Multivitamin use and cardiovascular disease in a prospective study of women[1–3]

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ABSTRACT

Background: Although multivitamins are widely used, there are limited prospective studies investigating their association with both long- and short-term risk of cardiovascular disease (CVD).

Objective: The objective was to investigate how multivitamin use is associated with the long- and short-term risk of CVD.

Design: A prospective cohort study was conducted of 37,193 women from the Women's Health Study aged ≥45 y and free of CVD and cancer at baseline who were followed for an average of 16.2 y. At baseline, women self-reported a wide range of lifestyle, clinical, and dietary factors. Women were categorized into *1*) no current use and *2*) current use of multivitamins. Duration and updated measures over the course of the follow-up to address short-term effects were also considered. Women were followed for major CVD events, including myocardial infarction (MI), stroke, and CVD death.

Results: During the follow-up, 1493 incident cases of CVD [defined as myocardial infarction (MI), stroke, and CVD death] occurred. In multivariable analyses, multivitamin use compared with no use was not associated with major CVD events (HR: 1.01; 95% CI: 0.89, 1.15), MI (HR: 1.04; 95% CI: 0.84, 1.27), stroke (HR: 0.99; 95% CI: 0.83, 1.18), or CVD death (HR: 1.10; 95% CI: 0.84, 1.45). A nonsignificant inverse association was observed between baseline multivitamin use and major CVD events among women aged ≥70 y (*P*-interaction = 0.04) and those consuming <3 servings/d of fruit and vegetables (*P*-interaction = 0.01). When updating information on multivitamin use during the course of follow-up, no associations were observed for major CVD events (HR: 0.91; 95% CI: 0.82, 1.02), MI (HR: 0.89; 95% CI: 0.74, 1.06), stroke (HR: 0.91; 95% CI: 0.78, 1.06), and CVD death (HR: 0.91; 95% CI: 0.71, 1.16).

Conclusions: In this study of middle-aged and elderly women, neither baseline nor time-varying multivitamin use was associated with the long-term risk of major CVD events, MI, stroke, cardiac revascularizations, or CVD death. Additional studies are needed to clarify the role of multivitamins on CVD. *Am J Clin Nutr* 2015;101:144–52.

Keywords multivitamin, cardiovascular disease, cohort, dietary supplements, epidemiology

INTRODUCTION

Cardiovascular disease (CVD)[4] is the most common cause of death worldwide, and it is therefore important to find preventive strategies against CVD development. Multivitamin supplements have been hypothesized to help prevent CVD because they include a wide range of lower-dose vitamins and minerals. The micronutrient doses in multivitamins tend to correspond to recommended dietary allowances and usual dietary intakes. Hypothesized pathways through which these vitamins and minerals may prevent CVD include inhibition of oxidative modification of low-density lipoproteins (1), lowering homocysteine concentrations (2), decreasing inflammation (3), and other mechanisms involving endothelial and vascular smooth cells (4). Despite the uncertainty of its purported benefits, the prevalence of multivitamin use has steadily increased during the past decade in the United States (5), with at least one-third of adults currently taking a daily multivitamin (6).

The Physicians' Health Study II, the only randomized controlled trial (RCT) testing daily multivitamins on total CVD events, found no effect on total CVD; however, a significant 39% reduction in fatal myocardial infarction (MI) was observed (7). Moreover, there was evidence of a significant effect modification by age, with a lower HR for total CVD among men aged ≥70 than among those <70 y (*P*-interaction by age = 0.04). In the absence of other randomized trials testing multivitamin supplements, we must rely on limited and inconsistent epidemiologic studies that have investigated how multivitamin use is associated with the risk of CVD events (8–11). Observational studies have mainly focused on coronary artery disease (CAD) (8, 12–18), with many reporting an inverse association (12–16), whereas others showed no association (8, 17, 18). To the best of our knowledge, only 2 prospective cohort studies have examined the association between multivitamin supplement use and stroke,

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[4] Abbreviations used: CAD, coronary artery disease; CVD, cardiovascular disease; FFQ, food-frequency questionnaire; MI, myocardial infarction; RCT, randomized controlled trial; WHS, Women's Health Study.

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both reporting no association (13, 17). To fully understand the studies and RCTs in both men and women, with data on dietary supplement use at multiple time points are needed.

We aimed to evaluate how short- and long-term multivitamin use was associated with the incidence of major CVD events, including MI, stroke, and CVD death in a long-term prospective cohort of middle-aged and older women.

