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Multivitamin Use and the Risk of Cardiovascular Disease in Men[1,2]

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Abstract

Background: Although multivitamins are widely used by US adults, few prospective studies have investigated their association with the long- and short-term risks of cardiovascular disease (CVD).

Objective: The aim of this study was to investigate how multivitamin use is associated with the risk of CVD in initially healthy men at baseline.

Methods: We studied 18,530 male physicians aged ≥40 y from the Physicians' Health Study I cohort who were free of CVD and cancer at baseline (1982). All men provided a wide range of self-reported lifestyle and clinical factors plus intake of selected foods and dietary supplements. Cox proportional hazards models were used to calculate multivariable-adjusted HRs (95% CIs).

Results: During a mean follow-up of 12.2 y (total of 225,287 person-years), there were 1697 incident cases of major CVD (defined as nonfatal myocardial infarction, nonfatal stroke, and CVD death). In multivariable-adjusted analyses, no significant associations were observed among baseline multivitamin users compared with nonusers for the risk of major CVD events (HR: 0.94; 95% CI: 0.84, 1.05), whereas a self-reported duration of ≥20 y at baseline was associated with lower risk (HR: 0.56; 95% CI: 0.35, 0.90; *P*-trend = 0.05). Baseline multivitamin use was also significantly inversely associated with the risk of cardiac revascularization (HR: 0.86; 95% CI: 0.75, 0.98). Baseline use of multivitamins was not significantly associated with other CVD endpoints.

Conclusion: In this long-term prospective study in initially healthy men, multivitamin use for ≥20 y was associated with a lower risk of major CVD events. *J Nutr* 2016;146:1235–40.

Keywords: nutrition, multivitamin supplements, cardiovascular diseases, prevention, epidemiology cohort

Introduction

Multivitamins are dietary supplements widely used under the assumption that they improve or maintain health (1). The prevalence of multivitamin use has steadily increased during the past decade in the United States (2), and more than one-third of adults report currently taking a daily multivitamin (3). Multivitamin supplements usually include a wide range of low-dose vitamins and minerals to match RDAs and/or usual dietary intakes. Multivitamins may prevent atherosclerosis and cardiovascular disease (CVD)[9] by inhibiting oxidative damage of low-density lipoproteins (4), reducing blood concentrations of homocysteine (5), lowering concentrations of inflammatory markers (6), and improving endothelial function (7).

Given the widespread use of multivitamin supplements and that many individuals take them in the belief of improving or maintaining health, surprisingly few prospective studies have investigated the potential role of multivitamins in CVD prevention. Prospective studies that investigated the risk of CVD incidence or mortality have reported inconsistent results (8–13). However, because the majority of them investigated only CVD mortality and not comprehensively the association with various CVD endpoints it is difficult to draw any overall conclusion on whether multivitamins may or may not prevent CVD. In the Women's Health Study, there was detailed information on

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[9] Abbreviations used: CVD, cardiovascular disease; IHD, ischemic heart disease; MI, myocardial infarction; PHS, Physicians' Health Study; RCT, randomized controlled trial.

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multivitamin use and different CVD endpoints and it was observed that neither baseline nor time-varying multivitamin use was significantly associated with total CVD incidence; however, there was a nonsignificant inverse association in time-varying models of multivitamin use (12). Among studies that focused on ischemic heart disease (IHD) incidence or mortality, some observed an inverse association (14–17) and others showed no association (8, 12, 18, 19). Only 3 studies examined multivitamin use and stroke and each found no association (12, 14, 18). In addition, only 1 randomized controlled trial (RCT), the Physicians' Health Study (PHS) II, tested a common multivitamin formulation with all essential low-dose vitamins and minerals and reported no effect on total CVD but found a significant 39% reduction in fatal myocardial infarction (MI) (20). The aim of this study was to evaluate whether multivitamin use was associated with the incidence of major CVD events, including MI, stroke, and CVD death, in a long-term, prospective cohort study in men.

Methods

The PHS was a 2 × 2 factorial RCT testing the effects of aspirin and β-carotene on cancer and CVD. Starting in 1982, 22,071 male physicians aged 40–84 y and free of cancer and CVD were randomly assigned into the trial. At baseline, all of the men completed questionnaires asking about different lifestyle and clinical factors plus intake of selected food and dietary supplements. We excluded men with missing information on dietary supplement use or selected lifestyle, clinical, and dietary factors. Thus, 18,530 men were followed from baseline through the end of 1995, when the PHS I trial ended but before the beginning of the PHS II trial, which included a multivitamin arm (21). All of the men provided written informed consent, and the PHS I was approved by the Institutional Review Board of Brigham and Women's Hospital, Boston, Massachusetts.

