays an important role in the development of cognitive impairment and Alzheimer's disease, but epidemiologic studies have produced conflicting results on the association between antioxidant vitamins and cognition in older adults (1–3). In particular, several large clinical trials of vitamin E, vitamin C, and beta-carotene supplements have shown little effect on cognitive function, with follow-up periods of 3–7 years (4–8). However, 1 trial suggested that long-term supplementation with beta-carotene, over approximately 18 years, can confer cognitive benefits, and an additional analysis by our research group indicated that long-term exposure to vitamin E supplements might be associated with cognitive health in the Nurses' Health Study (NHS) (9, 10). These findings are consistent with the prevailing notion that the pathology underlying cognitive impairment begins decades prior to onset of detectable symptoms; thus, long-term antioxidant intake could be most relevant for cognitive outcomes in later life (11). We took advantage of multiple, repeated dietary assessments administered over 2 decades in the NHS to examine relations between long-term antioxidant intake and subsequent cognition in approximately 16,000 older women.

MATERIALS AND METHODS

The NHS began in 1976, when 121,700 female registered nurses aged 30–55 years responded to a mailed questionnaire on health and lifestyle. Biennial questionnaires are used to update this information, and current follow-up exceeds 90%. In 1980, we added a food frequency questionnaire, which is administered approximately every 4 years. In addition, we initiated a telephone-based study of cognitive function in 1995–2001 and invited women to

participate if they were ≥70 years of age and had no history of stroke. Ninety-two percent of eligible women participated in the initial cognitive interview, and 3 subsequent follow-up interviews were conducted at approximately 2-year intervals (the median time between interviews 1 and 4 was 6.4 years). Follow-up was ≥90% among women who were still alive at each interview. The institutional review board of Brigham and Women's Hospital (Boston, Massachusetts) approved this study.

Population for analysis

Of the 19,415 nurse-participants who completed the initial cognitive interview, 3,405 were excluded from our analysis because they lacked dietary data; thus, we included 16,010 women in the current analysis. Key characteristics at the time of initial cognitive interview were similar among women who were included in our analysis and those who were excluded (e.g., mean age = 74.2 years vs. 74.4 years; mean body mass index (weight (kg)/height $(m)^2$) = 26.0 vs. 26.3).

Dietary assessment

We used a 61-item, Willett semiquantitative food frequency questionnaire to ascertain dietary habits in 1980 and an expanded 130-item version in 1984, 1986, and every 4 years thereafter (12). Food items were specified in common units or portion sizes (e.g., 1 tomato or a small, 1-ounce (28-g) packet of nuts) and detailed information was collected on methods of food preparation (e.g., types of cooking oils). Participants reported how often, on average, they had consumed each food item over the previous year, using 9 prespecified response categories that ranged from "almost never" to "≥6 times per day". For each food, we multiplied the reported consumption frequency by its nutrient content, which was determined using the Harvard University Food Composition Database (updated regularly). Each participant's nutrient intakes were aggregated across all dietary sources and adjusted for total energy intake using the residual method (13).

In a validation study, we found high correlations for major foods contributing to antioxidant intakes, comparing the food frequency questionnaire with four 1-week dietary records collected over a period of 1 year (14). In particular, correlation coefficients (corrected for within-person variation in dietary records) were 0.67 for chicken, 0.79 for cold cereal, and 0.75 for peanut butter (major sources of vitamin E in this cohort); 0.74 for oranges and 0.84 for orange juice (major sources of vitamin C); and 0.73 for tomatoes and 0.55 for carrots (major sources of carotenoids).

Cognitive function measurement

Initially, we administered the Telephone Interview for Cognitive Status (TICS), a telephone adaptation of the Mini-Mental State Examination; the two tests are highly correlated (ρ = 0.94) (15). After establishing high participation rates, we gradually added 5 other cognitive tests: the East Boston Memory Test—immediate and delayed recalls (16), category fluency (17, 18), delayed recall of the TICS 10-word list, and digit span backward (19). Despite the gradual introduction of cognitive tests, 87% of women completed all 6 tests in our cognitive battery during the initial cognitive interview. We found that our telephone-based cognitive battery was highly valid compared with detailed, in-person interviews (ρ = 0.81 for scores using the two methods in a validation study among 61 women). Inter-interviewer reliability was high across 10 interviewers (ρ > 0.95 for each cognitive test), and participation rates were virtually identical across all cognitive tests and remained stable over time.

