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Long-Term Multivitamin Supplementation and Cognitive Function in Men

A Randomized Trial

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Background: Despite widespread use of multivitamin supplements, their effect on cognitive health—a critical issue with aging—remains inconclusive. To date, no long-term clinical trials have studied multivitamin use and cognitive decline in older persons.

Objective: To evaluate whether long-term multivitamin supplementation affects cognitive health in later life.

Design: Randomized, double-blind, placebo-controlled trial of a multivitamin from 1997 to 1 June 2011. The cognitive function substudy began in 1998. Up to 4 repeated cognitive assessments by telephone interview were completed over 12 years. (ClinicalTrials.gov: NCT00270647)

Setting: The Physicians' Health Study II.

Patients: 5947 male physicians aged 65 years or older.

Intervention: Daily multivitamin or placebo.

Measurements: A global composite score averaging 5 tests of global cognition, verbal memory, and category fluency. The secondary end point was a verbal memory score combining 4 tests of verbal memory, which is a strong predictor of Alzheimer disease.

Results: No difference was found in mean cognitive change over time between the multivitamin and placebo groups or in the mean level of cognition at any of the 4 assessments. Specifically, for the global composite score, the mean difference in cognitive change over follow-up was −0.01 SU (95% CI, −0.04 to 0.02 SU) when treatment was compared with placebo. Similarly, cognitive performance did not differ between the multivitamin and placebo groups on the secondary outcome, verbal memory (mean difference in cognitive change over follow-up, −0.005 SU [CI, −0.04 to 0.03 SU]).

Limitation: Doses of vitamins may be too low or the population may be too well-nourished to benefit from a multivitamin.

Conclusion: In male physicians aged 65 years or older, long-term use of a daily multivitamin did not provide cognitive benefits.

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As the population ages, it is important to identify preventive strategies for cognitive decline, which is a step on the pathway to dementia (1). Multivitamins are the most commonly used dietary supplement in the United States and are consumed by more than one third of Americans (2). In addition to preventing vitamin and mineral deficiency, multivitamin supplements were found to reduce the risk for cancer in the Physicians' Health Study II (PHS II) trial (3) and are frequently marketed to prevent various chronic conditions (4).

A typical daily multivitamin contains a combination of nutrients that could help prevent cognitive decline (5, 6). For example, vitamins C and E and β-carotene may protect the brain from oxidative damage (7). B vitamins are involved in the synthesis of neurotransmitters, DNA, and neuronal membrane and prevent accumulation of homocysteine, which is a risk factor for cognitive decline (8). Vitamin A plays a role in neuronal survival and synaptic plasticity in the hippocampus (9). These vitamins, alone or combined, could delay the onset of cognitive decline, including at lower doses common in multivitamin supplements (10, 11).

Yet, randomized trials have been inconsistent about potential benefits of multivitamin supplementation on cognitive health (12). Some have found no effect of multivitamins on cognition (13, 14), whereas others have found modest benefits (15–17). However, these trials have important limitations, including fairly short treatment duration and small sample size.

The PHS II is a large-scale, randomized, double-blind, placebo-controlled trial testing long-term effects of a common multivitamin in the prevention of chronic disease. In this article, we present the results of the cognitive substudy of PHS II.

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METHODS

Study Design

The PHS II is a randomized, double-blind, placebo-controlled, $2 \times 2 \times 2 \times 2$ factorial trial testing β-carotene, vitamin E, ascorbic acid, and a multivitamin for their role in preventing chronic diseases among 14 641 male physicians aged 50 years or older. Cognitive function was a prespecified secondary outcome of PHS II.

Setting and Participants

Recruitment occurred in 2 phases. First, in July 1997, invitations to enroll in PHS II were mailed to eligible participants from PHS I who had been part of an earlier trial of aspirin and β-carotene among 22 071 physicians aged 40 to 84 years in 1982 (18, 19). Second, in July 1999, invitation letters were mailed to a new group of male physicians identified from a list provided by the American Medical Association. Men were ineligible if they had a history of cirrhosis or active liver disease, were receiving anticoagulants, or reported a serious illness that may interfere with study participation. Men were also required to forgo current use of multivitamins or individual supplements containing more than 100% of the recommended daily allowance of vitamin E, vitamin C, β-carotene, or vitamin A during PHS II follow-up. In total, 14 641 were randomly assigned into PHS II, including 7641 men from PHS I who agreed to enroll in PHS II and 7000 new participants. Original PHS I participants kept their original β-carotene assignments, and β-carotene assignment was not related to participation in PHS II (20). All participants provided written informed consent, and the Institutional Review Board at Brigham and Women's Hospital approved the PHS II research protocol.