SUBJECTS AND METHODS

The Women's Health Study (WHS) is a completed, 2 × 2 factorial trial of low-dose aspirin and vitamin E in the primary prevention of CVD and cancer among 39,876 female US health professionals aged ≥45 y who were postmenopausal or not intending to become pregnant (19–21). Women with no history of myocardial infarction (MI), stroke, transient ischemic attack, or cancer (except nonmelanoma skin cancer) were randomized into the WHS starting in 1992. At baseline, all WHS participants completed a questionnaire asking about their medical history and lifestyle factors. Women also completed a 131-item validated semiquantitative food-frequency questionnaire (FFQ), of whom 39,310 (98.6%) women responded. We excluded women with a history of MI, stroke, or transient ischemic attack at baseline (n = 13); missing information on dietary supplement use (n = 692) or lifestyle factors (n = 976) considered as covariates, and women who completed an insufficient number of food items or had a total energy intake outside the range of 600 to 3500 kcal/d (n = 1002). Thus, 37,193 women were followed-up from baseline through 2012. The trial ended in March 2004, and women who were still alive and eligible and willing to be followed on an observational basis (89%) were included in the observational follow-up. Written informed consent was obtained from all participants, and this research was approved by the institutional review board of Brigham and Women's Hospital, Boston, MA.

Multivitamin use status

Information on dietary supplement use and other dietary factors were collected from the enrollment questionnaires and the 131-item FFQ. Information was collected on the status, duration, and frequency of multivitamin use. We also collected information on the use of the following individual supplements: vitamin B-6, vitamin C, vitamin D, B-complex vitamins, folic acid, niacin, Brewer's yeast, selenium, calcium, iron, zinc, iodine, magnesium, cod liver oil, and other fish oil. Women were also asked to report current, past, and never use of multivitamins on a yearly basis on all annual questionnaires (except year 6) during both the randomized and observational period of the WHS follow-up. Information about dietary supplement use has been validated in women from the Nurses' Health Study (22) and men from the Health Professionals Follow-Up Study (23).

Other covariates

At baseline, women reported information on risk factors such as age, weight, height, smoking status, physical activity, postmenopausal status, postmenopausal hormone use, and clinical factors, including history of diabetes, hypercholesterolemia, and hypertension. Women also reported on a 131-item FFQ how often, on average, they consumed different foods or beverages during the past year by using 9 predefined response categories. BMI was calculated by dividing body weight (in kg) by square of height (in m). Total alcohol intake was calculated by summing alcohol content from beer, wine, and liquor consumed. Fruit and vegetable intake was calculated by summing individual fruit and vegetables. Other nutrients considered included total fiber (g/d), saturated fat (g/d), and omega-3 (n−3) fatty acids (g/d), which were each energy-adjusted by using the residual method (24).

Ascertainment of cardiovascular disease cases

Information about newly diagnosed CVD events, including nonfatal MI, nonfatal stroke, and cardiac revascularization (coronary artery bypass grafting and/or percutaneous transluminal coronary angioplasty), were collected from questionnaires sent to participants every 6 mo during the first year and annually thereafter. Confirmation of endpoints was done by an Endpoint Committee consisting of physicians. The diagnosis of MI was confirmed according to the World Health Organization criteria, electrocardiographic criteria, or abnormal concentrations of cardiac enzymes (25). A stroke event was defined as a typical neurological deficit, being sudden or rapid in onset and lasting >24 h. Strokes were also classified according to major subtype (ischemic, hemorrhagic, or unknown) with excellent interobserver agreement (Cohen's κ = 0.96) (26). CAD included a first event of nonfatal MI, nonfatal cardiac revascularization, and CAD death. Cardiac revascularization procedures were confirmed by hospital records. Deaths of women were identified through reports from family members, from postal authorities, and by the National Death Index.

Statistical analyses

All statistical analyses were performed with SAS 9.3 (SAS Institute Inc.). We categorized women into no and current use of multivitamins. We investigated the frequency and duration of multivitamin use per day by categorizing women into no current use, <6 pills/wk, or ≥6 pills/wk and no use, <10 y, or ≥10 y. In sensitivity analyses, we further categorized women into no supplement use, use of multivitamin supplements only, use of multivitamins with other individual vitamin/mineral supplements, and use of other individual vitamin/mineral supplement only. Age-standardized mean values for continuous variables and percentages for categorical variables were calculated and compared between groups of supplement use. We used the Cox proportional hazards models to calculate HRs with 95% CIs (27) by using the PHREG procedure. All HRs were adjusted for age at baseline (y, continuous), BMI (in kg/m^2, continuous), smoking status (never, past, current <15 cigarettes/d, or ≥15 cigarettes/d), vigorous exercise (rarely/never, <1 time/wk, 1–3 times/wk, or ≥4 times/wk), postmenopausal status (no, yes, biologically uncertain, or unclear), and hormone replacement therapy use (never, past, or current). In a second set of models, we also adjusted for family history of MI, diabetes history, hypertension history, and hypercholesterolemia history. In a third set of models, we adjusted for alcohol consumption (rarely/never, 1–3 drinks/mo, 1–6 drinks/wk, or ≤1 drink/d), fruit and vegetable intake (servings/d, continuous), and intakes of fiber (g/d, continuous), SFAs (g/d, continuous), and n–3 fatty acids (g/d, continuous).