Multivitamin use status and other covariates. At baseline, all of the men completed an enrollment questionnaire asking about lifestyle, clinical, and selected dietary factors, including 4 questions on dietary supplement use. Multivitamin supplement use was assessed by asking the participants "Have you ever taken multiple vitamins regularly?" with an option for "never," "past only," or "current." The questionnaire did not collect information on whether multivitamins included minerals. Those who reported current use were asked to provide the brand, years of use, and number of pills used per week. There were also questions on never, past, and current use for specific vitamin supplements of vitamins A, C, and E. At baseline, men also self-reported information on cardiovascular risk factors such as age, weight, height, smoking status, physical activity, and clinical factors including history of diabetes, hypercholesterolemia, hypertension, and alcohol use. BMI was calculated by dividing body weight (in kg) by square of height (in m). Vegetable intake was calculated by summing individual fruit and vegetables including broccoli, carrots, spinach, yellow squash, and tomatoes/tomato juice.

Ascertainment of CVD cases. Incident CVD events, including nonfatal MI, nonfatal stroke, and cardiac revascularization (coronary artery bypass grafting and/or percutaneous transluminal coronary angioplasty) were determined from self-reports on annual questionnaires. Reported CVD events were confirmed by an endpoints committee of physicians. For confirmation of MI, we used the WHO criteria, which use electrocardiogram criteria or abnormal concentrations of cardiac enzymes (22). Stroke was defined as a typical neurologic deficit, being sudden or rapid in onset and lasting >24 h, and classified as ischemic, hemorrhagic, or unknown. The evaluation of stroke in the PHS has previously shown excellent interobserver agreement (Cohen's $\kappa = 0.96$) for stroke subtypes (23, 24). Major CVD events were defined as first nonfatal MI, nonfatal stroke, or CVD death. We also examined the first occurrence of individual CVD events [MI, stroke (total, ischemic, and hemorrhagic), CVD death, cardiac revascularization, and IHD]. IHD included first events of nonfatal MI, cardiac revascularization, and IHD death. The identification of deaths was done through reports from family members, postal authorities, and by the National Death Index.

Statistical analyses. All statistical analyses were performed with SAS version 9.3 (SAS Institute). Men were categorized at baseline as *1*) no current use of multivitamins (including never and past) and *2*) current use of multivitamins. We also separately compared never, past, and current multivitamin users. To investigate the frequency and duration of multivitamin use, we further categorized current users into <4 or ≥4 pills/wk and <10, 10 to <20, or ≥20 y of multivitamin use, respectively. To assess trends across categories of duration, we used the median value of each category to create a single continuous variable. We compared baseline characteristics by calculating age-standardized mean values for continuous variables and percentages for categorical variables. We used Cox proportional hazards models to calculate HRs (95% CIs) (25) with the use of the PHREG procedure. HRs adjusted for baseline age (y, continuous), randomly assigned treatment (aspirin and β-carotene), BMI (kg/m^2, continuous), smoking status (never, past, or current), vigorous exercise (rarely/never, <1 time/wk, 1–3 times/wk, or ≥4 times/wk), and alcohol consumption (rarely/never, 1–3 drinks/mo, 1–6 drinks/wk, or ≥1 drinks/d). In a second model, we further adjusted for family history of MI, diabetes history, hypertension history, hypercholesterolemia history, and fruit and vegetable intake (continuous). We tested the proportional hazards assumption by entering the product of baseline multivitamin use and the natural logarithm of time in the model, and there was no evidence of violation of this assumption.

To investigate whether the association between multivitamin use and major CVD events was modified by potential CVD risk factors, we performed stratified analyses by age (<70 or ≥70 y), BMI (<25 or ≥25), smoking status (never, past, or current), history of diabetes (yes or no), hypertension (yes or no), hypercholesterolemia (yes or no), vegetable intake (<3 or ≥3 servings/d), and randomly assigned aspirin (yes or no) and β-carotene (yes or no) treatment. Multiplicative interactions were tested by using Wald chi-square tests.