In 1998, we initiated a substudy of cognitive function among men aged 65 years or older. Of the 7278 men eligible for the substudy, 249 were deceased before the selection date and 575 were no longer active PHS II participants or were unreachable. Of the 6454 PHS II participants contacted, 5947 (92%) completed an initial cognitive assessment, including 4046 original PHS I participants and 1901 new PHS II participants; 503 declined; and 4 partially completed the study (**Figure**). The participation rates for the initial cognitive interview were similar comparing multivitamin versus placebo groups and by PHS II group (range, 92% to 93% of those contacted).

After the initial cognitive assessment, there were up to 3 additional waves of follow-up: a second beginning in 2002, a third beginning in 2006, and a fourth beginning in 2010. We had a mean duration of about 2 years between the first and second assessments, 4 years between the second and third assessments, and about 4 years between the third and fourth assessments. High follow-up was maintained; 96%, 92%, and 90% of those contacted at waves 2, 3, and 4 completed cognitive testing, respectively. However, the fourth assessment was not attempted in many participants because of trial completion (that is, 2700 [45%] of the initial 5947 who completed the initial interview were invited to participate at the fourth assessment before the trial closed on 1 June 2011).

Randomization and Interventions

The design of PHS II, including randomization procedures, has been described (21). The interventions included β-carotene (Lurotin, 50 mg on alternate days, or its placebo; BASF, Florham Park, New Jersey); vitamin E (synthetic α-tocopherol, 400 IU on alternate days, or its placebo; BASF); ascorbic acid (synthetic ascorbic acid, 500 mg daily, or its placebo; BASF); or a multivitamin (Centrum Silver or its placebo daily; Pfizer, New York, New York) (**Appendix Table 1**, available at www.annals.org).

Context

Multivitamins are commonly used to prevent various chronic conditions. However, their benefit in preventing age-related cognitive decline is unclear.

Contribution

In a substudy of a large, randomized, double-blind clinical trial, use of a daily multivitamin compared with placebo did not improve performance on a validated test of cognitive function.

Caution

Study participants were older male physicians who were generally well-nourished.

Implication

This study does not support use of multivitamins to improve cognitive function.

