High-dose antioxidant supplements and cognitive function in community-dwelling elderly women[1–3]

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ABSTRACT

Background: Experimental data suggest that oxygen free radicals are probably involved in the deterioration of cognitive processes.
Objective: Our objective was to investigate the relation of high-dose antioxidant supplements to cognition.
Design: Information on the use of specific supplements containing vitamins E and C was collected biennially via mailed questionnaires beginning in 1980 from 14 968 community-dwelling women who participated in the Nurses' Health Study. From 1995 to 2000, telephone tests of cognitive function [Telephone Interview of Cognitive Status (TICS), delayed recall of the TICS 10-word list, immediate and delayed recall of a short paragraph, a test of verbal fluency, and a digit span backwards test] were administered to the women, who were 70–79 y of age at that time. We used linear and logistic regression models to calculate multivariate-adjusted mean differences in test scores and relative risks of a low score for specific supplement users compared with nonusers.
Results: Long-term, current users of vitamin E with vitamin C had significantly better mean performance, as judged by a global score that combined individual test scores, than did women who had never used vitamin E or C ($P = 0.03$); there was a trend for increasingly higher mean scores with increasing durations of use ($P = 0.04$). These associations were strongest among women with low dietary intakes of α-tocopherol. Benefits were less consistent for women taking vitamin E alone, with no evidence of higher scores with longer durations of use. Use of specific vitamin C supplements alone had little relation to performance on our cognitive tests.
Conclusion: The use of specific vitamin E supplements, but not specific vitamin C supplements, may be related to modest cognitive benefits in older women. *Am J Clin Nutr* 2003;77:975–84.

KEY WORDS Aging, epidemiology, cognitive function, women, antioxidant vitamins, vitamin E, Nurses' Health Study

INTRODUCTION

As the elderly become an increasingly large percentage of the US population, significant public health interest has been directed at identifying ways to maintain cognitive function in old age. Experimental data indicate that oxygen free radicals are probably involved in the deterioration of cognitive processes; in animal models, antioxidant vitamins appear to enhance the cholinergic and glutamatergic neurotransmitter systems (1, 2) and to directly increase neuron survival (3) and synaptic response (4). In addition, chronic administration of antioxidant vitamins in rats leads to greater learning and memory retention than does administration of a placebo (5). In recent observational studies (6, 7), dietary antioxidant intake appeared to decrease the risk of developing Alzheimer disease, and in a short-term, randomized clinical trial of Alzheimer patients (8), very high doses of vitamin E resulted in a longer time to institutionalization and a delayed time to deterioration of activities of daily living (although cognitive function did not appear to be improved).

The results of epidemiologic studies investigating the relation of antioxidants to cognitive function in generally healthy elderly subjects have been inconsistent (9–18); however, many of these studies did not have a large number of subjects who took supplements long term or detailed data on supplement use. Because any effect of vitamin supplements on cognition in a generally healthy population is likely to be modest (19), existing studies may not have adequate statistical power to identify effects. In the Nurses' Health Study, we have collected information regarding supplement use since 1980 from a large cohort of registered nurses; from 1995 to 2000, we administered a battery of cognitive tests to 14 968 of the oldest participants (aged 70–79 y) who had complete information on supplement intake. In the present study, we investigated the relation of specific vitamin E and vitamin C supplements, including the dose and duration, to performance on our cognitive tests.

SUBJECTS AND METHODS

The Nurses' Health Study cohort

The Nurses' Health Study began in 1976, when 121 701 female registered nurses, who were 30–55 y of age and lived in 11 US states, completed a mailed questionnaire about their lifestyle and medical history, including numerous diseases and risk factors. Every 2 y, we mail follow-up questionnaires to update information on risk factors and to identify newly diagnosed cases of major

illnesses. In 1980, we began collecting dietary information that included detailed assessment of vitamin supplements; ≈75% of the subjects participate in the diet cohort. The total follow-up for the diet cohort exceeds 94% to date.

Population for analysis

All Nurses' Health Study participants aged ≥70 y who were free of diagnosed stroke and who had answered the most recent mailed questionnaire were eligible to participate in the study of cognitive function. From 1995 to 2000, we telephoned 22 213 women to administer a brief telephone interview of cognitive function (described below); 19 510 (88%) agreed to complete the interview, 7% refused to be interviewed, and we were unable to obtain an accurate telephone number for 5% (ie, of those we contacted, 92% agreed to participate). The analyses presented here are based on the 14 968 subjects who were part of the diet cohort. This study was approved by the Institutional Review Board of Brigham and Women's Hospital, Boston.

Cognitive function assessment

The initial assessment consisted of the Telephone Interview for Cognitive Status (TICS; 20), which is modeled on the Mini-Mental State Examination. After we established a high degree of acceptance for the telephone interviewing, we gradually included additional tests: immediate and delayed recall of the East Boston Memory Test (EBMT; 21), delayed recall of the TICS 10-word list, a test of verbal fluency (22), and a digit span backwards test. Participation rates in the cognitive function study remained unchanged over time; thus, there was similar participation for each of the tests.