We next investigated whether the association between multivitamin use and major cardiovascular events was modified by potential CVD risk factors by performing stratified analysis by categories of age (<70 y or ≥70 y); BMI (<25 or ≥25); smoking status (never, past, or current); history of diabetes (no or yes), hypertension (no or yes), and hypercholesterolemia (no or yes); fruit and vegetable intake (<3, 3 to <7, or ≥7 servings/d); and treatment arm of aspirin, β-carotene, and vitamin E (no or yes). Multiplicative interactions were tested by using Wald chi-square tests. Furthermore, the 3-factor interactions between multivitamin use and age in combination with intakes of fruit and vegetables (<3, 3 to <7, or ≥7 servings/d), dairy products [<1.6 (median), ≥1.6 servings/d], dietary fiber [<18.2 (median), ≥18.2 mg/d], n−3 fatty acids [<1.4 (median), ≥1.4 mg/d], or folate [<349 (median), ≥349 μg/d] and the risk of major CVD events were investigated.

To investigate the relation between the short-term use of multivitamin supplements and incident major CVD events, a time-varying Cox model, was constructed by using information on current multivitamin use that was updated at each follow-up, and the most recent multivitamin use measurement was used to estimate risk in the following time period. In multivariable models, we also updated information on other covariates such as history of diabetes, hypertension, and hypercholesterolemia. If data were missing at a given time point, the last observation was carried forward. We further investigated whether the association between time-varying multivitamin use and major CVD was modified age (<70 y, ≥70 y).

The proportional hazards assumption was tested by entering the product of baseline multivitamin use and the natural logarithm of time in the model; we found no evidence of violation of this assumption. To investigate whether any observed association could be attributable to cardiovascular symptoms leading to changes in baseline vitamin supplement use, we excluded cases that occurred in the first 3 y of follow-up.

RESULTS

In the WHS, 14,264 of 37,193 women (38%) were taking a multivitamin supplement at baseline in 1992. In **Table 1**, women reporting current use of multivitamins had a lower BMI, were less likely to smoke, were more likely to be engaged in vigorous exercise, were more likely to be current users of hormone replacement therapy, and were more likely to have a family history of MI at age <60 y compared with women not taking multivitamins. They were also less likely to have a history of hypertension and diabetes and had higher intakes of fruit and vegetables, total fiber, and SFAs.

During a mean follow-up of 16.2 y (602,529 person-years), we identified 1493 cases of major CVD events, 586 cases of MI, 53 MI deaths, 752 cases of stroke (607 ischemic, 142 hemorrhagic, and 3 unknown), 350 cases of CVD death, 1435 cases of CAD, and 1274 cases of cardiac revascularization. In the multivariable-adjusted analyses, multivitamin use was not statistically significantly associated with the risk of major CVD events, MI, MI death, stroke (total, ischemic, or hemorrhagic), CVD death, or cardiac revascularization (**Table 2**). We also did not observe any statistically significant associations between longer duration of multivitamin use of ≥10 y as compared with no use and risk of CVD (**Table 3**). When investigating whether baseline frequency of taking <6 multivitamin pills/wk or ≥6 multivitamin pills/wk, as compared with no use, was associated with CVD, we observed no associations (data not shown).

In sensitivity analyses, we investigated a potential effect of reverse causation by excluding cases occurring in the first 3 y of

TABLE 1
Baseline characteristics according to the use of multivitamins (n = 37,193)[1]

Characteristics	No use (n = 22,929)	Baseline multivitamin use (n = 14,264)
Nondietary		
Age,[2] y	53.8 ± 7.0	54.1 ± 7.1
BMI,[3] kg/m^2	25.4 ± 0.2	25.0 ± 0.2*
Smoking, %		
Never	50.6	52.2*
Past	35.8	36.3*
Current	13.6	11.6*
Vigorous exercise ≥1 time/wk, %	59.6	65.6*
Current hormone replacement therapy, %	38.9	44.6*
Family history of MI <60 y, %	14.9	13.6*
Hypercholesterolemia, %	29.2	29.6
Hypertension, %	26.2	24.8*
Diabetes, %	2.8	2.2*
Dietary[3]		
Alcohol intake, g/d	4.7 ± 0.4	4.7 ± 0.4
Fruit and vegetables, servings/d	6.4 ± 0.1	6.7 ± 0.1*
Total fiber, g/d	19.9 ± 0.3	20.7 ± 0.3*
SFAs, g/d	18.7 ± 0.2	19.4 ± 0.2*
n−3 Fatty acids, g/d	1.4 ± 0.02	1.4 ± 0.02

[1]All variables except age are standardized to the age distribution in study population. *Significantly different from No use, $P < 0.05$ (ANOVA for quantitative data and Fisher's exact test for counts). MI, myocardial infarction.
[2]Values are means ± SDs.
[3]Values are means ± SEs.

