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ANTIOXIDANTS AND COGNITION

ANTIOXIDANT INTAKE AND COGNITIVE FUNCTION OF ELDERLY MEN AND WOMEN: THE CACHE COUNTY STUDY

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Abstract: *Objective:* We prospectively examined associations between intakes of antioxidants (vitamins C, vitamin E, and carotene) and cognitive function and decline among elderly men and women of the Cache County Study on Memory and Aging in Utah. *Participants and Design:* In 1995, 3831 residents 65 years of age or older completed a baseline survey that included a food frequency questionnaire and cognitive assessment. Cognitive function was assessed using an adapted version of the Modified Mini-Mental State examination (3MS) at baseline and at three subsequent follow-up interviews spanning approximately 7 years. Multivariate-mixed models were used to estimate antioxidant nutrient effects on average 3MS score over time. *Results:* Increasing quartiles of vitamin C intake alone and combined with vitamin E were associated with higher baseline average 3MS scores (p-trend = 0.013 and 0.02 respectively); this association appeared stronger for food sources compared to supplement or food and supplement sources combined. Study participants with lower levels of intake of vitamin C, vitamin E and carotene had a greater acceleration of the rate of 3MS decline over time compared to those with higher levels of intake. *Conclusion:* High antioxidant intake from food and supplement sources of vitamin C, vitamin E, and carotene may delay cognitive decline in the elderly.

Key words: Antioxidants, cognition, elderly, dementia-prevention.

Introduction

Cognitive impairment among the elderly, with or without dementia, represents a growing threat to the functional independence of aging populations worldwide. The main causes of severe cognitive impairment in the elderly are Alzheimer's Disease (AD) and vascular dementia (1). Lesser degrees of cognitive-impairment among the elderly are more common than dementia, may indicate early stages of disease development (2) and are strong predictors of decline to dementia (3). Strategies aimed at maintaining cognitive function with age may be especially important in the prevention of dementing disease among the elderly.

In the mid-1950's Harman (4) was among the first to suggest that the degenerative diseases of aging that progress to dementia may result from oxidative damage by the attacks of free radicals on cellular constituents. A common element of known risk factors for Alzheimer's disease and vascular dementia is the formation of free oxygen radicals (5-8). The hypothesis that antioxidant vitamins in the human diet may protect against degenerative diseases of aging, including those leading to cognitive impairment, has become popular in recent years, but supporting evidence from population studies is equivocal (9-17).

In prospective longitudinal analyses of data from the Cache County, Utah, Study on Memory, Health, and Aging, the authors examined associations between dietary intakes of antioxidant nutrients from both food and supplemental sources, cognitive function, and change in cognitive function over a seven-year period.

Subjects and Methods

Study Population

The Cache County Study on Memory, Health and Aging is a population-based longitudinal study of the prevalence and incidence of dementia among elderly residents of a single county in Utah. There were 5,677 permanent residents of Cache County, aged 65 or older on January 1, 1995 (per Health Care Financing Administration records and local public relations efforts), of which 5,092 (90%) enrolled in the study and completed the baseline interview (1995-1996). Additional follow-up surveys were conducted in 1997-1998, 1998-1999, and 2002-2003. The average length of follow-up for those completing all waves of follow-up was 7.2 years. The study was approved by the institutional review boards of Utah State University, The Johns Hopkins University, and Duke University. All participants or their relatives in the case of

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impaired persons gave written, informed consent to participate in the study.

The baseline survey instrument included information on demographic characteristics, health history, family history of dementia, use of medications, alcohol, tobacco, and other lifestyle factors. In addition, participants were asked to provide a cheek-swab DNA sample that was used for APOE genotyping. The Modified Mini-Mental State Examination (3MS) was used to assess cognitive function and to screen for dementia at the baseline and follow-up assessments (18, 19).

The baseline visit as well as follow-up visits two and three were conducted in person whereas the second follow-up visit was conducted over the telephone. In a previous analysis of data from the Cache study, the Telephone Modified Mini-Mental State Exam provided a reasonable substitute for the more costly in-person 3MS, at least among subjects without major cognitive syndromes (20). Participants who scored below an education and sensory adjusted cut-point on any of the three in-person administrations of the 3MS at any time point went on to a multi-stage assessment protocol to identify and diagnose prevalent and incident dementia. If dementia was ever diagnosed, participants did not go on to complete a 3MS at subsequent follow-ups. The details of this protocol have been published elsewhere (21, 22).

