Vitamin E, Vitamin C, Beta Carotene, and Cognitive Function Among Women With or at Risk of Cardiovascular Disease

The Women's Antioxidant and Cardiovascular Study

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Background—Cardiovascular factors are associated with cognitive decline. Antioxidants may be beneficial.

Methods and Results—The Women's Antioxidant Cardiovascular Study was a trial of vitamin E (402 mg every other day), beta carotene (50 mg every other day), and vitamin C (500 mg daily) for the secondary prevention of cardiovascular disease. From 1995 to 1996, women ≥40 years of age with cardiovascular disease or ≥3 coronary risk factors were randomized. From 1998 to 1999, a cognitive function substudy was initiated among 2824 participants ≥65 years of age. With 5 cognitive tests, cognition was assessed by telephone 4 times over 5.4 years. The primary outcome was a global composite score averaging all scores; repeated-measures analyses were used to examine cognitive change over time. Vitamin E supplementation and beta carotene supplementation were not associated with slower rates of cognitive change (mean difference in change for vitamin E versus placebo, −0.01; 95% confidence interval, −0.05 to 0.04; $P=0.78$; for beta carotene, 0.03; 95% confidence interval, −0.02 to 0.07; $P=0.28$). Although vitamin C supplementation was associated with better performance at the last assessment (mean difference, 0.13; 95% confidence interval, 0.06 to 0.20; $P=0.0005$), it was not associated with cognitive change over time (mean difference in change, 0.02; 95% confidence interval, −0.03 to 0.07; $P=0.39$). Vitamin C was more protective against cognitive change among those with new cardiovascular events during the trial (P for interaction=0.009).

Conclusions—Antioxidant supplementation did not slow cognitive change among women with preexisting cardiovascular disease or cardiovascular disease risk factors. A possible late effect of vitamin C or beta carotene among those with low dietary intake on cognition warrants further study. **(*Circulation*. 2009;119:2772-2780.)**

Key Words: antioxidants ■ brain ■ epidemiology ■ nutrition ■ risk factors ■ women

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Growing evidence supports the role of vascular disease and vascular risk factors in cognitive decline and Alzheimer dementia.[1] Given the high prevalence of vascular conditions in older persons, identifying modifiable approaches to prevent cognitive decline in this population is of vital importance.

Clinical Perspective on p 2780

Oxidative damage may play a key role in the neuropathology of dementia,[2] even in the earliest stages of cognitive impairments.[2,3] Several clinical trials of antioxidants and cognitive function have been published to date in generally healthy participants.[4–6] Few data are available on the effect of antioxidant supplementation on populations with existing vascular disease or vascular risk factors, a growing segment of our aging population. In the only previous study of antioxidant intervention among those with vascular conditions,[7] no effects were found. However, the findings are difficult to interpret because only a single cognitive test was administered at the end of the follow-up and because the treatment group was randomized to receive all 3 antioxidants combined, so the specific effects of individual antioxidants are unknown.

Therefore, we conducted a cognitive ancillary study within the Women's Antioxidant and Cardiovascular Study (WACS), a 2×2×2 factorial, randomized placebo-controlled trial of supplementation with vitamin E, vitamin C, and beta carotene in the secondary prevention of cardiovascular disease (CVD) among older women.

Methods

The WACS began in 1995 to 1996. WACS was a 2×2×2 randomized placebo-controlled trial of 3 antioxidants: 402 mg (600 IU) of

