ORIGINAL INVESTIGATION

A Randomized Trial of Vitamin E Supplementation and Cognitive Function in Women

Jae Hee Kang, ScD; Nancy Cook, ScD; JoAnn Manson, MD, DrPH; Julie E. Buring, ScD; Francine Grodstein, ScD

Background: Oxidative stress may play a key role in the development of cognitive impairment. Long-term supplementation with vitamin E, a strong antioxidant, may provide cognitive benefits.

Methods: The Women's Health Study is a randomized, double-blind, placebo-controlled trial of vitamin E supplementation (600 IU [α-tocopherol acetate], on alternate days) begun between 1992 and 1995 among 39 876 healthy US women. From 1998, 6377 women 65 years or older participated in a cognitive substudy. Three cognitive assessments of general cognition, verbal memory, and category fluency were administered by telephone at 2-year intervals. The primary outcome was a global composite score averaging performance on all tests. Repeated measures analyses were conducted to examine mean performance and mean differences in cognitive change, and logistic regression was used to estimate relative risks of substantial decline.

Results: There were no differences in global score between the vitamin E and placebo groups at the first assessment (5.6 years after randomization: mean difference, –0.01; 95% confidence interval [CI], –0.04 to 0.03) or at the last assessment (9.6 years of treatment: mean difference, 0.00; 95% CI, –0.04 to 0.04). Mean cognitive change over time was also similar in the vitamin E group compared with the placebo group for the global score (mean difference in change, 0.02; 95% CI, –0.01 to 0.05; *P*=.16). The relative risk of substantial decline in the global score in the vitamin E group compared with the placebo group was 0.92 (95% CI, 0.77 to 1.10).

Conclusion: Long-term use of vitamin E supplements did not provide cognitive benefits among generally healthy older women.

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Author Affiliations: Channing Laboratory (Drs Kang, Manson, and Grodstein) and Division of Preventive Medicine (Drs Cook, Manson, and Buring), Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, and Department of Epidemiology, Harvard School of Public Health (Drs Manson, Buring, and Grodstein), Boston, Mass.

OXIDATIVE STRESS MAY PLAY a key role in the pathogenesis of dementia.[1] Vitamin E is a powerful, lipid-soluble antioxidant. In vitro and in vivo studies have shown that vitamin E lowers levels of brain lipid peroxidation (the predominant form of oxidative damage in the brain[1]) and protects against neuronal damage.[2,3]

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Cognitive decline is associated with higher Alzheimer disease (AD) risk. Since oxidative neuronal damage is observed from the earliest stages in the pathologic process of AD,[1,4] it is likely that antioxidant intervention would also be most effective at the onset of the disease process. Biological[1,4,5] and epidemiologic[6,7] data indicate that antioxidant therapy may be successful only if initiated at young ages (ie, before the onset of major cognitive decline) and if given for long durations. Indeed, in clinical trials of subjects with AD[8] or mild cognitive impairment,[9] as well as in short-term trials of cognitively normal older participants,[10,11] antioxidant vitamins have provided no cognitive benefits.

We tested the effect of vitamin E supplements on cognitive function using data from the Women's Health Study (WHS), a randomized, double-blind, placebo-controlled trial of vitamin E supplementation of 10 years' duration. This large study included 6377 older healthy women, randomized to receive vitamin E or placebo, who were followed up for 4 years for changes in cognitive function.

METHODS

THE WOMEN'S HEALTH STUDY

The WHS is a double-blind, placebo-controlled randomized trial of vitamin E supplements (600 IU every other day; Natural Source Vitamin E Association, La Grange, Ill) and low-dose aspirin (100 mg every other day, provided by Bayer Healthcare, Elkhart, Ind) in a factorial design for the prevention of cardio-

vascular disease and cancer. The study design has been previously described in detail.[12] Briefly, women were eligible if they were at least 45 years old; had no history of coronary heart disease, cerebrovascular disease, cancer (except for nonmelanoma skin cancer), or other major chronic illnesses; and did not actively use any of the study medications or have any history of adverse effects from the medications.

Eligible women completed baseline questionnaires and were enrolled in a 3-month run-in period of placebo administration to determine those likely to maintain high compliance to treatment. From 1992 to 1995, a total of 39 876 women who were compliant during the run-in period were randomized to 4 treatment groups. All participants provided written informed consent. The trial was approved by the institutional review board of Brigham and Women's Hospital, Boston, Mass, and was monitored by an external data and safety monitoring board.

