A Randomized Trial of Beta Carotene Supplementation and Cognitive Function in Men

The Physicians' Health Study II

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Background: Oxidative stress contributes to brain aging. Antioxidant treatment, especially over the long term, might confer cognitive benefits.

Methods: We added cognitive testing to the Physicians' Health Study II (PHSII), a randomized trial of beta carotene and other vitamin supplements for chronic disease prevention. The PHSII is a continuation of the Physicians' Health Study (PHS), which had randomized male participants to low-dose aspirin and beta carotene. Participants include those continuing their original beta carotene assignment from the PHS, begun in 1982, and newer recruits randomized as of 1998. The beta carotene arm (50 mg, alternate days) was terminated; follow-up is ongoing for the remaining arms. Near the close of the beta carotene arm, we interviewed 5956 participants older than 65 years to assess general cognition, verbal memory, and category fluency. The primary end point was a global score averaging all tests (using *z* scores); the secondary end point was a verbal memory score combining results of 4 tests. We compared mean cognition among those assigned to beta carotene vs placebo. We separately examined new recruits and continuing participants.

Results: Among 1904 newly recruited subjects (mean treatment duration, 1 year), cognition was similar across treatment assignments. Among 4052 continuing participants from the PHS (mean treatment duration, 18 years), the mean global score was significantly higher in the beta carotene group than in the placebo group (mean difference in *z* scores, 0.047 standard units; $P = .03$). On verbal memory, men receiving long-term beta carotene supplementation also performed significantly better than the placebo group (mean difference in *z* scores, 0.063; $P = .007$).

Conclusion: We did not find an impact of short-term beta carotene supplementation on cognitive performance, but long-term supplementation may provide cognitive benefits.

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DEMENTIA IS A GROWING health issue. Studies have shown that modest decrements in cognitive function strongly predict eventual development of dementia[1-3]; these early stages of cognitive decline may be most susceptible to intervention. The Physicians' Health Study II (PHSII) is a randomized trial of beta carotene and other vitamin supplements for cardiovascular disease and cancer prevention; cognitive evaluations were added to the trial to assess the cognitive impact of supplementation. Beta carotene, a lipophilic, provitamin A carotenoid, is a potent antioxidant.

Long-term oxidative stress appears to be a major factor in declining cognition.[4] Nonetheless, epidemiologic data on antioxidant vitamins and cognition are not consistent. Some large observational investigations[5-10] have reported that high intake or high plasma levels of various antioxidants were associated with better cognitive performance, but several randomized trials[11-14] have not found neuroprotection. Impaired cognition likely takes many years, if not decades, to develop. Randomized trials of antioxidant vitamins have assessed from 3[12]

For editorial comment see page 2167

to 9 years[14] of treatment, which may be insufficient to detect notable benefits. In the PHSII, we evaluated short- and long-term beta carotene supplementation and cognitive performance, measured once at the close of the trial among healthy, older men.

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METHODS

PHYSICIANS' HEALTH STUDY

The original Physicians' Health Study (PHS) began in 1982, when 22 071 male physicians were randomized in a factorial design to receive aspirin, beta carotene, or placebo for prevention of cardiovascular disease and cancer. In January 1988, the aspirin component was terminated when it was clear that aspirin decreased heart disease.[15] The beta carotene arm continued until December 1995, with no observed relation of supplementation to cardiovascular disease or cancer.[15]

The PHSII is a randomized, placebo-controlled trial, extending the PHS. In the PHSII, supplementation with beta carotene (Lurotin; supplied by BASF Corporation, Florham Park, New Jersey) (50 mg, alternate days), vitamin E (400 IU, alternate days), daily ascorbic acid (500 mg), daily multivitamin, or placebo, is being tested in a factorial design. The design of the trial has been previously described.[16] Briefly, invitations to enroll in PHSII were mailed to PHS participants, who remained blinded to beta carotene assignment. In total, 7641 men from the PHS agreed to participate in the PHSII and, beginning in August 1997, were randomized to PHSII study treatments. Treatment assignment to beta carotene or beta carotene placebo was retained from the PHS (although participants may have stopped taking beta carotene during the 18-month interval between studies), and the men were newly randomized to receive vitamin E, ascorbic acid, multivitamin, or placebo. Importantly, participation of PHS subjects in the PHSII was not related to beta carotene; among nonparticipants, 49.5% had been assigned to active beta carotene and among participants, this figure was 50.6%.