We evaluated 3 primary outcomes selected a priori: 2 measures of general cognition (a global composite score and the TICS score) and a verbal composite score, as verbal memory is a strong predictor of the development of Alzheimer's disease (20–22). Because our 6 cognitive tests are scaled differently, we used z scores to create the 2 composite measures; specifically, we calculated the difference between each participant's individual score and the overall mean score for our study population and divided by the standard deviation of the study population. To create the global score, we averaged z scores for all 6 cognitive tests; we created the verbal score by averaging the immediate and delayed recalls of both the East Boston Memory Test and the TICS 10-word list. Composite scores were constructed only for women who completed all contributing tests.

Statistical analysis

Because of the long period of pathogenesis underlying cognitive decline, long-term dietary habits are likely to be most relevant; thus, we averaged antioxidant intakes from 1980 through each woman's last dietary report prior to her initial cognitive interview, to obtain the most stable measures reflecting long-term diet (11). Women had an average of 5 dietary assessments over a mean of 17 years. We evaluated total intakes of vitamin E, vitamin C, and carotenoids (derived from foods and supplements) and dietary intakes of vitamin E, vitamin C, and carotenoids (derived from foods only) in relation to cognitive decline; we also examined associations of antioxidant intake from supplements with cognitive decline. In addition to total carotenoids, we considered the following individual carotenoids: beta-carotene, alpha-carotene, lutein/zeaxanthin, lycopene, and beta-cryptoxanthin. Of the carotenoids, only beta-carotene was regularly included in vitamin supplements throughout the dietary reporting period; thus, we evaluated beta-carotene in foods and supplements but only dietary intakes of alpha-carotene, lutein/zeaxanthin, lycopene, and beta-cryptoxanthin.

In our analyses, we found nonlinearity in cognitive trajectories due to "learning effects," primarily between interviews 1 and 2 (i.e., there was an average increase in cognitive scores between assessments 1 and 2, followed by an average decline in scores at interviews 3 and 4); thus, we averaged test scores at cognitive assessments 1 and 2 to obtain a "robust baseline" score (23), yielding linear cognitive trajectories over time. Then, we used multivariable-adjusted mixed linear regression to estimate mean differences

Table 1. Characteristics of Participants at the Time of the Initial Cognitive Interview, According to Selected Quintiles of Total Vitamin E, Vitamin C, and Carotenoid Intake[a], Nurses' Health Study, 1995–2001

	Total Vitamin E			Total Vitamin C			Total Carotenoids		
	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5
Median intake[b]	7	31	159	124	244	761	8,631	13,841	21,310
Mean age, years	74.2	74.2	74.3	74.1	74.2	74.3	74.3	74.2	74.2
Education, % with graduate-level degree	5	6	6	5	7	7	4	6	9
Median alcohol intake, g/day	0	0.88	0.88	0	0.88	0.88	0	0.88	0.88
Current smoking, %	11	7	7	12	7	7	11	7	7
Median physical activity, MET-hours/week[c]	7.7	10.2	10.2	7.5	10.3	10.4	7.4	9.5	14.2
Obesity[d], %	19	19	16	19	18	16	17	17	17
Use of antidepressant medication, %	4	6	6	4	5	7	6	6	5
History of high blood pressure, %	56	55	55	54	56	56	54	55	56
History of high cholesterol, %	59	66	68	61	66	66	63	67	65
History of type 2 diabetes, %	10	10	9	11	11	9	9	10	10
History of myocardial infarction, %	6	6	6	7	5	6	7	6	6
Mean total energy intake, kcal/day	1,612	1,736	1,613	1,649	1,713	1,617	1,685	1,680	1,653
Mean baseline cognitive score[e]									
Global composite	−0.06	0.01	0.00	−0.03	0.01	0.02	−0.08	0.01	0.05
Verbal composite	−0.06	0.00	0.00	−0.03	0.00	0.01	−0.09	0.00	0.07
TICS	33.7	33.9	33.9	33.8	33.9	33.9	33.7	33.9	34.0

Abbreviations: MET, metabolic equivalent of task; Q, quintile; TICS, Telephone Interview for Cognitive Status.
[a] Total intake includes the contributions of foods and supplements.
[b] Median intakes are expressed in g/day for vitamins E and C and in μg/day for carotenoids.
[c] One MET-hour is proportional to the amount of energy spent sitting quietly for 1 hour.
[d] Obesity was defined as body mass index (weight (kg)/height $(m)^2$) ≥30.
[e] Average of cognitive scores from cognitive interviews 1 and 2.

in rates of cognitive decline over 3 time points across quintiles of various antioxidant intakes. Specifically, we used repeated-measures models with random intercepts and slopes, which permits description of individual cognitive trajectories over time and provides explicit tests regarding the relation of antioxidant intakes and rates of cognitive decline. We calculated 95% confidence intervals and performed linear tests of trend using the median values of quintiles.

