Multivitamins in the Prevention of Cardiovascular Disease in Men
The Physicians’ Health Study II Randomized Controlled Trial

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Despite uncertainty regarding the long-term health benefits of vitamins, many US adults take vitamin supplements to prevent chronic diseases or for general health and well-being. Because multivitamins are the most common supplement taken by US adults, there are broad public health implications regarding their everyday use. Individuals who believe they are deriving benefits from supplements may be less likely to engage in other preventive health behaviors, and chronic use of daily supplements poses a financial burden, with annual vitamin supplement sales in the billions of US dollars.

A daily multivitamin, with its combination of essential vitamins and minerals that meet minimum recommended

Context Although multivitamins are used to prevent vitamin and mineral deficiency, there is a perception that multivitamins may prevent cardiovascular disease (CVD). Observational studies have shown inconsistent associations between regular multivitamin use and CVD, with no long-term clinical trials of multivitamin use.

Objective To determine whether long-term multivitamin supplementation decreases the risk of major cardiovascular events among men.

Design, Setting, and Participants The Physicians’ Health Study II, a randomized, double-blind, placebo-controlled trial of a common daily multivitamin, began in 1997 with continued treatment and follow-up through June 1, 2011. A total of 14 641 male US physicians initially aged 50 years or older (mean, 64.3 [SD, 9.2] years), including 754 men with a history of CVD at randomization, were enrolled.

Intervention Daily multivitamin or placebo.

Main Outcome Measures Composite end point of major cardiovascular events, including nonfatal myocardial infarction (MI), nonfatal stroke, and CVD mortality. Secondary outcomes included MI and stroke individually.

Results During a median follow-up of 11.2 (interquartile range, 10.7-13.3) years, there were 1732 confirmed major cardiovascular events. Compared with placebo, there was no significant effect of a daily multivitamin on major cardiovascular events (11.0 and 10.8 events per 1000 person-years for multivitamin vs placebo, respectively; hazard ratio [HR], 1.01; 95% CI, 0.91-1.10; P = .91). Further, a daily multivitamin had no effect on total MI (3.9 and 4.2 events per 1000 person-years; HR, 0.93; 95% CI, 0.80-1.09; P = .39), total stroke (4.1 and 3.9 events per 1000 person-years; HR, 1.06; 95% CI, 0.91-1.23; P = .48), or CVD mortality (5.0 and 5.1 events per 1000 person-years; HR, 0.95; 95% CI, 0.83-1.09; P = .47). A daily multivitamin was also not significantly associated with total mortality (HR, 0.94; 95% CI, 0.88-1.02; P = .13). The effect of a daily multivitamin on major cardiovascular events did not differ between men with or without a baseline history of CVD (P = .62 for interaction).

Conclusion Among this population of US male physicians, taking a daily multivitamin did not reduce major cardiovascular events, MI, stroke, and CVD mortality after more than a decade of treatment and follow-up.

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dietary allowance levels, may replicate broader, healthier dietary and food patterns identified in epidemiologic studies for prevention of cardiovascular disease (CVD).7-8 However, observational studies of multivitamin use and cardiovascular incidence and mortality have been limited and inconsistent.9-16

Randomized clinical trials have tested the effect of high-dose individual vitamins and minerals—including beta carotene;17-19 vitamin E;19,20 vitamin C,20-22 selenium,23 and B vitamins24,25—with the vast majority showing no effect on CVD end points. Only a few large-scale trials have tested combinations of a few vitamins or minerals, typically selected from those already tested individually and equivocally;26-28 for which there has been a lack of effect. There have been no large-scale trials of a multivitamin in CVD prevention. Accordingly, a National Institutes of Health conference panel29 and the proceedings of 2010 Dietary Guidelines stated that there is no evidence to support use of a daily multivitamin in disease prevention, including CVD.30

The Physicians’ Health Study (PHS) II is to our knowledge the only large-scale trial testing the effects of long-term use of a common multivitamin on the risk of major cardiovascular events and cancer. In this article, we present the findings for the effects of multivitamin use on major cardiovascular events. Results for cancer,31 eye disease, and cognitive decline will be published separately.