In addition, 7000 physicians 55 years and older were newly recruited to the PHSII and randomized from 1998 to 2001 to the study treatments or placebo; as in the original PHS, men had no history of cancer, active liver disease, current renal disease, peptic ulcer, or gout.

FOLLOW-UP

Every 12 months, men were sent questionnaires on compliance and health factors. In the original PHS, plasma beta carotene concentrations were measured during unannounced visits to a sample of participants; beta carotene levels were significantly higher among men assigned to treatment than to placebo, and there was a highly significant correlation between self-reported compliance and plasma beta carotene levels.[17] Thus, in the PHSII, all compliance data were established via mailed questionnaire only.

The beta carotene arm of the PHSII continued until May 2003, its planned stopping date; the remaining arms are ongoing. In this report, we provide results of a substudy of cognitive function.

COGNITIVE FUNCTION STUDY

A cognitive component was added to the PHSII during the final years of beta carotene treatment. Beta carotene dose in the trial was originally chosen based on hypothesized effects across cardiovascular diseases and cancers. There is limited literature on beta carotene and cognition, yet evidence[5,18,19] indicated that the dose would also be adequate for neuroprotection. This study was approved by the institutional review board of Partners HealthCare, Boston, Massachusetts. All 7045 PHSII participants older than 65 years were eligible for the cognitive substudy (**Figure**). Cognitive testing began in November 1998 (only a small number of interviews were conducted from 1998 to 2000, as part of a pilot to establish subjects' willingness to participate). Of the 7045 eligible participants, 271 were no longer active PHSII participants (3.8%) and 4 were deceased (0.06%). Of the remaining 6770, we were unable to reach 315 (4.7%). Of the 6455 participants contacted, 5956 (92.3%) completed a cognitive assessment: 4052 from the original PHS and 1904 new recruits. Participation was virtually identical in those assigned to beta carotene (92.0%) vs placebo (92.6%) and in continuing participants (92.1%) vs new recruits (92.7%). Second cognitive assessments were begun in 2002. The beta carotene arm was terminated prior to completion of second assessments (second and third assessments were planned to allow further data collection in the continuing trial of other vitamins). Nonetheless, some data from the second interview were available (n=4074, with 88.3% participation of those who were contacted before termination of the beta carotene study).

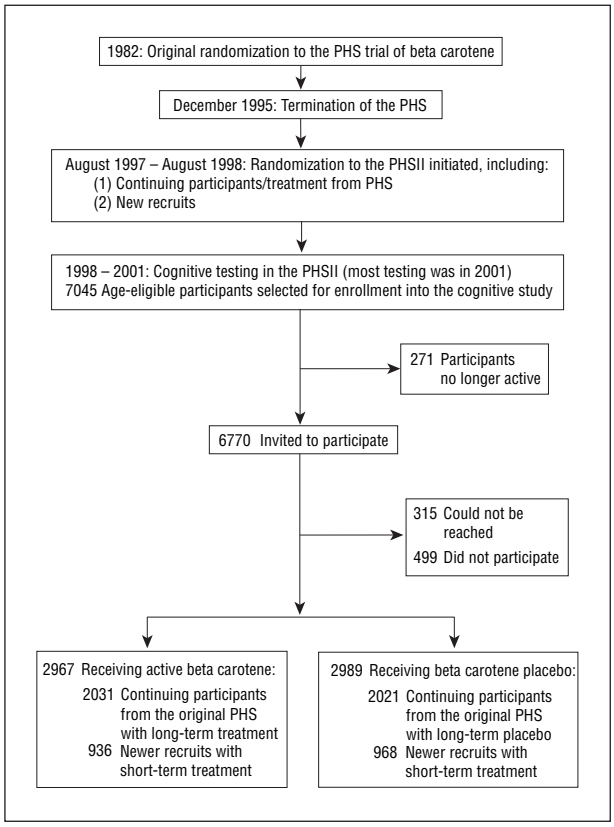

Figure. Study flow of the Physicians' Health Study (PHS) II cognitive study.