In our analyses, we considered multiple potential confounders: age (years; continuous), education (registered nurse degree, bachelor's degree, or graduate degree), antidepressant use (yes, no), alcohol intake (none, 0–14 g/day, ≥15 g/day, or missing data), smoking (never, past, or current), physical activity (quintiles of metabolic equivalent of task-hours/week, or missing data), total energy intake (quintiles of kcal/day), body mass index (<22, 22–24, 25–30, ≥30, or missing data), history of high blood pressure (yes, no), history of high cholesterol (yes, no), history of type 2 diabetes (yes, no), and history of myocardial infarction (yes, no). When relevant, to consider possible confounding by vitamin supplements, we controlled for vitamin E supplement use (yes, no, or missing data), vitamin C supplement use (yes—regularly, yes—seasonally, no, or missing data), and multivitamin supplement use (yes, no, or missing data), except when doing so would have adjusted for the exposure of interest (e.g., we did not adjust for vitamin E supplement use in analyses of total vitamin E). In addition, we adjusted analyses of total and dietary vitamin E for polyunsaturated fat intake (quintiles) because vitamin E and polyunsaturated fat are found in common food sources. Levels of all covariates were determined at the time of initial cognitive interview, except total energy intake, which was averaged to correspond with the method used to calculate antioxidant intakes.

We conducted additional analyses of cognitive status as well. Specifically, we evaluated an alternative outcome by averaging all 4 of our repeated cognitive assessments to obtain "average" cognition in later life. Given the very long exposure period over which we evaluated antioxidant intake (approximately 15–20 years), it seemed plausible that any impact of antioxidants on brain health may have occurred prior to our initial cognitive assessment; thus, relations might be better reflected by a measure of "average" cognition in later life than by analyses of change in cognition over a relatively short period of 6 years subsequent to the initial cognitive assessment. Thus, the average of all 4 repeated cognitive measurements was considered a representation

Table 2. Mean Difference[a] in Rates of Cognitive Decline Over the Follow-Up Period Across Quintiles of Total[b] and Dietary[c] Intake of Vitamin E, Vitamin C, and Carotenoids, Nurses' Health Study, 1995–2001

Antioxidant and Quintile	Median Intake[d]	Global Composite		Verbal Composite		TICS	
		Mean Difference	95% CI	Mean Difference	95% CI	Mean Difference	95% CI
Total vitamin E[e,f]							
1	7	0.00	Referent	0.00	Referent	0.00	Referent
2	12	−0.02	−0.07, 0.03	0.00	−0.06, 0.06	0.08	−0.13, 0.29
3	31	−0.01	−0.06, 0.04	0.01	−0.05, 0.08	0.21	−0.01, 0.42
4	69	0.00	−0.05, 0.05	0.02	−0.04, 0.09	0.29	0.07, 0.51
5	159	−0.03	−0.08, 0.03	−0.01	−0.08, 0.05	0.06	−0.17, 0.29
P-trend[g]			0.44		0.51		0.75
Dietary vitamin E[e,h]							
1	6.2	0.00	Referent	0.00	Referent	0.00	Referent
2	7.1	0.02	−0.02, 0.07	0.03	−0.03, 0.09	0.20	0.00, 0.40
3	7.8	0.04	−0.01, 0.09	0.04	−0.02, 0.09	0.15	−0.05, 0.35
4	8.5	0.03	−0.02, 0.07	0.03	−0.02, 0.09	0.10	−0.10, 0.30
5	9.9	0.04	−0.01, 0.09	0.06	0.00, 0.12	0.14	−0.06, 0.34
P-trend			0.20		0.09		0.50
Total vitamin C[e,i]							
1	124	0.00	Referent	0.00	Referent	0.00	Referent
2	178	0.00	−0.05, 0.05	0.02	−0.04, 0.07	0.02	−0.18, 0.21
3	244	−0.02	−0.06, 0.03	−0.01	−0.07, 0.05	0.00	−0.20, 0.20
4	389	−0.03	−0.08, 0.02	−0.03	−0.09, 0.03	−0.03	−0.23, 0.18
5	761	−0.06	−0.11, −0.01	−0.05	−0.11, 0.01	−0.24	−0.46, −0.03
P-trend			0.006		0.04		0.006
Dietary vitamin C[e,j]							
1	95	0.00	Referent	0.00	Referent	0.00	Referent
2	126	0.01	−0.04, 0.06	0.01	−0.04, 0.07	0.08	−0.11, 0.27
3	149	−0.03	−0.07, 0.02	0.00	−0.06, 0.05	−0.04	−0.23, 0.16
4	173	0.01	−0.04, 0.06	0.01	−0.04, 0.07	0.11	−0.09, 0.30
5	213	0.00	−0.05, 0.05	0.01	−0.05, 0.07	0.08	−0.12, 0.28
P-trend			0.99		0.76		0.40