Every 12 months during follow-up, the women were sent a year's supply of monthly calendar packs containing active agents or placebo. Women were asked to complete mailed questionnaires annually to update information on compliance, adverse effects, health and lifestyle characteristics, and the occurrence of clinical end points. The trial continued through the scheduled end (March 31, 2004); the overall follow-up of the cohort exceeded 99%.[13]

COGNITIVE COHORT

In 1998, a mean of 5.6 years after randomization, a substudy of cognitive function was initiated among active WHS participants 65 years or older (n=7175) at that time. Of these, 296 women (4%) were unreachable and 502 (7%) declined participation; thus, 6377 women (89%) completed the initial telephone cognitive assessment. Participation rates in the initial cognitive interview were virtually identical in the treatment and placebo groups.

We conducted 2 follow-up assessments, in 2000 and in 2002. High follow-up was maintained: 5845 (92%) of those who completed the initial assessment also completed at least 1 follow-up assessment (2% died, 1% were unreachable, and 5% refused), and 5073 women (80%) completed all 3 assessments. Follow-up rates were nearly identical by treatment groups.

COGNITIVE FUNCTION ASSESSMENT

The telephone cognitive battery (**Table 1**) included 5 tests measuring general cognition, verbal memory, and category fluency. To assess general cognition, we administered the Telephone Interview of Cognitive Status (TICS),[14] a telephone adaptation of the Mini-Mental State Examination. To test verbal memory, we administered the immediate and delayed recalls of the East Boston Memory Test,[15] in which a short paragraph is read and 12 key elements must be repeated immediately and 15 minutes later. To further evaluate delayed verbal memory, we also added a delayed recall of the TICS 10-word list. Finally, to assess category fluency (used to measure executive retrieval functions),[16] women were asked to name as many animals as possible in 1 minute.

Our primary, prespecified outcome was a global composite score averaging performance across all 5 cognitive tests using *z* scores. Because verbal memory is strongly associated with the risk of AD,[17] our key secondary outcome was a composite score of verbal memory, averaging performance across 4 measures of verbal memory (the immediate and delayed recalls of both the East Boston Memory Test and the TICS 10-word list). For participants who did not complete all tests (0.4% for the global composite score and 0.3% for the verbal memory score), we took the mean of the *z* scores of the tests that were completed.

Table 1. Characteristics of Participants in the Women's Health Study Cognitive Cohort*

Characteristic†	Vitamin E Group (n = 3184)	Placebo Group (n = 3193)	*P* Value
Age at randomization, y	66.2 ± 4.0 (60.4-89.9)	66.3 ± 4.1 (60.4-87.1)	.82
Age at initial cognitive assessment, y	71.8 ± 4.0 (66.1-95.5)	71.9 ± 4.1 (66.0-92.8)	.78
Vitamin E intake from diet, mg/d	7.0 ± 4.5 (1.9-67.9)	7.3 ± 6.0 (2.0-92.2)	.63
Self-reported perceived change in memory at the run-in period			
No change or improved	83.3	82.5	.39
Worsened	16.7	17.5	
Highest attained education			
LPVN, AD, RN	68.6	65.7	.01
BA, MA, DR	31.4	34.3	
Cigarette smoking			
Never smoker	53.6	51.3	.14
Past smoker	36.9	38.2	
Current smoker	9.5	10.5	
Alcohol drinking			
<Weekly	59.6	59.1	.90
Weekly	28.2	28.6	
Daily	12.1	12.3	
BMI			
<25	50.3	50.0	.94
25-29	34.6	34.7	
≥30	15.1	15.3	
Physical exercise, times/wk			
<1	60.2	58.9	.28
≥1	39.8	41.2	
Postmenopausal hormones			
Never user	40.6	39.4	.38
Past user	19.8	19.2	
Current user	39.7	41.4	
History of depression as of 4 years after randomization	6.0	5.8	.82
History of diabetes mellitus	3.4	3.5	.85
History of hypertension	40.3	39.8	.69
History of hyperlipidemia	43.2	42.7	.69

Abbreviations: AD, associate's degree; BA, bachelor's degree; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DR, doctoral degree; LPVN, licensed practical or vocational nurse; MA, master's degree; RN, registered nurse.