Telephone Interview of Cognitive Status

The TICS is a telephone version of the Mini-Mental State Examination; Brandt et al (20) reported a strong linear relation between scores on the 2 tests (Pearson correlation = 0.94). Test-retest reliability has been shown to be high ($r = 0.97$; 20). In our population, TICS scores ranged from 8 to 41 (41 is a perfect score); the mean ($\pm$SD) score was 33.8 ± 2.7, and 9.8% of the women scored < 31, which has been established as a cutoff for poor cognitive function. Because there is particular interest in verbal memory [verbal memory appears to be an important predictor of future development of Alzheimer disease (23)], we also separately analyzed a subsection of the TICS, immediate recall of a 10-word list; scores for the immediate recall of the 10-word list ranged from 0 to 10 ($\bar{x} = 4.7 \pm 1.7$). Results from the TICS and the test of immediate recall of the 10-word list are based on the 14 968 women in the diet cohort who completed the TICS.

Delayed recall of 10-word list

We administered a test of delayed recall of the TICS 10-word list at the end of our interview (≈15 min later); scores ranged from 0 to 10 ($\bar{x} = 2.4 \pm 2.0$). The test of delayed recall of the 10-word list was added to our battery after the TICS and was completed by 12 838 women in the diet cohort.

East Boston Memory Test

A short paragraph was read; the score was based on the ability to repeat 12 key elements. A test of delayed recall was given at the end of the interview (≈15 min later). In our population, scores for immediate recall ranged from 0 to 12; the mean was 9.4 ± 1.7. For delayed recall, scores ranged from 0 to 12 ($\bar{x} = 9.0 \pm 2.0$).

Analyses of the EBMT are based on the 14 281 women in the diet cohort who were administered those tests.

Test of verbal fluency

The women were asked to name as many animals as they could during 1 min. Scores ranged from 2 to 38 animals named; the mean was 17.0 ± 4.6. Analyses of this test are based on the 14 275 women in the diet cohort to whom it was administered (4 women in the diet cohort who completed a cognitive assessment refused to complete this test).

Digit span backwards test

The women were asked to repeat backwards increasingly long series of digits; scoring was based on the ability to repeat 12 series for a total of 12 points. In our population, the mean score was 6.8 ± 2.4, and scores ranged from 1 to 12. We administered this test to 12 834 women in the diet cohort (6 women in the diet cohort who completed a cognitive assessment refused to complete this test).

Global score

To estimate overall cognitive performance, we calculated a global cognitive score by combining the results from each of the 6 primary tests we administered: TICS, delayed recall of the TICS 10-word list, immediate and delayed recalls of the EBMT, the test of verbal fluency, and the digit span backwards test. The global score was calculated only for the women who were administered all these tests. We could not add the scores together because a point is not equivalent for each test; thus, we created z scores by taking the difference between the participant's score on each test and the mean score and dividing by the SD. We added these z scores to acquire a global score. Because of issues of multiple comparisons when separately examining each of the cognitive tests individually, we focused our data interpretation on the results for this global score.

Clinical significance of test scores

The clinical significance of a given difference in test scores for the tests we administered has not been established in a generally healthy population. Thus, we chose to use age as a benchmark of clinical significance; for a given cognitive test, we calculated the mean difference in scores between subjects 2 y apart in age, allowing evaluation of the effect of age in contrast to the effect of specific vitamin supplements. The magnitude of age effects on cognitive test scores was determined from the data in our study by using a continuous term for age (in 2-y increments) in multivariate linear regression models adjusted for all factors described below.

The telephone cognitive assessments were administered by registered nurses who were trained to conduct these interviews. In a small study of inter-interviewer reliability, we found correlations > 0.95 for each test included in our battery.

Ascertainment of specific antioxidant supplement use

In 1980, the women were first asked about their use, including dose and duration, of specific vitamin E and vitamin C supplements. On each subsequent biennial questionnaire, information on specific supplement use and dose was updated. For all analyses, supplement status was updated until the most recent questionnaire completed before the cognitive interview (ie, up to 2 y before).

For each vitamin, we calculated duration on the basis of reported years of use from the 1980 questionnaire; we then added time according to the women's responses to subsequent questionnaires such that *1*) if use of a given vitamin was reported on the current questionnaire as well as on the preceding questionnaire, then we assumed continual use between questionnaires and added 2 y; *2*) if use was reported on the current questionnaire and not on the preceding questionnaire, then we added 1 y. For specific vitamin C use, we also considered seasonal use, such that when seasonal use was reported on 2 subsequent questionnaires, we added 1 y of use, and if seasonal use was reported on a single questionnaire, we added 6 mo; however, only 9% of the women reported seasonal use.

Daily doses of vitamin E were determined by using the categories from the self-reported questionnaires: < 100, 100–250, 300–500, and ≥ 600 mg. We defined a very high dose of vitamin E as ≥ 600 mg. Daily doses of vitamin C were based on the following questionnaire categories: < 400, 400–700, 750–1250, and ≥ 1300 mg; we considered ≥ 750 mg a very high dose.

Some multivitamins contain antioxidant vitamins. Because we did not have information on the exact multivitamin taken and because there is substantial variation in the antioxidant component of multivitamins (although they generally contain low doses), we chose not to consider these as antioxidant supplementation. However, when we excluded from the reference group women who reported current use of a multivitamin, results were unchanged (*see* Results); thus, we did not make such exclusions in the results presented here (we do, however, adjust for multivitamin use in all multivariate models; *see* below).

Statistical analysis

We compared the results on the cognitive function tests from current users of vitamins E and C, current users of vitamin E alone, current users of vitamin C alone, and past antioxidant vitamin users with the results from the women who had never used either vitamin E or C supplements. In analyses of current duration of supplement use, we excluded the women currently taking both vitamins E and C who had not always taken the combination (eg, 5 y of vitamin E with vitamin C, preceded by 8 y of vitamin C alone). We did not consider duration of past use, because most past users had taken supplements for < 10 y.