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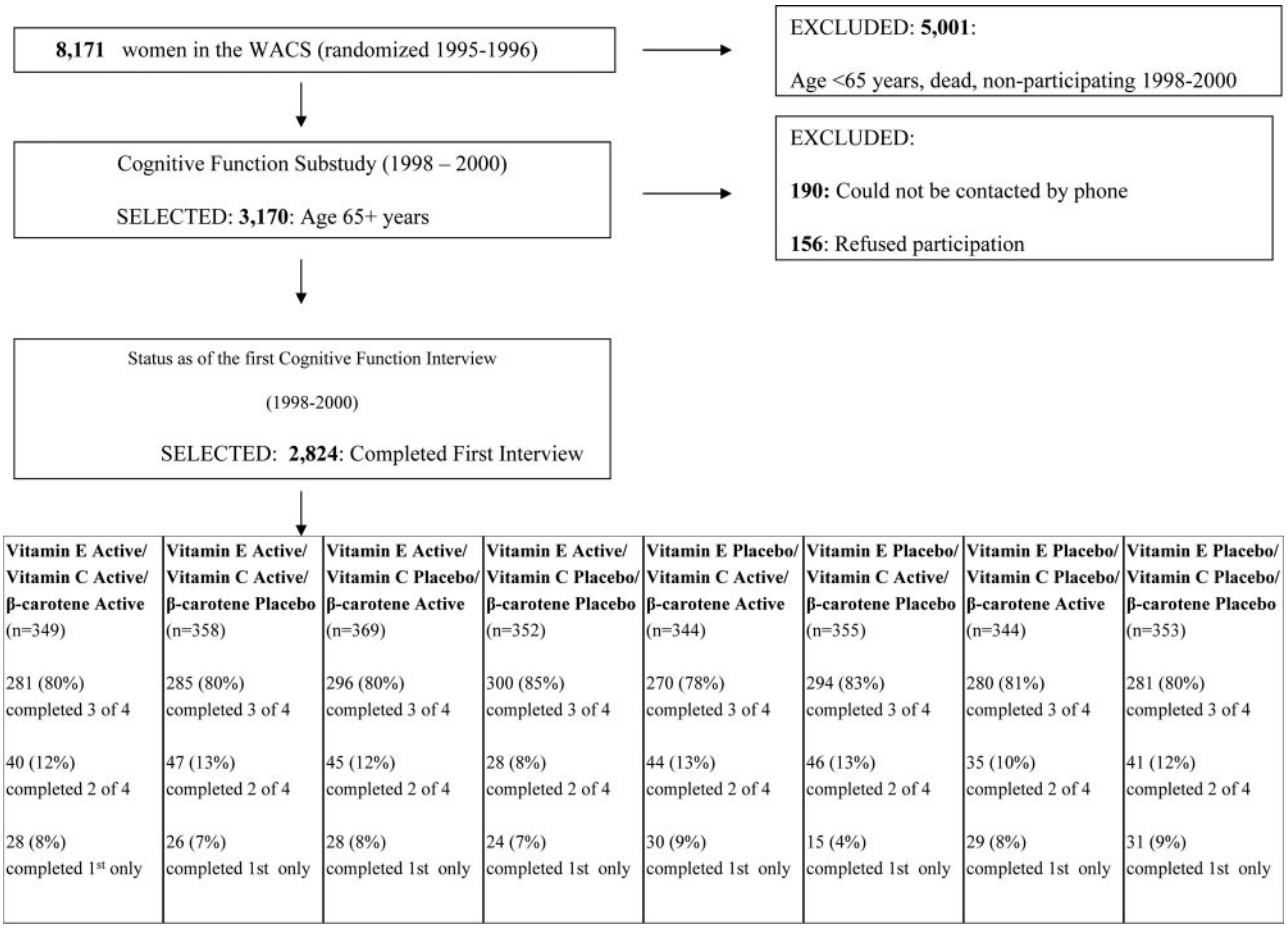

Figure 1. Flow chart of participation in the cognitive cohort of WACS.

vitamin E every other day, 500 mg of vitamin C daily, and 50 mg of beta carotene every other day for the secondary prevention of CVD. Eligible participants were female health professionals ≥40 years of age with at least 3 coronary risk factors or prevalent CVD. The women were 94.0% white, 3.3% black, 0.9% Latino American, 0.7% Asian American, and 1.1% other/multiple race. Coronary risk factors included parental history of premature myocardial infarction, diabetes mellitus, hypertension, high cholesterol, and obesity (body mass index ≥30 kg/m^2). CVD included myocardial infarction, stroke, revascularization procedures (percutaneous transluminal angioplasty, coronary artery bypass graft, carotid endarterectomy, or peripheral artery surgery), and symptomatic angina pectoris or transient cerebral ischemia. In a 3-month run-in phase to assess compliance, women received placebo caplets. Women (n=8171) who reported good compliance; had no history of cancer in the past 10 years, active liver disease, chronic kidney failure, or use of anticoagulants; and expressed willingness to forgo the use of out-of-study vitamin supplements beyond the recommended daily allowance were randomized.

Every year during follow-up, the women were sent a 12-month supply of calendar packs containing active agents or placebo. Women completed annual mailed questionnaires on compliance, side effects, health and lifestyle characteristics, and clinical end points. Participants were followed up through the scheduled end (January 31, 2005).[8] When assessed on annual questionnaires, participants' compliance to assigned study agents was high and comparable between the active and placebo groups; average compliance (defined as taking at least two thirds of assigned study medications) during follow-up was 83% and did not differ significantly between the two groups.[8] Participants provided written informed consent; the trial was approved by the institutional review board of Brigham and Women's Hospital, Boston, and was monitored by an external data and safety monitoring board.

The results of the primary trial have been published[8]; briefly, antioxidant supplementation did not protect against CVD, and it did not cause any major adverse side effects.[8]

Cognitive Cohort

After a mean 3.5 years after randomization, from December 1998 to July 2000, we initiated a substudy of cognitive function. The substudy was focused on the oldest women, all active participants ≥65 years of age (n=3170). Of these women, we could not contact 190 by telephone; of the 2980 women we contacted, 156 (5%) declined participation, and 2824 (95%) completed the initial telephone cognitive assessment (Figure 1). Participation in our initial cognitive interview was virtually identical across all the treatment and placebo groups (range, 94% to 95%).

Participants received 3 follow-up cognitive assessments every ≈2 years. High follow-up was maintained across the groups (Figure 1): 93% completed at least 1 follow-up assessment, and 81% completed at least 3 assessments. In the fourth assessment, 24% of participants were not contacted for their interview because only a short interval had passed between their third interview and the end of the trial in January 2005. Follow-up rates were nearly identical across treatment groups at each assessment.

Cognitive Function Assessment

Substantial research implicates vascular factors in cognitive health, including cognitive outcomes not traditionally associated with vascular health such as general cognition, episodic memory, and Alzheimer dementia.[1] Thus, the emphasis of this study was not on executive function measures but on general cognition. We hypothe-

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sized that if CVD and cognitive decline share similar pathways of development, then antioxidants that may protect against the development of CVD may also confer benefits for the maintenance of general cognitive function.