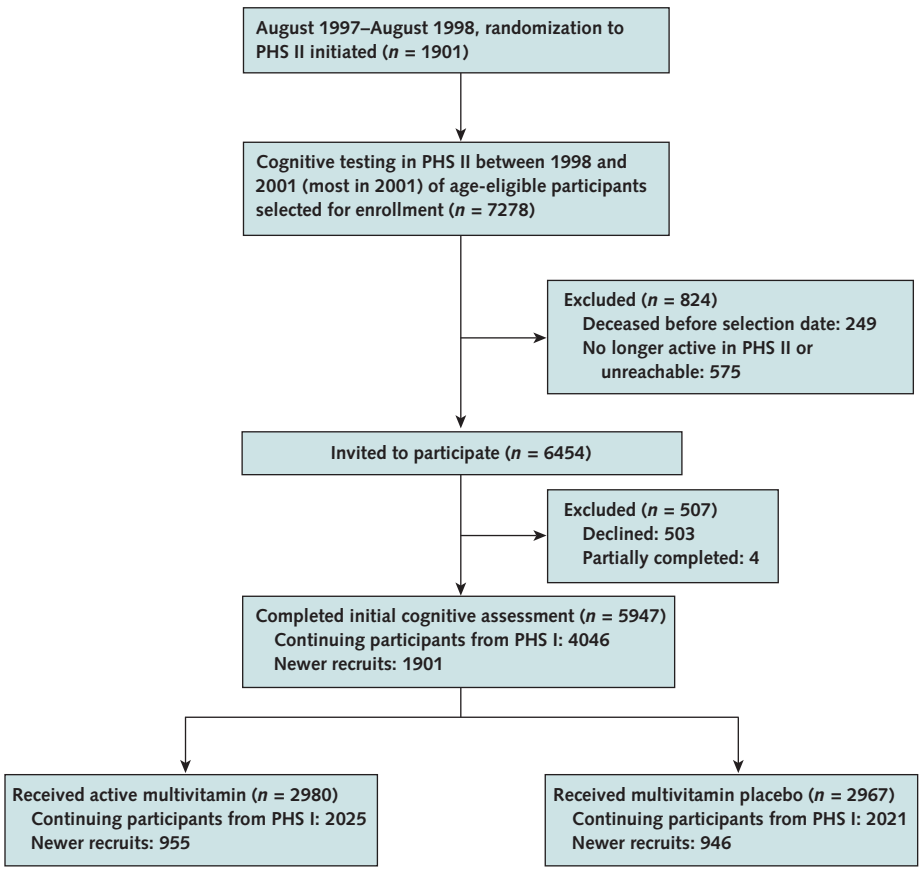
—The Editors

Outcomes and Follow-up

Cognition was assessed using a validated telephone interview (22–24). The cognitive battery included the Telephone Interview for Cognitive Status (TICS) (25), which is a telephone adaptation of the Mini-Mental State Examination (26); immediate and delayed recalls of the East Boston Memory Test (EBMT) (27) to assess verbal memory; the delayed recall of a 10-word list in the TICS to test verbal memory; and a category fluency task (28). The primary prespecified outcome of the cognitive substudy was a composite score of global cognition (that is, an average of all cognitive tests). We created the composite global score by standardizing results of each cognitive test using Z scores and averaging them (see the **Appendix**, available at annals.org). Because verbal memory is strongly associated with risk for Alzheimer disease (1, 29–31), we assessed a secondary outcome of a verbal memory composite score, which was calculated by averaging the Z scores from the immediate and delayed recalls of the EBMT and TICS 10-word list. In a previous validation study of the telephone cognitive testing, the correlation between the global composite score from the telephone interview versus an extensive in-person assessment was 0.81 (23). Moreover, reliability of TICS performance was high between 50 women who were given the test twice 31 days apart (test–retest correlation, 0.7) (23).

Every 6 months for the first year, then annually thereafter, participants received monthly calendar packs containing a multivitamin or placebo (taken daily). Partici-

Figure. **Study flow diagram.**



PHS = Physicians' Health Study.

pants completed annual questionnaires on adherence, risk factors, and study outcomes. The β-carotene group of the PHS II continued as planned through May 2003, and results on cognitive function have been reported (20). Treatment and follow-up of the vitamin E and C components continued through August 2007, with benefits reported for cancer (32) and findings of no effect for cardiovascular disease (33). The multivitamin intervention continued through 1 June 2011, the scheduled end of the multivitamin component of the PHS II, with findings reported to date for cancer (3) and cardiovascular disease (34).

Statistical Analysis

Characteristics at randomization by treatment group were compared by using Wilcoxon rank-sum tests for continuous variables and chi-square tests for proportions.

We first examined mean performance at each cognitive assessment in the treatment versus placebo groups by using repeated measures analysis of means, which allows examination of each time point and accounts for correlation between assessments. For our primary, prespecified analysis, we examined mean change in cognitive function in as many as 4 assessments. We treated mean scores and mean change in scores at each assessment as repeated continuous outcomes and modeled the treatment effect with a time-by-treatment interaction. Because trajectories of test scores were nonlinear, we used general linear models of response profiles, modeling time with indicator variables rather than linearly (35). This approach imposes minimal structure on outcome trends over time and permits valid estimation of effects in nonlinear data. The nonlinearity of cognitive data due to "learning effects" is common in studies of cognitive function (there was a mean increase in scores from the first to second assessment) (36). We fitted all models by maximum likelihood, incorporating longitudinal correlations in participants by using unstructured covariance structures. For statistical testing, we used Wald tests. For all statistical analyses, we used Proc Mixed in SAS, version 9.2 (SAS Institute, Cary, North Carolina).

In secondary analyses, we tested for effect modification by possible risk factors of cognitive decline by including interaction terms in our models for cognitive change (age, smoking, alcohol consumption, body mass index, history of diabetes, hypertension, high cholesterol, folate intake

with and without supplements, intake of fruits and vegetables, and history of depression). We also evaluated the differences in cognitive change by comparing participants assigned to active multivitamins with those assigned to placebo for all other groups of the trial (that is, placebo for the β-carotene, vitamin C, vitamin E, and multivitamin groups), although the sample size for the placebo-only group was small ($n = 372$).

Role of the Funding Source

The National Institutes of Health, BASF, Pfizer, and DSM Nutritional Products had no role in the study design; conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

RESULTS

Characteristics at randomization were similar between the multivitamin and placebo groups ($P > 0.05$ for all groups) (**Table 1**). The average time from randomization to initial cognitive assessment was 2.5 years (range, 0.18 to 5.3 years), although this time was shorter for the newly recruited PHS II participants (mean time from randomization to initial assessment was 1.1 years for new participants and 3.2 years for original PHS I participants). The average duration of follow-up from randomization to the final cognitive evaluation was 8.5 years (range, 0.3 to 14.2 years), and 83.5% of the multivitamin group and 84.2% of the placebo group reported taking at least two thirds of their study pills.