COGNITIVE TESTING

Cognitive assessments were administered using a validated telephone interview.[20] The cognitive battery included: (1) Telephone Interview of Cognitive Status[21] (TICS), a telephone version of the Mini-Mental State Examination, with possible scores from 0 to 41 points; (2) immediate and (3) delayed recall measures of the East Boston Memory Test (EBMT)[22] to assess verbal memory, with possible scores from 0 to 12 points; (4) delayed recall of a 10-word list to test verbal memory, with possible scores from 0 to 10 points; and (5) category fluency, naming animals in 1 minute. Our primary prespecified outcome was a global score combining results of all cognitive tests. Since a point is not equivalent across the different tests, this global score was calculated by normalizing results of each cognitive test using z scores and averaging the z scores.

Subsequent to our design of the cognitive substudy, several studies reported that losses of verbal memory were among

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Table 1. Characteristics of Newly Recruited Participants in the Physicians' Health Study II Cognitive Function Cohort[a]

Characteristic	Beta Carotene Group	Placebo Group	*P* Value
Participants, No.	936	968	NA
Age, mean, y	72.9	72.8	.93
BMI, mean	26.1	25.9	.18
Alcohol intake daily, %	36.4	38.0	.69
Current smoker, %	2.5	2.8	.30
Diastolic BP, mean, mm Hg	78.6	78.8	.20
Systolic BP, mean, mm Hg	131.0	131.8	.55
Prevalence of angina, %	1.5	1.8	.63
Prevalence of type 2 diabetes, %	5.3	5.0	.93
Prevalence of MI, %	2.1	2.6	.52
Prevalence of stroke, %	1.0	0.8	.75

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; MI, myocardial infarction; NA, not applicable.
[a]All variables defined as of randomization, beginning in 1998.

the strongest predictors of Alzheimer disease development[1-3]; thus, a key added secondary outcome was a verbal memory score, calculated by averaging the *z* scores from immediate and delayed recall assessments of the EBMT and 10-word list.

VALIDATION STUDIES

We have established the validity of our telephone cognitive battery in educated, high-functioning subjects. Among 61 persons, we found a correlation of 0.81 when comparing the global composite score from our brief telephone interview with the global score from an extensive in-person interview.

We also tested clinical validity. In a sample of 88 participants in our study of registered nurses, we administered the Dementia Questionnaire.[23] Over 3 years of follow-up, there was almost an 8-fold increased risk of dementia diagnosis among women who scored poorly on general cognitive function (odds ratio [OR], 7.6; 95% confidence interval [CI], 2.2-25.0), with a statistically significant, 11.6-fold increase for those performing poorly on verbal memory ($P<.001$).

STATISTICAL ANALYSIS

Because continuing participants from the original PHS had substantially longer assignment to treatment or placebo compared with the newly recruited subjects in PHSII, our prespecified analysis plan included separate analyses within each group. All analyses are based on the intention-to-treat principle. Our primary, prespecified comparisons were of mean differences between treatment and placebo groups. We used unpaired *t* tests to assess mean differences in cognitive performance, measured at a single point near the trial's close.

In secondary analyses, we examined the second cognitive assessments for the 3023 continuing participants and 1051 new recruits who had these data. We compared mean cognitive performance scores on the second assessment for beta carotene vs placebo. These were specified a priori as secondary analyses. Because the majority of men had been randomized to beta carotene or placebo for a mean of 18 years before we initiated cognitive testing, it seemed biologically implausible that any notable change in cognition would be detected over the 1.9 years of follow-up between the first and second cognitive interviews. In addition, the sample size was limited, with almost one-third fewer subjects.