*Data are given as mean ± SD (range) or percentage unless otherwise specified.

†Characteristics as of randomization unless otherwise noted.

The cognitive interviews were administered by trained nurses. In a test-retest reliability study of the TICS administered twice, 31 days apart, we found a correlation of 0.7 ($P<.001$) among 35 high-functioning, educated women. In a validation study of our telephone instrument, 61 nuns from the Religious Order Study[18] who had completed an extensive in-person interview were administered our brief telephone-administered assessment; we found a correlation of 0.81 comparing the overall performance on those 2 measures, demonstrating high validity of our telephone method. In addition, among 88 older female health professionals, cognitive impairment as determined by our telephone assessment was strongly associated with later dementia after 3 years; poor performance in the TICS and in verbal memory were both associated with significant 8- and 12-fold increases, respectively, of later dementia diagnosis.

Table 2. Mean Cognitive Performance at Initial Assessment*

Cognitive Test	Vitamin E Group (n = 3184)	Placebo Group (n = 3193)	*P* Value
TICS	34.2 ± 2.7 (4.0-41.0)	34.2 ± 2.7 (15.0-41.0)	.84
East Boston Memory Test: immediate recall	9.5 ± 1.6 (0.0-12.0)	9.6 ± 1.6 (0.0-12.0)	.09
East Boston Memory Test: delayed recall	9.3 ± 1.8 (0.0-12.0)	9.3 ± 1.8 (0.0-12.0)	.75
TICS 10-word list: delayed recall	3.0 ± 2.1 (0.0-10.0)	3.0 ± 2.1 (0.0-10.0)	.47
Category fluency, animal naming test	17.6 ± 5.0 (0.0-37.0)	17.5 ± 4.9 (0.0-43.0)	.60

Abbreviation: TICS, Telephone Interview of Cognitive Status.
*Data are given as mean ± SD (range) unless otherwise specified. Initial cognitive testing was conducted a mean of 5.6 years after randomization.

STATISTICAL ANALYSIS

We first evaluated mean performance at each cognitive assessment by treatment assignment using repeated measures analysis of means, which permits examination at each time point, taking into account correlations between assessments. Second, we examined mean change in cognitive function over the 3 cognitive assessments by treatment assignment. Because of a "learning effect," test scores generally improved with time, particularly at the second assessment; however, this common, well-recognized phenomenon in cognitive function studies[19] does not prohibit detection of differences between treatment groups in long-term studies. To address this nonlinearity of the changes in the scores over time, we used general linear models of response profiles, modeling time with indicator variables for assessment rather than with a linear variable.[20] This approach imposes minimal structure on outcome trends over time and it permits valid estimation of effects in nonlinear data. We fitted all models by maximum likelihood, incorporating the longitudinal correlation within study subjects using unstructured covariance structures; for statistical testing, we used Wald tests.[20] All linear models were fit using SAS PROC MIXED (SAS release 9.1; SAS Institute Inc, Cary, NC).

We also examined effect modification by the following key risk factors (all assessed prior to randomization except when indicated) for cognitive decline: age, baseline score, dietary vitamin E intake, perceived change in memory, education, cigarette smoking, alcohol drinking, body mass index, physical activity, postmenopausal hormone use, history of diabetes, hypertension, elevated cholesterol level, depression (as of 4 years after randomization), and cardiovascular disease (all incident occurrences after randomization). Cardiovascular disease included nonfatal myocardial infarction, nonfatal stroke, cardiovascular-related deaths, or vascular disease as evidenced by either a coronary artery bypass graft or percutaneous transluminal coronary angioplasty or vascular stenting, confirmed by medical record review.[13] Tests of effect modification were performed by evaluating the interaction terms in the models of mean change.

In addition, to assess the impact of vitamin E treatment on the risk of "substantial decline," we used logistic regression models in which substantial cognitive decline was defined as the worst 10% of the distribution of change from the initial to the final cognitive assessment. In these models, we adjusted for the follow-up time between the first and third assessments. We did not control for cognitive performance at the first assessment; however, results were very similar to results from alternate models when it was included in models.

Finally, in models adjusting for aspirin assignment (the second intervention tested in this trial), results did not change materially; thus, we did not include aspirin as a covariate in any models for the main analyses. Effect modification by aspirin assignment was also not observed.