Results

Among 18,530 men included in our analyses, 3790 (20%) were currently taking a multivitamin supplement at baseline in 1982. In **Table 1**, we present the baseline characteristics according to multivitamin use status. Men reporting current use were more likely to smoke, more likely to be physically active, and less likely to consume alcohol than were men not taking multivitamins. We also investigated baseline characteristics according to never, past, and current use of multivitamins and observed that never and past users were similar in their characteristics and differed from current users with regard to smoking and alcohol consumption as above.

TABLE 1 Age-adjusted characteristics at baseline (1982) among 18,530 men in the Physicians' Health Study[1]

	Baseline multivitamin use	
	No (n = 14,740)	Yes (n = 3790)
Age, y	52.8 ± 9.1	53.2 ± 9.0
Current smokers, %	10	12
Vigorous exercise (≥1 time/wk), %	72	77
BMI, kg/m^2	24.8 ± 2.8	24.6 ± 2.8
Parental history of myocardial infarction, %	10	9
History of diabetes, %	3	4
History of hypercholesterolemia, %	12	12
History of hypertension, %	23	25
Alcohol use (≥1 drink/mo),[2] %	77	73
Vegetable intake, servings/d	2.4 ± 1.2	2.5 ± 1.3

[1] Values are means ± SDs or percentages and were standardized to the age distribution of the study population. Values were not age adjusted.
[2] Ethanol content estimated as 13.2 g for 360 mL (12 ounces) of beer, 10.8 g for 120 mL (4 ounces) of red or white wine, and 15.1 g for 45 mL of liquor.

During a mean follow-up of 12.2 y (225,287 person-years), we identified 1697 cases of major CVD events, 815 cases of MI (101 MI deaths), 670 cases of stroke (569 ischemic, 93 hemorrhagic, and 8 unknown), and 566 cases of CVD death. We also identified 1400 cases of cardiac revascularization and 1706 cases of IHD (including MI and cardiac revascularization).

The multivariable-adjusted association between current multivitamin use at baseline compared with no use did not substantially differ from the age-adjusted association. No significant associations were observed for major CVD events (HR: 0.94; 95% CI: 0.84, 1.05) or for MI, total stroke, ischemic stroke, hemorrhagic stroke, and CVD death (**Table 2**). However, baseline multivitamin use was significantly and inversely associated with the risk of cardiac revascularization (HR: 0.86; 95% CI: 0.75, 0.98) and IHD (HR: 0.89; 95% CI: 0.79, 1.00). When investigating the duration of multivitamin use, we found that multivitamin use for ≥20 y compared with no use was inversely associated with total CVD (HR: 0.56; 95% CI: 0.35, 0.90; *P*-trend = 0.05), total stroke (HR: 0.43; 95% CI: 0.19, 0.96; *P*-trend = 0.20), cardiac revascularization (HR: 0.35; 95% CI: 0.17, 0.74; *P*-trend = 0.10), and IHD (HR: 0.43; 95% CI: 0.24, 0.77; *P*-trend = 0.08) (**Table 3**). The number of multivitamin pills used (≥4 or <4 pills/wk) compared with no use was not associated with the risk of major CVD events or individual CVD components (data not shown).

We further investigated whether the association between multivitamin use and CVD was modified by other potential CVD risk factors such as age, BMI, smoking, history of diabetes, history of hypertension, history of hypercholesterolemia, vegetable intake, and randomized treatment assignment (**Table 4**). In these analyses, we found evidence that the association was modified by baseline history of diabetes (*P*-interaction = 0.009), in which an inverse association was observed among men with no history (HR: 0.88; 95% CI: 0.78, 1.00) and a higher risk was observed among men with a history of diabetes (HR: 1.43; 95% CI: 1.05, 1.96). We also investigated whether there was any effect modification by the above-mentioned factors for the association between multivitamin use and IHD. The association was consistent across categories of age, smoking, history of diabetes, history of hypertension, history of hypercholesterolemia, vegetable intake, and randomized treatment assignment. However, a significant interaction was observed for BMI (*P*-interaction = 0.03), in which multivitamin use was inversely associated with the risk of IHD (HR: 0.77; 95% CI: 0.67, 0.94) among men with a BMI ≥25, and no association was observed among men with a BMI <25.