METHODS

Study Design

The PHS II was a randomized, double-blind, placebo-controlled, 2 × 2 × 2 factorial trial evaluating the balance of risks and benefits of a multivitamin (Centrum Silver or placebo daily [Pfizer; formerly Wyeth, American Home Products, and Lederle]), vitamin E (400-UI synthetic α-tocopherol or placebo on alternate days [BASF Corporation]), vitamin C (500-mg synthetic ascorbic acid or placebo daily [BASF Corporation]), and beta carotene (50-mg Lutroin or placebo on alternate days [BASF Corporation]) in the prevention of CVD, cancer, eye disease, and cognitive decline among 14 641 male physicians initially aged 50 years or older.32 The beta carotene component ended as scheduled in March 2003, and the vitamin E and C components ended as scheduled in 2007, with a lack of effect reported for CVD and cancer.33

As detailed previously,22,32,33 PHS II recruitment, enrollment, and randomization occurred in 2 phases (FIGURE I). In phase 1, starting in July 1997, we invited 18 763 living participants from PHS I, a randomized trial of low-dose aspirin34 and beta carotene17 among 22 071 male physicians, to participate in PHS II. Men were ineligible if they reported a history of cirrhosis or active liver disease, were taking anticoagulants, or reported a serious illness that might preclude participation. Men also must have been willing to forgo current use of multivitamins or individual supplements containing more than 100% of the recommended dietary allowance of vitamin E, vitamin C, beta carotene, or vitamin A. Men with a history of myocardial infarction (MI), stroke, or cancer remained eligible. We randomized 7641 (41%) willing and eligible PHS I participants into PHS II.

Phase 2 of the PHS II began in July 1999 with invitational letters and baseline questionnaires sent to 254 597 additional US male physicians 50 years or older identified from a list from the American Medical Association that exceeded PHS I participants. By July 2001, 42 165 men (16.6%) had completed the baseline PHS II questionnaire, of whom 11 128 (26.4%) were willing and eligible to participate based on the same eligibility criteria as PHS I participants. Of 11 128 physicians who entered a run-in phase, 7000 (63%) were adherent with their pills and were randomized into PHS II.

A total of 14 641 men were randomized into PHS II in blocks of 16 and stratified by age, prior diagnosis of cancer, prior diagnosis of CVD, and, for 7641 PHS I participants, their original beta carotene treatment assignment. There were 754 (5.1%) men with a history of MI or stroke before randomization. All participants provided written informed consent, and the institutional review board at Brigham and Women’s Hospital approved the research protocol.

Study Treatment, Follow-up, and Adherence

Every 6 months for the first year, then annually thereafter, PHS II participants were sent monthly calendar packs containing a multivitamin or placebo. Annual mailed questionnaires asked about adherence, adverse events, end points, and risk factors. Blinded treatment and follow-up continued through June 1, 2011, the scheduled end of the PHS II multivitamin component. Data analyses include follow-up and validation of reported end points through August 2012. Morbidity and mortality follow-up in PHS II were high—98.2% and 99.9%, respectively. In addition, morbidity and mortality follow-up as a percentage of person-time each exceeded 99.9%. Adherence with the multivitamin component was defined from participant self-report, which has been shown to be highly reliable in physicians,35 as taking at least two-thirds of the pills.

Confirmation of CVD End Points

For the multivitamin component, a primary end point was major cardiovascular events (including nonfatal MI, nonfatal stroke, and CVD mortality). Prespecified secondary end points included in this report include total MI and total stroke. Other end points considered in these analyses included fatal and nonfatal MI and stroke, cardiovascular death, ischemic and hemorrhagic stroke, and total mortality.

For each of the above self-reported end points, we requested permission from the participant to examine all relevant medical records. On receipt of consent, medical records were requested and reviewed by an end points committee of physicians blinded to randomized treatment assignment. We were unable to obtain adequate medi-
The diagnosis of MI was confirmed by evidence of symptoms in the presence of either diagnostic elevations of cardiac enzyme levels or diagnostic changes on electrocardiograms. For fatal events, the diagnosis of MI was also accepted based on autopsy findings. We confirmed diagnoses of stroke defined as a typical neurologic deficit of sudden or rapid onset and vascular origin, lasting more than 24 hours. Stroke was classified according to National Survey of Stroke criteria into ischemic, hemorrhagic, and unknown subtype, with high interobserver agreement.

Participant deaths were usually reported by family members or postal authorities. Following a report of a participant death, we obtained death certificates, autopsy reports, or both. Total mortality was confirmed by the end points committee or by death certificate. Mortality attributable to CVD was additionally documented by convincing evidence of a cardiovascular mechanism from all available sources. For men with unknown vital status, we used web and National Death Index searches to identify deaths.

Only confirmed end points of MI, stroke, and CVD death were included in this analysis. We also collected data on participant self-reports of congestive heart failure, angina pectoris, and revascularization (including coronary artery bypass graft surgery and percutaneous coronary intervention) for inclusion in our analyses.

**Statistical Analyses**

All primary analyses were based on the intention-to-treat principle, in which all 14,641 randomized PHS II participants were classified according to their randomized multivitamin treatment assignment and underwent follow-up until the occurrence of major cardiovascular events, death, loss to follow-up, or the end of the study.