At the first cognitive assessment, performance did not differ between the multivitamin and placebo groups (**Table 2**). (For raw scores at each cognitive assessment, see **Appendix Table 2** [available at www.annals.org]). For example, the global composite score for the multivitamin group was 0.01 SU (SD, 0.7), and the global composite score for the placebo group was −0.005 SU (SD, 0.7). When performance was examined at each follow-up assessment, there were no differences between the mean global composite score of cognitive function for men taking a daily multivitamin versus placebo at any point (**Table 3**). That is, the mean difference in global composite score between multivitamin and placebo groups at the fourth assessment (after an average of 8.5 years of follow-up) was 0.02 SU (95% CI, −0.04 to 0.08 SU). Likewise, for our secondary outcome of verbal memory, no differences were observed between groups at any of the assessments. For example, at the fourth assessment, the mean difference for the multivitamin compared with placebo group was 0.01 SU (CI, −0.05 to 0.07 SU). Similarly, in secondary analyses, the multivitamin group did not show any differences in mean performance versus the placebo group on the TICS or category fluency.

For our primary, prespecified outcome of change in cognitive function over follow-up, no differences were observed according to treatment group for any outcome

Table 1. **Self-Reported Characteristics at Randomization***

Characteristic	Multivitamin Group	Placebo Group
Participants, *n*	2980	2967
Mean age (SD), *y*	71.6 (6.0)	71.6 (5.9)
Age		
65–74 *y*	2129 (71.4)	2146 (72.3)
75–85 *y*	790 (26.5)	757 (25.5)
≥85 *y*	61 (2.1)	64 (2.2)
Mean BMI (SD), *kg/m²*	25.8 (3.2)	25.7 (3.3)
Alcohol intake		
Rarely or never	559 (18.9)	521 (17.6)
≥1 drink/mo	2404 (81.1)	2436 (82.4)
History of cigarette smoking		
Never	1453 (48.8)	1427 (48.1)
Former	1417 (47.6)	1431 (48.3)
Current	107 (3.6)	106 (3.6)
Vigorous exercise ≥1/wk		
No	1214 (41.2)	1196 (40.9)
Yes	1733 (58.8)	1728 (59.1)
Hypertension		
No	1387 (46.7)	1359 (45.9)
Yes	1585 (53.3)	1602 (54.1)
High cholesterol		
No	1744 (59.2)	1685 (57.6)
Yes	1203 (40.8)	1239 (42.4)
Type 2 diabetes mellitus		
No	2724 (91.5)	2737 (92.4)
Yes	253 (8.5)	225 (7.6)
History of MI		
No	2818 (94.6)	2799 (94.4)
Yes	162 (5.4)	167 (5.7)
History of stroke		
No	2897 (97.2)	2899 (97.7)
Yes	83 (2.8)	68 (2.3)
History of angina		
No	2702 (90.7)	2674 (90.1)
Yes	278 (9.1)	293 (9.9)
History of depression		
No	2704 (91.1)	2687 (91.0)
Yes	263 (8.9)	265 (9.0)
Mean fruit and vegetable intake (SD), *servings/d*†	4.9 (2.6)	4.9 (2.9)

BMI = body mass index; MI = myocardial infarction.
* 5947 participants aged ≥65 y participating in the Cognitive Substudy of the Physicians' Health Study II. Data are numbers (percentages) unless otherwise indicated. All variables defined as of Physicians' Health Study II randomization. Numbers do not always sum to group totals because of missing information for some variables, and $P > 0.05$ for all comparisons between multivitamin and placebo groups.
† Among 5575 participants with available dietary data on fruit and vegetable intake.

Table 2. **Mean (SD) Cognitive Test Scores at Initial Assessment***

Cognitive Test	Multivitamin Group (n = 2980)	Placebo Group (n = 2967)
Global composite (*Z* score), *SU*	0.01 (0.7)	−0.005 (0.7)
Verbal memory composite (*Z* score), *SU*	0.00 (0.7)	−0.005 (0.7)
TICS	34.3 (2.7)	34.3 (2.7)
EBMT		
Immediate recall	9.7 (1.9)	9.7 (1.9)
Delayed recall	9.4 (2.1)	9.3 (2.2)
Delayed recall of 10-word list	2.6 (2.0)	2.6 (2.0)
Category fluency	20.1 (6.0)	20.0 (6.1)

EBMT = East Boston Memory Test; TICS = Telephone Interview for Cognitive Status.
* Initial cognitive testing was conducted at a mean of 2.5 y (range, 0.18–5.3 y) after randomization.

(**Table 4**). That is, the average difference in change over follow-up between the multivitamin and placebo groups was −0.01 SU (CI, −0.04 to 0.02 SU) for the global score and in secondary analyses was −0.005 SU (CI, −0.04 to 0.03 SU) for the verbal memory score, 0.02 points (CI, −0.11 to 0.15 points) for the TICS, and −0.07 points (CI, −0.35 to 0.20 points) for category fluency. To help interpret these mean differences, we contrasted the effect of the multivitamin to the effect of time. Across the study population, there were mean annual changes of −0.046 SU on the global score, −0.044 SU on the verbal score, and −0.16 points on the TICS. Therefore, the mean differences we saw were smaller than the decline we would expect with 1 year of aging.