A dietary food frequency questionnaire (FFQ) was left with all participants who completed their own baseline interview. The FFQ, based on the methods developed by the Nurses' Health Study (23) and later evaluated among elderly women, (24) was used to assess the usual dietary intake of participants. It included queries on 141 food items and use of vitamin and mineral supplements. Participants were instructed to complete the dietary questionnaire and to return it in a pre-addressed, postage-paid envelope. Daily intake of each nutrient was computed by multiplying the nutrient content of the food item by the reported frequency of intake and summing over all food items. Nutrient analysis was completed using the nutrient database and computer programs provided by the Nurses' Health Study. All nutrients from foods were adjusted for total caloric intake using the regression-residual method (25). To obtain a measure of total nutrient intake, nutrient intake from supplements were added to energy adjusted nutrient intake from foods. In addition, use of dietary supplements providing vitamin C, vitamin E, or carotene were categorized into groups of no, low-moderate (< 500 mg vitamin C per day, < 400 IU vitamin E per day, < 10,000 IU carotene per day) or high (≥ 500 mg vitamin C per day, ≥ 400 IU vitamin E per day, ≥ 10,000 IU carotene per day) daily dose of individual supplements.

Of the 5092 participants who were screened during the baseline survey, 355 scored below the cutoff for the 3MS and did not receive an FFQ. Of the remaining 4737 participants, 3831 (81%) completed and returned the FFQ. Of the returned dietary questionnaires, 74 were excluded because of implausible caloric intakes (less than 600 or greater than 5000 kcal per day); an additional 123 were identified as having prevalent dementia after clinical assessment and were also excluded. Complete data that allowed estimation of usual dietary intake of antioxidants at the baseline interview and at least one assessment of cognitive function represented by the 3MS score were available for 3632 participants including 1566 men and 2066 women. Non-dietary covariates were obtained during the baseline interview and included self-reported age, gender, level of education (years of school completed), APOE genotype, history of tobacco and alcohol use, physical activity (indicator of vigorous physical activity at least once per week), and history of diabetes, myocardial infarction, and stroke.

Statistical Analyses

Mixed-models in the SAS statistical software package were used to examine associations between antioxidant nutrient intakes and average 3MS score over the period of study. Associations were examined for nutrient intake from foods alone and for foods and supplements combined. A variable representing the periods in which the four 3MS data assessments were conducted (time) was included in all mixed models. All models included both linear and quadratic terms for time in order to account for curvilinear trajectories of 3MS performance over time. Intakes of the antioxidant nutrients were modeled as quartiles of intake. Interactions between the time variables and the nutrient variables of interest were tested by comparing the likelihood ratio test statistics between models with and without the interaction terms. Associations were then examined in models adjusting for age and gender and then in more complex models adjusting for other important risk factors including education, APOE status (yes or no indicator of the presence of an ε4 allele), physical activity, body mass index (BMI; weight in kg/height in M^2), and history of diabetes, myocardial infarction, and stroke. In addition, the possible confounding effect of other antioxidant nutrients were examined by including other antioxidants, modeled as continuous variables, in the multivariable models examining the main effect of a specific antioxidant (for example continuous variables for vitamin E and carotene were included in the model testing the association of vitamin C intake). Effect modification by gender, age (split at median age of population; < 80 years vs. >= 80 years), education (<12 years, >= 12 years), and APOE status were examined in separate models that included terms for quartiles of nutrient intake, the potential effect modifier, time variables, and the interaction terms between these variables. None of the above interaction terms were statistically significant. Reported p-values are 2-sided, and the type I error rate for statistical significance was 0.05.

Results

At baseline, participants were aged 65 years and older (mean = 74.6, SD = 6.7) and had a mean education level of 13.3 years (SD = 2.8). Additional characteristics of participants by gender are listed in Table 1.

Table 1
Characteristics of participants in the Cache County, Utah, Study on Memory, Health and Aging by gender; baseline interview conduced in 1995.