Figure 1. Flow Diagram of Participants From Screening to Completion of the Multivitamin Component of the Physicians’ Health Study II
We performed all analyses using SAS version 9.2 (SAS Institute Inc) and S-Plus (Insightful Corp), with statistical significance set at \( P < .05 \) using 2-sided tests. The PHS II was estimated to have 80% power to detect a 12% reduction in the primary end point of major cardiovascular events.

We initially compared baseline characteristics by multivitamin treatment assignment to ensure that randomization equally distributed baseline characteristics by active vs placebo groups. As done in previous PHS II trial analyses, Cox proportional hazards models estimated hazard ratios (HRs) and 95% CIs, comparing event rates in the multivitamin and placebo groups. For each pre-specified end point, we stratified on the presence of CVD at randomization and adjusted for PHS II study design variables, including age (in years), PHS cohort (original PHS I participant, new PHS II participant), and randomized vitamin E, vitamin C, and beta carotene assignments. For analyses of total major cardiovascular events, all new events were included, regardless of whether the participant had a baseline history of CVD. Analyses of individual cardiovascular endpoints did not censore men on occurrence of another cardiovascular end point. For analyses of total and cardiovascular mortality, we included all 14,641 PHS II participants; for total mortality, we additionally stratified by history of cancer at randomization.

We tested the proportional hazards assumptions by including an interaction term for multivitamin treatment with the logarithm of time; this assumption was not violated for major cardiovascular events, total MI, and total stroke (\( P > .05 \) for each). Cumulative incidence curves compared the overall effect of the multivitamin component on major cardiovascular events, total MI, and total stroke using a crude log-rank test. We investigated the effect of adherence to the multivitamin inter-

### Table 1. Self-reported Baseline Characteristics According to Multivitamin Treatment Assignment of 14,641 Men From the Physicians’ Health Study II

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Multivitamin (n = 7317)</th>
<th>Placebo (n = 7324)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>64.2 (9.1)</td>
<td>64.3 (9.2)</td>
</tr>
<tr>
<td>Age, y</td>
<td>50-59</td>
<td>2944 (40.2)</td>
</tr>
<tr>
<td>60-69</td>
<td>2348 (32.1)</td>
<td>2348 (32.1)</td>
</tr>
<tr>
<td>≥70</td>
<td>2025 (27.7)</td>
<td>2029 (27.7)</td>
</tr>
<tr>
<td>Body mass index, mean (SD)</td>
<td>25.9 (3.4)</td>
<td>26.0 (3.4)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>4145 (56.7)</td>
<td>4107 (56.1)</td>
</tr>
<tr>
<td>Former</td>
<td>2908 (39.8)</td>
<td>2944 (40.2)</td>
</tr>
<tr>
<td>Current</td>
<td>255 (3.5)</td>
<td>269 (3.7)</td>
</tr>
<tr>
<td>Exercise ≥1 time/wk</td>
<td>2699 (37.8)</td>
<td>2806 (39.3)</td>
</tr>
<tr>
<td>No</td>
<td>4444 (62.2)</td>
<td>4328 (60.7)</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>1391 (19.2)</td>
<td>1339 (18.4)</td>
</tr>
<tr>
<td>Rarely/never</td>
<td>5874 (80.9)</td>
<td>5942 (81.6)</td>
</tr>
<tr>
<td>No</td>
<td>1625 (22.5)</td>
<td>1636 (22.7)</td>
</tr>
<tr>
<td>Yes</td>
<td>5602 (77.5)</td>
<td>5565 (77.3)</td>
</tr>
<tr>
<td>Medical history</td>
<td>4229 (58.2)</td>
<td>4177 (57.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3039 (41.8)</td>
<td>3117 (42.7)</td>
</tr>
<tr>
<td>No</td>
<td>4534 (64.0)</td>
<td>4432 (62.7)</td>
</tr>
<tr>
<td>Yes</td>
<td>2549 (36.0)</td>
<td>2641 (37.3)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6838 (93.5)</td>
<td>6883 (94.1)</td>
</tr>
<tr>
<td>No</td>
<td>472 (6.5)</td>
<td>433 (5.9)</td>
</tr>
<tr>
<td>Parental MI at &lt;60 y</td>
<td>5941 (90.0)</td>
<td>5928 (89.4)</td>
</tr>
<tr>
<td>No</td>
<td>661 (10.0)</td>
<td>701 (10.6)</td>
</tr>
<tr>
<td>Yes</td>
<td>1391 (19.2)</td>
<td>1339 (18.4)</td>
</tr>
<tr>
<td>Self-reported CVD</td>
<td>6941 (94.9)</td>
<td>6946 (94.8)</td>
</tr>
<tr>
<td>No</td>
<td>376 (5.1)</td>
<td>378 (5.2)</td>
</tr>
<tr>
<td>Plasma cholesterol, mean (SD), mg/dL</td>
<td>203.3 (35.5)</td>
<td>203.7 (36.0)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>44.3 (14.4)</td>
<td>44.0 (14.7)</td>
</tr>
</tbody>
</table>