We assessed cognitive function by telephone and administered 5 tests measuring general cognition, verbal memory, and category fluency. For general cognition, we used the Telephone Interview of Cognitive Status (TICS)[9] a telephone adaptation of the Mini-Mental State Examination. For verbal memory, we administered the delayed recall of the TICS 10-word list and the immediate and delayed recalls of the East Boston Memory Test,[10] in which a short paragraph is read and 12 key elements are repeated immediately and 15 minutes later. Finally, in a test of category fluency (used to measure executive retrieval functions),[11] women were asked to name as many animals as possible in 1 minute.

The primary, prespecified outcome of this trial was the change from baseline of the global composite score, which is an average of all 5 cognitive tests made into z scores. In addition, because verbal memory is strongly associated with risk of Alzheimer disease,[12] our key secondary outcome was the change from baseline of the verbal memory composite score; this composite score was calculated by averaging scores across 4 measures of verbal memory (the immediate and delayed recalls of both the East Boston Memory Test and 10-word list). To calculate the composite scores for participants who did not complete all tests (only 0.5% for both the global composite score and the verbal memory score), we used the mean of the z scores of the tests that were completed.

The telephone cognitive interviews were administered by trained interviewers who were masked to the participants' randomized treatment assignment. Our telephone cognitive test battery had high reliability and validity. In a test-retest reliability study of the TICS, administered twice 31 days apart, we found a correlation of 0.7 ($P<0.001$) among 35 high-functioning, educated women. In a validation study of our telephone instrument, 61 women who had completed an extensive in-person interview were administered our brief telephone-administered assessment; we found a correlation of 0.81 comparing the global composite scores on those 2 measures, demonstrating high validity of our telephone method. Importantly, among 88 older female health professionals, cognitive impairment as determined by our telephone assessment was strongly associated with dementia diagnosis after 3 years; poor performances on the TICS and verbal memory were associated with significant 8- and 12-fold increases, respectively, of dementia.

Statistical Analysis

Characteristics at baseline between randomized groups were compared by use of Wilcoxon rank-sum tests and χ^2 tests for proportions. Mean performance at each assessment by treatment assignment was evaluated using repeated-measures analysis of means, which takes into account correlations between assessments. The mean for each intervention group at each time was estimated, allowing for an interaction of group and time and modeling the correlation of measures over time with an unstructured covariance matrix. Such general linear models of response profiles address the nonlinearity of scores and impose minimal structure on outcome trends over time.[13] Second, the primary analytic outcome was the mean difference in cognitive change from the initial to the second through fourth assessments. The mean difference in change was basically calculated by subtracting the baseline score from follow-up scores and then taking the difference of cognitive change between the treatment and placebo groups. Thus, a negative value for the mean difference in cognitive change indicates an adverse effect of treatment. The mean differences in cognitive change were evaluated by treatment assignment in a repeated-measures model. This included fixed effects for time and a common intervention effect over time for each group, reflecting the average difference between groups over time. All models were fitted by maximum likelihood, incorporating the longitudinal correlation within study subjects using unstructured covariance structures; for statistical testing, we used Wald tests.[13] For statistical analyses, Proc Mixed in SAS (SAS release 9.1, SAS Institute Inc, Cary, NC) was used.

We also evaluated the differences in cognitive change between those assigned to any of the 3 antioxidants compared with those assigned to all placebos. We further evaluated taking various combinations of antioxidants (eg, vitamin E and vitamin C versus placebos for both).

We examined effect modification by key risk factors for cognitive change at randomization and by incident CVD during the trial. We also selected factors that may affect the metabolism of antioxidants (eg, smoking). Tests of effect modification were performed by evaluating interaction terms in models of mean change in cognition.

In secondary analyses, we examined the influence of noncompliance by repeating the main analyses after excluding women who were taking fewer than two thirds of their assigned study medications.

We also constructed models adjusting for assignment to other antioxidant agents or B vitamins, but results were essentially unchanged (data not shown); thus, we did not include assignment to other supplements as covariates in the models. In addition, effect modification by assignment to other trial agents was not observed.

Finally, to assess the impact of antioxidant supplementation on the risk of substantial cognitive change, we fitted logistic regression models adjusting for follow-up time between the first and last assessments, defining the outcome as those in the worst 10% of the distribution of cognitive change from the initial to the final cognitive assessment.

Results

The average time from randomization to the initial cognitive assessment was 3.5 years (range, 3.1 to 4.7) and from randomization to the last assessment was 8.9 years (range, 7.8 to 9.6). At the end of the study, compliance (defined as taking at least two thirds of study pills) was comparable across all groups (range, 64% to 68%). No race/ethnicity-based differences were present. Other demographic and health characteristics at randomization were similar between all treatment and placebo groups, with a few minor exceptions (Table 1).

Mean Score at Each Time Point

Mean scores over time by assignment group are shown in Figure 2. At the first cognitive assessment, after an average of 3.5 years of treatment, cognition did not differ significantly by treatment groups for vitamin E or beta carotene but was borderline significant for vitamin C (Table 2) (mean difference in the global composite score between treatment and placebo groups for vitamin C, 0.05; 95% confidence interval [CI], 0.00 to 0.10; $P=0.05$). At the final assessment, for vitamin E and beta carotene, there was no difference by assignment; however, for vitamin C, the treatment group had higher scores than the placebo group for the global composite score (mean difference, 0.13; 95% CI, 0.06 to 0.20; $P=0.0005$), verbal memory score (mean difference at last assessment, 0.14; 95% CI, 0.06 to 0.21; $P=0.0004$), and TICS (mean difference at last assessment, 0.46; 95% CI, 0.14 to 0.78; $P=0.006$). Overall, the vitamin C active group performed better than the vitamin C placebo group from the first through the last assessments as determined by the difference in pattern of performance in global score over time; however, this was of borderline significance ($P=0.06$). The overall mean performance on global score over the 4 assessments did not differ between the active and placebo groups for vitamin E ($P=0.54$) and beta carotene ($P=0.54$).