We examined effect modification by key risk factors for cognitive decline (**Table 5**). No evidence was found that the differences in the magnitude of cognitive decline across the treated versus placebo groups were influenced by any of these factors.

In analyses comparing men assigned to multivitamin treatment versus placebo across all of the treatment groups (that is, not receiving any other active vitamin supplement), we saw a suggestion of higher scores at the first cognitive assessment for the multivitamin group (for example, the global composite score at the first assessment was 0.01 for the multivitamin group and −0.03 for the placebo group), although the differences were not significant for any cognitive test ($P > 0.05$ for all tests). We also found significantly worse cognitive decline in the multivitamin than in the placebo group for the global and verbal composite scores but not for the TICS or category fluency task (for example, the mean difference in decline in global score was −0.08 SU [CI, −0.14 to −0.01 SU] and the mean difference in decline in verbal memory score was

Table 3. **Cognitive Function at Each Assessment**

Cognitive Test	Multivitamin Group		Placebo Group		Mean Difference in Score Between Multivitamin and Placebo Groups (95% CI)*
	Participants, *n*	Least-Squares Mean (SE)	Participants, *n*	Least-Squares Mean (SE)	
Global composite score†					
1	2978	0.01 (0.01)	2964	−0.00 (0.01)	0.01 (−0.02 to 0.05)
2	2657	0.02 (0.01)	2639	0.01 (0.01)	−0.01 (−0.05 to 0.03)
3	2091	−0.13 (0.02)	2015	−0.15 (0.02)	0.02 (−0.03 to 0.06)
4	1165	−0.26 (0.02)	1159	−0.28 (0.02)	0.02 (−0.04 to 0.08)
Verbal memory composite score†					
1	2978	0.00 (0.01)	2964	−0.00 (0.01)	0.01 (−0.03 to 0.05)
2	2657	0.03 (0.01)	2639	0.03 (0.02)	−0.00 (−0.05 to 0.04)
3	2091	−0.08 (0.02)	2015	−0.10 (0.02)	0.02 (−0.03 to 0.07)
4	1165	−0.16 (0.02)	1159	−0.18 (0.02)	0.01 (−0.05 to 0.07)
TICS score					
1	2980	34.3 (0.05)	2967	34.3 (0.05)	0.04 (−0.09 to 0.18)
2	2657	34.5 (0.05)	2639	34.5 (0.06)	0.10 (−0.05 to 0.24)
3	2091	34.0 (0.07)	2015	34.0 (0.07)	0.00 (−0.18 to 0.19)
4	1165	33.2 (0.09)	1159	33.1 (0.09)	0.12 (−0.14 to 0.38)
Category fluency score					
1	2978	20.1 (0.11)	2964	20.0 (0.11)	0.02 (−0.29 to 0.33)
2	2657	20.0 (0.11)	2639	20.2 (0.12)	−0.21 (−0.53 to 0.12)
3	2091	18.8 (0.12)	2015	18.7 (0.13)	0.04 (−0.31 to 0.40)
4	1165	18.5 (0.15)	1159	18.3 (0.15)	0.22 (−0.21 to 0.65)

TICS = Telephone Interview for Cognitive Status.
* Difference from longitudinal models of mean cognitive performance.
† Global score is a composite of TICS, immediate and delayed recalls of the East Boston Memory Test, category fluency, and delayed recall of the TICS 10-word list. 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. Values are reported in standardized units.

−0.10 SU [CI, −0.17 to −0.02 SU]). However, these results must be interpreted cautiously given the small number of participants in the placebo group ($n = 372$) and the probably random increase in cognitive performance at the first cognitive assessment for the multivitamin group.

DISCUSSION

In this long-term, randomized, placebo-controlled trial with more than a decade of treatment among 5947 men aged 65 years or older, those assigned to a daily multivitamin had similar overall cognitive performance as those receiving a placebo.

Few observational studies have examined multivitamin use and cognition. Some epidemiologic research suggests that moderate doses of antioxidant vitamins (similar to those found in a multivitamin supplement) are associated with a slower rate of cognitive decline (38). For example, in 2889 participants from the Chicago Health and Aging Project with a mean follow-up of 3.2 years, higher total vitamin E and vitamin E from food intake (mean intake of vitamin E was 90 IU and 17% of participants used vitamin E supplements) was associated with slower cognitive decline (10). Nonetheless, findings for antioxidant vitamins are not consistent. An analysis of 16 010 women in the Nurses' Health Study found no association between total antioxidant intake or antioxidant intake from foods alone and cognitive decline over 4 years (39).