TABLE 2
Baseline multivitamin use and risk of cardiovascular disease (n = 37,193)[1]

	No use (n = 22,929)	Multivitamin use (n = 14,264)
Major cardiovascular events		
Cases	923	570
Age-adjusted HR (95% CI)	1.00 (reference)	0.96 (0.87, 1.07)
+ Lifestyle factors[2]	1.00 (reference)	1.00 (0.88, 1.14)
+ Lifestyle and clinical factors[3]	1.00 (reference)	1.01 (0.89, 1.14)
+ Lifestyle, clinical, and dietary factors[4]	1.00 (reference)	1.01 (0.89, 1.15)
Myocardial infarction		
Cases	363	223
Age-adjusted HR (95% CI)	1.00 (reference)	0.97 (0.82, 1.14)
+ Lifestyle factors[2]	1.00 (reference)	1.04 (0.84, 1.27)
+ Lifestyle and clinical factors[3]	1.00 (reference)	1.04 (0.85, 1.28)
+ Lifestyle, clinical, and dietary factors[4]	1.00 (reference)	1.04 (0.84, 1.27)
Myocardial infarction death		
Cases	32	21
Age-adjusted HR (95% CI)	1.00 (reference)	1.01 (0.58, 1.75)
+ Lifestyle factors[2]	1.00 (reference)	1.15 (0.59, 2.27)
+ Lifestyle and clinical factors[3]	1.00 (reference)	1.15 (0.59, 2.25)
+ Lifestyle, clinical, and dietary factors[4]	1.00 (reference)	1.24 (0.64, 2.42)
Total stroke		
Cases	457	295
Age-adjusted HR (95% CI)	1.00 (reference)	1.01 (0.87, 1.17)
+ Lifestyle factors[2]	1.00 (reference)	0.97 (0.81, 1.16)
+ Lifestyle and clinical factors[3]	1.00 (reference)	0.97 (0.82, 1.16)
+ Lifestyle, clinical, and dietary factors[4]	1.00 (reference)	0.99 (0.83, 1.18)
Ischemic stroke		
Cases	376	231
Age-adjusted HR (95% CI)	1.00 (reference)	0.96 (0.81, 1.13)
+ Lifestyle factors[2]	1.00 (reference)	0.94 (0.77, 1.15)
+ Lifestyle and clinical factors[3]	1.00 (reference)	0.95 (0.78, 1.16)
+ Lifestyle, clinical, and dietary factors[4]	1.00 (reference)	0.96 (0.79, 1.17)
Hemorrhagic stroke		
Cases	79	63
Age-adjusted HR (95% CI)	1.00 (reference)	1.26 (0.91, 1.76)
+ Lifestyle factors[2]	1.00 (reference)	1.11 (0.75, 1.64)
+ Lifestyle and clinical factors[3]	1.00 (reference)	1.11 (0.74, 1.64)
+ Lifestyle, clinical, and dietary factors[4]	1.00 (reference)	1.12 (0.76, 1.66)
Cardiovascular disease death		
Cases	210	140
Age-adjusted HR (95% CI)	1.00 (reference)	1.02 (0.82, 1.26)
+ Lifestyle factors[2]	1.00 (reference)	1.11 (0.86, 1.44)
+ Lifestyle and clinical factors[3]	1.00 (reference)	1.11 (0.85, 1.44)
+ Lifestyle, clinical, and dietary factors[4]	1.00 (reference)	1.10 (0.84, 1.45)
Coronary artery disease		
Cases	897	538
Age-adjusted HR (95% CI)	1.00 (reference)	0.94 (0.85, 1.05)
+ Lifestyle factors[2]	1.00 (reference)	1.02 (0.89, 1.16)
+ Lifestyle and clinical factors[3]	1.00 (reference)	1.03 (0.90, 1.18)
+ Lifestyle, clinical, and dietary factors[4]	1.00 (reference)	1.03 (0.90, 1.17)
Cardiac revascularization		
Cases	801	473
Age-adjusted HR (95% CI)	1.00 (reference)	0.93 (0.83, 1.04)
+ Lifestyle factors[2]	1.00 (reference)	1.01 (0.88, 1.16)
+ Lifestyle and clinical factors[3]	1.00 (reference)	1.03 (0.89, 1.18)
+ Lifestyle, clinical, and dietary factors[4]	1.00 (reference)	1.03 (0.89, 1.18)

[1]All statistical tests were conducted by using Cox proportional hazards regression models.

[2]Multivariable models were adjusted for age, BMI, smoking, physical activity, hormone replacement therapy use, postmenopausal status, randomized treatment assignment, and number of supplements used.

[3]Multivariable models were adjusted for variables in footnote 2 plus family history of myocardial infarction, diabetes history, hypertension history, and hypercholesterolemia history.

[4]Multivariable models were adjusted for variables in footnote 3 plus alcohol consumption and intakes of fruit and vegetables, dietary fiber, SFAs, and PUFAs.