RESULTS

Among 4052 continuing participants from the PHS, the mean time from randomization to cognitive assessment was 18 years (range, 15-20 years) and was 1 year in 2021 new recruits (range, 2 months–3 years). Overall, 79.3% reported taking at least 2 of 3 of their study pills; this was similar in those assigned to active treatment (79.1%) or placebo (79.5%), and in the continuing participants from the PHS (79.2%) vs new recruits (79.4%).

Baseline characteristics of those assigned to beta carotene and placebo were virtually identical. For newly recruited participants (**Table 1**), the mean age at randomization to PHSII was 72.9 years for those assigned to beta carotene and 72.8 years for the placebo group. There was low prevalence of angina, type 2 diabetes mellitus, or cardiovascular disease.

For the continuing participants from the PHS (**Table 2**), there were no significant differences in baseline characteristics by treatment. The mean age at original randomization was 55.9 years among those assigned to beta carotene and 56.0 years for those assigned to placebo; the mean age at recruitment into the PHSII was 70.9 years for beta carotene group and 71.0 years for the placebo group. At the original randomization, participants were healthy, with low prevalence of angina or type 2 diabetes; at enrollment into the PHSII almost 15 years later, the prevalence of these conditions had increased, and a small proportion had developed coronary disease or stroke. Among continuing participants, we also examined major characteristics at the cognitive interview (approximately 3 years after enrollment into the PHSII). The prevalence of comorbid conditions had further increased, although there were no significant differences between those assigned to beta carotene vs placebo (data not given in Table 2); for example, at cognitive testing, the prevalence of coronary disease was 5.1% in the treatment group vs 4.9% in the placebo group ($P=.84$), and the prevalence of stroke was 3.2% in the treatment group vs 3.3% in the placebo group ($P=.80$).

When we examined together all data from the continuing plus newly recruited participants, with beta carotene treatment ranging from 2 months to 20 years, we found slightly better cognition for those assigned to beta carotene than to placebo (global score: mean difference in *z* scores, 0.028 standard units; 95% CI, –0.01 to 0.06 [$P=.12$]; verbal memory: mean difference in *z* scores, 0.037 standard units; 95% CI, 0.00 to 0.07 [$P=.049$]). In analyses specifically examining the newly recruited PHSII participants (**Table 3**), there was no evidence of cognitive benefits with short-term beta carotene supplementation. Because many participants had only been randomized to beta carotene for several months at their cognitive assessment, in secondary analyses, we examined treatment duration. However, there was no suggestion of increased cognitive benefits with increased treatment duration in this group (data not shown).

In participants continuing from the PHS (**Table 4**), with long-term treatment, those assigned to beta carotene performed significantly better on the global score compared with the placebo group (mean difference in *z*

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Table 2. Characteristics and Medical History of Participants in the Physicians' Health Study II (PSHII) Cognitive Function Substudy, Who Continued Treatment Assignment From the Physicians' Health Study

Characteristic	Characteristics at Original Randomization[a]			Characteristics at Entry Into the PHSII[b]		
	Beta Carotene Group	Placebo Group	*P* Value	Beta Carotene Group	Placebo Group	*P* Value
Participants, No.	2031	2021	NA	2031	2021	NA
Age, mean, y	55.9	56.0	.48	70.9	71.0	.45
BMI, mean	25.1	25.0	.13	25.7	25.6	.48
Current smoker, %	9.0	9.4	.86	3.1	3.5	.79
Alcohol intake daily, %	25.3	25.8	.48	41.3	42.0	.67
Diastolic BP, mean, mm Hg	78.7	78.6	.55	80.8	80.9	.91
Systolic BP, mean, mm Hg	125.4	125.8	.39	132.6	133.1	.72
Prevalence of angina, %	1.3	1.0	.41	17.0	17.2	.91
Prevalence of diabetes, %	2.0	1.6	.46	7.5	6.9	.42
Prevalence of MI, %	0	0	NA	3.6	3.1	.45
Prevalence of stroke, %	0	0	NA	2.0	2.3	.57

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; MI, myocardial infarction; NA, not applicable.
[a] Characteristics at original randomization into Physicians' Health Study, beginning in 1982.
[b] Characteristics at continuation into PHSII, beginning in 1997.