RESULTS

PRIMARY ANALYSES

The mean time since randomization to treatment or placebo as of the initial cognitive assessment was 5.6 years (range, 4.4-6.8 years), and the mean time between the first and the last assessment was 4.0 years (range, 2.6-5.7 years). Compliance was comparable between the 2 groups; as of the final cognitive assessment, the percentage that reported taking at least two thirds of the assigned pills was 75.4% for the vitamin E group and 76.9% for the placebo group. Demographic and health characteristics at randomization were similar between treatment and placebo groups, except for education: the placebo group included more women with higher levels of education (34.3%) than the vitamin E group (31.4%) (Table 1). When we compared analyses adjusted for education with unadjusted analyses, results were not materially different; thus, we present herein only unadjusted analyses.

At the first assessment, scores on the 5 tests did not differ by treatment (**Table 2**). Similarly at each follow-up assessment, there were no mean differences in global score between the vitamin E and placebo groups (**Table 3**). For example, at the initial assessment, the mean difference between the vitamin E and placebo groups was –0.01 (95% CI, –0.04 to 0.03); at the final assessment (after a mean of 9.6 years of treatment), this difference was 0.00 (95% CI, –0.04 to 0.04). Similarly, for our secondary end point of verbal memory, we observed no differences in score between the groups at any of the 3 assessments: at the final assessment, the mean difference in performance was 0.01 (95% CI, –0.03 to 0.05). The vitamin E group also did not show better performance in either the TICS or category fluency.

When we compared the mean change in cognitive performance from initial through the final assessments, we observed similar results (**Table 4**), with no differences by treatment assignment. The mean difference in cognitive change between the vitamin E and placebo groups was 0.02 (95% CI, –0.01 to 0.05) for the global score; 0.02 (95% CI, –0.01 to 0.06) for the verbal memory score; 0.10 (95% CI, –0.03 to 0.23) for the TICS; and 0.05 (95% CI, –0.18 to 0.28) for category fluency score.

Compared with the placebo group, the vitamin E group did not have a lower risk of substantial cognitive decline from the first through third assessment and had a relative risk (RR) of substantial decline in global score of 0.92 (95% CI, 0.77 to 1.10) (**Table 5**). For the verbal memory score, the vitamin E group had a borderline significant 15% lower risk of substantial decline compared with the placebo group (RR, 0.85; 95% CI, 0.71 to 1.02).

Table 3. Cognitive Function at Each Cognitive Assessment by Vitamin E Treatment

Cognitive Test*	Treatment Assignment: Vitamin E Group No. of Subjects	Vitamin E Group Mean ± SE†	Placebo Group No. of Subjects	Placebo Group Mean ± SE†	Difference in Score, Mean (95% CI), Vitamin E Group – Placebo Group‡
Primary end point: global score					
1	3184	0.00 ± 0.01	3193	0.00 ± 0.01	–0.01 (–0.04 to 0.03)
2	2837	0.08 ± 0.01	2855	0.06 ± 0.01	0.02 (–0.02 to 0.05)
3	2596	0.02 ± 0.01	2630	0.02 ± 0.01	0.00 (–0.04 to 0.04)
Key secondary end point: verbal memory score					
1	3184	0.00 ± 0.01	3193	0.00 ± 0.01	–0.01 (–0.04 to 0.03)
2	2837	0.13 ± 0.01	2855	0.12 ± 0.01	0.01 (–0.03 to 0.05)
3	2596	0.10 ± 0.02	2630	0.09 ± 0.02	0.01 (–0.03 to 0.05)
TICS score					
1	3176	34.21 ± 0.05	3186	34.23 ± 0.05	–0.01 (–0.15 to 0.12)
2	2835	34.15 ± 0.05	2853	34.05 ± 0.05	0.10 (–0.05 to 0.25)
3	2596	34.12 ± 0.06	2630	34.08 ± 0.06	0.04 (–0.12 to 0.21)
Category fluency score					
1	3171	17.55 ± 0.09	3182	17.49 ± 0.09	0.06 (–0.18 to 0.31)
2	2835	18.14 ± 0.10	2853	18.01 ± 0.10	0.13 (–0.14 to 0.41)
3	2595	17.59 ± 0.10	2630	17.55 ± 0.10	0.04 (–0.24 to 0.31)

Abbreviations: CI, confidence interval; TICS, Telephone Interview of Cognitive Status.
*Verbal memory score is a composite score of the immediate and delayed recalls of both the TICS 10-word list and the East Boston Memory Test; global score is a composite score of TICS, immediate and delayed recalls of the East Boston Memory Test, category fluency, and delayed recall of the TICS 10-word list.
†Least squares mean and standard errors.
‡From longitudinal linear models of mean cognitive performance.