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Table 1. Baseline Characteristics of Participants in the WACS Cognitive Cohort

	Vitamin E		Vitamin C		β-Carotene	
Characteristics*	Active (n=1428)	Placebo (n=1396)	Active (n=1406)	Placebo (n=1418)	Active (n=1406)	Placebo (n=1418)
Age at randomization, y	69.1 (4.3; 62.6–87.4)	69.0 (4.2; 62.6–87.9)	69.0 (4.2; 62.6–86.9)	69.1 (4.3; 62.6–87.9)	69.1 (4.3; 62.6–87.9)	69.0 (4.2; 62.6–87.6)
Age at initial cognitive assessment, y	72.6 (4.3; 66.1–90.9)	72.5 (4.2; 66.1–91.3)	72.5 (4.2; 66.1–90.5)	72.6 (4.3; 66.1–91.3)	72.6 (4.3; 66.2–91.3)	72.5 (4.2; 66.1–91.2)
Total vitamin E intake, mg/d	132.7 (204.6; 1.5–864.8)	117.2 (184.1; 1.24–884.10.5)	123.2 (193.8; 1.24–864.8)	126.9 (195.9; 1.39–884.1)	129.2 (198.3; 1.4–864.8)	121.0 (191.4; 1.2–884.1)
Total vitamin C intake, mg/d	245.9 (214.2; 34.1–1793.9)	248.7 (229.8; 25.1–1890.9)	247.6 (228.1; 25.1–1890.9)	247.0 (215.88; 28.1–1793.8)	248.1 (218.8; 25.1–1775.3)	246.6 (225.2; 27.9–1890.9)
Total carotenoid intake, mg/d	6.8 (5.1; 0.4–74.5)	6.6 (4.6; 0.1–35.4)	6.8 (5.2; 0.4–74.5)	6.6 (4.5; 0.1–35.4)	6.8 (5.0; 0.4–74.5)	6.6 (4.8; 0.1–41.8)
Total alcohol intake, g/d	3.7 (8.1; 0–66.7)	3.8 (8.7; 0–85.7)	3.7 (8.5; 0–83.9)	3.8 (8.3; 0–85.7)	3.8 (8.3; 0–85.7)	3.7 (8.5; 0–72.4)
Total physical activity, kcal/wk	862.9 (1086.4; 0-14 669.3)	938.4 (1240.0; 0–19 017.4)	890.5 (1109.2; 0-14 669.3)	909.8 (1218.5; 0–19 017.4)	901.8 (1208.4; 0–19 017.4)	898.6 (1121.1; 0–14 669.3)
Body mass index, kg/m^2	28.6 (5.6; 15.9–56.7)	28.7 (5.7; 15.4–58.6)	28.7 (5.6; 15.4–56.7)	28.7 (5.7; 15.5–58.6)	28.6 (5.8; 15.4–54.9)	28.8 (5.6; 16.0-58.6)
Highest attained education, %						
LPVN/AD/RN	71.1	69.4	69.9	70.6	70.7	69.9
BA/MA/DR	28.9	30.6	30.1	29.4	29.4	30.1
Current cigarette smoking, %	9.9	9.7	10.2	9.4	10.0	9.5
History of MI, %	19.4†	22.8	21.2	21.1	21.7	20.6
History of stroke, %	9.0	8.3	9.7‡	7.6	9.0	8.3
History of revascularization surgery, %	21.8	20.2	21.9	20.1	21.8	20.2
History of angina, %	45.0	44.5	44.5	45.0	43.9	45.6
History of transient ischemic attack, %	15.2	15.5	15.2	15.5	15.2	15.5
History of diabetes mellitus, %	18.1	17.1	17.0	18.2	17.7	17.5
History of hypertension, %	77.3	78.0	77.7	77.6	79.6§	75.7
History of hyperlipidemia, %	72.9	76.7	74.2	75.3	72.8§	76.7

LPVN indicates licensed practical or vocational nurse; AD, associate's degree; RN, registered nurse; BA, bachelor's degree; MA, master's degree; DR, doctoral degree. Values are mean (SD; range) when appropriate.

*Characteristics as of randomization.

†$P<0.05$ for the difference between vitamin E active group and placebo.

‡$P<0.05$ for the difference between vitamin C active group and placebo.

§$P<0.05$ for the difference between beta carotene active group and placebo.

Change From Baseline During Follow-Up

The primary, prespecified analyses were of change in cognitive function over time in the treated compared with placebo groups. When we evaluated the differences in the mean rate of change from baseline in cognitive performance from the second through the fourth assessments, we did not observe differences by treatment assignment for any of the antioxidants across all cognitive outcomes (Table 3). On the global composite score, the mean difference in cognitive change from baseline between the vitamin E treatment and placebo groups was −0.01 standard unit (95% CI, −0.05 to 0.04; $P=0.78$); for vitamin C, the difference was 0.02 (95% CI, −0.03 to 0.07; $P=0.39$); and for beta carotene, the difference was 0.03 (95% CI, −0.02 to 0.07; $P=0.28$).