TABLE 2 Baseline multivitamin use and HRs (95% CIs) of CVD among 18,530 men from the Physicians' Health Study followed from 1982 to 1995[1]

	No use (*n* = 14,740)	Multivitamin use (*n* = 3790)
Major cardiovascular events		
Cases, *n*	1293	404
Age-adjusted HR	1.00 (ref)	0.96 (0.86, 1.08)
+ Lifestyle factors[2]	1.00 (ref)	0.96 (0.85, 1.07)
+ Lifestyle, clinical, dietary factors[3]	1.00 (ref)	0.94 (0.84, 1.05)
Myocardial infarction		
Cases, *n*	643	172
Age-adjusted HR	1.00 (ref)	0.88 (0.75, 1.05)
+ Lifestyle factors[2]	1.00 (ref)	0.89 (0.75, 1.05)
+ Lifestyle, clinical, dietary factors[3]	1.00 (ref)	0.88 (0.74, 1.04)
Myocardial infarction death		
Cases, *n*	74	27
Age-adjusted HR	1.00 (ref)	1.09 (0.70, 1.70)
+ Lifestyle factors[2]	1.00 (ref)	1.06 (0.68, 1.66)
+ Lifestyle, clinical, dietary factors[3]	1.00 (ref)	1.04 (0.66, 1.62)
Total stroke		
Cases, *n*	502	168
Age-adjusted HR	1.00 (ref)	0.97 (0.82, 1.16)
+ Lifestyle factors[2]	1.00 (ref)	0.96 (0.81, 1.15)
+ Lifestyle, clinical, dietary factors[3]	1.00 (ref)	0.94 (0.79, 1.13)
Ischemic stroke		
Cases, *n*	426	143
Age-adjusted HR	1.00 (ref)	0.97 (0.80, 1.18)
+ Lifestyle factors[2]	1.00 (ref)	0.96 (0.79, 1.16)
+ Lifestyle, clinical, dietary factors[3]	1.00 (ref)	0.94 (0.77, 1.14)
Hemorrhagic stroke		
Cases, *n*	73	20
Age-adjusted HR	1.00 (ref)	0.83 (0.50, 1.36)
+ Lifestyle factors[2]	1.00 (ref)	0.83 (0.50, 1.37)
+ Lifestyle, clinical, dietary factors[3]	1.00 (ref)	0.83 (0.50, 1.36)
CVD death		
Cases, *n*	408	158
Age-adjusted HR	1.00 (ref)	1.09 (0.91, 1.31)
+ Lifestyle factors[2]	1.00 (ref)	1.08 (0.89, 1.30)
+ Lifestyle, clinical, dietary factors[3]	1.00 (ref)	1.04 (0.87, 1.26)
Cardiac revascularization		
Cases, *n*	1121	279
Age-adjusted HR	1.00 (ref)	0.86 (0.76, 0.99)
+ Lifestyle factors[2]	1.00 (ref)	0.87 (0.76, 0.99)
+ Lifestyle, clinical, dietary factors[3]	1.00 (ref)	0.86 (0.75, 0.98)
Ischemic heart disease		
Cases, *n*	1350	356
Age-adjusted HR	1.00 (ref)	0.89 (0.79, 1.00)
+ Lifestyle factors[2]	1.00 (ref)	0.89 (0.80, 1.01)
+ Lifestyle, clinical, dietary factors[3]	1.00 (ref)	0.89 (0.79, 1.00)

[1] CVD, cardiovascular disease; ref, reference.
[2] Adjusted for age at baseline, randomly assigned aspirin and β-carotene treatment, BMI, smoking status, vigorous exercise, and alcohol consumption.
[3] Additionally adjusted for family history of myocardial infarction, diabetes history, hypertension history, hypercholesterolemia history, and vegetable intake.

Discussion

In this prospective cohort study in male physicians, there was no association between current multivitamin use and the risk of major CVD events, MI, stroke, or CVD death. However, multivitamin use was significantly associated with a 14% lower risk of cardiac revascularization. In addition, there were potentially stronger reductions in major CVD events among men who reported ≥20 y of multivitamin use with a significant trend; however, these observations should be interpreted with caution due to the low number of cases.