Observational studies of B vitamins and cognitive status have also been inconsistent (40). Some studies have shown better cognitive performance among persons with higher blood levels of folate (41, 42) or other B vitamins (43–45), but other studies have shown no association (46–48). Studies of dietary intake and supplements have also varied. One cohort study of 321 participants with a mean follow-up of 3 years found that dietary folate (mean intake, 440 μg), vitamin B_6 (mean intake, 3.98 mg), and vitamin B_{12} (mean intake, 9.57 μg) from food and supplement sources were related to better performance on a spatial copying task but not other memory-related tests (49). Another study found that vitamin B_{12} intake was not related to cognitive decline in 3718 participants with a median follow-up of 5.5 years, except for a potential benefit limited to the oldest participants (50).

Results from previous randomized, controlled trials of multivitamin supplements and cognition have not found clear benefits in well-nourished populations. In a recent meta-analysis of 10 smaller, shorter-term, randomized, controlled trials of multivitamin supplements, there was no effect on 7 cognitive domains except for immediate free recall memory, which was not a specific a priori hypothesis (12). Trials testing high doses of individual vitamin supplements have generally had null results for cognition as well, including large-scale trials of antioxidant supplements (51–55) and B vitamins (56–59).

Table 4. **Mean Difference in Cognitive Decline Between Multivitamin and Placebo Groups**

Cognitive Test	Mean Difference in Cognitive Decline Between Multivitamin and Placebo Groups (95% CI)*	*P* Value
Global composite score†		
From initial cognitive assessment to:		
Second cognitive assessment	−0.02 (−0.05 to 0.02)	0.28
Third cognitive assessment	0.01 (−0.04 to 0.05)	0.79
Fourth cognitive assessment	0.01 (−0.05 to 0.06)	0.77
Average over follow-up	−0.01 (−0.04 to 0.02)	0.53
Verbal memory composite score†		
From initial cognitive assessment to:		
Second cognitive assessment	−0.02 (−0.06 to 0.02)	0.43
Third cognitive assessment	0.01 (−0.03 to 0.06)	0.57
Fourth cognitive assessment	0.01 (−0.05 to 0.07)	0.84
Average over follow-up	−0.005 (−0.04 to 0.03)	0.80
TICS score		
From initial cognitive assessment to:		
Second cognitive assessment	0.04 (−0.10 to 0.18)	0.59
Third cognitive assessment	−0.04 (−0.21 to 0.13)	0.64
Fourth cognitive assessment	0.07 (−0.18 to 0.32)	0.59
Average over follow-up	0.02 (−0.11 to 0.15)	0.79
Category fluency score		
From initial cognitive assessment to:		
Second cognitive assessment	−0.22 (−0.52 to 0.09)	0.165
Third cognitive assessment	0.05 (−0.30 to 0.40)	0.77
Fourth cognitive assessment	0.22 (−0.21 to 0.65)	0.31
Average over follow-up	−0.07 (−0.35 to 0.20)	0.59

TICS = Telephone Interview for Cognitive Status.
* From longitudinal models of least-squares means of change in cognitive performance from the initial assessment and averaged over follow-up. Number of participants in each assessment is shown in **Table 3**.
† Global score is a composite of TICS, immediate and delayed recalls of the East Boston Memory Test, category fluency, and delayed recall of the TICS 10-word list. 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. Values are reported in standardized units.

Yet, one issue with many of the trials is that supplementation may be administered too late or for an inadequate duration to prevent cognitive decline, which is a process that begins years before symptoms are detected. In a cognitive substudy of the SU.VI.MAX (Supplementation in Vitamins and Mineral Antioxidants) trial ($n = 4447$), investigators assessed cognition 6 years after the conclusion of an 8-year trial of antioxidant supplementation and found better performance for the supplement group on a test of episodic memory (17). However, results were not significant for the 5 other cognitive outcomes tested. Therefore, findings are difficult to interpret. Stronger evidence comes from a report of the β-carotene component from the PHS II trial. Participants randomly assigned to β-carotene had significantly better performance on global cognitive and verbal memory after an average of 18 years of supplementation, suggesting that very long-term vitamin supplementation or exposure at younger ages before substantial neuropathology has accumulated may be required to maintain brain health (20, 60).