Table 3. Mean Cognitive Performance With Short-term Treatment Assignment[a]: the Physicians' Health Study II

Cognitive Measure	Placebo Group (n = 968)	Beta Carotene Group (n = 936)	*P* Value
Global score[b]			
Mean *z* score (SD)[c]	0.007 (0.67)	−0.007 (0.67)	
Mean difference (95% CI)	0 [Reference]	−0.014 (−0.07 to 0.05)	.65
Verbal memory[b]			
Mean *z* score (SD)[c]	0.008 (0.72)	−0.008 (0.72)	
Mean difference (95% CI)	0 [Reference]	−0.015 (−0.08 to 0.05)	.64
TICS[b]			
Mean points (SD)[c]	34.29 (2.64)	34.15 (2.57)	
Mean difference (95% CI)	0 [Reference]	−0.13 (−0.37 to 0.10)	.26
Category fluency[b]			
Mean points (SD)[c]	20.09 (6.15)	20.02 (6.14)	
Mean difference (95% CI)	0 [Reference]	−0.06 (−0.62 to 0.49)	.82

Abbreviations: CI, confidence interval; TICS, Telephone Interview of Cognitive Status.
[a] Short-term treatment is a mean of 1 year among subjects newly recruited to the Physicians' Health Study II.
[b] The global score is the primary outcome and combines results of all cognitive tests; verbal memory is the key secondary outcome and combines results of immediate and delayed recalls of 10-word list and East Boston Memory Test; additional secondary outcomes are the TICS and category fluency.
[c] For the global score and the verbal memory score, the outcome is obtained by deriving *z* scores for each relevant cognitive test and averaging *z* scores across component tests; the unit for these measures is a standard unit. For TICS and category fluency, the outcome is the number of points scored on that test. On the TICS, scores can range from 0 to 41 points, and on category fluency, scores can range from 0 to infinity, with 1 point assigned for each distinct animal named during 1 minute.

Table 4. Mean Cognitive Performance With Long-term Treatment Assignment[a]: the Physicians' Health Study II

Cognitive Measure	Placebo Group (n = 2021)	Beta Carotene Group (n = 2031)	*P* Value
Global score[b]			
Mean *z* score (SD)[c]	−0.024 (0.71)	0.023 (0.69)	
Mean difference (95% CI)	0 [Reference]	0.047 (0.00 to 0.09)	.03
Verbal memory[b]			
Mean *z* score (SD)[c]	−0.032 (0.74)	0.031 (0.73)	
Mean difference (95% CI)	0 [Reference]	0.063 (0.02 to 0.11)	.007
TICS[b]			
Mean points (SD)[c]	34.23 (2.80)	34.41 (2.73)	
Mean difference (95% CI)	0 [Reference]	0.18 (0.01 to 0.35)	.04
Category fluency[b]			
Mean points (SD)[c]	20.04 (6.04)	20.03 (5.94)	
Mean difference (95% CI)	0 [Reference]	−0.012 (−0.38 to 0.35)	.95

Abbreviations: CI, confidence interval; TICS, Telephone Interview of Cognitive Status
[a] Long-term treatment is a mean of 18 years among subjects continuing from the original Physicians' Health Study.
[b] The global score is the primary outcome and combines results of all cognitive tests; verbal memory is the key secondary outcome and combines results of immediate and delayed recalls of 10-word list and East Boston Memory Test; additional secondary outcomes are the TICS and category fluency.
[c] For the global score and the verbal memory score, the outcome is obtained by deriving *z* scores for each relevant cognitive test and averaging *z* scores across component tests; the unit for these measures is a standard unit. For TICS and category fluency, the outcome is the number of points scored on that test. On the TICS, scores can range from 0 to 41 points, and on category fluency, scores can range from 0 to infinity, with 1 point assigned for each distinct animal named during 1 minute.