TABLE 3
Baseline duration of multivitamin use and risk of cardiovascular disease[1]

	Duration of multivitamin use		
	No use	<10 y	≥10 y
Major cardiovascular events			
Cases	923	372	162
Age-adjusted HR (95% CI)	1.00	0.99 (0.88, 1.12)	0.91 (0.77, 1.07)
Multivariable-adjusted HR (95% CI)	1.00	1.01 (0.88, 1.17)	0.97 (0.80, 1.17)
Myocardial infarction			
Cases	363	149	58
Age-adjusted HR (95% CI)	1.00	1.01 (0.83, 1.22)	0.85 (0.64, 1.12)
Multivariable-adjusted HR (95% CI)	1.00	1.04 (0.83, 1.30)	0.93 (0.68, 1.27)
Myocardial infarction death			
Cases	32	17	3
Age-adjusted HR (95% CI)	1.00	1.32 (0.74, 2.39)	0.45 (0.14, 1.49)
Multivariable-adjusted HR (95% CI)	1.00	1.56 (0.79, 3.08)	0.56 (0.16, 2.01)
Total stroke			
Cases	457	191	89
Age-adjusted HR (95% CI)	1.00	1.03 (0.87, 1.22)	1.00 (0.80, 1.26)
Multivariable-adjusted HR (95% CI)	1.00	1.00 (0.83, 1.21)	0.99 (0.76, 1.28)
Ischemic stroke			
Cases	376	154	67
Age-adjusted HR (95% CI)	1.00	1.01 (0.84, 1.22)	0.91 (0.70, 1.18)
Multivariable-adjusted HR (95% CI)	1.00	1.00 (0.81, 1.24)	0.92 (0.69, 1.24)
Hemorrhagic stroke			
Cases	79	36	22
Age-adjusted HR (95% CI)	1.00	1.11 (0.75, 1.65)	1.52 (0.95, 2.44)
Multivariable-adjusted HR (95% CI)	1.00	1.00 (0.64, 1.56)	1.33 (0.77, 2.29)
CVD death			
Cases	210	93	39
Age-adjusted HR (95% CI)	1.00	1.10 (0.87, 1.41)	0.90 (0.64, 1.27)
Multivariable-adjusted HR (95% CI)	1.00	1.16 (0.87, 1.53)	0.99 (0.67, 1.46)
Coronary artery disease			
Cases	897	361	144
Age-adjusted HR (95% CI)	1.00	0.98 (0.87, 1.11)	0.86 (0.72, 1.03)
Multivariable-adjusted HR (95% CI)	1.00	1.05 (0.91, 1.22)	0.98 (0.80, 1.20)
Cardiac revascularization			
Cases	801	319	127
Age-adjusted HR (95% CI)	1.00	0.97 (0.85, 1.11)	0.85 (0.71, 1.03)
Multivariable-adjusted HR (95% CI)	1.00	1.06 (0.91, 1.23)	0.99 (0.80, 1.23)

[1]All statistical tests were conducted by using Cox proportional hazards regression models. Multivariable models were adjusted for age, BMI, smoking, physical activity, postmenopausal status, randomized treatment assignment, number of supplements used, family history of myocardial infarction, diabetes history, hypertension history, hypercholesterolemia history, alcohol consumption, and intakes of fruit and vegetables, dietary fiber, SFAs, and PUFAs. CVD, cardiovascular disease.

follow-up because cardiovascular symptoms may lead to changes in multivitamin use. Similar results were observed after cases during the first 3 y of follow-up for major CVD events were excluded (HR: 0.98; 95% CI: 0.85, 1.12), MI (HR: 0.99; 95% CI: 0.79, 1.24), total stroke (HR: 0.95; 95% CI: 0.78, 1.15), ischemic stroke (HR: 0.97; 95% CI: 0.78, 1.19), hemorrhagic stroke (HR: 0.89; 95% CI: 0.89, 1.38), CVD death (HR: 1.05; 95% CI: 0.80, 1.39), and cardiac revascularization (HR: 0.99, 95% CI: 0.85, 1.15). We also investigated whether the associations differed if women were using multivitamins only or multivitamins with other supplements by comparing them with women who were not using any supplements, and similar associations were observed for major CVD events, MI, total stroke, ischemic stroke, hemorrhagic stroke, CVD death, and cardiac revascularizations (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, fruit and vegetable intake, and randomized treatment assignment (**Table 4**). We observed that the association differed by age (P-interaction = 0.04) because women aged <70 y had an HR of major CVD events of 1.03 (95% CI: 0.90, 1.19) and women aged ≥70 y had an HR of major CVD events of 0.72 (95% CI: 0.48, 1.08). Moreover, a statistically significant interaction was observed between duration of multivitamin use and age on the risk of major CVD events (P = 0.03). We observed among women aged <70 y HRs of 1.04 (95% CI: 0.90, 1.20) and 1.02 (95% CI: 0.83, 1.25) for <10 and ≥10 y of multivitamin use as compared with no multivitamin use, respectively. The corresponding HRs among women aged ≥70 y were 0.74 (95% CI: 0.46, 1.17) and 0.57 (95% CI: 0.32, 1.03) for <10 and ≥10 y of multivitamin use as compared with no multivitamin use,