Characteristics	Men (n=1566)	Women (n=2066)
Age (yrs)	74.2 (6.5)[a]	75.0 (6.8)
BMI (wt kg/ht m^2)	26.4 (3.9)	26.0 (4.8)
3MS scores		
1995-1996	90.5 (6.9)	91.7 (6.1)
1997-1998	90.0 (8.2)	90.9 (7.4)
1999-2000	91.1 (8.1)	91.4 (8.8)
2002-2003	88.6 (8.2)	89.2 (11.1)
Years of education	13.8 (3.4)	12.7 (2.3)
APOE status (ε4 allele present) (%)	32%	31%
Ever regularly drink alcohol (%)	27%	7%
Ever regularly smoked (%)	34.7%	6.9%
Ever used estrogen (%; women only)	–	58%
Diabetes (%)	14%	12%
Heart attack (%)	18%	9%
Stroke (%)	4%	4%
Vigorous physical activity at least once per week (%)	28%	15%
Calories (kcals/day)	2045 (750)	1887.5 (720)
Fruit and vegetable intake (servings/day)	5.8 (3.4)	6.5 (4.1)
Vitamin C (mg/day)	169.4 (93.6)	195.1 (95.8)
Vitamin E (mg/day)	10.3 (5.8)	11.1 (6.5)
Carotene (mg/day)	10517 (8533)	13512 (11719)
Supplemental vitamin C use[b] (%)	19.5%	24%
Supplemental vitamin E use[c] (%)	14.6%	15.3%
Supplemental carotene use[d] (%)	6%	7%

a. Mean (standard deviation); b. Supplemental vitamin C use = regular intake of at least 500 mg supplemental vitamin C per day; c.Vitamin E supplement use = regular intake of at least 400 IU supplemental vitamin E per day; d. Carotene supplement use = regular intake of at last 10,000 IU supplemental carotene per day

Table 2 includes characteristics of participants with complete and probable dietary intake by quartile of antioxidant intake from food. Participants consuming antioxidants in the higher quartiles of antioxidant intake (quartiles 2, 3, and 4) were more educated, scored higher on the baseline 3MS, and were more likely to be female as compared to participants in the lowest quartiles of antioxidant intake. In addition, participants in the highest quartiles of each specific antioxidant were more likely to take that antioxidant in supplement form and had higher mean intakes of other antioxidants from both food and supplemental sources compared to participants consuming in the lowest quartiles of intake.

In mixed models that controlled for age and gender, participants in the higher quartiles (quartile 3(Q3) and Q4) of vitamin C intake from both foods alone and foods and supplements combined had average baseline 3MS scores 0.74 – 0.89 points higher than those in the lowest quartile of intake (table 3). This association was attenuated but remained statistically significant in models that controlled for additional factors including APOE status, smoking and drinking status, BMI, education, physical activity, and history of diabetes, stroke, and myocardial infarction and intakes of vitamin E and carotene. High vitamin C supplement use (≥500 mg) was not associated with difference in mean baseline 3MS score (average 3MS scores of high vitamin C supplement uses was 0.122 (0.22) points higher than non-Vitamin C supplement users; p-value = 0.96) and vitamin C intake from food remained protective in models that controlled for vitamin C supplement use. In the multivariable model, the difference in mean 3MS scores from the lowest quartile to the highest quartiles of Vitamin C intake from foods were 0.0 (quartile 1, reference group), 0.24, 0.47, and 0.49 (p-trend = 0.04). The effect of Vitamin C intake from food was modified by time (p-value = 0.0014) such that those in the higher quartiles of Vitamin C intake (Q2-4) had slower rates of cognitive decline and thus higher 3MS scores than those in the lowest quartile of vitamin C intake at times 0, 1.5, and 3 years. The protective association of higher intakes of food sources of vitamin C appeared to be attenuated by the time of the last 3MS assessment at 7-years (figure, table 4).

In similar multivariable analyses that examined the effects of increasing quartiles of intake of vitamin E and carotene on 3MS scores, there was little evidence that higher intakes of either vitamin E or carotene were associated with higher 3MS scores at the baseline interview (time = 0-years) (table 3). However, the effects of higher intakes of both vitamin E and carotene

Table 2

Baseline characteristics by quartile of vitamin C, vitamin E and carotene intake from food among 3632 elderly men and women of the Cache County Study on Memory Health and Aging.