In secondary analyses, those on at least 1 of the 3 antioxidant supplements (n=2471) did not differ in cognitive change from baseline compared with those assigned to all placebos (n=353); mean difference in cognitive change over time was 0.02 standard units (95% CI, −0.04 to 0.09; $P=0.64$). We also examined those taking various combinations of 2 of the 3 supplements and compared them with those on the corresponding placebos and did not observe any associations; eg, the mean difference in cognitive change over time for those on both active vitamin C and active vitamin E was 0.01 (95% CI, −0.05 to 0.08; $P=0.67$). When we compared those assigned to all 3 active antioxidant agents (n=349) with those assigned to all placebos (n=353), those on all 3 antioxidants showed a suggestion of cognitive benefits; however, the difference in cognitive change was not significant (0.08; 95% CI, −0.01 to 0.17; $P=0.08$).

We investigated the risk of substantial cognitive change, defined as those in the worst 10% of the distribution of change from the first to the final assessment. Compared with placebo, the relative risk was 1.20 (95% CI, 0.86 to 1.66) for the vitamin E group and 1.04 (95% CI, 0.75 to 1.44) for the beta carotene group. The relative risk for the vitamin C group was 0.73 (95% CI, 0.52 to 1.01).

In further secondary analyses, we investigated whether the influence of antioxidants differed by various participant characteristics at randomization (Table 4). We observed effect modification by new cardiovascular events occurring after randomization for vitamin C (P for interaction=0.009). Vitamin C supplementation was associated with better change from baseline (difference in change from baseline in global score for active versus placebo, 0.15; 95% CI, 0.04 to 0.26) among those who developed cardiovascular events

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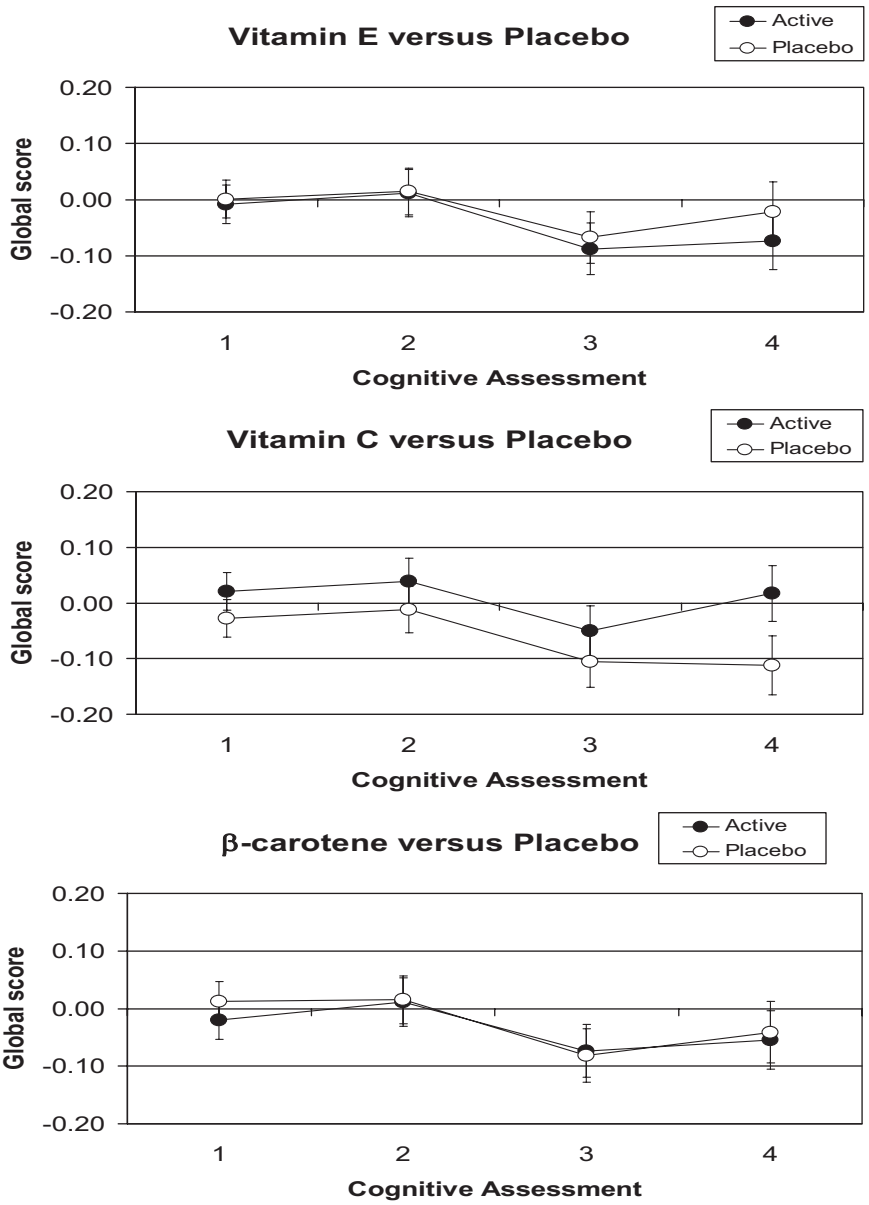

Figure 2. Mean global scores during follow-up (1998 to 2000 through 2004 to 2005) by active or placebo assignment for vitamin E, vitamin C, and beta carotene.