SECONDARY ANALYSES

We investigated whether vitamin E assignment influenced mean cognitive decline within groups defined by various risk factors (**Table 6**). We observed that the vitamin E group experienced less adverse cognitive change compared with the placebo group among women with dietary intake below the median of 6.1 mg/d (the difference in mean change in global score over time between the vitamin E and placebo groups was 0.05 [95% CI, 0.01 to 0.09]) but among women with high intakes of dietary vitamin E, the 2 groups were similar in their change. Also among women who exercised less than once per week, the vitamin E group experienced a more favorable cognitive change than did the placebo group: the difference in mean change in global score over time was 0.06 (95% CI, 0.03 to 0.10). In contrast, among women who exercised at least once per week, there was no difference in mean change in global score over time (mean difference, –0.04; 95% CI, –0.09 to 0.01). We also observed that vitamin E treatment appeared beneficial among women without diabetes (mean difference, 0.03; 95% CI, 0.00 to 0.06) but not among women with diabetes (mean difference, –0.15; 95% CI, –0.31 to 0.01).

Finally, to assess the influence of compliance, we repeated analyses after excluding participants who reported taking less than two thirds of their assigned treatment as of the third cognitive assessment (24% of participants). In both treatment arms, noncompliant subjects were more likely to be current smokers, to have depression at enrollment, and to have developed cardiovascular disease during follow-up. After excluding noncompliant subjects, the mean difference in global score for cognitive decline between the vitamin E and placebo groups was 0.03 (95% CI, 0.00 to 0.07), and for the verbal memory score, the difference was 0.04 (95% CI, 0.00 to 0.08). The RR of substantial decline in the global score in the vitamin E treatment compared with the placebo group was 0.95 (95% CI, 0.76 to 1.19); for the verbal memory score, the RR was 0.79 (95% CI, 0.63 to 1.00).

COMMENT

In this large randomized, placebo-controlled trial, with 10 years of treatment and 4 years of follow-up, vitamin E supplementation did not provide overall cognitive benefits; at each cognitive assessment, we observed no material difference in global score by vitamin E or placebo assignment. In secondary analyses, we found a suggestion that those who were compliant with treatment assignment or low in dietary vitamin E at randomization may have received some cognitive benefits with vitamin E supplementation, and there were other suggestions of effect modification with physical activity and history of diabetes. However, chance cannot be ruled out as explanations, given that we performed multiple subgroup analyses.

Previous clinical trials of vitamin E supplementation have also not demonstrated obvious cognitive benefits. For example, in a 2-year placebo-controlled trial among 341 patients with AD,[8] high-dose vitamin E (2000 IU/d) supplementation helped delay nursing home placement, death, and disability but did not delay cognitive decline, making the mechanism of putative beneficial effects unclear. Similarly, in a recent randomized clinical

Table 4. Mean Cognitive Decline Over Follow-up by Vitamin E Treatment

Cognitive Test*	Difference in Rate of Cognitive Decline, Mean (95% CI), Vitamin E Group – Placebo Group	*P* Value
Primary end point: global score		
From initial cognitive assessment to:		
Second cognitive assessment	0.03 (–0.01 to 0.06)	.12
Third cognitive assessment	0.01 (–0.02 to 0.05)	.46
Mean over follow-up	0.02 (–0.01 to 0.05)	.16
Key secondary end point: verbal memory score		
From initial cognitive assessment to:		
Second cognitive assessment	0.02 (–0.01 to 0.06)	.22
Third cognitive assessment	0.02 (–0.02 to 0.06)	.31
Mean over follow-up	0.02 (–0.01 to 0.06)	.19
TICS score		
From initial cognitive assessment to:		
Second cognitive assessment	0.12 (–0.02 to 0.27)	.10
Third cognitive assessment	0.07 (–0.09 to 0.23)	.39
Mean over follow-up	0.10 (–0.03 to 0.23)	.13
Category fluency score		
From initial cognitive assessment to:		
Second cognitive assessment	0.10 (–0.16 to 0.36)	.46
Third cognitive assessment	–0.01 (–0.28 to 0.26)	.93
Mean over follow-up	0.05 (–0.18 to 0.28)	.69