**Abbreviations:** CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; MI, myocardial infarction.

*SI conversion factors: To convert total cholesterol and HDL-C values to mmol/L, multiply by 0.0259.*

*Numbers do not always sum to group totals because of missing information for some variables. \( P < .05 \) for all comparisons between multivitamin and placebo groups.*

*Calculated as weight in kilograms divided by height in meters squared.*

*Defined as self-reported systolic blood pressure of 140 mm Hg or greater, diastolic blood pressure of 90 mm Hg or greater, or past or current treatment for hypertension.*

*Defined as self-reported total cholesterol level of 240 mg/dL or greater or past or current treatment for high cholesterol level.*

*Excludes 1410 men with missing information on parental history of MI at ages younger than 60 y.*

*Among 8609 and 8615 men with available biomarker data for plasma total cholesterol and HDL-C, respectively.*

*Among 13,310 men with available dietary data on fruit and vegetable intake, 13,280 with data on whole grain intake, and 13,268 with data on red meat intake.*
TABLE 2. Association Between Randomized Multivitamin Assignment and Risk of Major Cardiovascular Events and Mortality in the Physicians’ Health Study II

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Multivitamin (n = 7317)</th>
<th>Placebo (n = 7324)</th>
<th>Adjusted HR (95% CI)b</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major cardiovascular events c</td>
<td>876</td>
<td>856</td>
<td>1.01 (0.91-1.10)</td>
<td>.91</td>
</tr>
<tr>
<td>Total MI d</td>
<td>317</td>
<td>335</td>
<td>0.93 (0.80-1.09)</td>
<td>.39</td>
</tr>
<tr>
<td>MI death</td>
<td>27</td>
<td>43</td>
<td>0.61 (0.38-0.99)</td>
<td>.048</td>
</tr>
<tr>
<td>Total stroke d</td>
<td>332</td>
<td>311</td>
<td>1.06 (0.91-1.23)</td>
<td>.48</td>
</tr>
<tr>
<td>Stroke death</td>
<td>89</td>
<td>76</td>
<td>1.16 (0.85-1.58)</td>
<td>.34</td>
</tr>
<tr>
<td>Ischemic stroke d</td>
<td>277</td>
<td>250</td>
<td>1.10 (0.92-1.30)</td>
<td>.29</td>
</tr>
<tr>
<td>Hemorrhagic stroke d</td>
<td>49</td>
<td>45</td>
<td>1.08 (0.72-1.63)</td>
<td>.69</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>408</td>
<td>421</td>
<td>0.95 (0.83-1.09)</td>
<td>.47</td>
</tr>
<tr>
<td>Total mortality d</td>
<td>1345</td>
<td>1412</td>
<td>0.94 (0.88-1.02)</td>
<td>.13</td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; MI, myocardial infarction.

a Mean follow-up of 11.2 years for all 14,641 men through June 1, 2011.

b Adjusted for age, Physicians’ Health Study (PHS) cohort (original PHS I participant, new PHS II participant), randomized beta carotene assignment, randomized vitamin E assignment, and randomized vitamin C assignment and stratified on cardiovascular disease at baseline.

c Defined as a composite end point consisting of the first of any of the following individual events: nonfatal MI, nonfatal stroke, and cardiovascular death. The individual events do not sum to the total because each individual analysis assesses the first event that occurs during follow-up. Therefore, a participant who for example has an MI and then dies of cardiovascular disease would be counted for both individual events but only once for the primary end point of major cardiovascular events.

d Includes both nonfatal and fatal events.

e Stroke type was unknown for 6 men in the active multivitamin group and 16 men in the placebo group.

f Additionally stratified on baseline cancer.

We then conducted additional exploratory analyses on the effect of the multivitamin intervention on major cardiovascular events, total MI, and total stroke after excluding the first 2 or 5 years of follow-up to explore a possible early or late benefit associated with long-term multivitamin use. We also conducted subgroup analyses stratified by major risk factors, parental history of MI at ages younger than 60 years, and selected coronary biomarkers and dietary factors available in a subgroup of PHS II participants. We evaluated the effect of a daily multivitamin within the prespecified subgroups of 754 men with and 13,887 men without a baseline history of CVD. Effect modification was assessed using interaction terms between subgroup indicators and randomized multivitamin treatment assignment.