Table continues

of overall cognitive status at older ages. Finally, we examined the possibility that smoking—a major contributor to oxidative stress—might modify the association between antioxidant intake and cognition.

All statistical analyses were conducted in SAS, version 9 (SAS Institute Inc., Cary, North Carolina), and all statistical tests were 2-sided.

RESULTS

Key health and lifestyle characteristics of participants at the time of initial cognitive interview are presented in Table 1. Overall, characteristics were generally similar across increasing quintiles of long-term total vitamin E, vitamin C, and carotenoid consumption. However, overall, women had slightly higher physical activity levels and baseline cognitive scores across increasing quintiles of antioxidant intake; these trends were most pronounced for total carotenoids. Trends were similar when we considered dietary intakes of vitamin E, vitamin C, and carotenoids from foods only (data not shown in table).

In models adjusted for multiple potentially confounding factors, total vitamin E intake was not related to cognitive decline (e.g., for the global score, P-trend = 0.44) (Table 2). We initially observed a modest association between greater intake of dietary vitamin E and slower cognitive decline in multivariable-adjusted models (e.g., P-trend = 0.07 for the global score), but further adjustment for polyunsaturated fat intake attenuated this association (e.g., P-trend = 0.20 for the global score). Similarly, no association was found for long-term intake of vitamin E from supplements and cognitive decline (e.g., for the global score in multivariable-adjusted models, P-trend = 0.37; results not shown in table). However, with adjustment for covariates, greater consumption of total vitamin C was related to worse cognitive decline in the global score (P-trend = 0.006), the verbal

Table 2. Continued

Antioxidant and Quintile	Median Intake[d]	Global Composite		Verbal Composite		TICS	
		Mean Difference	95% CI	Mean Difference	95% CI	Mean Difference	95% CI
Total carotenoids[e,j]							
1	8,631	0.00	Referent	0.00	Referent	0.00	Referent
2	11,436	0.02	−0.03, 0.06	0.01	−0.04, 0.07	0.12	−0.07, 0.32
3	13,841	0.02	−0.03, 0.07	0.01	−0.04, 0.07	0.10	−0.09, 0.30
4	16,594	0.05	0.00, 0.10	0.05	−0.01, 0.11	0.18	−0.01, 0.38
5	21,310	0.01	−0.04, 0.06	0.01	−0.05, 0.07	0.09	−0.11, 0.29
P-trend		0.51		0.44		0.36	
Dietary carotenoids[e,j]							
1	8,326	0.00	Referent	0.00	Referent	0.00	Referent
2	11,095	0.04	0.00, 0.09	0.04	−0.02, 0.10	0.13	−0.06, 0.33
3	13,407	0.00	−0.05, 0.05	0.00	−0.06, 0.05	−0.03	−0.23, 0.16
4	16,044	0.06	0.02, 0.11	0.07	0.01, 0.13	0.17	−0.03, 0.36
5	20,506	0.01	−0.03, 0.06	0.02	−0.03, 0.08	0.09	−0.10, 0.29
P-trend		0.48		0.29		0.34	

Abbreviations: CI, confidence interval; TICS, Telephone Interview for Cognitive Status.