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

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

Table 5. Relative Risk of Substantial Decline*

Cognitive Test	Substantial Decline, RR (95% CI)	*P* Value
Primary end point: global score†		
Placebo group	1.00	.36
Vitamin E group	0.92 (0.77-1.10)	
Key secondary end point: verbal memory score†		
Placebo group	1.00	.08
Vitamin E group	0.85 (0.71-1.02)	
TICS†		
Placebo group	1.00	.82
Vitamin E group	0.98 (0.83-1.16)	
Category fluency†		
Placebo group	1.00	.23
Vitamin E group	1.12 (0.93-1.35)	

Abbreviations: CI, confidence interval; RR, relative risk; TICS, Telephone Interview of Cognitive Status.

*Substantial decline is defined as the worst 10% of the distribution of decline from the first to third assessment (global score, –0.8 points; verbal memory score, –0.9 points; TICS score, –4 points; and category fluency, –7 points). Adjusted for time between first and third cognitive interview.

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

study among patients with mild cognitive impairment (n=769), vitamin E supplementation (2000 IU/d) did not reduce the rate of progression to AD or delay cognitive decline over a 3-year period.[9] In the Age-Related Eye Disease Study (AREDS) trial[11] in which a combination of antioxidants including vitamin E (400 IU/d), zinc, and copper was tested for slowing progression of age-related macular degeneration and 2166 participants completed cognitive testing, no differences were observed in the likelihood of cognitive impairment by treatment assignment over 6.9 years of follow-up. Finally, in the largest randomized study to date (n=20 536) among those at high risk for cardiovascular disease,[10] there were no treatment differences after 5 years between placebo and a combination of antioxidants including vitamin E (>800 IU/d) in relation to cognitive impairment. Thus, overall, the current body of trial data, including our study results with almost 10 years of treatment, does not indicate any cognitive benefits of vitamin E supplementation.

Several possibilities related to supplement dose, antioxidant agent, and timing of study initiation may explain the lack of overall cognitive benefits found in this trial. First, the dose of vitamin E for this trial was 600 IU taken every other day. It is possible that the dose used in this study was not high enough, given that previous studies[8,9,21,22] have investigated very high doses of vitamin E (eg, 2000 IU/d[8,9]). Although there is not enough evidence to determine what the optimal dose may be for neuroprotection, studies of very high doses of vitamin E have not demonstrated cognitive benefits either; thus, it seems unlikely that our largely null findings could be explained by the vitamin E dose. Second, most vitamin E supplements are largely composed of α-tocopherol. It has been suggested that tocopherols such as γ-tocopherol that is found in foods rather than in supplements[23] may be more important for delaying brain aging. Although α-tocopherol has stronger antioxidant properties, γ-tocopherol has important additional anti-inflammatory effects that may enhance neuroprotection.[23,24] Finally, although this trial was of long duration and most women in the cognitive study initiated vitamin E treatment in their 60s, it is possible that an even longer duration or earlier initiation is required. For example, in a transgenic mouse model of AD, a significant reduction in amyloid deposition in the brain was observed only when vitamin E supplementation was provided at young ages (5-13 months) but not at older ages (14-20 months).[5] In addition, 2 observational studies of cognitive function[6,7] both found that less than 10 years of vitamin E use was not strongly associated with better cognitive performance. Also, a recent randomized trial of supplementation with the antioxidant beta carotene reported protection against cognitive impairment after a mean of 18 years of treatment but no protection if taken for shorter durations.[25]

Limitations of this study should be considered. Cognitive testing began a mean of 5.6 years after randomization; thus, we were unable to evaluate change in cognitive performance from randomization. However, at randomization, the distribution of the various risk factors for cognitive impairment was comparable across treatment groups; thus, it is unlikely in this large trial that

Table 6. Mean Difference in Rate of Decline in Global Score Between Vitamin E and Placebo Groups: Effect Modification by Major Risk Factors for Cognitive Decline