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during follow-up, whereas it was not associated among those who had not developed incident events (difference in change, 0.00; 95% CI, −0.05 to 0.05). We also found a benefit of beta carotene supplements among those with low dietary intakes of total carotenoids but not among those with higher intakes (P for interaction=0.02). Because there are no recommended dietary allowance values for total carotenoids, we defined low total carotenoids intake as consuming at the lowest 20th percentile (<3.09 mg). There were no such significant interactions by dietary intake with vitamin C and vitamin E.

We did not observe major differences in the effect of supplementation for any of the antioxidants when we excluded women with poor compliance. Among those who reported good compliance, the mean difference in cognitive change from baseline was −0.02 standard units (95% CI, −0.07 to 0.03; P=0.49) for vitamin E, 0.02 (95% CI, −0.03 to 0.07; P=0.49) for vitamin C, and 0.03 (95% CI, −0.02 to 0.08; P=0.23) for beta carotene.

Discussion

In this randomized placebo-controlled trial of 2824 older women at high risk of cognitive decline caused by existing CVD or cardiovascular risk factors, use of antioxidant supplements was not clearly associated with slowing of cognitive decline. With our a priori determined outcome of differences in cognitive change over the entire follow-up period, we did not observe effects with any of the individual antioxidants. However, in secondary analyses, a suggestive late effect of vitamin C was observed in which women assigned to active vitamin C performed better than women assigned to vitamin C placebo across several cognitive measures at the last assessment.

The late protective effect of vitamin C particularly among those who developed CVD during follow-up should be interpreted with caution because this result could be due to chance. Furthermore, it is not clear that the water-soluble vitamin C may have stronger neuroprotective actions over the lipid-soluble vitamin E or beta carotene. Biologically, the

Table 2. Mean Difference in Cognitive Function at Each Cognitive Assessment for Each Antioxidant

		Vitamin E		Vitamin C		β-Carotene	
Cognitive Assessment	n	Mean Difference in Score, Active Group−Placebo Group (95% CI)*	P	Mean Difference in Score, Active Group−Placebo Group (95% CI)*	P	Mean Difference in Score, Active Group−Placebo Group (95% CI)*	P
Primary endpoint: Global score† (difference in score associated with being 1 y older=−0.03)							
1	2824	−0.01 (−0.06–0.04)	0.71	0.05 (0.00–0.10)	0.05	−0.03 (−0.08–0.02)	0.19
2	2511	0.00 (−0.06–0.06)	0.94	0.05 (−0.01–0.11)	0.09	0.00 (−0.06–0.05)	0.89
3	2271	−0.02 (−0.09–0.05)	0.55	0.05 (−0.01–0.12)	0.10	0.01 (−0.06–0.07)	0.82
4	1586	−0.05 (−0.13–0.02)	0.17	0.13 (0.06–0.20)	0.0005	−0.01 (−0.09–0.06)	0.71
Key secondary endpoint: Verbal memory score† (difference in score associated with being 1 y older=−0.03)							
1	2824	0.02 (−0.03–0.07)	0.43	0.05 (0.00–0.10)	0.06	−0.01 (−0.07–0.04)	0.62
2	2511	0.02 (−0.04–0.09)	0.45	0.05 (−0.01–0.11)	0.13	0.00 (−0.06–0.06)	0.99
3	2271	−0.01 (−0.08–0.06)	0.75	0.07 (0.00–0.13)	0.05	0.02 (−0.04–0.09)	0.50
4	1586	−0.06 (−0.13–0.02)	0.13	0.14 (0.06–0.21)	0.0004	−0.02 (−0.09–0.06)	0.68
TICS score† (difference in score associated with being 1 y older=−0.13)							
1	2824	−0.01 (−0.25–0.23)	0.95	0.16 (−0.08–0.39)	0.20	−0.18 (−0.42–0.06)	0.14
2	2511	0.03 (−0.23–0.29)	0.80	0.15 (−0.11–0.41)	0.24	0.06 (−0.20–0.32)	0.63
3	2270	−0.08 (−0.37–0.21)	0.61	0.15 (−0.14–0.44)	0.31	0.14 (−0.15–0.43)	0.35
4	1586	−0.16 (−0.49–0.16)	0.33	0.46 (0.14–0.78)	0.006	−0.13 (−0.46–0.19)	0.42
Category fluency score (difference in score associated with being 1 y older=−0.18)							
1	2819	−0.42 (−0.78–−0.06)	0.02	0.03 (−0.33–0.39)	0.87	−0.22 (−0.58–0.14)	0.23
2	2504	−0.45 (−0.83–−0.06)	0.02	0.03 (−0.36–0.41)	0.90	−0.05 (−0.44–0.34)	0.80
3	2261	−0.25 (−0.66–0.16)	0.24	0.05 (−0.36–0.46)	0.80	−0.05 (−0.46–0.36)	0.80
4	1583	−0.35 (−0.80–0.10)	0.13	0.25 (−0.20–0.70)	0.27	−0.01 (−0.46–0.44)	0.96

*From longitudinal linear models of adjusted mean cognitive performance.