	Quartiles (Q) of intake				
Characteristic	**Q1**	**Q2**	**Q3**	**Q4**	**p-value**
Vitamin C from food					
Range (mg/d)	< 125	125 - 171	172 - 224	>224	
Age (yr)	74.7 (6.9)[a]	74.5 (6.7)	74.7 (6.6)	74.8 (6.5)	0.802
Education (yr)	13.1 (3.0)	13.2 (2.7)	13.6 (2.7)	13.5 (2.8)	<0.001
Baseline 3MS score	90.5 (7.0)	91.2 (6.4)	91.6 (6.3)	91.35 (6.4)	<0.001
Female (%)	44%	56%	63%	64%	<0.001
Calories (kcal/d)	2231 (792)	1754 (647)	1771 (638)	2066 (750)	<0.001
Vitamin C from food (mg/g)	85 (39)	148 (13)	196 (15)	306 (92)	<0.001
Vitamin E from food (IU/d)	9.7 (3.5)	10.5 (4.0)	11.2 (5.5)	11.6 (9.6)	0.002
Carotene from food, (IU/d)	8609 (9737)	11261 (8606)	13495 (9101)	15518 (12999)	<0.001
Vitamin C supplement use	19%	21%	22%	26%	<0.001
Vitamin E from food					
Range, IU/d	<8.4	8.4 – 9.8	9.9 – 11.6	>11.6	
Age (yr)	74.6 (6.9)[a]	74.6 (6.5)	74.4 (6.5)	75.0 (6.7)	0.29
Education (yr)	13.2 (3.0)	13.3 (2.7)	13.3 (2.7)	13.4 (2.8)	0.42
Baseline 3MS score	90.7 (6.9)	91.2 (6.2)	91.7 (6.2)	91.1 (6.6)	0.017
Female (%)	47	57	60	64	<0.001
Calories (kcal/d)	2239 (755)	1780 (626)	1717 (649)	2087 (778)	<0.001
Vitamin E from food (IU/d)	6.9 (1.5)	9.1 (0.42)	10.6 (0.49)	16.4 (10.0)	<0.001
Vitamin C from food (mg/d)	180.3 (119)	177.4 (84)	182.6 (71.7)	195.6 (99.6)	<0.001
Carotene from food (IU/d)	9197 (6941)	11213 (7353)	12986 (8813)	16487 (15204)	<0.001
Vitamin E supplement use	9.9%	15%	16.3%	18.7%	<0.001
Carotene from food					
Range, IU/d	<6776	6775 - 10111	10111 - 15145	>15145	
Education (yr)	13.0 (2.9)[a]	13.2 (2.7)	13.5 (2.8)	13.6 (2.7)	<0.001
Age, mean (yr)	74.6 (7.0)	73.9 (6.3)	74.8 (6.6)	75.2 (6.6)	<0.001
Baseline 3MS score	90.4 (7.2)	71.6 (6.2)	91.3 (6.4)	91.5 (6.1)	<0.001
Female (%)	43%	57%	62%	66%	<0.001
Calories (kcal/d)	2291 (782)	1732 (634)	1791 (670)	2009 (721)	<0.001
Vitamin C from food (mg/d)	148 (104)	176 (81)	191 (78)	220 (102)	<0.001
Vitamin E from food (IU/d)	9.1 (4.0)	10.4 (6.0)	10.7 (4.4)	12.8 (8.6)	<0.001
Carotene supplement use	13%	13%	14%	20%	<0.001

a. Means (standard deviation)

Figure 1

Multivariable adjusted average change in 3MS score over 7 years of follow-up by quartile of food sources of vitamin C.