To the best of our knowledge, only 1 previous trial investigated the effect of a wide-spectrum, low-dose multivitamin supplement on CVD incidence (20). The PHS II, which enrolled 14,641 men and followed them for 11.2 y, reported no effect between random assignment for multivitamin use and total major CVD events, which is consistent with our findings. However, there was some evidence that the effect between randomly assigned multivitamin use and total CVD may be modified by age (*P*-interaction = 0.04), with a stronger effect among men aged ≥70 y. In our analyses, we did not see any effect modification by age. However, this could be explained by

TABLE 3 Self-reported duration of multivitamin use at baseline and HRs (95% CIs) of CVD among men from the Physicians' Health Study followed from 1982 to 1995[1]

	Duration of multivitamin use				
	No use	<10 y	10 to <20 y	≥20 y	*P*-trend
Major cardiovascular events					
Cases	1293	211	67	18	
Age-adjusted HR	1.00 (ref)	0.95 (0.82, 1.10)	0.96 (0.75, 1.23)	0.58 (0.37, 0.93)	0.12
+ Lifestyle factors[2]	1.00 (ref)	0.95 (0.82, 1.10)	0.95 (0.74, 1.22)	0.58 (0.36, 0.92)	0.10
+ Lifestyle, clinical, dietary factors[3]	1.00 (ref)	0.94 (0.81, 1.09)	0.91 (0.71, 1.17)	0.56 (0.35, 0.90)	0.05
Myocardial infarction					
Cases	643	98	28	7	
Age-adjusted HR	1.00 (ref)	0.93 (0.75, 1.15)	0.91 (0.62, 1.33)	0.54 (0.25, 1.13)	0.17
+ Lifestyle factors[2]	1.00 (ref)	0.94 (0.76, 1.16)	0.92 (0.63, 1.35)	0.54 (0.25, 1.13)	0.19
+ Lifestyle, clinical, dietary factors[3]	1.00 (ref)	0.93 (0.75, 1.15)	0.89 (0.61, 1.30)	0.53 (0.25, 1.13)	0.14
Total stroke					
Cases	502	86	31	6	
Age-adjusted HR	1.00 (ref)	0.96 (0.77, 1.21)	1.05 (0.73, 1.51)	0.45 (0.20, 1.00)	0.36
+ Lifestyle factors[2]	1.00 (ref)	0.96 (0.76, 1.20)	1.02 (0.71, 1.47)	0.44 (0.19, 0.98)	0.29
+ Lifestyle, clinical, dietary factors[3]	1.00 (ref)	0.95 (0.75, 1.19)	0.97 (0.67, 1.40)	0.43 (0.19, 0.96)	0.20
CVD death					
Cases	408	76	24	9	
Age-adjusted HR	1.00 (ref)	1.03 (0.81, 1.32)	0.95 (0.63, 1.44)	0.80 (0.41, 1.55)	0.63
+ Lifestyle factors[2]	1.00 (ref)	1.02 (0.80, 1.30)	0.93 (0.62, 1.41)	0.80 (0.41, 1.55)	0.55
+ Lifestyle, clinical, dietary factors[3]	1.00 (ref)	1.00 (0.78, 1.28)	0.89 (0.59, 1.36)	0.73 (0.38, 1.42)	0.36
Cardiac revascularization					
Cases	1121	146	52	7	
Age-adjusted HR	1.00 (ref)	0.81 (0.68, 0.96)	1.07 (0.81, 1.41)	0.34 (0.16, 0.71)	0.09
+ Lifestyle factors[2]	1.00 (ref)	0.81 (0.69, 0.97)	1.08 (0.82, 1.43)	0.34 (0.16, 0.72)	0.11
+ Lifestyle, clinical, dietary factors[3]	1.00 (ref)	0.81 (0.68, 0.96)	1.06 (0.80, 1.40)	0.35 (0.17, 0.74)	0.10
Ischemic heart disease					
Cases	1350	194	63	11	
Age-adjusted HR	1.00 (ref)	0.88 (0.76, 1.03)	1.02 (0.79, 1.31)	0.41 (0.23, 0.75)	0.08
+ Lifestyle factors[2]	1.00 (ref)	0.89 (0.77, 1.04)	1.03 (0.80, 1.33)	0.42 (0.23, 0.76)	0.10
+ Lifestyle, clinical, dietary factors[3]	1.00 (ref)	0.88 (0.76, 1.03)	1.00 (0.78, 1.30)	0.43 (0.24, 0.77)	0.08

[1] CVD, cardiovascular disease; ref, reference.
[2] Adjusted for age at baseline, randomly assigned aspirin and β-carotene treatment, BMI, smoking status, vigorous exercise, and alcohol consumption.
[3] Additionally adjusted for family history of myocardial infarction, diabetes history, hypertension history, hypercholesterolemia history, and vegetable intake.

the low number of cases, limiting the statistical power to detect such associations. Moreover, in the PHS II trial, a significant 39% lower risk was observed for fatal MI (20), which is not consistent with our observations of no association.