RESULTS

We randomized a total of 14,641 men into PHS II; the mean age of participants was 64.3 (SD, 9.2) years. Factors measured at baseline were similar between the multivitamin and placebo groups (TABLE 1). Among coronary risk factors, there was a low proportion (3.6%) of current smokers and a relatively high proportion (59.9%) of men who exercised 1 time/wk or more, which was countered with 42.0% of men reporting a history of hypertension, 33.4% a history of high cholesterol levels, and 6.2% a history of diabetes. Baseline aspirin use was high (77.4%) in this population of physicians, in part reflective of their previous participation and results of the PHS I trial assessing aspirin use and CVD.34 There were 754 men (5.1%) with a baseline history of CVD and 1312 (9.0%) with a baseline history of cancer.

Median follow-up of PHS II participants was 11.2 years (interquartile range, 10.7-13.3 years; maximum, 13.8 years), totaling 164,320 person-years. Adherence was 76.8% in the multivitamin group and 77.1% in the placebo group at 4 years (P = .71); 72.3% in the multivitamin group and 70.7% in the placebo group at 8 years (P = .15); and 67.5% in the multivitamin group and 67.1% in the placebo group at the end of follow-up (P = .70). There were small differences between the multivitamin and placebo groups when comparing the avoidance of individual nontrial multivitamin use (<30 days/y) at 4 years of follow-up (86.7% and 85.4%, respectively; P = .03) and 8 years of follow-up (78.5% and 75.8%, P = .01) but not by the end of multivitamin follow-up (81.0% and 80.3%; P = .35). During multivitamin treatment, we confirmed that 1732 men had major cardiovascular events, including 652 cases (first events) of MI and 643 cases of stroke (527 ischemic stroke, 94 hemorrhagic stroke), and 829 had cardiovascular death, with some men experiencing multiple events. A total of 2757 men (18.8%) died during follow-up.

Multivitamin Use and Major Cardiovascular Events

The rates of major cardiovascular events were 11.0 per 1000 person-years in the multivitamin group and 10.8 per 1000 person-years in the placebo group. Men taking a daily multivitamin experienced no benefit for the primary end point of major cardiovascular events (HR, 1.01; 95% CI, 0.91-1.10; P = .91) (TABLE 2), with similar cumulative incidence curves (crude log-rank P = .69) (FIGURE 2). There was a similar lack of significant benefit for the secondary end points of total MI (3.9 and 4.2 events per 1000 person-years for multivitamin and placebo groups).
MULTIVITAMINS IN PREVENTION OF CVD IN MEN

Figure 2. Cumulative Incidence Rates of Major Cardiovascular Events, Total Myocardial Infarction, and Total Stroke by Randomized Multivitamin Assignment in the Physicians’ Health Study II

![Graph showing cumulative incidence rates of major cardiovascular events, total myocardial infarction, and total stroke by randomized multivitamin assignment.](image)

| Y-axis range shown in blue indicates cumulative incidence from 0 to 0.06. The reduction in the numbers at risk from 10 to 12 years reflects the 2 phases of Physicians’ Health Study II recruitment; men in the Physicians’ Health Study I initially enrolled in phase 1 starting in 1997 were followed up longer on average (mean, 13 years) than the men recruited in phase 2 starting in 1999 (mean, 10 years). |

In secondary analyses, there were fewer MI deaths among multivitamin users (HR, 0.61; 95% CI, 0.38-0.995; \( P = .048 \)). Among stroke subtypes, a daily multivitamin had no effect on either ischemic stroke (HR, 1.10; 95% CI, 0.92-1.30; \( P = .29 \)) or hemorrhagic stroke (HR, 1.08; 95% CI, 0.72-1.63; \( P = .69 \)). We found no significant effect of a daily multivitamin on rates of congestive heart failure (HR, 0.95; 95% CI, 0.83-1.09; \( P = .47 \)), angina (HR, 1.00; 95% CI, 0.91-1.09; \( P = .96 \)), and coronary revascularization (HR, 1.03; 95% CI, 0.94-1.13; \( P = .50 \)). Taking a daily multivitamin was not significantly associated with CVD mortality (5.0 and 5.1 events per 1000 person-years for multivitamin and placebo, respectively; HR, 0.95; 95% CI, 0.83-1.09; \( P = .47 \)). There were fewer death deaths among multivitamin users (HR, 0.94; 95% CI, 0.88-1.02; \( P = .13 \)), but this was not statistically significant.