scores, 0.047 standard units; 95% CI, 0.00 to 0.09 [*P* = .03]). The mean performance score for verbal memory was substantially better among men assigned to long-term beta carotene use than to placebo (mean difference in *z* scores, 0.063 standard units; 95% CI, 0.02 to 0.11 [*P* = .007]). In secondary analyses, we found a signifi-

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cantly higher mean TICS score for those with long-term use of beta carotene. Thus, performance on the majority of cognitive measures was better with long-term beta carotene supplementation than with placebo. To help interpret these mean differences, we contrasted the effect of beta carotene to the effect of time: across the study population, on the global score, there was a mean decrease of –0.045 standard units per year; on the verbal score, there was a mean decrease of –0.044 standard units; on the TICS, the yearly mean decrease was –0.16 points. Thus, in general, the effect of long-term beta carotene treatment was comparable to delaying cognitive aging by 1 to 1.5 years. Finally, these findings were consistent in analyses excluding participants who developed cardiovascular disease prior to their cognitive interview.

In secondary analyses, using the limited data from second cognitive assessments, we found better performance for men assigned to beta carotene than to placebo, although the results were not statistically significant. At the second assessment, the mean difference in global score for men assigned to beta carotene vs placebo was 0.010 standard units (95% CI, –0.03 to 0.05). On verbal memory, those given beta carotene performed better by 0.019 standard units (95% CI, –0.03 to 0.06). These apparent benefits were stronger in the participants continuing from the PHS; however, these findings were not statistically significant. These analyses are difficult to interpret with combined issues of decreased sample size and short follow-up, as well as increased measurement error (resulting from learning effects over the short interval between cognitive assessments).

COMMENT

Overall, when we examined together all participants in the PHSII, men assigned to beta carotene had slightly better cognition compared with the placebo group. As expected, results appeared strongest with long-term supplementation. While treatment with beta carotene for 3 years or less had no impact on cognitive performance, at least 15 years' treatment provided significant benefits consistently across several cognitive measures. In this generally healthy population, the extent of protection conferred by long-term treatment appeared modest; nonetheless, studies have established that very modest differences in cognition, especially verbal memory, predict substantial differences in eventual risk of dementia[1-3]; thus, the public health impact of long-term beta carotene use could be large.[24]

In addition, biological data reveal a role for vitamin A in the adult brain.[25,26] Retinoic acid normalizes β-amyloid precursor protein processing in vitro[27] (β-amyloid accumulation in the brain is involved in the pathogenesis of Alzheimer disease[28]). More generally, substantial biological data support cognitive benefits of antioxidant vitamins. Neurologic function, neuron survival, and synaptic response are all improved in the presence of antioxidants.[29,30] Expression of amyloid-β precursor protein is decreased and resistance to amyloid-β toxicity is increased in culture treated with antioxidant vitamins.[31,32] Furthermore, in animal models, cognitive performance improves with administration of antioxidants.[33]

Yet, no cognitive benefits were observed in a trial of 20 536 adults randomized to a combination of vitamin E (600 mg), ascorbic acid (250 mg), and beta carotene (20 mg) or placebo for 5 years,[11] and there was no effect of vitamin E (2000 IU) on cognition performance among subjects with mild cognitive impairment, followed up for 3 years.[12] In a trial of 2166 adults,[13] followed up for a mean of 6.9 years, there were no significant differences in cognitive performance between those assigned to a combination of vitamin E (400 mg), ascorbic acid (500 mg), and beta carotene (15 mg) vs placebo. In the longest trial (6377 women assigned to vitamin E [600 mg, alternate days] for 9.6 years), there were also no differences in the rate of cognitive decline between treatment and placebo groups.[14]