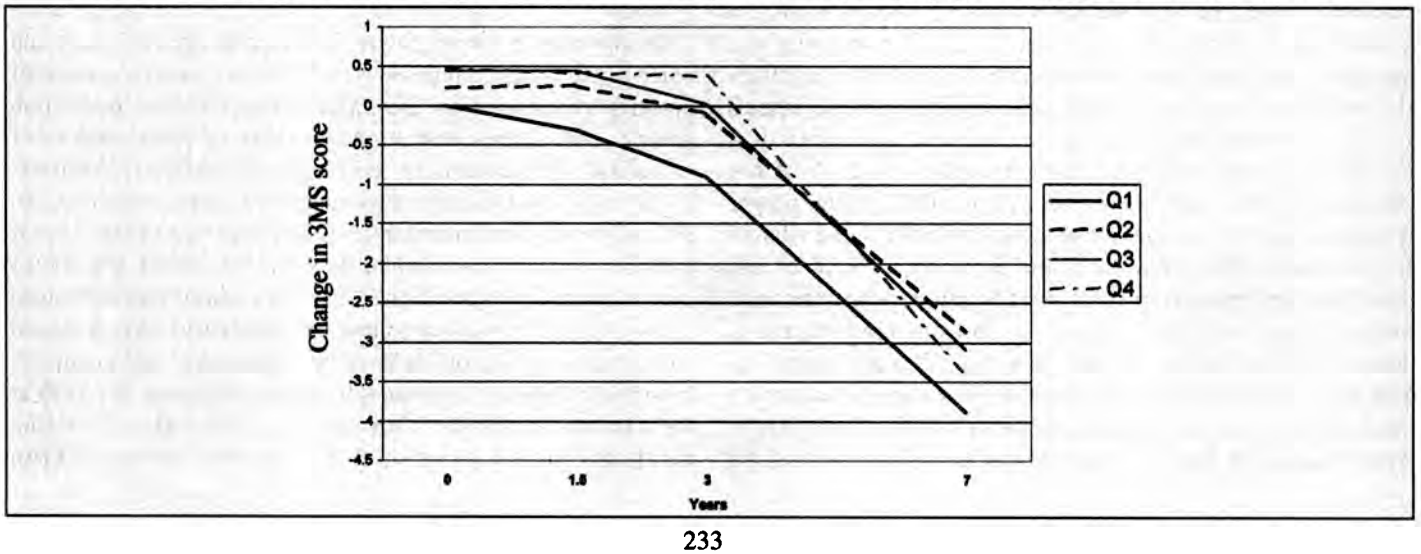

Table 3
Difference in mean baseline 3MS score across increasing quartile of intake of vitamin C, vitamin E, and carotene among 3632 men and women of the Cache County Study on Memory, Health, and Aging.

	Quartiles of intake				
Characteristic	**Q1**	**Q2**	**Q3**	**Q4**	**p-trend[d]**
Food vitamin C					
Age-gender adjusted	0 (Ref)	0.58 (0.27)[a]	0.86 (0.27)	0.84 (0.27)	0.0012
Multivariable [b]	0 (Ref)	0.24 (0.25)	0.47 (0.26)	0.49 (0.26)	0.04
Total vitamin C					
Age-gender adjusted	0 (Ref)	0.28 (0.27)	0.89 (0.27)	0.74 (0.27)	0.001
Multivariable	0 (Ref)	-0.13 (0.26)	0.43 (0.26)	0.13 (0.29)	0.23
Food Vitamin E					
Age-gender adjusted	0 (Ref)	0.35 (0.27)	0.58 (0.27)	0.35 (0.27)	0.13
Multivariable	0 (Ref)	0.24 (0.25)	0.34 (0.25)	0.18 (0.26)	0.43
Total Vitamin E					
Age-gender adjusted	0 (Ref)	-0.05 (0.27)	0.41 (0.27)	0.39 (0.27)	0.05
Multivariable	0 (Ref)	-0.21 (0.25)	-0.09 (0.26)	0.03 (0.26)	0.50
Food Carotene					
Age-gender adjusted	0 (Ref)	0.64 (0.227)	0.29 (0.27)	1.01 (0.27)	0.003
Multivariable	0 (Ref)	0.24 (0.25)	0.07 (0.26)	0.27 (0.26)	0.35
Total Carotene					
Age-gender adjusted	0 (Ref)	1.06 (0.27)	0.62 (0.27)	1.18 (0.27)	0.003
Multivariable	0 (Ref)	0.50 (0.25)	-0.004 (0.26)	0.50 (0.26)	0.40

a. Mean (standard deviation); b. Multivariable model includes gender, age, education, body mass index, level of physical activity, APOE status, history of drinking, smoking, heart attack, stroke, and diabetes, intakes of other antioxidants modeled as continuous variable (for example, vitamin E and carotene are included in the model examining the main effect of vitamin C) time, time^2 and two way interactions between time variables and the antioxidant variable of interest; c. Intake from foods and supplements combined; d. A test of the monotonic trend of the association in which each participant is assigned the median nutrient level for the quartile and nutrient intake is modeled as a continuous variable.