Characteristic*	Difference in Rate of Cognitive Decline, Mean (95% CI) Vitamin E Group – Placebo Group	*P* Value for Interaction
Age at first assessment, y		
<75	0.01 (–0.02 to 0.04)	.36
≥75	0.05 (–0.02 to 0.12)	
Dietary vitamin E intake		
Below median (<6.1 mg/d)	0.05 (0.01 to 0.09)	.04
Above median (≥6.1 mg/d)	–0.01 (–0.06 to 0.03)	
Cognitive performance at first assessment		
Below median	0.04 (–0.01 to 0.08)	.26
Above median	0.00 (–0.03 to 0.04)	
Self-reported perceived change in memory†		
No change or improved	0.03 (0.00 to 0.06)	.12
Worsened	–0.03 (–0.10 to 0.04)	
Highest attained education		
LPVN, AD, RN	0.02 (–0.01 to 0.06)	.71
BA, MA, DR	0.01 (–0.04 to 0.06)	
Cigarette smoking		
Never smoker	0.04 (0.00 to 0.08)	.40
Past smoker	–0.01 (–0.05 to 0.04)	
Current smoker	0.04 (–0.06 to 0.13)	
Alcohol drinking		
<Weekly	0.03 (–0.01 to 0.06)	.52
Weekly	0.00 (–0.06 to 0.05)	
Daily	0.05 (–0.03 to 0.13)	
BMI		
<30	0.02 (–0.01 to 0.05)	.49
≥30	0.05 (–0.03 to 0.12)	
Physical exercise, times/wk		
<1	0.06 (0.03 to 0.10)	<.001
≥1	–0.04 (–0.09 to 0.01)	
Postmenopausal hormones		
Never user	–0.01 (–0.06 to 0.04)	.09
Past + current user	0.04 (0.00 to 0.08)	
Diabetes mellitus		
Absent	0.03 (0.00 to 0.06)	.03
Present	–0.15 (–0.31 to 0.01)	
Hypertension		
Absent	0.03 (0.00 to 0.07)	.33
Present	0.00 (–0.04 to 0.05)	
Hyperlipidemia		
Absent	0.00 (–0.04 to 0.04)	.18
Present	0.04 (0.00 to 0.09)	
Cardiovascular disease during follow-up‡		
Absent	0.02 (–0.01 to 0.05)	>.99
Present	0.02 (–0.10 to 0.14)	
History of depression†		
Absent	0.02 (–0.01 to 0.05)	.16
Present	0.11 (–0.01 to 0.24)	

Abbreviations: See Table 1.

*Characteristics as of randomization unless noted otherwise.

†Change in memory was assessed at run-in phase; depression was assessed as of fourth year after randomization.

‡Cardiovascular disease includes nonfatal myocardial infarction, nonfatal stroke, revascularization surgery, or cardiovascular death.

baseline cognitive function was also similar in the vitamin E and placebo groups. Hence, the lack of cognitive function assessment at randomization should not greatly affect our ability to detect effects of long-term vitamin E treatment on cognitive decline. If, however, vitamin E confers cognitive benefits in the short term, then our cognitive data collected after 5.6 years on treatment would not be able to capture these early differences. Yet, this possibility seems biologically implausible given that cognitive impairment develops slowly over decades. Another limitation was noncompliance (23%-25%), which may bias associations toward the null; indeed, our secondary analyses including only compliant subjects suggested some potential cognitive benefits of vitamin E supplementation. However, these analyses themselves may be inherently biased and thus should be interpreted with caution.

In conclusion, in this randomized placebo-controlled trial among more than 6000 healthy women, vitamin E supplementation did not provide overall cognitive benefits or reduce cognitive decline over 4 years. Although some questions remain (eg, the possibility of using mixed tocopherols or initiating use at young ages for very long durations), the findings of this trial, combined with results of other studies, indicate that vitamin E supplementation of 10 years or less does not provide neuroprotection.

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Correspondence: Jae Hee Kang, ScD, Channing Laboratory, 181 Longwood Ave, Boston, MA 02115 (nhjhk@channing.harvard.edu).

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REFERENCES

1. Pratico D, Clark CM, Liun F, Rokach J, Lee VY, Trojanowski JQ. Increase of brain oxidative stress in mild cognitive impairment: a possible predictor of Alzheimer disease. *Arch Neurol.* 2002;59:972-976.
2. Yokota T, Igarashi K, Uchihara T, et al. Delayed-onset ataxia in mice lacking α-tocopherol transfer protein: model for neuronal degeneration caused by chronic oxidative stress. *Proc Natl Acad Sci U S A.* 2001;98:15185-15190.