TABLE 4
Multivitamin supplement use and major cardiovascular disease events by subgroups of individuals[1]

	No. of events			
	No use	Multivitamin use	Multivitamin use compared with no use[2]	*P*-interaction
Age				
<70 y	826	513	1.03 (0.90, 1.19)[3]	
≥70 y	98	57	0.72 (0.48, 1.08)	0.04
BMI				
<25 kg/m^2	387	272	1.10 (0.91, 1.34)	
≥25 kg/m^2	536	282	0.96 (0.81, 1.14)	0.45
Smoking status				
Nonsmokers	383	250	0.97 (0.80, 1.17)	
Past smokers	285	200	1.11 (0.89, 1.39)	
Current smokers	255	120	0.98 (0.75, 1.29)	0.56
History of diabetes				
No	819	515	0.99 (0.87, 1.14)	
Yes	104	55	1.13 (0.76, 1.69)	0.96
History of hypertension				
No	494	287	0.91 (0.76, 1.08)	
Yes	429	283	1.14 (0.95, 1.38)	0.11
History of hypercholesterolemia				
No	536	345	1.03 (0.87, 1.22)	
Yes	387	225	0.98 (0.80, 1.20)	0.19
Fruit and vegetables				
<3 servings/d	291	143	0.77 (0.55, 1.09)	
3 to <7 servings/d	386	227	0.99 (0.83, 1.17)	
≥7 servings/d	246	200	1.20 (0.95, 1.51)	0.01
Aspirin arm				
No	471	296	1.06 (0.89, 1.27)	
Yes	452	274	0.95 (0.79, 1.15)	0.74
β-Carotene arm				
No	480	269	0.93 (0.77, 1.11)	
Yes	443	301	1.09 (0.91, 1.30)	0.24
Vitamin E arm				
No	466	273	0.98 (0.82, 1.18)	
Yes	457	297	1.02 (0.86, 1.22)	0.31

[1]All statistical tests were conducted by using Cox proportional hazards regression models. Interaction test were done by using the Wald's statistics.

[2]Multivariable models were adjusted for age, BMI, smoking, physical activity, postmenopausal status, randomized treatment assignment, number of supplements used, family history of myocardial infarction, diabetes history, hypertension history, hypercholesterolemia history, alcohol consumption, and intakes of fruit and vegetables, dietary fiber, SFAs, and PUFAs.

[3]HR; 95% CI in parentheses (all such values).

respectively. We also observed that the association between multivitamin use and CVD appeared to differ according to fruit and vegetable intake (*P*-interaction = 0.01), where the HRs of major CVD events for multivitamin use were 0.77 (95% CI: 0.55, 1.09), 0.99 (95% CI: 0.83, 1.17), and 1.20 (95% CI: 0.95, 1.51) in groups of women consuming <3, 3 to <7, and ≥7 servings of fruit and vegetables per day, respectively. We also investigated whether the association was modified by other dietary factors, including dairy products, dietary fiber, n−3 fatty acids, and folate. We observed a statistically significant interaction between multivitamin use and dairy product intake on the risk of major CVD ($P = 0.04$), with HRs of CVD among women with a dairy intake of <1.62 and ≥1.62 servings/d of 0.93 (95% CI: 0.78, 1.12) and 1.07 (95% CI: 0.89, 1.29), respectively. We found no evidence of effect modification by dietary fiber ($P = 0.69$), n−3 fatty acids ($P = 0.38$), or folate ($P = 0.63$). We next performed 3-factor interaction tests among multivitamin use, age, and fruit and vegetable intake on major CVD events and did not observe a statistically significant interaction ($P = 0.09$). We also investigated additional 3-factor interactions by combining multivitamin use and age with categories dairy products ($P = 0.11$), dietary fiber ($P = 0.009$), n−3 fatty acids ($P = 0.03$), and folate ($P = 0.14$).

To investigate the time-varying association between multivitamin use and major CVD events, we updated information on current multivitamin use during follow-up (**Table 5**). We still found no association between updated multivitamin use and the risk of major CVD events (HR: 0.91; 95% CI: 0.82, 1.02), MI (HR: 0.89; 95% CI: 0.74, 1.07), MI death (HR: 0.49; 95% CI: 0.22, 1.06), total stroke (HR: 0.91; 95% CI: 0.78, 1.07), ischemic stroke (HR: 0.85; 95% CI: 0.71, 1.01), hemorrhagic stroke (HR:1.26; 95% CI: 0.86, 1.83), CVD death (HR: 0.91; 95% CI: 0.71, 1.16), CAD (HR: 0.96; 95% CI: 0.86, 1.08), or cardiac revascularization (HR: 1.00; 95% CI: 0.89, 1.12). In stratified analyses, we investigated whether the time-varying association