In observational investigations, apparent cognitive benefits of antioxidant vitamins, including beta carotene, have been reported.[5,7,9,34] This could be due to uncontrolled confounding or perhaps because antioxidant measures in observational studies better represent long-term intake. For example, in the Rotterdam Study,[5] beta carotene was associated with reduced odds of poor score on the Mini-Mental State Examination (OR, 0.53 [95% CI, 0.32-0.85] for highest vs lowest quintile), and in the Etude du Vieillissement Artériel (EVA)[9] and Rotterdam studies,[34] there were nonsignificant decreases in risk of diminished cognition for those with higher levels of plasma carotenoids (relative risk, 0.85 [95% CI, 0.55-1.33], and OR, 0.87 [95% CI, 0.64-1.19], respectively). In addition, higher plasma carotenoid levels have been strongly associated with fewer periventricular white matter lesions (relative risk, 0.4 [95% CI, 0.2-0.9] per 1 SD increase in carotenoid level)[35]; these lesions appear to predict the development of Alzheimer disease.

In 2 observational investigations, duration of vitamin use was specifically examined, and the results support the hypothesis that long-term supplementation may be necessary to achieve cognitive benefits. The Nurses' Health Study[6] reported that 10 or more years of vitamin E supplementation was associated with significantly better cognition, while shorter-term use was not related to cognition. In the Honolulu-Asia Aging study,[10] inverse associations between vitamin E and C supplements and cognitive impairment were evident only after 10 or more years. Indeed, the development of cognitive impairment appears to take years, if not decades, and data from animal models[36] indicate that brain aging starts early in adult life. Thus, it is biologically plausible that long-term exposure, beginning at midlife, is required for neuroprotection.

Limitations to our study should be considered. First, the addition of cognitive testing was initiated near the termination of the beta carotene arm; thus, we had a single measure of cognition and no cognitive data prior to randomization. This might be a particular issue for the continuing PHS participants, who began treatment 15 or more years prior to the cognitive assessment. Still, in this large trial, it is highly likely that cognitive function was similar at baseline in those assigned to placebo and to active treatment; indeed risk factors for diminished cognition

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were virtually identical in all groups, both at randomization and at later points (eg, near cognitive testing). Therefore, our primary findings should represent a prospective investigation of differences in cognition from the initiation of treatment through cognitive assessment. Second, since we could not evaluate cognitive function in all subjects who had participated in the original PHS, we could not conduct a true intention-to-treat analysis of long-term beta carotene supplementation; nonetheless, beta carotene assignment in the original participants had no apparent relation to their continued participation in the PHSII, suggesting that it is unlikely that this materially biased our findings. In addition, our cognitive battery did not measure all cognitive systems. Still, in a validation study, we found high correlation between performance on our brief assessment compared with an extensive interview,[20] indicating that our battery provides a reasonable measure of overall cognition.

Overall, risks and benefits of beta carotene supplementation should be considered in interpreting our study. Two randomized trials found that beta carotene supplementation increases mortality and lung cancer among smokers.[37,38] However, in the PHS, beta carotene had no impact on cardiovascular disease, cancer, or overall mortality after 12 years of follow-up among primarily nonsmokers,[39] and after the extended follow-up in the PHSII, findings were not appreciably different (unpublished data, April 2006, J.M.G.). Existing biological and epidemiologic data, in combination with findings from this randomized trial, indicate that long-term beta carotene supplementation may provide cognitive benefits. The extent of benefits that we found for long-term beta carotene use appeared modest, but the mean differences in cognitive performance we observed were substantially greater compared with those in a trial of donepezil among nondemented subjects (eg, for verbal memory, mean difference of 0.02 standard units, comparing donepezil use with placebo, vs our findings for verbal memory, mean difference of 0.063 standard units, comparing long-term beta carotene use with placebo).[12] Thus, the public health value of beta carotene supplementation merits careful evaluation. Moreover, as these data support the possibility of successful interventions at early stages of brain aging in well-functioning subjects, investigations of additional agents that might also provide such neuroprotection should be initiated.

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