were similar to the effect observed for food source of vitamin C as described above. Regardless of their baseline level of performance on the 3MS, participants consuming in the highest quartile of either vitamin E or carotene (from food alone or from food and supplements combined) had slower rates of cognitive decline and thus higher 3MS scores than those in the lowest quartiles of intake at times 1, 1.5, and 3 years. The protective association of vitamin E and carotene over time also appeared to be attenuated by the time of the last 3MS assessment at 7-years.

Additional analyses were performed to examine the combined effect of antioxidants vitamin C and vitamin E, a combination explored in several studies examining the synergistic effect of these antioxidants on cognitive outcomes (9, 26). In multivariable models, participants with the highest intakes of food sources of both vitamin C and vitamin E (intakes of both vitamin C and E in the top 25% of the distribution of intake) scored on average 0.92 points higher than those with the lowest intake of both vitamin C and vitamin E (intakes of both vitamin C and E in lowest 25% of the distribution of intakes) (p-value = 0.05). Those who consumed dietary supplements containing high doses of both vitamin C and vitamin E together (vitamin E > 200 IU and vitamin C > 500 mg) scored 0.56 points higher than those consuming neither vitamin C nor vitamin E (p-value = 0.08). These effects were modified by time in a pattern similar to that observed for food source of vitamin C and other antioxidants (p-value = 0.02 and 0.03, respectively). No similar association was observed among participants with the highest intakes of both vitamin E and vitamin C from food and supplements combined.

The results described above remained largely unchanged when we restricted our analyses to include only 3MS scores that were collected by in-person interviews, thus excluding the telephone assessment conducted in 1997-1998 (n=2821 data points; mean(standard deviation) = 91.1(7.2)).

Discussion

In this large cohort of elderly participants aged 65 years and older at the baseline interview in 1995, we found evidence of better performance on the 3MS at baseline and over time among participants with higher intakes of food sources of vitamin C. Participants in the highest quartile of vitamin C intake from food scored on average 0.49 points higher on the 3MS at the baseline interview (0-years) than those in the lowest quartile of intake and, unlike those in the lowest quartile of intake, maintained this higher level of cognitive performance across the first 3 years of follow-up. Similarly, participants in the highest quartiles of intake of both vitamin C and vitamin E from food scored on average 0.92 points higher on the 3MS at the baseline interview, with slower acceleration of decline across the first 3 years of follow-up. We observed little

Table 4

Multivariable adjusted[a] average cumulative change in 3MS score by year of study follow-up across increasing quartile of intake of vitamin C, vitamin E, and carotene among 3632 men and women of the Cache County Study on Memory, Health and Aging.

	Time in years of follow-up			p-value[b]
	1.5	3	7	
Food Vitamin C				0.0015
Q1	-0.28	-0.99	-3.65	
Q2	+0.01	-0.50	-3.10	
Q3	+0.03	-0.52	-3.33	
Q4	+0.04	+0.08	-3.48	
Total Vitamin C				0.004
Q1	-0.31	-0.95	-3.20	
Q2	+0.08	-0.49	-3.56	
Q3	+0.17	-0.34	-3.14	
Q4	-0.10	-0.20	-3.77	
Food Vitamin E				0.0028
Q1	-0.06	-0.58	-2.97	
Q2	+0.02	-0.54	-3.39	
Q3	-0.24	-0.98	-3.94	
Q4	+0.09	+0.19	-3.23	
Total Vitamin E				0.0022
Q1	-0.13	-0.69	-3.06	
Q2	-0.14	-0.80	-3.61	
Q3	-0.05	-0.59	-3.10	
Q4	+0.12	+0.24	-3.74	
Food Carotene				0.034
Q1	-0.26	-0.92	-3.39	
Q2	-0.15	-0.64	-2.70	
Q3	+0.15	-0.47	-4.01	
Q4	+0.06	+0.13	-3.49	
Total Carotene				0.011
Q1	-0.29	-0.86	-2.86	
Q2	+0.08	-0.42	-3.14	
Q3	+0.002	-0.658	-3.97	
Q4	+0.009	+0.018	-3.57	