For current supplement users, we also examined lower-dose users (< 600 mg vitamin E or < 750 mg vitamin C) and very-high-dose users (≥ 600 mg vitamin E or ≥ 750 mg vitamin C). In these analyses, we excluded the women who were currently taking vitamins E and C but in different doses (eg, lower-dose vitamin E with very-high-dose vitamin C).

We analyzed the relation of various categories of specific antioxidant use to mean scores on each of the cognitive tests; we used linear regression models to adjust the mean difference in scores for age, education, and other potential confounders (*see* below). We also examined the results of each test as a categorical outcome by using logistic regression to estimate multivariate-adjusted relative risks of a low score and corresponding 95% CIs. In these analyses, for the TICS, we used a score of < 31 points to define low scorers [on the basis of a previously established cutoff (20)] and compared the women scoring < 31 points to those scoring ≥ 31 points. For the remaining tests, we defined a low score as the bottom 10th percentile and compared low scorers to all other women (ie, the remaining 90%). The following cutoffs were used: immediate and delayed recall of the TICS 10-word list, ≤ 3

and ≤ 2, respectively; immediate and delayed recall of the EBMT, ≤ 7 and ≤ 6, respectively; the test of verbal fluency, ≤ 11; and the digit span backwards test, ≤ 3.

In both the linear and logistic regression models, we included the following confounding variables: age at interview (five 2-y age groups), years of education after high school (1–4, > 4), history of diabetes (yes, no), history of high blood pressure (yes, no), history of heart disease (yes, no), multivitamin use (yes, no), regular aspirin use (yes, no), postmenopausal hormone use (never, current, past), body mass index (in kg/m^2; < 22, 22–24.9, 25–29.9, ≥ 30), cigarette smoking (current, past, never), and antidepressant use (yes, no). We also adjusted for the mental health index (0–51, 52–100) and energy-fatigue index (0–49, 50–100) from the Medical Outcomes Short Form-36. These indexes combine items on questions such as feeling hopeless or feeling downhearted (for the mental health index), being worn-out or having a lot of energy (for the energy-fatigue index), etc; < 52 on the mental health index is a standard cutoff for low mental health, and < 50 on the energy-fatigue index is a standard cutoff for low vitality. Information on each of these confounding variables, except antidepressant use (which we began requesting in 1996) and the indexes from the Medical Outcomes Short Form-36 (which we administered in 1992 and 1996), was updated until the most recent questionnaire completed before the women's cognitive assessment.

Finally, we were concerned that healthy diets in our population of registered nurses might mask the effects of vitamin supplements. To address this issue, we included in some analyses only the women in the bottom 30% of α-tocopherol or vitamin C dietary intake (ie, food only). These analyses were based on reported dietary intakes from our food-frequency questionnaire (24) in 1994; this validated questionnaire included questions about usual intakes of 118 different foods during the previous year. We adjusted for multivitamin use in these models; as in the main analysis, the exclusion of the women taking multivitamins from the reference group did not change the results. All analyses were conducted with the use of SAS statistical software, version 6.1 (SAS Institute Inc, Cary, NC).

RESULTS

The women who currently used both specific vitamin E and C supplements represented 33% of our cohort, an additional 20% were current users of vitamin E alone, 9% were current users of vitamin C alone, 14% were past users of either vitamin, and 24% had never used vitamins E or C (**Table 1**). Among the women currently taking specific vitamin E supplements, 30% had been taking them for ≥ 10 y; for vitamin C, 37% were long-term users. Few of the women were taking very low or very high doses of these vitamins: among those currently taking specific vitamin E supplements, 2% took < 100 mg and 15% took ≥ 600 mg; among those taking vitamin C, 11% took < 400 mg and 34% took ≥ 750 mg.

The characteristics of specific supplement users and nonusers are shown in Table 1. In general, significantly higher percentages of supplement users than of nonusers received hormone therapy and took antidepressants. The percentages of subjects who took aspirin or smoked cigarettes were significantly higher and lower, respectively, among the current users of specific vitamin E supplements than among the women who had never taken specific vitamin E or C supplements.

TABLE 1
Characteristics of vitamin E and vitamin C supplement users and nonusers among Nurses' Health Study participants aged 70–79 y[1]

	Nonusers (n = 3649)	Current users of E and C (n = 4961)	Current users of C alone (n = 1364)	Current users of E alone (n = 2969)	Past users (n = 2025)
Age at interview (y)[2]	74.1 ± 2.3	74.2 ± 2.3	74.4 ± 2.2[3]	74.1 ± 2.3	74.2 ± 2.2
Mental health index[4] <52 (%)	9.3	9.4	10.1	9.3	8.5
Energy fatigue index[5] <50 (%)	22.1	20.8	24.6	20.7	23.5
Master's or doctoral degree (%)	23.1	26.2[6]	25.5	23.8	24.2
Current postmenopausal hormone use (%)	26.5	40.4[6]	33.3	37.4[6]	34.9[6]
Antidepressant use (%)	4.7	6.6[6]	6.4[6]	5.8	7.5[6]
Current smoker (%)	12.3	7.5[6]	10.8	7.7[6]	10.5
BMI ≥ 30 (%)	21.6	17.6[6]	19.5	20.6	22.6
High blood pressure (%)	53.8	54.0	53.2	56.6[6]	57.0[6]
Diabetes (%)	10.0	9.3	9.3	9.1	9.9
Current aspirin use (%)	32.7	45.7[6]	38.5	44.3[6]	35.1

[1] All characteristics were determined on the basis of the most recent questionnaire completed before the subject's cognitive interview, except for antidepressant use, which was determined on the basis of the 1996 questionnaire, and mental health and energy-fatigue indexes, which were determined on the basis of the 1992 and 1996 questionnaires.