†Verbal score is a composite score of the z scores of the immediate and delayed recalls of both the TICS 10-word and the East Boston Memory Test; global score is a composite score of the z scores of TICS, immediate and delayed recalls of the East Boston Memory Test, category fluency, and delayed recall of the TICS 10-word list.

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brain has a high concentration of vitamin C,[14] and within the brain, the highest levels are in the cerebral cortex and hippocampus (important in memory).[15] In the brain extracellular fluid, vitamin C is involved in broad-spectrum radical scavenging and acts with vitamin E to inhibit peroxidation of membrane phospholipids, particularly in cerebral ischemia.[16] However, supplementation with ascorbic acid is unlikely to greatly increase brain levels of vitamin C because ascorbic acid itself does not readily penetrate the blood-brain barrier (only the oxidized form of ascorbic acid does).[17] In human

Table 3. Mean Differences in Cognitive Change Over Follow-Up for Each Antioxidant*

Vitamin E		Vitamin C		β-Carotene	
Mean Difference in Change in Score, Active Group−Placebo Group (95% CI)	P	Mean Difference in Change in Score, Active Group−Placebo Group (95% CI)	P	Mean Difference in Change in Score, Active Group−Placebo Group (95% CI)	P
Primary endpoint: Global score† (difference in change associated with being 1 y older=−0.02)					
−0.01 (−0.05–0.04)	0.78	0.02 (−0.03–0.07)	0.39	0.03 (−0.02–0.07)	0.28
Key secondary endpoint: Verbal memory score† (difference in change associated with being 1 y older=−0.02)					
−0.03 (−0.08–0.03)	0.33	0.03 (−0.03–0.08)	0.32	0.01 (−0.04–0.07)	0.61
TICS score† (difference in change associated with being 1 y older=−0.07)					
−0.01 (−0.24–0.23)	0.96	0.08 (−0.15–0.32)	0.49	0.20 (−0.03–0.44)	0.09
Category fluency score (difference in change associated with being 1 y older=−0.05)					
0.11 (−0.22–0.44)	0.52	0.06 (−0.27–0.39)	0.70	0.16 (−0.17–0.49)	0.36

*From longitudinal linear models of adjusted mean cognitive change. Cognitive change is defined as the follow-up score minus the baseline score, with negative values indicating worsened scores. Mean difference in change in score is defined as the cognitive change in the active group minus the cognitive change in the placebo group, with negative values indicating an adverse effect of the active agent.

†Verbal score is a composite score of the z scores of the immediate and delayed recalls of both the TICS 10-word and the East Boston Memory Test; global score is a composite score of the z scores of TICS, immediate and delayed recalls of the East Boston Memory Test, category fluency, and delayed recall of the TICS 10-word list.

Table 4. Mean Difference in Cognitive Change Between Antioxidant and Placebo Groups by Subgroups*

Characteristics	Mean Difference in Cognitive Change, Active Group−Placebo Group (95% CI)		
	Vitamin E	Vitamin C	β-Carotene
Age at first assessment, y			
≤72 (n=1440)	−0.03 (−0.09–0.04)	0.05 (−0.01–0.12)	0.03 (−0.03–0.10)
>72 (n=1384)	0.02 (−0.05–0.08)	−0.01 (−0.08–0.05)	0.02 (−0.05–0.09)
P	0.34†	0.34†	0.80
First cognitive assessment score			
Below median (n=1412)	−0.01 (−0.08–0.06)	0.05 (−0.02–0.12)	0.05 (−0.02–0.12)
Above median (n=1412)	−0.01 (−0.07–0.05)	0.01 (−0.05–0.07)	0.00 (−0.06–0.05)
P	1.00	0.37	0.21
Highest attained education			
LPVN/AD/RN (n=1861)	−0.04 (−0.10–0.01)	0.03 (−0.03–0.08)	0.01 (−0.05–0.06)
BA, MA, DR (n=788)	0.06 (−0.03–0.15)	−0.01 (−0.10–0.08)	0.04 (−0.05–0.13)
P	0.05	0.53	0.50
Prevalent CVD event/risk factors‡			
CVD event (n=2120)	0.00 (−0.06–0.05)	0.04 (−0.01–0.10)	0.03 (−0.02–0.09)
Risk factors (n=704)	−0.01 (−0.10–0.08)	−0.04 (−0.13–0.05)	0.00 (−0.09–0.09)
P	0.91	0.12	0.51
Incident CVD§			
Present (n=501)	0.06 (−0.05–0.17)	0.15 (0.04–0.26)	0.00 (−0.11–0.11)
Absent (n=2323)	−0.02 (−0.07–0.03)	0.00 (−0.05–0.05)	0.03 (−0.02–0.08)
P	0.17	0.009	0.64
Dietary intake of specific antioxidant‖			
Low	0.01 (−0.05–0.08)	−0.06 (−0.27–0.14)	0.14 (0.04–0.24)
Adequate	−0.01 (−0.08–0.05)	0.03 (−0.02–0.07)	0.00 (−0.05–0.06)
P	0.62	0.40	0.02
Cigarette smoking			
Never smoker (n=1314)	−0.03 (−0.10–0.04)	0.00 (−0.07–0.06)	0.03 (−0.04–0.10)
Ever smoker (n=1510)	0.01 (−0.05–0.07)	0.04 (−0.02–0.10)	0.02 (−0.04–0.09)
P	0.40	0.34	0.96
Alcohol drinking			
Nondrinker (n=1416)	−0.01 (−0.08–0.06)	0.02 (−0.04–0.09)	0.04 (−0.03–0.11)
Drinker (n=1280)	0.01 (−0.06–0.08)	0.02 (−0.05–0.08)	0.02 (−0.05–0.08)
P	0.64	0.85	0.64
Multivitamin use			
No (n=1970)	−0.01 (−0.06–0.05)	0.01 (−0.05–0.06)	0.02 (−0.04–0.07)
Yes (n=833)	0.00 (−0.09–0.09)	0.05 (−0.04–0.13)	0.03 (−0.05–0.12)
P	0.91	0.46	0.79

Abbreviations as in Table 1.