In secondary analyses, exclusion of the first 2 or 5 years of follow-up did not alter the results for major cardiovascular events, total MI, or total stroke. Analyses adjusting for adherence either during follow-up or averaged over the whole trial, or adjusting for drop-ins, did not materially change the effect of multivitamin use on risk of major cardiovascular events.

Modifiers of the Effect Between Multivitamin Use and Major Cardiovascular Events

In subgroup analyses, we examined whether baseline clinical, lifestyle, familial, biochemical, and dietary risk factors for CVD, along with the other randomized PHS II interventions, modified the effect of a daily multivitamin on major cardiovascular events (eTable 1). There was a suggestion of a differential effect across age groups (\( P = .041 \) for interaction), with possible differences among men aged 50 to 59 years (HR, 1.27; 95% CI, 0.99-1.63; \( P = .06 \)) and men 70 years or older (HR, 0.91; 95% CI, 0.81-1.03; \( P = .14 \)). We found no other evidence of effect modification by baseline risk factors on major cardiovascular events (\( P > .05 \) for interaction for all). There also were no multiplicative or subadditive interactions of the multivitamin component with randomized vitamin C, vitamin E, or beta carotene treatment in PHS II (\( P > .05 \) for interaction for all).

We found no significant interaction by baseline CVD history status (\( P = .62 \) for interaction) for primary (HR, 1.02; 95% CI, 0.92-1.13) vs secondary (HR, 0.96; 95% CI, 0.75-1.22) prevention (TABLE 3). The cumulative incidence curves did not differ for primary (crude log-rank \( P = .71 \)) or secondary (crude log-rank \( P = .94 \)) prevention during up to 14 years of treatment and follow-up (FIGURE 3). The apparent lower rate of MI death among multivitamin users persisted (HR, 0.56; 95% CI, 0.33-0.95; \( P = .03 \)), whereas power was limited, with only 9 cases of MI death among those with baseline CVD (\( P = .31 \) for interaction). The effect of a daily multivitamin on total MI, total stroke, and other cardiovascular end points did not differ between men with and without baseline CVD (\( P > .05 \) for interaction for all).

Potential Adverse Effects of Daily Multivitamin Use

Besides the primary and secondary end points, we assessed several potential adverse effects of daily multivitamin use and found no significant effects on gastrointestinal tract symptoms (peptic ulcer, constipation, diarrhea, gastritis, and nausea), fatigue, drowsiness, skin discoloration, and migraine (\( P > .05 \) for all). Participants taking the multivitamin vs placebo were more likely to have skin rashes (2125 in the multivitamin
group and 2002 in the placebo group; HR, 1.07; 95% CI, 1.01-1.14; \(P = .03\)). In addition, findings were inconsistent for effects of daily multivitamin use on minor bleeding, suggesting the role of chance. There was a reduction in hematuria (1194 men in the multivitamin group and 1292 in the placebo group; HR, 0.91; 95% CI, 0.84-0.98; \(P = .02\)), an increase in epistaxis (1579 in the multivitamin group and 1451 in the placebo group; HR, 0.91; 95% CI, 0.84-0.98; \(P = .02\)), an increase in bruising or other bleeding (2786 in the multivitamin group and 2806 in the placebo group; HR, 0.99; 95% CI, 0.94-1.05; \(P = .77\)).

**COMMENT**

The PHS II represents to our knowledge the only large-scale, randomized, double-blind, placebo-controlled trial testing the long-term effects of a commonly available multivitamin on the prevention of chronic disease. We found that after more than a decade of daily multivitamin use among middle-aged and older men, daily multivitamin use did not reduce the primary end point of major cardiovascular events. Multivitamin use also did not reduce the risk of total MI; total, ischemic, or hemorrhagic stroke; cardiovascular death; or other cardiovascular end points, including congestive heart failure, angina, or coronary revascularization. The reduction observed in fatal MI \((P = .048)\) may have been attributable to chance.

### Table 3. Association Between Randomized Multivitamin Assignment and Risk of Major Cardiovascular Events and Mortality Among 13 887 Men Without and 754 Men With Baseline Cardiovascular Disease in the Physicians’ Health Study II\(^a,b\)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No Baseline History of CVD</th>
<th>Baseline History of CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Multivitamin (n = 6941)</td>
<td>Placebo (n = 6946)</td>
</tr>
<tr>
<td>Major cardiovascular events(^d)</td>
<td>745</td>
<td>728</td>
</tr>
<tr>
<td>Total MI(^e)</td>
<td>253</td>
<td>302</td>
</tr>
<tr>
<td>MI death</td>
<td>22</td>
<td>39</td>
</tr>
<tr>
<td>Total stroke(^f)</td>
<td>281</td>
<td>265</td>
</tr>
<tr>
<td>Stroke death</td>
<td>64</td>
<td>60</td>
</tr>
<tr>
<td>Ischemic stroke(^f)</td>
<td>239</td>
<td>213</td>
</tr>
<tr>
<td>Hemorrhagic stroke(^f)</td>
<td>40</td>
<td>43</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>319</td>
<td>335</td>
</tr>
<tr>
<td>Total mortality(^g)</td>
<td>1166</td>
<td>1233</td>
</tr>
</tbody>
</table>