[2] $\bar{x} \pm$ SD.

[3] Significantly different from never, $P < 0.05$ (ANOVA).

[4] 0–100; a score <52 is considered indicative of low mental health.

[5] 0–100; a score <50 is considered indicative of low vitality.

[6] Significantly different from never, $P < 0.05$ (chi-square test).

In analyses of the cognitive tests as continuous data (**Figure 1**), we found that the current users of vitamins E and C and the current users of vitamin E alone had higher ($P = 0.07$ and 0.03, respectively) mean global scores than did the women who had never taken either vitamin E or vitamin C. On the basis of the performance of the women in our Nurses' Health Study cohort, the mean differences we observed between the users and nonusers were equivalent to an ≈1-y difference in age. On the individual cognitive tests, users of vitamins E and C or of vitamin E alone scored higher on the immediate ($P = 0.02$ for users of vitamins E and C, $P = 0.02$ for users of vitamin E alone) and delayed ($P = 0.04$ and $P = 0.07$, respectively) recalls of the 10-word list, and the women who took vitamin E alone also scored significantly ($P = 0.04$) higher on the test of verbal fluency than did the nonusers; these mean differences were equivalent to a difference in age of 1–2 y. However, on the remaining tests we administered, mean scores were not significantly different between the supplement users and nonusers. Past use of vitamin E had little consistent relation with cognitive performance. Although we had less statistical power to detect effects of vitamin C alone (because of the smaller number of women taking only vitamin C supplements), we found little evidence of better results on the cognitive tests; the global score for the women taking vitamin C only was not significantly different from that for the nonusers ($P = 0.7$). In addition, the scores for the past users of vitamin C were not significantly different from those for the women who had never used vitamin C.

When we examined long duration of current supplement use (**Figure 2**), the global score was significantly ($P = 0.03$) higher among the women who had taken vitamins E and C for ≥10 y than among those who had never taken vitamins E or C, and there was a significant trend of increasingly higher mean scores with increasing durations (P for trend = 0.04 with categories of <5 y, 5–9 y, and ≥10 y); for the longest-term users, the effect of taking vitamins E and C was cognitively equivalent to being ≈1.5 y younger. However, for the women taking vitamin E alone, there was little evidence of increasing benefits with increasing duration of use. On the global score, there was no significant difference between those taking vitamin E for ≥10 y and those who had

never taken vitamins E or C, and on the individual tests, the long-term users performed significantly ($P = 0.02$) better only on the immediate recall of the TICS 10-word list. For the women taking vitamin C alone, there was no significant difference in global scores between the long-term users and those that had never used vitamin C ($P = 0.6$). We also examined whether very high doses of either vitamin affected our results; we found no added benefits at very high doses, although our statistical power to detect such effects was modest.

We were concerned that in this population of educated health professionals, a good diet may have masked some of the benefits of supplement use and that our results may have therefore underestimated the true relation between antioxidant use and cognitive function. Thus, we examined the effects of vitamin E and C supplements specifically among the women in the bottom 30% of α-tocopherol or vitamin C dietary intake (**Figure 3**). Indeed, among the women with a low dietary intake of α-tocopherol, mean global scores were substantially and significantly ($P = 0.01$) higher for those using vitamin E and C supplements than for those who had never taken vitamin E or C supplements; this mean difference in score was equivalent to a difference in age of 2 y. Furthermore, on the individual cognitive measures, mean scores were higher on most of the tests (TICS: $P = 0.04$; immediate recall of a 10-word list: $P = 0.001$; delayed recall of a 10-word list: $P = 0.003$; immediate recall of EBMT: $P = 0.001$; verbal fluency: $P = 0.08$). For vitamin E alone, there was no significant difference between supplement users and nonusers ($P = 0.2$) on the global score, and on the individual tests, scores were significantly higher for supplement users than for nonusers on only 2 of the tests. Among the women in the bottom 30% of vitamin C dietary intake, we still did not find any notable effect of vitamin C supplementation.