Only 1 previous study, to our knowledge, investigated the association between multivitamin use and total CVD incidence. This study, which was performed in the Women's Health Study cohort and included 37,193 women followed for 16.2 y, did not observe an association between baseline multivitamin use and total CVD, defined as nonfatal MI, nonfatal stroke, or CVD death (12).

Most prospective cohort studies that investigated the association between multivitamin use and CVD mortality observed no association (8–10, 12), which is consistent with our findings. In contrast, 1 other US study found a 16% lower risk of CVD mortality in women and men who had a 10-y average frequency of 6–7 multivitamin pills/wk compared with nonusers (11). Moreover, the NHANES III study with detailed information on supplement use reported a 44% significantly lower CVD mortality risk among women and no significant associations among men (13).

In our analyses, we observed a significant 11% lower risk of IHD defined as incident MI or cardiac revascularization. This is consistent with previous prospective studies that investigated multivitamin use in association with IHD (14–17). In a prospective cohort study in 31,671 Swedish women followed for 10.2 y, multivitamin supplement use was inversely associated with incident MI (15). In addition, in the Nurses' Health Study, regular multivitamin use was significantly associated with a 24% lower risk of incident IHD among women (16). Another US prospective study in women and men found that the combined use of multivitamins and supplements of vitamin A, C, or E was associated with a 25% lower risk of IHD mortality (14). Moreover, the Women's Health Initiative in >90,000 American women observed no overall association with incident MI; however, a significant inverse association was observed for multivitamins containing vitamin and mineral amounts >200% of RDAs (18). Only a few prospective cohort studies examined the association between multivitamin supplement use and the risk of stroke (12, 14, 18). All of the studies reported no associations, which is in agreement with our observations.

Although our results suggest that continuous multivitamin use over a longer duration may be significantly associated with a lower risk of major CVD, the low number of cases supporting these results indicates that they should be interpreted with caution. A lower risk of IHD associated with long-term multivitamin use for ≥20 y is consistent with findings in men of the Health Professionals Follow-Up Study, in whom ≥10 y of

TABLE 4 Multivitamin supplement use and major cardiovascular disease events by subgroups of men from the Physicians' Health Study followed from 1982 to 1995

	Events, *n*			
	No use	Multivitamin use	Multivitamin use vs. no use[1]	*P*-interaction
Age, y				
<70	1051	293	0.96 (0.85, 1.10)	
≥70	242	111	0.87 (0.69, 1.09)	0.43
BMI, kg/m^2				
<25	614	210	0.95 (0.81, 1.11)	
≥25	679	194	0.94 (0.80, 1.10)	0.36
Smoking status				
Never smokers	540	163	0.94 (0.79, 1.13)	
Past smokers	528	178	0.96 (0.81, 1.15)	
Current smokers	225	63	0.86 (0.65, 1.14)	0.39
History of diabetes				
No	1185	336	0.88 (0.78, 1.00)	
Yes	108	68	1.43 (1.05, 1.96)	0.009
History of hypertension				
No	701	212	1.03 (0.88, 1.20)	
Yes	592	192	0.88 (0.74, 1.03)	0.10
History of hypercholesterolemia				
No	1066	336	0.96 (0.84, 1.08)	
Yes	227	68	0.86 (0.65, 1.13)	0.45
Vegetables, servings/d				
<3	921	278	0.96 (0.83, 1.10)	
≥3	372	126	0.90 (0.73, 1.11)	0.62
Aspirin arm				
No	669	202	0.89 (0.76, 1.05)	
Yes	624	202	1.00 (0.85, 1.17)	0.30
β-Carotene arm				
No	657	207	0.94 (0.80, 1.10)	
Yes	636	197	0.94 (0.80, 1.11)	0.86

[1] Values are multivariate HRs (95% CIs) adjusted for age at baseline, randomly assigned aspirin and β-carotene treatment, BMI, smoking status, vigorous exercise, alcohol consumption, family history of myocardial infarction, diabetes history, hypertension history, hypercholesterolemia history, and vegetable intake.

self-reported multivitamin use at baseline was associated with a significant 25% reduced risk of IHD (17). Another study in American women and men found that ≥5 y of combined use of multivitamins and supplements of vitamin A, C, or E was inversely associated with IHD mortality (14). In the Swedish Mammography Cohort, a stronger inverse association for MI was also observed among women who used multivitamins for ≥5 y (15). Finally, in the Women's Health Study, a longer duration of reported multivitamin use at baseline was not associated with the risk of major CVD, MI, stroke, or CVD death (12).