*Characteristics as of randomization, except for cumulative CVD, which occurred during follow-up and compliance. Mean difference in change in score is defined as the change in the global composite score from baseline in the active group minus the change in the global composite score from baseline in the placebo group, with negative values indicating an adverse effect of the active agent.

†*P* value for interaction for testing effect modification.

‡Nonfatal myocardial infarction, nonfatal stroke, revascularization surgery, or CVD as of randomization.

§Incident CVD refers to an updated history of CVD as of each follow-up assessment.

‖Low dietary intake refers to intake from diet and supplements and is defined for vitamin C as <75 mg/d (recommended daily allowance; n=164), for vitamin E as <15 mg/d (recommended daily allowance; n=1315), and for total carotenoids as <3.09 mg/d (lowest quintile cut point; n=539); Adequate refers to intakes greater than the cut points for low.

studies, the evidence for vitamin C protecting against cognitive impairment or dementia is inconsistent, with studies finding both protective associations[18,19] and null associations.[20–23] If there was a putative vitamin C–specific neuroprotective effect, particularly among those with recent development of cardiovascular events, these data suggest that long-term treatment might be necessary for any effects; this is consistent with a recent antioxidant trial showing protective

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associations only with long durations.[6] Clearly, further research on specific effects of vitamin C is needed.

Neurons contain oxidizable lipids that need protection by lipophilic antioxidants such as beta carotene and vitamin E.[24] Vitamin E has been studied extensively in relation to cognitive function, including several randomized trials in different populations with different durations (2 to 10 years) and dosages (134 to 1340 mg or 200 to 2000 IU).[4,5,7,25,26] Consistent with the results of these trials, our study among women with cardiovascular conditions showed no cognitive benefits with vitamin E when used for ≈9 years. β-Carotene has been less studied; however, a recent trial by Grodstein et al[6] among 4052 healthy male physicians showed that men treated with 50 mg on alternate days (same dose as this study) for 18 years had significantly better performance compared with men on placebo, whereas no association was observed among 1904 men treated for a short duration (1 year). This raises the possibility that either the duration of this study was too short (8.9 years) or the effect of beta carotene on cognition is different among those with CVD. There was some evidence that beta carotene supplementation may be beneficial among those with the lowest dietary intake of carotenoids; however, this finding needs replication.

This present study has important strengths. WACS is unique in that it provides cognitive data from a large study sample (n=2824) of older women at elevated risk of cognitive decline as a result of vascular disease or vascular risk factors. There was a long duration of treatment (8.9 years of treatment and 5.4 years of follow-up), and follow-up and compliance were high. This study provides unique data in that other similar trials of antioxidants have not specifically tested the effect of vitamin C. Finally, cognitive assessments included tests measuring a variety of cognitive domains.

A primary limitation of this study was initiating cognitive testing 3.5 years after randomization, which did not allow us to evaluate cognitive change from randomization. However, at randomization, the distribution of various risk factors for cognitive decline was comparable across treatment groups. Thus, it is highly likely that cognitive function at randomization also was similar across treatment groups. Finally, because this study was limited to women with cardiovascular conditions, the results may not be generalizable to men or healthy women.

Conclusions

Supplementation with vitamin E, vitamin C, or beta carotene did not slow cognitive decline among women with preexisting CVD or risk factors. A late effect of vitamin C or an effect of beta carotene supplements among those with low dietary intake may have been due to chance, but further study with trials of long treatment durations (>10 years) is warranted. The clinical interpretation and implications of this study are that supplementation with vitamin E, vitamin C, or beta carotene for older women with cardiovascular conditions is unlikely to reduce their risk of cognitive decline.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Substantial research implicates vascular factors in cognitive health, including cognitive outcomes not traditionally associated with vascular health such as general cognition, episodic memory, and Alzheimer's dementia. Thus, if cardiovascular disease and cognitive decline share similar pathways of development, then antioxidants that may protect against the development of cardiovascular disease may also confer benefits for the maintenance of general cognitive function. Data from an ancillary cognitive function study within the setting of a randomized placebo-controlled trial of 2824 older women at high risk of cognitive decline as a result of existing cardiovascular disease or cardiovascular risk factors showed that the use of supplements of vitamin E, vitamin C, or beta carotene was not clearly associated with slowing of cognitive decline over 5.4 years. For older women with cardiovascular conditions, in whom it remains critically important to control cardiovascular risk factors, the clinical interpretation and implications of this study are that supplementation with vitamin E, vitamin C, or beta carotene is unlikely to reduce their risk of cognitive decline.

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Vitamin E, Vitamin C, Beta Carotene, and Cognitive Function Among Women With or at Risk of Cardiovascular Disease: The Women's Antioxidant and Cardiovascular Study

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