[a] Mean differences compare the mean rates of cognitive decline over follow-up for women in the quintile of interest with women in quintile 1 (the referent). Therefore, a positive mean difference indicates that women in the quintile of interest have less decline than those in quintile 1; a negative mean difference indicates that women in the quintile of interest have more decline than those in quintile 1.

[b] Total intake includes the contributions of foods and supplements.

[c] Dietary intake includes the contribution of foods only.

[d] Median intakes are expressed in g/day for vitamins E and C and in μg/day for carotenoids.

[e] Adjusted for age, education, antidepressant use (yes, no), alcohol intake (none, 0–14 g/day, ≥ 15 g/day, or missing data), smoking (never, past, or current), physical activity (quintiles of metabolic equivalent of task-hours/week, or missing data), total energy intake (quintiles of kcal/day), body mass index (<22, 22–24, 25–30, ≥30, or missing data), history of high blood pressure (yes, no), history of high cholesterol (yes, no), history of type 2 diabetes (yes, no), and history of myocardial infarction (yes, no).

[f] Additionally adjusted for use of vitamin C supplements (yes—regularly, yes—seasonally, no, or missing data), use of multivitamins (yes, no, or missing data), and polyunsaturated fat intake (quintiles).

[g] Linear tests for trend were performed using the median value of each quintile as a continuous variable in regression models.

[h] Additionally adjusted for use of vitamin E supplements (yes, no, or missing data), vitamin C supplements, and multivitamins and polyunsaturated fat intake (quintiles).

[i] Additionally adjusted for use of vitamin E supplements and multivitamins.

[j] Additionally adjusted for use of vitamin E supplements, vitamin C supplements, and multivitamins.

score (*P*-trend = 0.04), and TICS score (*P*-trend = 0.006)—a finding that was inconsistent with our a priori hypothesis. Although dietary consumption of vitamin C was not associated with cognitive decline (e.g., *P*-trend = 0.99 for the global score), higher intake of supplemental vitamin C was related to worse cognitive decline over the follow-up period (e.g., *P*-trend = 0.001 for the global score; comparing extreme quintiles of intake, mean difference = − 0.07, 95% confidence interval (CI): −0.13, 0.02) (supplement results not shown in table), which explained the finding for total vitamin C and cognitive decline. In addition, no associations were observed between total carotenoid intake (from supplements and foods) or dietary carotenoid intake (from foods only) and cognitive decline in models adjusted for multiple potentially confounding factors (e.g., *P*-trend = 0.51 and *P*-trend = 0.48 for the global score). Supplemental carotenoid intake (from beta-carotene supplements) was unrelated to cognitive decline as well (e.g., *P*-trend = 0.32 for the global score) (results not shown in table).

In analyses of individual carotenoids, we found that higher long-term consumption of lycopene from food sources was related to slower cognitive decline (i.e., a better outcome) in the global score (*P*-trend = 0.05) and the verbal score (*P*-trend = 0.009) (results not shown in tables). For example, participants in the highest quintile of lycopene intake had a mean decline in the verbal score that was 0.08 standard units less over follow-up (95% CI: 0.03, 0.14) than participants in the lowest quintile. To help interpret the mean differences observed with greater lycopene intake, we found that 1 year of age was associated with a mean decline of 0.05 standard units on the verbal score; thus, the mean difference that we observed between extreme quintiles of lycopene intake over the follow-up period of 6 years was equivalent to approximately 1–2 years of cognitive aging. Long-term intakes of total

Table 3. Mean Difference[a] in "Average" Cognition Score (Average of Scores From All 4 Cognitive Assessments) in Later Life Across Quintiles of Total[b] and Dietary[c] Intake of Vitamin E, Vitamin C, and Carotenoids, Nurses' Health Study, 1995–2001