Finally, we investigated effect modification by cigarette smoking status because cigarettes are known to be a potent oxidizing agent. Although there were relatively few current cigarette smokers in this age group (9% of the population), the point estimate for
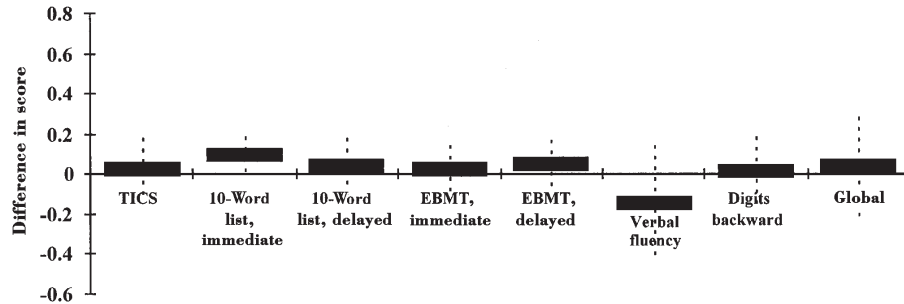
Vitamin E and vitamin C supplement users compared with nonusers
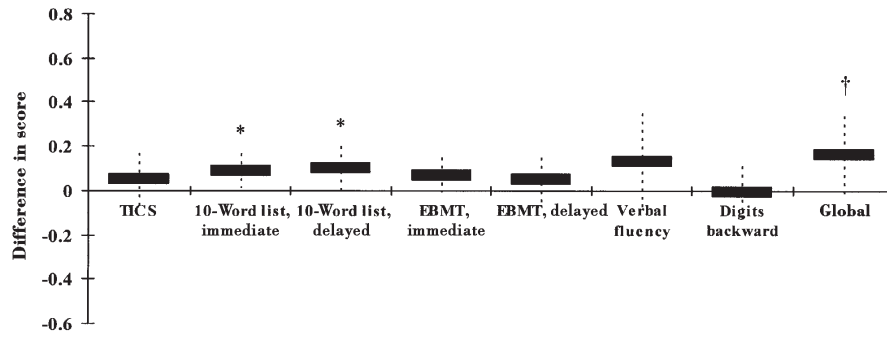
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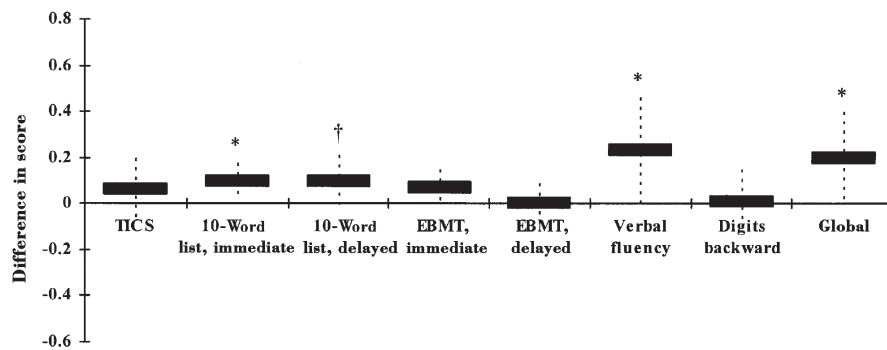
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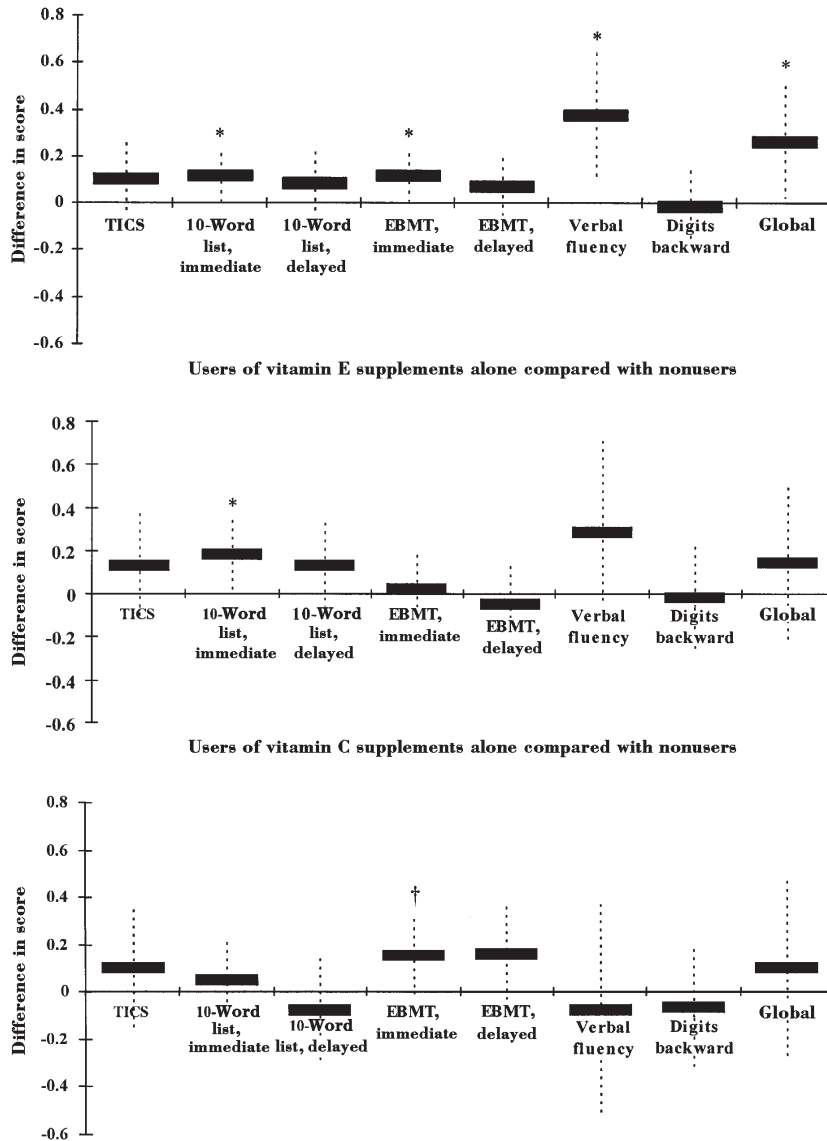

FIGURE 1. Multivariate-adjusted mean differences in cognitive test scores between current users and nonusers of specific antioxidant supplements among 14 968 women in the Nurses' Health Study. The horizontal bars represent mean differences derived from linear regression analysis, and the dashed vertical lines represent 95% CIs. TICS, Telephone Interview for Cognitive Status; EBMT, East Boston Memory Test. *$P < 0.05$; †$P < 0.08$.

the global score indicated a tendency toward additional benefits of antioxidant supplement use among current smokers (the adjusted mean difference between the women taking vitamins E and C and the women who never used either was 0.30; 95% CI: −0.23, 0.84); however, the results were not significant and the CI was wide.