**Abbreviations:** CVD, cardiovascular disease; HR, hazard ratio; MI, myocardial infarction.

\(^a\)Mean follow-up of 11.3 years for 13 887 men free of baseline cardiovascular disease through June 1, 2011.

\(^b\)Mean follow-up of 9.3 years for 754 men with baseline cardiovascular disease through June 1, 2011.

\(^c\)Adjusted for age, Physicians’ Health Study (PHS) cohort (original PHS I participant, new PHS II participant), and randomized treatment assignment (beta carotene, vitamin E, and vitamin C).

\(^d\)Defined as a composite end point consisting of the first of any of the following individual events: nonfatal MI, nonfatal stroke, and cardiovascular death. The individual events do not sum to the total because each individual analysis assesses the first event that occurs during follow-up. Therefore, a participant who for example has an MI then dies of MI death will be counted for both individual events but only once for the primary end point of major cardiovascular events.

\(^e\)Includes both nonfatal MI and fatal MI.

\(^f\)Stroke type was unknown for 2 men in the multivitamin group and 9 men in the placebo group among men with no history of CVD, and for 4 men in the multivitamin group and 7 men in the placebo group among men with a history of CVD.

\(^g\)Additionally stratified on baseline cancer.

### Figure 3. Cumulative Incidence Rates of Major Cardiovascular Events Among 13 887 Men With No Baseline History of Cardiovascular Disease (CVD) and 754 Men With a Baseline History of Cardiovascular Disease in the Physicians’ Health Study II

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MULTIVITAMINS IN PREVENTION OF CVD IN MEN

These findings on CVD and the decision to take a multivitamin should be considered in the context of initial nutritional status and other outcomes to be considered in this trial. The lack of an effect of a daily multivitamin on CVD appears consistent with what is known to date. Basic research indicates several mechanisms by which specific micronutrients contained in multivitamins may prevent CVD through modifications in platelet activity, reductions in thrombotic potential, and modifications in vascular reactivity. The consistent observation that people consuming greater amounts of fruits and vegetables tend to have lower rates of coronary heart disease and stroke supports the idea that combinations of vitamins at moderate doses may offer protection against CVD.

Observational data examining multivitamin use and CVD are sparse and inconsistent. Among 1,063,023 US adults from the Cancer Prevention Study II, men without CVD taking a multivitamin had an age-adjusted relative risk of death from ischemic heart disease of 0.91 (P = .001), attenuated on multivariate adjustment; similar results were noted for women. In 80,082 Nurses' Health Study participants, multivitamin use was associated with a significant reduction in coronary heart disease incidence (relative risk, 0.76; 95% CI, 0.65-0.90) after 14 years, a result further confirmed with additional follow-up. In a Swedish population-based case-control study in adults aged 45 to 70 years, the multivariate odds ratio of MI comparing regular users vs nonusers of multivitamins was 0.79 (95% CI, 0.63-0.98) among 2053 men and 0.66 (95% CI, 0.48-0.91) among 928 women.

In contrast, in the PHS II enrollment cohort of 83,936 initially healthy male physicians, there was no association between baseline multivitamin use and either CVD or coronary heart disease mortality. Among 161,808 Women's Health Initiative participants, of whom 41.5% took a multivitamin, there was no association between multivitamin use and the risk of CVD, MI, or stroke after a median of 8 years of follow-up. Last, there was also no association between multivitamin use and cardiovascualr mortality in 182,099 men and women from the Multiethnic Cohort Study after a mean follow-up of 11 years.

Several large trials of single agents or combinations of vitamins and minerals, generally at doses well above recommended dietary allowances and the multivitamin dose used in PHS II, have not demonstrated no effect on CVD. Primary prevention trials that have examined smaller combinations of vitamins and minerals, including the Linxian Chinese Cancer Prevention Trial and the Supplementation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) trial as well as secondary prevention trials such as the Heart Protection Study, found no effect on CVD. Other randomized trials have tested combinations of B vitamins with folic acid at high doses, particularly in the secondary prevention of CVD, but have found no protective effect. Moreover, the Women's Health Initiative calcium and vitamin D trial, testing vitamin D3 (400 IU/d) plus calcium (1000 mg/d), found no effect on CVD.