Antioxidant and Quintile	Median Intake[d]	Global Composite		Verbal Composite		TICS	
		Mean Difference	95% CI	Mean Difference	95% CI	Mean Difference	95% CI
Total vitamin E[e,f]							
1	7	0.00	Referent	0.00	Referent	0.00	Referent
2	12	0.04	0.01, 0.07	0.03	0.00, 0.07	0.17	0.04, 0.30
3	31	0.05	0.02, 0.08	0.05	0.01, 0.08	0.21	0.07, 0.34
4	69	0.08	0.05, 0.11	0.09	0.05, 0.12	0.31	0.17, 0.45
5	159	0.05	0.02, 0.08	0.05	0.02, 0.09	0.16	0.02, 0.31
P-trend[g]		0.12		0.06		0.49	
Dietary vitamin E[e,h]							
1	6.2	0.00	Referent	0.00	Referent	0.00	Referent
2	7.1	0.03	0.00, 0.05	0.03	0.00, 0.06	0.08	−0.04, 0.21
3	7.8	0.04	0.01, 0.06	0.04	0.00, 0.07	0.12	0.00, 0.25
4	8.5	0.04	0.01, 0.07	0.05	0.01, 0.08	0.12	0.00, 0.25
5	9.9	0.05	0.02, 0.08	0.08	0.04, 0.11	0.14	0.02, 0.27
P-trend		0.0008		< 0.0001		0.03	
Total vitamin C[e,i]							
1	124	0.00	Referent	0.00	Referent	0.00	Referent
2	178	−0.02	−0.05, 0.01	−0.02	−0.06, 0.01	−0.09	−0.22, 0.03
3	244	0.01	−0.02, 0.04	0.01	−0.02, 0.04	0.01	−0.11, 0.14
4	389	0.01	−0.02, 0.04	0.02	−0.02, 0.05	0.00	−0.13, 0.13
5	761	0.00	−0.03, −0.04	0.00	−0.04, 0.03	−0.06	−0.20, 0.07
P-trend		0.51		0.77		0.54	
Dietary vitamin C[e,j]							
1	95	0.00	Referent	0.00	Referent	0.00	Referent
2	126	0.03	0.00, 0.05	0.02	−0.01, 0.05	0.16	0.04, 0.28
3	149	0.01	−0.02, 0.03	0.01	−0.03, 0.04	0.05	−0.07, 0.18
4	173	0.02	−0.01, 0.05	0.03	0.00, 0.06	0.10	−0.02, 0.23
5	213	0.03	0.00, 0.06	0.04	0.01, 0.07	0.16	0.03, 0.28
P-trend		0.12		0.009		0.05	

Table continues

beta-carotene, dietary beta-carotene, alpha-carotene, lutein/zeaxanthin, and beta-cryptoxanthin were not related to cognitive decline (e.g., *P*-trend values for the global score were 0.76, 0.77, 0.61, 0.88, and 0.69, respectively, after adjustment for multiple potential confounders).

In alternate analyses of cognitive function averaged across all 4 time points, greater intake of total vitamin E was not related to cognitive status measured by our 3 primary outcomes (e.g., *P*-trend = 0.12 for the global score), whereas the relation with dietary vitamin E was significant for these outcomes (e.g., *P*-trend = 0.0008 for the global score) (Table 3). However, findings for dietary vitamin E were attenuated after polyunsaturated fat intake was included in the models. Because polyunsaturated fat intake is measured with error, there is concern that residual confounding may explain these results. In contrast to our finding above for total vitamin C and cognitive decline, there was no association for total vitamin C intake and average cognitive status after controlling for possible confounding factors (e.g., for the global score, *P*-trend = 0.51). A positive association between greater dietary vitamin C intake and better cognitive status was observed only for the verbal score (*P*-trend = 0.009). Furthermore, higher intakes of total and dietary carotenoids were both associated with better cognition at older ages as assessed by the global score (*P*-trend = 0.0001 and *P*-trend = 0.0005 for total and dietary intakes of carotenoids, respectively) and the verbal score (*P*-trend < 0.0001 for both). When we explored associations between individual carotenoids and overall cognition, we found that greater intakes of lutein/zeaxanthin and lycopene were related to better cognitive status (e.g., in multivariable-adjusted models, *P*-trend = 0.0002 and *P*-trend < 0.0001, respectively, for the global score) (results not shown in table).