In analyses of the cognitive function tests as categorical data (**Table 2**), the risk of a low global score was not significantly different for the current users of vitamins E and C than for those who had never taken either vitamin [relative risk (RR): 1.04; 95% CI: 0.88, 1.22]; however, there was a 16% lower risk of a low score for the longest-term users (RR: 0.84; 95% CI: 0.66, 1.07 for ≥10 y of use), which was of borderline significance ($P = 0.1$). For the women who had taken vitamins E and C for ≥10 y, the

RR estimates were < 1.0 for 4 (delayed recall of a 10-word list, immediate and delayed recalls of EBMT, verbal fluency) of the 7 individual tests (RRs ranging from 0.77 to 0.82), and the P values were < 0.08 for 3 of these. For vitamin E alone, there was no significant difference in the risk of a low global score between current users and those who had never used vitamins E and C (RR: 0.97) and no evidence of decreasing risk with increasing duration (RR: 1.03 for ≥10 y of use); on the individual tests, the women who had used vitamin E for ≥10 y had RRs < 1.0 for 2 (immediate recall of EBMT and verbal fluency) of the 7 tests, although only the results for the immediate recall of the EBMT were significant. For the women taking vitamin C alone, there was little evidence of any benefit; on the global score, the RRs for current use and long-term current use were 1.21 (95% CI:

Vitamin E and vitamin C supplement users compared with nonusers

Users of vitamin E supplements alone compared with nonusers

Users of vitamin C supplements alone compared with nonusers

FIGURE 2. Multivariate-adjusted mean differences in cognitive test scores between current users of specific antioxidant supplements who had used them for ≥10 y and nonusers among 14 968 women in the Nurses' Health Study. The horizontal bars represent mean differences derived from linear regression analysis, and the dashed vertical lines represent 95% CIs. TICS, Telephone Interview for Cognitive Status; EBMT, East Boston Memory Test. [*]$P < 0.05$; [†]$P < 0.08$.

0.96, 1.52) and 1.16 (95% CI: 0.82, 1.63), respectively. In addition, we found no relation between past use of vitamins E or C and the risk of a low score on our cognitive tests. Analyses of the effects of supplement use in the women with a low dietary intake of α-tocopherol or vitamin C and of effect modification by cigarette smoking were generally consistent with those for the continuous data reported above.

The categorical results did not appear to be an artifact of our chosen cutoff (ie, defining a low score as one in the bottom 10% of the distribution); our findings were robust with other cutoffs as well. For example, when we defined a low score as one in the bottom 5% of the distribution and examined the association between current vitamin E and C use and performance on our cognitive

tests, we found similar results (although the statistical power was reduced because of the smaller number of "cases"); for the global score, the RRs of a low score for current users of vitamins E and C and for those who had used the vitamins ≥10 y were 0.87 (95% CI: 0.70, 1.09) and 0.81 (95% CI: 0.57, 1.15), respectively.

Finally, because multivitamins often contain low doses of vitamins E and C, we conducted an alternate analysis in which we excluded multivitamin users from the reference group of women who had never taken antioxidant vitamins. However, this had no influence on our results; for example, relative to the reference group, the RRs of a low global score for current users of specific vitamin E and C supplements, for current users of specific vitamin E supplements alone, and for current users of specific vitamin C
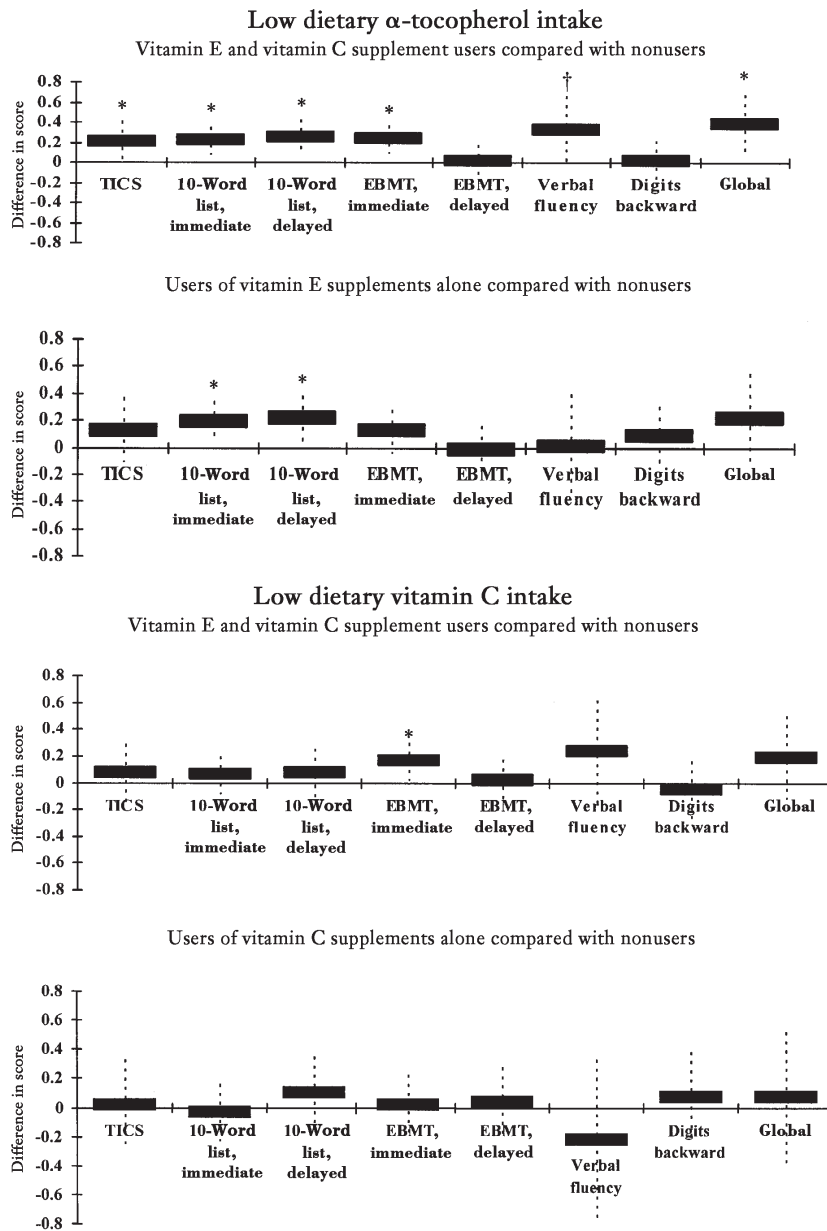
FIGURE 3. Multivariate-adjusted mean differences in cognitive test scores between current users and nonusers of specific antioxidant supplements who had a low dietary intake (bottom 30%) of α-tocopherol or vitamin C among 14 968 women in the Nurses' Health Study. The horizontal bars represent mean differences derived from linear regression analysis, and the dashed vertical lines represent 95% CIs. TICS, Telephone Interview for Cognitive Status; EBMT, East Boston Memory Test. $^*P < 0.05$; $^†P < 0.08$.