a. Multivariable model includes gender, age, education, body mass index, level of physical activity, APOE status, history of drinking, smoking, heart attack, stroke, and diabetes, intakes of other antioxidants modeled as continuous variable (for example, vitamin E and carotene are included in the model examining the main effect of vitamin C) time, time^2 and two way interactions between time variables and the antioxidant variable of interest; b. p-value of the Chi-square distribution (6 df) of the difference between the likelihood ratio test statistic of models with and without time interaction terms. The p-value is an indication of the statistical significance of whether cognitive trajectories across increasing quartile of antioxidant intake are modified by time.

evidence of baseline associations between supplemental or food and supplemental intakes of vitamin E or carotene or other combinations of antioxidants. However, participants in the lowest quartiles of these antioxidants had a greater acceleration of the rate of 3MS decline compared to those with highest levels of intake.

Much of the epidemiologic evidence of associations between antioxidant intake or status and cognitive performance among the non-demented elderly is from cross-sectional studies (13-17, 27). A handful of large prospective studies have examined associations between antioxidant intake or status and change in cognitive function over time (9, 11, 12, 28). Results from both types of study designs provide inconsistent evidence of associations between dietary antioxidants and cognitive function. For example, cross-sectional analyses of data from the Rotterdam study (16) found low intake of beta-carotene (but not vitamin C or vitamin E) was associated with cognitive impairment at baseline, but additional prospective analyses found higher intakes of vitamin C and vitamin E (but not beta-carotene) were associated with decreased risk of Alzheimer's disease (29). More recently from the Rotterdam study, Engelhart et al. (12) reported no association between plasma levels of vitamin A or vitamin E and incidence of Alzheimer's disease or cognitive decline. In a cross-sectional analysis Berr et al. (10) reported an association between low serum levels of total carotenoids (but not blood levels of thiobarbituric-reactive substances, selenium, or vitamin E) and poor cognitive test performance among participants of the EVA study (Etude du Viellissement Arteriel). Prospective analyses of the same baseline data showed low plasma levels of selenium and high thiobarbituric-reactive substances (but not total carotenoids) were associated increased risk of cognitive decline over a

follow-up period of 4 years (28). A prospective study from the Chicago Health and Aging Project (CHAP) found a 36% reduction in the rate of cognitive decline among participants in the highest quintile of vitamin E intake from both foods and supplements but little evidence of associations with vitamin C or carotene intake from either foods or supplements (11). Others have examined the use of supplemental antioxidant intake and cognitive function or decline in cognitive function but failed to examine, or in most cases, to control for dietary intake of antioxidants (30, 9).

The variable results from studies of antioxidant intake and cognitive function are likely a result of differences in study design, difficulties in the definition and measurement of cognitive function, errors in the measurement of dietary intake, or confounding by factors related to both antioxidant intake and cognitive function.

The hypothesis that dietary intake of antioxidants is related to cognitive function and dementia is biologically plausible and deserves further study. B-amyloid and tau proteins, pathological hallmarks of Alzheimer's disease, may induce oxidative stress that contributes to damage and degeneration of neuronal and glial cells (31, 6). Reactive oxygen species may activate the receptor for advanced glycation end products (RAGE) and contribute to endothelial and neuronal damage in addition to encouraging lipid peroxidation of plaque forming low-density lipoproteins, pathways likely related to progression of vascular dementia (8, 32, 33). Antioxidants may thus protect against cognitive impairment by influencing several different metabolic pathways.