TABLE 5
The association between time-varying multivitamin use and cardiovascular disease (n = 37,193)[1]

	No use	Multivitamin use
Major cardiovascular events		
Cases	670	823
Age-adjusted HR (95% CI)	1.00 (reference)	0.85 (0.77, 0.95)
+ Lifestyle, clinical, and dietary factors[2]	1.00 (reference)	0.91 (0.82, 1.02)
Myocardial infarction		
Cases	216	370
Age-adjusted HR (95% CI)	1.00 (reference)	0.81 (0.69, 0.96)
+ Lifestyle, clinical, and dietary factors[2]	1.00 (reference)	0.89 (0.74, 1.06)
Myocardial infarction death		
Cases	30	23
Age-adjusted HR (95% CI)	1.00 (reference)	0.46 (0.22, 0.99)
+ Lifestyle, clinical, and dietary factors[2]	1.00 (reference)	0.49 (0.22, 1.06)
Total stroke		
Cases	368	752
Age-adjusted HR (95% CI)	1.00 (reference)	0.88 (0.76, 1.03)
+ Lifestyle, clinical, and dietary factors[2]	1.00 (reference)	0.91 (0.78, 1.06)
Ischemic Stroke		
Cases	304	303
Age-adjusted HR (95% CI)	1.00 (reference)	0.82 (0.69, 0.97)
+ Lifestyle, clinical, and dietary factors[2]	1.00 (reference)	0.85 (0.71, 1.01)
Hemorrhagic stroke		
Cases	62	80
Age-adjusted HR (95% CI)	1.00 (reference)	1.27 (0.88, 1.82)
+ Lifestyle, clinical, and dietary factors[2]	1.00 (reference)	1.26 (0.86, 1.83)
CVD death		
Cases	183	167
Age-adjusted HR (95% CI)	1.00 (reference)	0.83 (0.66, 1.05)
+ Lifestyle, clinical, and dietary factors[2]	1.00 (reference)	0.91 (0.71, 1.16)
Coronary artery disease		
Cases	528	907
Age-adjusted HR (95% CI)	1.00 (reference)	0.88 (0.79, 0.98)
+ Lifestyle, clinical, and dietary factors[2]	1.00 (reference)	0.96 (0.86, 1.08)
Cardiac revascularization		
Cases	464	810
Age-adjusted HR (95% CI)	1.00 (reference)	0.91 (0.81, 1.02)
+ Lifestyle, clinical, and dietary factors[2]	1.00 (reference)	1.00 (0.89, 1.12)

[1]Current multivitamin use that was updated at each follow-up and the most recent multivitamin use measurement was used to estimate risk in the following time period. All statistical tests were conducted by using Cox proportional hazards regression models.

[2]Multivariable models were adjusted for age, BMI, smoking, physical activity, hormone replacement therapy use, postmenopausal status, randomized treatment assignment, number of supplements used, family history of myocardial infarction, diabetes history (time-varying), hypertension history, hypercholesterolemia history (time-varying), alcohol consumption, and intakes of fruit and vegetables, dietary fiber, SFAs, and PUFAs.

between multivitamin use and major CVD was modified by age. The HR among women aged <70 y was 0.89 (95% CI: 0.79, 1.00), and the corresponding HR among women aged ≥70 y was 1.11 (95% CI: 0.78, 1.58). However, no statistically significant interaction was observed (P = 0.65).

DISCUSSION

In this prospective cohort of middle-aged and elderly women, we observed that baseline multivitamin use was not associated with risk of major CVD events, MI, stroke, or CVD death. Moreover, no significant association was observed for women taking multivitamins ≥10 y at baseline. However, the association between baseline multivitamin use and major CVD events seemed to vary by age and fruit and vegetable intake, but no significant associations in either of the subgroups were observed. When investigating short-term risk of CVD from multivitamins by updating information over the course of the study, we found no association with major CVD events and its associated endpoints.

Our results agree with the Physicians' Health Study II, the first RCT investigating the effect of multivitamins on CVD incidence (7). In that study, no association was observed for total major CVD events; however, there was some evidence that the effect between multivitamin use and total CVD may be modified by age (P-interaction = 0.04). Moreover, a significant 39% lower risk was observed for fatal MI (7). No previous observational studies have investigated the association between multivitamin use and total CVD incidence; however, our results agree with 3 other studies in US populations examining CVD mortality (8–10). In contrast, one American prospective cohort study observed a 16% lower risk of CVD mortality in women and men

who had a 10-y average frequency of 6 to 7 multivitamin pills per week compared with nonusers (11). Observational studies that have investigated how multivitamins are associated with CAD have reported mixed results (8, 12–18). In a prospective cohort study of Swedish women and another Swedish case-control study of women and men, multivitamin supplement use was inversely associated with incident MI (12, 14). The Nurses' Health Study reported that regular multivitamin use was associated with a 24% lower risk of incident CAD among women (16). In the Health Professionals Follow-Up Study, multivitamin use for ≥10 y was associated with 25% lower risk of CAD incidence (15). An American prospective study of women and men observed that combined use of multivitamins and supplements of vitamins A, C, or E was associated with a 25% lower risk of CAD mortality, and the association was somewhat stronger for duration of ≥5 y (13). In contrast, one prospective cohort study of >90,000 American women observed no association with incident MI (17). To the best of our knowledge, only 2 prospective cohort studies have examined the association between multivitamin supplement use and the risk of stroke (13, 17). Both studies, one in women and men and one in only women, reported no associations, in agreement with our observations.