supplements alone were 0.95 (95% CI: 0.76, 1.20), 0.93 (95% CI: 0.73, 1.20), and 1.19 (95% CI: 0.90, 1.58).

DISCUSSION

In this large cohort of community-dwelling women aged 70–79 y, we found evidence of better overall performance on our cognitive tests among long-term users of vitamins E and C combined than among women who had never taken either vitamin, and performance improved significantly with increasing duration of use. For those taking vitamin E alone, the benefits appeared to be weaker and there was no evidence of a trend with duration of use.

Apparent benefits were most marked among women with a low dietary intake of α-tocopherol, among whom taking vitamins E and C together was cognitively equivalent to being 2 y younger. However, we found little support for vitamin C supplements alone or past use of either supplement having an influence on cognitive function. These findings all pertain to the use of specific antioxidant supplements, because we did not consider the lower doses of vitamins E or C in most multivitamin preparations.

Information on supplement use was self-reported, perhaps leading to some misclassification. Nonetheless, we believe the reports were accurate because the participants were registered nurses with a demonstrated interest in medical research. Validation studies of

TABLE 2
Relative risk (RR) of a low global cognitive score according to current antioxidant supplement use among Nurses' Health Study participants aged 70–79 y[1]

	Never used	Vitamin E and C supplements	Vitamin E alone	Vitamin C alone
Current supplement use				
Low scorers (n)	255	385	116	225
RR adjusted for age and education	1.0	1.04 (0.88, 1.22)	0.98 (0.81, 1.18)	1.21 (0.96, 1.53)
Multivariate-adjusted RR[2]	1.0	1.02 (0.86, 1.21)	0.97 (0.80, 1.18)	1.17 (0.92, 1.48)
≥10 y of use				
Low scorers (n)	255	103	41	44
RR adjusted for age and education	1.0	0.84 (0.66, 1.06)	0.99 (0.70, 1.40)	1.21 (0.86, 1.70)
Multivariate-adjusted RR[2]	1.0	0.84 (0.66, 1.07)	1.03 (0.73, 1.47)	1.16 (0.82, 1.63)

[1] 95% CI in parentheses. The global score reflects combined performance on 6 cognitive tests; a low score is defined as one in the bottom 10% of the distribution.

[2] Derived from logistic regression models with adjustment for age, education, postmenopausal hormone use, antidepressant use, aspirin use, multivitamin use, diabetes, hypertension, history of heart disease, cigarette smoking, BMI, and the mental health index and energy-fatigue index from the Medical Outcomes Short Form-36.

several of the self-reported items on our questionnaires support this belief; for example, a validation study comparing the vitamin E intakes (including supplement use) obtained with our food-frequency questionnaire with those obtained with four 1-wk diet records collected over a 1-y period from a sample of the nurses found a correlation of 0.92 (24).

Information on cognitive function was collected by using telephone interviews rather than in-person interviews. However, substantial data support the validity of telephone tests of cognitive function containing items similar to those in our interview. Roccaforte et al (25) reported a correlation of 0.85 between the results from telephone and in-person administrations of a telephone version of the Mini-Mental State Examination. Kawas et al (26) gave the Blessed Information-Memory-Concentration test by telephone and in person; they found a correlation of 0.96 for the different modes of interview. In addition, on the basis of results from 61 nuns from the Rush Religious Order Study (27) who were of similar age and educational status to our Nurses' Health Study participants, we found a correlation of 0.81 between the global scores from the telephone-administered interview in our study and the global score from an in-person interview consisting of 21 tests that was also administered to the same nuns. Furthermore, established predictors of cognitive function, such as age, also distinguished scores in our population; for example, nurses aged 77–79 y were twice as likely to score poorly on the TICS than those aged 70–72 y (RR: 2.10; 95% CI: 1.27, 3.48).