Biological evidence supports synergistic antioxidant functions of vitamin C and vitamin E. Vitamin E, a fat-soluble nutrient, readily donates electrons to neutralize reactive oxygen species and may be especially important in protecting lipid membranes in the oxygen rich environment of the brain. In the process of neutralizing free radicals vitamin E becomes oxidized, losing its oxidative ability; vitamin C, a water-soluble nutrient, readily donates electrons to vitamin E to restore its oxidative ability. A previous report from the Cache Study based on supplements reported in a medication inventory found use of vitamin E and C supplements in combination was associated with reduced prevalence and incidence of AD (26). Our current report from the Cache Study is different from this previous report in that the current findings are based on food sources of antioxidant vitamins in addition to supplement sources. A recent report from the Canadian Study of Health and Aging found that a combination vitamin E and C use or use of multivitamins significantly reduced the odds of cognitive decline defined by a decrease in 3MS score by 10 points or more over 5-years of follow-up (9). Results from the present study lend support to the importance of antioxidant-nutrient interactions as participants in the highest quartiles of intake of both vitamin E and vitamin C scored an average of 0.92 points higher than those in the lowest quartiles of both, an effect greater than that observed for either vitamin C or vitamin E alone from either food or supplement sources.

Several limitations of the present study should be noted. Despite our attempt to control for many potential confounders in statistical models, the observed protective effect of vitamin C intake from food alone and in combination with vitamin E could be due to uncontrolled confounding. Higher total vitamin C intake may be a marker for a healthier lifestyle. Participants with higher vitamin C intake were likely to consume higher intakes of other antioxidants, fruits and vegetables, were more likely to exercise, to take dietary supplements, and to participate in other healthy behaviors; control for these factors however did not change the overall results. Citrus fruit and juice, the main source of vitamin C intake in this population, is also a good source of potassium and folate, other nutrients with potential benefits for the brain. The present study had a rather limited length of follow-up (mean = 7.2 years) and was conducted relatively late in life; observations earlier in the lifespan and for a greater length of time may be important. Others have detected differences in the trajectory of change in cognitive status by antioxidant status over a shorter period of follow-up than reported in the present study (11). Although life-time exposure to antioxidants seems a likely factor in late-life cognition, Laurin et al (34) found no evidence for associations between mid-life dietary antioxidant intake and later life cognitive function.

The health effects of specific antioxidant vitamins may be difficult to identify in observational studies because the common sources (e.g. fruits, vegetables and vitamin supplements) are also sources of other beneficial vitamins, minerals and other compounds; this is an inherent weakness of the use of specific nutrient intakes derived from dietary data collected in observational studies. Food-group specific analyses are an important focus of future studies. In addition, cognitive status is a broad concept and one test of global cognitive function, such as the 3MS used in the present study, may not provide a complete measure of cognitive function in the non-demented elderly. Finally, selective survival may influence the results because dementia disorders and cognitive impairment are accompanied by an increased mortality (35, 36).

Several strengths of the study should be noted. The study participants were drawn from a geographically defined population with a high response rate, known to reduce bias (37). Dietary intakes of antioxidants were measured with use of a well-established food-frequency questionnaire. Further, the effects of several potential confounding factors were evaluated in the multivariable analyses. A unique feature of this study is that 90 percent of the participants are members of the Church of Jesus Christ of Latter-Day Saints (LDS or Mormon) religion (38). The LDS population have low rates of alcohol or tobacco use and low rates of cardiovascular disease, (39) smoking-related cancer and other chronic diseases (40). As a result the median life expectancy of LDS populations exceeds that of the U.S. population as a whole by about 10-12 years (41). Almost two thirds of the men and 93 percent of the women in our study had never smoked. Thus, the Cache County population was comparatively free from this confounding variable and

competing risks from smoking-related disease.

In summary, the findings from the Cache County Study, a large, population-based prospective study, provides evidence that higher intakes of antioxidants including vitamin C, vitamin E, and carotene from food alone or from food and supplements combined may help preserve cognitive function and thus delay cognitive decline in the elderly. Vitamin C intake from food, alone or in combination with vitamin E from food, seemed especially beneficial as participants with the highest intake had higher baseline 3MS scores and maintained higher function over the first 3-years of follow-up. Further longitudinal follow-up and study of food-groups and dietary patterns may provide more insight into the role of antioxidant and other nutrients in maintaining cognitive function and preventing dementia in later-life.

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