We also found suggestions that the association between baseline multivitamin use and major CVD events may be modified by age and fruit and vegetable intake. Women aged ≥70 y had a lower risk of major CVD, especially among those reporting use ≥10 y, where a nonsignificant 43% lower risk was observed compared with nonusers. Multivitamin supplementation may be inversely related to CVD development among older women for several reasons, including difficulties in meeting nutritional requirements and a higher prevalence of CVD risk factors. Furthermore, among women consuming <3 servings of fruit and vegetables per day, a nonsignificant 22% lower risk of major CVD events was observed. Fruit and vegetable intake may be a proxy for an overall quality of diet and therefore, women with low intake may benefit from multivitamins.

To the best of our knowledge, this was the first study investigating the time-varying association between multivitamin use and CVD using information that was updated on almost a yearly basis. In these analyses, we found suggestions that multivitamin use may be inversely associated with different CVD endpoints; however, the results were not statistically significant in the multivariable-adjusted analyses. Thus, our results indicate that, in addition to baseline assessment, it may be important to examine both short- and long-term effects of multivitamins to better understand their potential protective role in CVD prevention.

Nutritional deficiencies are suggested to be central components in CVD development; therefore, multivitamins have been hypothesized to fill nutritional gaps and to be promising supplements and potentially reduce CVD risk. Multivitamins typically seek to replicate the combination of low-dose essential vitamins and minerals that parallel what would be obtained through a healthy diet. The doses of included nutrients in multivitamins are lower than high-dose individual supplements given in previous randomized trials, which had no effect on CVD risk (19, 28–32). However, many of the trials were conducted among participants with existing, well-managed atherosclerosis in whom further benefits from supplementation may not be seen. There are several hypothesized mechanisms through which individual vitamins and minerals included in multivitamin supplements may prevent CVD. Antioxidants such as α-tocopherol and β-carotene are transported in LDL particles and may inhibit oxidative modifications (1). In vitro studies show that vitamin C can protect LDL from oxidation and reduce harmful oxidants in the stomach (33). Folate, vitamin B-6, and vitamin B-12 are involved in homocysteine metabolism and may inhibit atherosclerotic and thrombotic events (2). Vitamin D may modulate immune function, have direct effects on cardiomyocytes, and have indirect effects on circulating hormone and calcium concentrations (3). Magnesium deficiency has been shown to induce oxidative stress but may also accelerate the atherosclerotic process through other mechanisms involving endothelial and vascular smooth cells (4). Endothelial selenoproteins are involved in the regulation of vascular tone, cell adhesion, and apoptosis and may be important targets in inflammatory processes and atherogenesis (34).

Our study had several strengths. We studied a large prospective cohort with almost complete follow-up, where all women provided high-quality information on different lifestyle, clinical, and dietary factors. We had access to updated measures of multivitamin use and important confounders. There are also some limitations of our study. The lack of association may be explained by the fact that women in our study are health professionals who may, on average, be better nourished than the general population. Moreover, we cannot exclude the possibility that our results are biased by measurement error in self-reported multivitamin use. However, previous studies have shown reasonable validity and reproducibility of the included variables (22). We were not able to adjust for the use of medications (e.g., lipid-lowering and antihypertensive drugs), which may have some effect on our results, especially in the time-varying analyses. Moreover, we did not adjust our results for other CVD risk factors such as serum total cholesterol, blood pressure, and fasting blood glucose, which may have confounded our results. However, we did adjust for CVD intermediates such as diabetes, hypertension, and hypercholesterolemia; thus, some potential confounding from these factors we may already have accounted for.

In conclusion, in this prospective study of middle-aged and elderly women, we found that baseline multivitamin use was not associated with the risk of major CVD events, MI, stroke, or CVD death. This lack of effect on CVD risk extended to when updating multivitamin use over the course of follow-up. Future RCTs and observational studies are needed to confirm or refute our findings.

The authors' responsibilities were as follows—SR and HDS: designed the research; SR, I-ML, JEB, and HDS: conducted the research; SR, I-ML, PMR, JMG, JEM, JEB, and HDS: analyzed the data; SR and HDS: wrote the manuscript; and HDS: had primary responsibility for the final content. All authors read and approved the final manuscript. The funding organizations had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript. None of the authors had any conflicts of interest.

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