Table 5. **Mean Difference in Cognitive Decline in Global Score Between Multivitamin and Placebo Groups, by Subgroups**

Characteristic*	Mean Difference in Cognitive Decline Between Multivitamin and Placebo Groups (95% CI)†	Interaction *P* Value‡
Age at first assessment		
<74 *y*	−0.02 (−0.06 to 0.02)	0.50
≥74 *y*	0.00 (−0.05 to 0.05)	
Cognitive performance at first assessment		
Below median	0.01 (−0.04 to 0.06)	0.26
Above median	−0.03 (−0.06 to 0.01)	
Cigarette smoking		
Never	0.01 (−0.04 to 0.05)	0.25
Ever	−0.03 (−0.07 to 0.02)	
Alcohol consumption		
Rare or never	−0.04 (−0.11 to 0.03)	0.38
≥1 drink/mo	−0.00 (−0.04 to 0.03)	
BMI		
<30 kg/m^2	−0.01 (−0.04 to 0.03)	0.57
≥30 kg/m^2	−0.04 (−0.15 to 0.07)	
Diabetes		
Yes	−0.04 (−0.15 to 0.08)	0.64
No	−0.01 (−0.04 to 0.02)	
Hypertension		
Yes	−0.01 (−0.05 to 0.03)	0.99
No	−0.01 (−0.05 to 0.04)	
High cholesterol		
Yes	−0.02 (−0.07 to 0.03)	0.56
No	−0.00 (−0.04 to 0.04)	
Folate without supplements§		
<279 μg/d	0.01 (−0.08 to 0.10)	0.67
≥279 μg/d	−0.01 (−0.04 to 0.03)	
Folate with supplements§		
<279 μg/d	0.02 (−0.08 to 0.11)	0.67
≥279 μg/d	−0.01 (−0.04 to 0.03)	
Fruit and vegetable intake		
<4 servings/d	−0.02 (−0.07 to 0.02)	0.31
4–7 servings/d	−0.02 (−0.06 to 0.03)	
≥7 servings/d	0.05 (−0.03 to 0.13)	
History of depression		
Yes	−0.08 (−0.18 to 0.02)	0.142
No	−0.00 (−0.04 to 0.03)	

* Characteristics as of randomization unless otherwise noted.
† From longitudinal models of least-squares means of change in cognitive performance from the initial assessment and averaged over follow-up. Values are reported in standardized units.
‡ From testing effect modification in longitudinal models.
§ Cutoff for low folate intake was determined from intakes found to be significantly associated with elevated homocysteine in the Framingham study (37).

A limitation of this study is that the male physician participants may have been too well-nourished to observe benefits of supplementation. When cognitive benefits have been observed in other trials of nutriceuticals, these benefits are usually in groups with inadequate dietary intakes of the relevant vitamin (52, 61). Future studies are needed to clarify whether multivitamin supplementation may be more beneficial in persons with less optimal nutritional status or vitamin deficiencies. This is of particular interest in an aging population because older persons are often at risk for nutritional deficiencies due to reduced micronutrient intake, altered absorption, and the metabolic requirements of vitamins (62).

This population is also unique in that the participants are all highly educated men, so it is possible that effects of multivitamins could have been different in a study population with varying levels of educational attainment. Nevertheless, our large sample size gave us sufficient power to detect the effects of the multivitamin supplement on changes in cognition, and we have identified many risk factors for cognitive decline in previous studies using PHS II data, including β-carotene treatment and type 2 diabetes mellitus (20, 63).

Furthermore, cognitive testing began an average of 2.5 years (range, 0.18 to 5.3 years) after randomization. This prevented evaluating change in performance from randomization, and it is possible that we missed acute benefits of multivitamins during initial follow-up. However, risk factors for cognitive decline were similarly distributed among treatment groups at randomization, and cognition was similar at the initial cognitive assessment (including among newly recruited participants with a mean of only 1 year from randomization to initial cognitive testing). Therefore, it is likely that cognitive function was similar between the 2 groups at randomization. Given the length of time over which cognitive changes occur, it is unlikely that we missed any meaningful changes due to multivitamin supplementation in the period between randomization and initial cognitive testing.

Finally, the formulation of the multivitamin used in PHS II has changed since it began, reflecting evolving perspectives and priorities in nutrition. For example, vitamin D increased from 400 to 500 IU, vitamin A (percentage as β-carotene) decreased from 5000 IU (50%) to 2500 IU (40%), and 250 μg of lutein and 300 μg of lycopene were added. However, the formulation of the multivitamin used throughout PHS II (**Appendix Table 1**) has remained the same throughout its duration.

Strengths of this trial include the large population of men with a long duration of randomized treatment. Additional strengths include completion of 4 repeated cognitive assessments over nearly a decade, with high rates of follow-up and a validated neuropsychological test battery covering various cognitive domains based on the same cognitive domains used in the National Institute on Aging's Uniform Data Set Neuropsychological Test Battery (64). The PHS II also benefited from high levels of adherence to multivitamin treatment, with two thirds of men still adherent to their treatment regimen after more than a decade of follow-up.