Baseline nutritional status among our physician participants remains a critical consideration in the interpretation of our findings. PHS II participants likely represent, on average, a well-nourished population who already have adequate or optimum intake levels of nutrients, for which supplementation may offer no additional benefit. However, the requirement for PHS II participants to avoid personal use of multivitamin supplements also lowered their in-trial intake of essential vitamins and minerals. Additional studies are needed to understand how the range of baseline nutritional status among PHS II participants and other populations may modify the effect of a daily multivitamin on cardiovascular end points. Further, several behavioral (eg, exercise, weight loss) and pharmacological (eg, lipid-lowering therapies) interventions are available to effectively lower CVD risk. This may make it difficult for vitamin supplements such as a multivitamin to meaningfully contribute toward risk reduction.

Several unique strengths of this trial include more than a decade of treatment and follow-up, high statistical power for our primary end point of major cardiovascular events, consistently good adherence in taking a daily multivitamin, and the inclusion of physician participants providing high-quality reporting of health information. We are unaware of any other long-term clinical trials that have tested use of a multivitamin in the prevention of CVD and other chronic diseases, highlighting the importance of trials like PHS II to test the efficacy of supplements and assess potential causality across a range of clinically relevant outcomes. In addition, we selected a commonly used multivitamin formulation when we initiated PHS II to increase the generalizability of our findings.

This trial also has important potential limitations to be considered. We relied on a specific, constant multivitamin formulation (eTable 2), which is one of many multivitamin formulations. There was an observed reduction in total cancer found for the PHS II multivitamin, suggesting that the formulation used may be adequate for cancer but not for CVD. This highlights the need to understand how essential vitamins and minerals may differentially interact and influence cardiovascular and cancer mechanisms, even at usual levels of vitamin and mineral intake. Although PHS II included more than a decade of treatment, an even longer duration of multivitamin use may be required to derive any cardiovascular benefits. Existing epidemiologic data can provide insight on this concept, while PHS II remains the only trial of its kind for which extended follow-up of CVD end points can provide important longer-term mechanistic perspectives.

The PHS II also may have limited generalizability, because our study population was confined to middle-aged and older, predominantly white, male physicians. Despite some multi-
vitamin nonadherence and drop-ins during PHS II, adjusted analyses adjusted for adherence and drop-ins reiterated a lack of effect of multivitamin use on major cardiovascular events. As with any trial, chance may be important when multiple hypotheses are tested; thus, cautious interpretation of secondary analyses is warranted. In addition, long-term multivitamin use may be more effective when initiated earlier in life to counter the initiation and progression of atherosclerosis that often begins at an earlier age.

After a mean of 11.2 years of treatment and follow-up in 14641 men, daily multivitamin supplementation in this trial did not reduce the risk of major cardiovascular events. These data do not support multivitamin use to prevent CVD, demonstrating the importance of long-term clinical trials of commonly used nutritional supplements. Whether to take a daily multivitamin requires consideration of an individual’s nutritional status, because the aim of supplementation is to prevent vitamin and mineral deficiency, plus consideration of other potential effects, including a modest reduction in cancer16 and other important outcomes in PHS II that will be reported separately.

Author Contributions: Drs Sesso and Gaziano had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study design and design: Sesso, Christen, Bubes, Manson, Glynn, Buring, Gaziano. Acquisition of data: Sesso, Bubes, Smith, MacFadyen, Schwartz, Manson, Buring, Gaziano. Analysis and interpretation of data: Sesso, Christen, Bubes, Manson, Glynn, Buring, Gaziano. Drafting of the manuscript: Sesso, Gaziano. Critical revision of the manuscript for important intellectual content: Christen, Bubes, Smith, MacFadyen, Schwartz, Manson, Glynn, Buring, Gaziano. Statistical analysis: Sesso, Bubes, Glynn, Gaziano. Obtained funding: Sesso, Buring, Gaziano. Administrative, technical, or material support: Sesso, Bubes, Smith, MacFadyen, Schwartz, Manson, Gaziano. Study supervision: Sesso, Bubes, MacFadyen, Schwartz, Gaziano.

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Data and Safety Monitoring Board: Voting members over the course of the Physicians’ Health Study (PHS) II trial included Lawrence Cohen, Roy Collins, Theodore Collins, Colin Co霜, Andrea LaCroix, Ross Prentice, and Nanette Wenger (chair); ex-officio members included Mary Francis Cotch, Jeffrey Cutler, Frederick Ferris, Jerome Fleg, Peter Greenwald, Natalie Kurlin, Howard Lebowitz, Pearl Rimer, Eleanor Schon, and Alan Zonderman.

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