We were also concerned that women with poor cognitive function may have selectively begun taking antioxidant supplements if they believed that supplementation might improve their condition. To examine this possibility, we conducted an analysis in which we updated data on supplements through the questionnaire 5–6 y before the cognitive assessment. However, results from this alternate analysis were quite similar to those reported above; for example, current users of vitamins E and C had higher mean global scores than did women who had never used the vitamins (mean difference = 0.14; P = 0.09).

The Nurses' Health Study is a cohort of educated women, and the participants in this cognitive function substudy ranged in age from 70 to 79 y. Thus, it is possible that we may be underestimating differences in cognitive function between supplement users and nonusers because of an insufficient range of abilities or exposures in our select population. There was a large distribution of scores on the tests that we administered; for example, ≈10% of subjects scored < 31 on the TICS, which has been established as a cutoff value for poor cognitive function (20).

Nonetheless, we found substantially stronger results for vitamin E and C supplementation, specifically among the women with a low dietary intake of α-tocopherol, suggesting that our overall results may indeed somewhat underestimate the effect of supplements in a more general population with poorer nutrition than that of our nurses.

Finally, in this observational study, it is possible that results were influenced by confounding. However, we adjusted for several potential confounders. Furthermore, multivariate-adjusted results did not differ substantially from those adjusted for age and education, rendering it unlikely that residual confounding was completely responsible for our findings.

Limited data from other studies also support modest cognitive benefits of vitamin E supplementation, in particular long-term use. In a large epidemiologic study of antioxidant supplements, Masaki et al (9) observed a decrease in the risk of a low CASI (Cognitive Abilities Screening Instrument) score (RR: 0.80; 95% CI: 0.67, 0.96) with vitamin E or C supplement use 3 y before the cognitive interview, and the use of vitamins E and C together also resulted in a similar reduction (RR: 0.85); long-term use of vitamins E and C together appeared to be associated with a further decrease (RR: 0.57; 95% CI: 0.42, 0.79). In another large-scale study of supplement use, Mendelsohn et al (10) found no relation between antioxidant supplementation and results on 15 cognitive tests among 1509 participants in the MoVIES (Monongahela Valley Independent Elders Survey) Project, but all supplements (multivitamins or specific antioxidant vitamins) were considered together; thus, if there is a specific effect of vitamin E or if the very low doses of vitamin E found in multivitamins were not sufficient, then their null results could be explained. Finally, in a recent randomized clinical trial of antioxidant supplements (vitamins E and C and β-carotene together) and heart disease (17), the investigators reported no difference in TICS scores between subjects assigned to treatment and those assigned to placebo after 5 y; however, this follow-up may have been too short to observe effects.

Studies of plasma antioxidant concentrations have also been suggestive, although not decisive. In the third National Health and Nutrition Examination Survey, Perkins et al (16) measured serum antioxidant concentrations and administered 2 tests of verbal memory to 4809 multiethnic men and women sampled from the US general population. They found that the risk of a low score on their 2 tests was significantly lower among subjects with the highest vitamin E concentrations than among those with

the lowest concentrations (RR: 0.48; 95% CI: 0.34, 0.98) but that vitamin C had no effect; those in the highest categories of plasma vitamin E concentration were largely specific supplement users. Schmidt et al (12) reported a 2% increase in score with each unit (1 μmol/L) increase in plasma vitamin E concentration (95% CI: 1%, 4%) but no association between plasma vitamin C and scores on the Mattis Dementia Rating Scale among 1769 participants in the Austrian Stroke Prevention Study. Yet, Perrig et al (15) found conflicting results when measuring antioxidant vitamins at 2 points 22 y apart among 442 men and women in Switzerland; plasma vitamin C was correlated with better semantic memory (but not with 3 other cognitive tests), and plasma vitamin E was not associated with better performance on any of the tests. However, vitamin E concentrations were low in this population (ie, there were probably few specific supplement users). Two studies of dietary antioxidant intake both found no effect of vitamin E or C on cognition (13, 14), although a third (18) found a significant inverse relation between vitamin E, but not vitamin C, intake and cognitive decline.

There is biological plausibility for our data and those of others showing a greater effect of vitamin E than of vitamin C on cognitive function; α-tocopherol is a lipid-soluble vitamin that is absorbed directly by tissue, whereas vitamin C is water-soluble and excreted after maximum absorption (> 400 mg). Although we could not establish statistical evidence of a difference between the cognitive benefits of taking vitamin E alone and those of taking vitamin E combined with vitamin C, there is also biological support for believing that there are additional benefits with the combination; for example, Sato et al (3) showed in rat brains that the promoting effect of α-tocopherol on neuronal survival was more than doubled when vitamin C was added. Furthermore, in humans, it is well established that vitamin E requires the presence of vitamin C for optimal metabolism (although relatively low amounts of vitamin C are sufficient).

In conclusion, there is currently support for a modest effect of high-dose supplementation with antioxidant vitamins on cognitive function; we found overall better cognitive performance among women taking specific vitamin E supplements along with specific vitamin C supplements for ≥ 10 y than among those not taking these supplements. More marked benefits were evident among women with a low dietary intake of α-tocopherol. Although the effect of supplementation was modest, it is likely that even small cognitive effects in a generally healthy "young-old" population (such as ours) carry substantial public health implications over time (28). In the future, large prospective studies of the association between specific antioxidant supplements and changes in cognitive function over several years will be helpful in better understanding the potential of supplement use to prevent cognitive impairment.

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