In this large, randomized, placebo-controlled trial among 5947 men aged 65 years or older, we saw no benefit of a daily multivitamin in slowing cognitive decline after more than a decade of treatment and follow-up. These data do not provide support use of multivitamin supplements in the prevention of cognitive decline. However, it is important to consider other health effects of multivitamin supplementation, including modest protection against overall cancer risk in the PHS II with long-term use (3) and any potential effects on other important health outcomes yet to be evaluated. Moreover, further research is needed in other populations, such as those with nutrient deficiencies, to determine whether there are cognitive benefits specific to daily multivitamin use.

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Appendix Table 1. **Vitamins and Minerals Contained in the Centrum Silver* Formulation Used in the PHS II Trial**

Vitamin or Mineral	Amount
Vitamin A, *IU*	5000†
Vitamin C, *mg*	60
Vitamin D, *IU*	400
Vitamin E, *IU*	45
Vitamin K, *μg*	10
Thiamin, *mg*	1.5
Riboflavin, *mg*	1.7
Niacin, *mg*	20
Vitamin B_6, *mg*	3
Folic acid, *μg*	400
Vitamin B_{12}, *μg*	25
Biotin, *μg*	30
Pantothenic acid, *mg*	10
Calcium, *mg*	200
Iron, *mg*	4
Phosphorus, *mg*	48
Iodine, *μg*	150
Magnesium, *mg*	100
Zinc, *mg*	15
Selenium, *μg*	20
Copper, *mg*	2
Manganese, *mg*	3.5
Chromium, *μg*	130
Molybdenum, *μg*	160
Chloride, *mg*	72.6
Potassium, *mg*	80
Boron, *μg*	150
Nickel, *μg*	5
Vanadium, *μg*	10
Silicon, *mg*	2

PHS = Physicians' Health Study II.
* Pfizer, New York, New York.
† 50% as β-carotene.

Appendix: Score Methods

Global Composite Score Method

To create the global composite score, we combined results from each of the 5 primary tests: the TICS, the delayed recall of the 10-word list, the immediate and delayed recalls of the EBMTs, and the test of verbal fluency. Because we could not combine the raw scores together (a point is not equal for each test), we created *Z* scores by taking the difference between the participant's score on each test and the mean for that test at the initial assessment and divided this by the SD at the initial assessment.

Verbal Memory Composite Score Method

The verbal composite score was created by using the same method as above; however, it is an average of the *Z* scores of the verbal memory tests only (immediate and delayed recall of the EBMT and the 10-word list from the TICS).

Appendix Table 2. **Mean (SD) Cognitive Scores at Each Assessment***

Cognitive Test	Initial Assessment		Second Assessment		Third Assessment		Fourth Assessment	
	Multivitamin	Placebo	Multivitamin	Placebo	Multivitamin	Placebo	Multivitamin	Placebo
Global composite, *SU*	0.01 (0.68)	−0.00 (0.70)	0.05 (0.70)	0.05 (0.74)	−0.02 (0.76)	−0.03 (0.73)	−0.05 (0.77)	−0.07 (0.75)
Verbal memory composite, *SU*	0.00 (0.73)	−0.00 (0.73)	0.05 (0.75)	0.05 (0.79)	−0.00 (0.78)	−0.01 (0.77)	−0.03 (0.76)	−0.03 (0.76)
TICS	34.3 (2.7)	34.3 (2.7)	34.6 (2.6)	34.5 (2.8)	34.3 (3.0)	34.3 (2.9)	33.9 (3.3)	33.8 (3.3)
Delayed 10-word list recall	2.6 (2.0)	2.6 (2.0)	2.8 (2.1)	2.9 (2.1)	2.7 (2.0)	2.6 (2.0)	2.5 (2.1)	2.5 (2.1)
EBMT (immediate recall)	9.7 (1.9)	9.7 (1.9)	9.7 (1.9)	9.7 (1.9)	9.7 (1.9)	9.7 (1.9)	9.7 (1.8)	9.8 (1.8)
EBMT (delayed recall)	9.4 (2.1)	9.3 (2.2)	9.3 (2.2)	9.3 (2.3)	9.3 (2.4)	9.3 (2.3)	9.3 (2.2)	9.3 (2.3)
Category fluency	20.1 (6.0)	20.0 (6.1)	20.1 (6.0)	20.4 (6.2)	19.3 (5.9)	19.3 (6.1)	19.6 (6.0)	19.3 (5.9)

EBMT = East Boston Memory Test; TICS = Telephone Interview for Cognitive Status.