3. Milgram NW, Head E, Zicker SC, et al. Learning ability in aged beagle dogs is preserved by behavioral enrichment and dietary fortification: a two-year longitudinal study. *Neurobiol Aging*. 2005;26:77-90.
4. Nunomura A, Perry G, Aliev G, et al. Oxidative damage is the earliest event in Alzheimer disease. *J Neuropathol Exp Neurol*. 2001;60:759-767.
5. Sung S, Yao Y, Uryu K, et al. Early vitamin E supplementation in young but not aged mice reduces Aβ levels and amyloid deposition in a transgenic model of Alzheimer's disease. *FASEB J*. 2004;18:323-325.
6. Grodstein F, Chen J, Willett WC. High-dose antioxidant supplements and cognitive function in community-dwelling elderly women. *Am J Clin Nutr*. 2003; 77:975-984.
7. Masaki KH, Losonczy KG, Izmirlian G, et al. Association of vitamin E and C supplement use with cognitive function and dementia in elderly men. *Neurology*. 2000; 54:1265-1272.
8. Sano M, Ernesto C, Thomas RG, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease: the Alzheimer's Disease Cooperative Study. *N Engl J Med*. 1997;336:1216-1222.
9. Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med*. 2005;352:2379-2388.
10. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:23-33.
11. Yaffe K, Clemons TE, McBee WL, Lindblad AS. Impact of antioxidants, zinc, and copper on cognition in the elderly: a randomized, controlled trial. *Neurology*. 2004; 63:1705-1707.
12. Buring JE, Hennekens CH. The Women's Health Study: summary of the design. *J Myocardial Ischemia*. 1992;4:27-29.
13. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med*. 2005; 352:1293-1304.
14. Brandt J, Folstein MF. *Telephone Interview for Cognitive Status: Professional Manual*. Lutz, Fla: Psychological Assessment Resources Inc; 2003.
15. Scherr PA, Albert MS, Funkenstein HH, et al. Correlates of cognitive function in an elderly community population. *Am J Epidemiol*. 1988;128:1084-1101.
16. Morris JC, Heyman A, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD), I.: clinical and neuropsychological assessment of Alzheimer's disease. *Neurology*. 1989;39:1159-1165.
17. Small BJ, Fratiglioni L, Viitanen M, Winblad B, Backman L. The course of cognitive impairment in preclinical Alzheimer disease: three- and 6-year follow-up of a population based sample. *Arch Neurol*. 2000;57:839-844.
18. Bennett DA, Wilson RS, Schneider JA, et al. Natural history of mild cognitive impairment in older persons. *Neurology*. 2002;59:198-205.
19. Espeland MA, Rapp SR, Shumaker SA, et al. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. *JAMA*. 2004;291:2959-2968.
20. Fitzmaurice GM, Laird NM, Ware JH. *Modelling the Mean: Analyzing Response Profiles: Applied Longitudinal Analysis*. Hoboken, NJ: John Wiley & Sons Inc; 2004:103-139.
21. Luchsinger JA, Tang M-X, Shea S, Mayeux R. Antioxidant vitamin intake and risk of Alzheimer disease. *Arch Neurol*. 2003;60:203-208.
22. Baker H, De Angelis B, Baker ER, Frank O, Jaslowdagger SP. Lack of effect of 1 year intake of a high-dose vitamin and mineral supplement on cognitive function of elderly women. *Gerontology*. 1999;45:195-199.
23. Morris MC, Evans DA, Tangney CC, et al. Relation of the tocopherol forms to incident Alzheimer disease and to cognitive change. *Am J Clin Nutr*. 2005;81: 508-514.
24. Liu M, Wallmon A, Olsson-Mortlock C, Wallin R, Saldeen T. Mixed tocopherols inhibit platelet aggregation in humans: potential mechanisms. *Am J Clin Nutr*. 2003;77:700-706.
25. Grodstein F, Kang JH, Gaziano JM. A large randomized trial of beta-carotene supplements and Cognitive Function [abstract]. *Neurobiol Aging*. 2004;25:S54.