The precise mechanisms through which long-term multivitamin use may be more strongly associated with CVD are unclear from observational studies and may reflect residual confounding by healthy behaviors. Alternatively, a longer period of time may be necessary for multivitamins to affect the long-term development of CVD.

We observed that the association between multivitamin use and the risk of major CVD events was modified by baseline history of diabetes, with a reduced risk of major CVD among nondiabetic men and an increased risk among diabetic men. Effect modification by diabetes may be explained by the possibility that men might start taking multivitamins after they are diagnosed with diabetes and therefore a stronger inverse association is observed when restricting analyses to nondiabetic men.

Multivitamins are supplements that typically include a wide range of vitamins and minerals in doses that correspond to those found in the usual diet. Many of the included vitamins and minerals may prevent CVD development through several hypothesized mechanisms. Low-density lipoproteins transport antioxidants such as α-tocopherol and β-carotene, which may inhibit oxidative damage of these particles (4). In vitro studies have shown that vitamin C may also protect low-density lipoproteins from oxidation by interacting with α-tocopherol and β-carotene (26). Folate, vitamin B-6, and vitamin B-12 are important components in homocysteine metabolism and deficiencies of these vitamins may therefore contribute to atherosclerotic and thrombotic events (5). Vitamin D deficiency may cause CVD mediated through mechanisms involved in atherosclerosis and endothelial dysfunction (6). Magnesium is a cofactor included in antioxidant enzymes and therefore of importance in preventing oxidative stress and may also act through other mechanisms involving endothelial and vascular smooth cells (7). Endothelial selenoproteins regulate vascular tone, cell adhesion, and apoptosis and may also be involved in inflammatory processes and atherogenesis (27).

Strengths of our study include the use of a large prospective cohort with high-quality information on different lifestyle and clinical factors. We also had detailed data on various endpoints, including MI, stroke, CVD death, and cardiac revascularization,

allowing us to comprehensively examine a potential role of multivitamins in CVD prevention. Moreover, we had minimal loss to follow-up, with morbidity and mortality follow-up rates >99%.

There are also important limitations to our study. We investigated only self-reported multivitamin use at baseline and did not account for time-varying multivitamin use. Moreover, the definition of multivitamin use is extremely broad and includes supplements with varying doses and included vitamins and minerals, which complicates the interpretation of study results and the comparability of findings across studies. Next, the present study included male physicians, who may differ from the general population in terms of lifestyle and clinical risk factors as well as baseline nutritional status, which affects generalizability to other populations. As in any observational study we cannot exclude the possibility that measurement error in self-reported multivitamin use may have biased our results toward the null. In addition, our observed findings may be driven by uncontrolled and residual confounding from other healthy behavior–related factors. It was previously observed in a cross-sectional study in PHS II participants that self-reported use of multivitamins was positively associated with healthy lifestyle and dietary factors as well as with having a history of cancer and cardiovascular intermediates such as hypercholesterolemia and hypertension (28). A well-designed RCT may alleviate concerns about residual and unmeasured confounding. However, the generalizability of the study results and the ability to test a range of exposures may be limited. In contrast, an observational study may allow for a broader exploration of multivitamin doses and usage habits. Thus, observational studies and RCTs can complement each other and be used together to help determine the potential benefits and risks of daily multivitamin use in adults.

In conclusion, in this prospective study in men, we observed that baseline multivitamin use was associated with a lower risk of cardiac revascularization. No association was observed with major CVD events, including MI, stroke, or CVD death. However, men who reported ≥20 y of use at baseline had a lower risk of major CVD events. Future large-scale RCTs and focused observational studies with detailed information on multivitamin use are needed to confirm or refute our findings.

Acknowledgments

SR and HDS designed the research; SR, JEB, JMG, and HDS conducted the research; SR, PMR, RJG, JEB, JMG, and HDS analyzed the data; SR and HDS wrote the manuscript; and HDS had primary responsibility for final content. All authors read and approved the final manuscript.

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