Table 3. Continued

Antioxidant and Quintile	Median Intake[d]	Global Composite		Verbal Composite		TICS	
		Mean Difference	95% CI	Mean Difference	95% CI	Mean Difference	95% CI
Total carotenoids[e,j]							
1	8,631	0.00	Referent	0.00	Referent	0.00	Referent
2	11,436	0.03	0.01, 0.06	0.04	0.01, 0.07	0.09	−0.03, 0.22
3	13,841	0.05	0.02, 0.08	0.05	0.02, 0.09	0.13	0.01, 0.26
4	16,594	0.05	0.02, 0.08	0.07	0.03, 0.10	0.11	−0.02, 0.23
5	21,310	0.06	0.03, 0.09	0.09	0.06, 0.13	0.13	0.00, 0.25
P-trend		0.0001		< 0.0001		0.08	
Dietary carotenoids[e,j]							
1	8,326	0.00	Referent	0.00	Referent	0.00	Referent
2	11,095	0.05	0.02, 0.08	0.07	0.04, 0.10	0.13	0.01, 0.25
3	13,407	0.05	0.02, 0.08	0.06	0.03, 0.09	0.12	0.00, 0.25
4	16,044	0.06	0.03, 0.09	0.08	0.05, 0.12	0.14	0.02, 0.27
5	20,506	0.06	0.03, 0.09	0.10	0.07, 0.13	0.11	−0.01, 0.24
P-trend		0.0005		< 0.0001		0.13	

Abbreviations: CI, confidence interval; TICS, Telephone Interview for Cognitive Status.

[a] Mean differences compare the mean "average cognition" in later life for women in the quintile of interest with women in quintile 1 (the referent). Therefore, a positive mean difference indicates that women in the quintile of interest have higher "average cognition" than those in quintile 1; a negative mean difference indicates that women in the quintile of interest have lower "average cognition" than those in quintile 1.

[b] Total intake includes the contributions of foods and supplements.

[c] Dietary intake includes the contribution of foods only.

[d] Median intakes are expressed in g/day for vitamins E and C and in μg/day for carotenoids.

[e] Adjusted for age (years; continuous), education (registered nurse degree, bachelor's degree, graduate degree), time span between cognitive interviews (years; continuous), antidepressant use (yes, no), alcohol intake (none, 0–14 g/day, ≥15 g/day, or missing data), smoking (never, past, or current), physical activity (quintiles of metabolic equivalent of task-hours/week, or missing data), total energy intake (quintiles of kcal/day), body mass index (<22, 22–24, 25–30, ≥30, or missing data), history of high blood pressure (yes, no), history of high cholesterol (yes, no), history of type 2 diabetes (yes, no), and history of myocardial infarction (yes, no).

[f] Additionally adjusted for use of vitamin C supplements (yes—regularly, yes—seasonally, no, or missing data), use of multivitamins (yes, no, or missing data), and polyunsaturated fat intake (quintiles).

[g] Linear tests for trend were performed using the median value of each quintile as a continuous variable in regression models.

[h] Additionally adjusted for use of vitamin E supplements (yes, no, or missing data), vitamin C supplements, and multivitamins and polyunsaturated fat intake (quintiles).

[i] Additionally adjusted for use of vitamin E supplements and multivitamins.

[j] Additionally adjusted for use of vitamin E supplements, vitamin C supplements, and multivitamins.

Finally, there was no evidence of effect modification by smoking status for antioxidant intakes in relation to cognitive decline (e.g., for decline on the global score, *P* values for interaction were 0.24 for total vitamin E intake, 0.87 for total vitamin C intake, and 0.68 for total carotenoid intake).

DISCUSSION

We found no clear or consistent evidence that greater consumption of vitamin E or vitamin C was associated with cognition in this cohort of older women. However, higher lycopene intake was related to less cognitive decline in this study, and in analyses of overall cognition at older ages (i.e., averaging all 4 of our repeated cognitive measures), we confirmed the relation with lycopene and observed similar associations for total carotenoids and lutein/zeaxanthin as well.

There have been several previous randomized clinical trials of antioxidant supplements and cognition in older adults. In the Age-Related Eye Disease Study ($n = 2{,}166$), participants who were given a combination of vitamin E, vitamin C, and beta-carotene over a period of 7 years demonstrated similar levels of cognitive function compared with a placebo group (e.g., mean scores on the Mini-Mental State Examination were 92.7 and 92.1, respectively; $P > 0.05$) (5). Another trial, the Women's Health Study ($n = 6{,}377$), identified a virtually identical risk of substantial cognitive decline in the vitamin E supplement group versus the placebo group over 10 years of supplementation (relative risk = 0.98, 95% CI: 0.83, 1.16) (7). In addition, 2 trials of antioxidants in women with existing cardiovascular risk factors or cardiovascular disease yielded null results. In the Women's Antioxidant and Cardiovascular Study ($n = 2{,}824$), Kang et al. (8) found that 9 years of supplementation with vitamin E, vitamin C, and beta-carotene did little to slow cognitive decline (e.g., comparing vitamin E and placebo groups, mean difference in TICS score = −0.01, 95% CI: −0.24, 0.23), and investigators in the Heart

Protection Study ($n = 20,536$) detected no significant differences in mean TICS scores (24.1 vs. 24.0) for persons receiving a combined vitamin E, vitamin C, and beta-carotene supplement versus placebo over a period of 5 years (4). Our data on intakes of vitamins E and C over 15–20 years are generally similar to the results of these trials.

For carotenoids, our data suggest a possible relation between higher levels of very long-term intake and better cognition, especially in our analyses of overall cognitive status at older ages. These results are generally consistent with those of Physicians' Health Study II ($n = 4,052$), the longest-term antioxidant trial to date, in which men received beta-carotene supplementation for 18 years and had higher cognitive function scores than those receiving placebo (e.g., mean difference in TICS score = 0.18, 95% CI: 0.01, 0.35) (9). These findings certainly merit further consideration in future research, as increased carotenoid intake would be a simple intervention for maintaining cognitive function, although it appears that consistent consumption over at least 15 years is needed.

Previous observational studies of dietary antioxidants and cognitive decline have yielded inconsistent results, with 2 studies producing null results (24, 25) and 2 others finding inverse relations (26, 27). However, none of these studies focused specifically on long-term diet, and all employed a single measure of diet to estimate antioxidant intakes. In contrast, a major strength of our study is that we collected information on dietary antioxidant intake over 2 decades, allowing us to obtain stable estimates of long-term diet beginning in midlife—a particularly relevant exposure period during which dementia pathogenesis is thought to begin (11).

To our knowledge, the association between higher lycopene intake and slower cognitive decline has not been previously reported in a large, prospective study, although we found consistent relations between higher lycopene intake and cognition across all analyses. Lycopene is a strong antioxidant in the presence of oxygen free radicals (28), and 2 studies have identified a relation between higher levels of plasma lycopene and better cognitive function (29, 30). Growing evidence also indicates that lycopene has multiple microvascular benefits, including prevention of endothelial injury, reduction of inflammatory factors, and inhibition of smooth muscle cell proliferation (31). Furthermore, a recent meta-analysis demonstrated that lycopene significantly reduced serum total cholesterol, low density lipoprotein cholesterol, and systolic blood pressure in human intervention trials (32). Because strong evidence has linked vascular factors and cognitive decline (33), these benefits might represent mechanisms by which lycopene could help to mitigate cognitive decline. Nonetheless, among the various carotenoids that we considered, we did not have any specific a priori hypothesis regarding lycopene, and this finding should be interpreted cautiously.

Several important limitations of this study should be discussed. First, the dietary information used in our analysis was reported by the participants, and therefore nondifferential misclassification of our exposures may have caused us to underestimate the associations of interest. Although this could possibly explain our null findings for most of the antioxidant nutrients, our averaging of multiple dietary assessments helped to reduce random measurement error (34). In addition, we have previously established our ability to detect important diet-cognition associations for other self-reported nutrients in this cohort (35, 36). Second, this was an observational study, and therefore residual confounding could explain our findings, although we would expect such confounding to create rather than obscure associations. In particular, physical activity levels increased across increasing quintiles of carotenoid intake, and although we controlled for physical activity levels and other indicators of healthy lifestyle, we cannot entirely rule out residual confounding by these factors. Third, residual confounding might particularly influence analyses of average cognition due to factors that persist over time (e.g., education) and affect the cognitive level a person achieves more than a person's cognitive trajectory in later life. However, we carefully adjusted for many potentially confounding variables in all analyses, and for the most part these adjustments did not meaningfully change our results for average cognition, which suggests that residual confounding, or unknown confounding factors, would be unlikely to completely explain our findings. In addition, our conclusions regarding a potential association of carotenoid intake and cognition were based on associations observed for both cognitive decline and average cognition, which provides some reassurance that our results are valid. Nonetheless, residual confounding cannot be ruled out entirely, and therefore our findings should be interpreted with caution.

In summary, this study found that long-term consumption of vitamins E and C was not consistently related to cognition in this cohort. However, there appeared to be a relation between higher intake of lycopene and slower cognitive decline, as well as strong associations between greater carotenoid intake and better overall cognition. Future studies should further investigate the potential association between carotenoids and cognitive decline, especially long-term patterns of intake, which are most likely to influence cognitive health.

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