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Multivitamin use and the risk of hypertension in a prospective cohort study of women

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Abstract

Objective—Despite the widespread use of multivitamin supplements, little is known regarding its effects on blood pressure (BP) and the development of hypertension. We therefore sought to prospectively investigate how multivitamin use was associated with incident hypertension among middle-aged and older women.

Methods—We studied 28,157 women from the Women's Health Study aged ≥45 years and free of cardiovascular disease, cancer and hypertension at baseline. Women reported information on a wide range of lifestyle, clinical and dietary factors, including multivitamin and other supplement use at baseline. Hypertension was identified on baseline and annual follow-up questionnaires. Incident hypertension was defined as either a new diagnosis of hypertension by a physician, initiation of antihypertensive medication, newly reported systolic BP ≥140 mmHg, or diastolic BP ≥90 mmHg during follow-up.

Results—During a mean follow-up of 11.5 years, we identified 16,316 cases of incident hypertension. We found that neither baseline (hazard ratio (HR) =1.01, 95% confidence interval (CI): 0.98, 1.05) nor time-varying multivitamin use (HR=0.97, 95% CI: 0.94–1.00) were associated with the risk of incident hypertension in multivariable-adjusted models. When we

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Conflicts of Interest

For the remaining authors none were declared.

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

investigated the duration of multivitamin use reported at baseline, we also observed no association with the risk of hypertension.

Conclusion—The results from this prospective study of middle-aged and older women suggest that neither baseline multivitamin use nor time-varying multivitamin use is associated with the risk of developing hypertension.

Keywords

Multivitamins; hypertension; blood pressure; cohort; epidemiology

INTRODUCTION

Hypertension is a common chronic disease worldwide and a major risk factor for cardiovascular disease (CVD) [1]. It is characterized by several pathophysiologic pathways including endothelial dysfunction, vascular inflammation, increased arterial stiffness [2]. A diet including high amounts of fruits, vegetables, and fish and lower amounts of saturated fatty acids and sodium contributes to adequate intakes of essential vitamins and minerals and has been linked to lower blood pressure (BP) and reductions in the risk of hypertension [3, 4]. However, little is known whether supplementation of vitamins and minerals may have a preventive role in hypertension development. Multivitamins are supplements including a wide-range of essential nutrients at amounts typically found in a healthy diet. Multivitamins are the most commonly used dietary supplement in the US and its prevalence has steadily increased during the past few decades [5]. In the National Health and Nutrition Examination Survey (NHANES) study, more than one-third of US adults reported current daily multivitamin use [6]. Multivitamins were also commonly taken in several countries in European Prospective Investigation into Cancer and Nutrition (EPIC) study. Thus, these data highlight the importance of monitoring dietary supplement use and evaluating its benefits and risks in chronic disease prevention including hypertension.

Although previous prospective studies have been conducted to investigate the preventive role of multivitamin use in the prevention of CVD [7–19], there are surprisingly very few prospective studies investigating its association with blood pressure (BP) or the risk of hypertension. Only two trials have been conducted, which were performed in highly selective populations limiting the generalizability of findings. One trial reported reduced risk of hypertension among women and men with esophageal dysplasia [20] and the other reported short-term decreases in both systolic BP (SBP) and diastolic BP (DBP) among obese women with increased risk of CVD [21], with multivitamin supplement use. To the best of knowledge our present study is the first examining whether baseline and time-varying multivitamin use is associated with the risk of incident hypertension in a long-term prospective cohort of middle-aged and older women.

METHODS AND SUBJECTS

The Women’s Health Study (WHS) was a 2×2 factorial trial testing a low-dose aspirin and vitamin E in the primary prevention of CVD and cancer among 39,876 female U.S. health professionals aged ≥45 y and with no history of myocardial infarction (MI), stroke, transient

ischemic attack, or cancer (except nonmelanoma skin cancer) [22–24]. At baseline in September 1992 to May 1995, all participating women completed a questionnaire asking about their medical history and lifestyle factors as well as a 131-item validated semiquantitative food-frequency questionnaire (FFQ), of whom 39,310 (98.6%) women responded. In the present study, we excluded 10,227 women with baseline history of hypertension defined as having a self-reported SBP ≥140 mm Hg or DBP ≥90 mm Hg, or being on antihypertensive treatment. We also excluded 926 women with missing information on multivitamin supplement use and lifestyle, clinical and dietary factors considered as covariates. Thus, 28,157 women were included in analysis with follow-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.

Assessment of multivitamin use

Information on the status, duration, and frequency of multivitamin supplement use and other dietary factors were reported on questionnaires completed at the start of the study. The following individual supplements were reported: vitamin B6, 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 intervention period and observational follow-up period of WHS. Nutrient intake from dietary supplement use and food consumption assessed by FFQ has been validated in women from the Nurse's Health Study [25] and in men from the Health Professionals Follow-up Study [26]. In these validation studies, the Pearson's correlation coefficients between the FFQ and two 1-week dietary records ranged from 0.32 to 0.72 for vitamins and minerals from diet and dietary supplements. When reproducibility was investigated by comparing responses to the same FFQ twice one year apart, the intraclass correlation coefficients ranged from 0.52 to 0.80.

Other covariates

At WHS baseline, we collected information on age, weight, height, as well as lifestyle factors such as smoking status, physical activity, postmenopausal status, postmenopausal hormone use, and clinical factors including history of diabetes and hypercholesterolemia. Women also reported on a 131-item FFQ how often, on average, they consumed different foods or beverages during the last year by using 9 predefined response categories. Body mass index (BMI) was calculated by dividing body weight (in kilograms) by square of height (in meters). Intakes of whole grains and fruits and vegetables were calculated by summing individual food items.

Ascertainment of incident hypertension and blood pressure change

Cases of incident hypertension were identified from annual follow-up questionnaires where information on the month and year of hypertension diagnosis were reported. Incident hypertension was defined as meeting at least 1 of the following 4 criteria: a new physician's

diagnosis of hypertension, initiation of antihypertensive medication; self-reported SBP ≥140 mm Hg, or self-reported DBP ≥90 mm Hg. If there was missing information on dates of physician diagnosis or hypertension defined by other criteria, the time of event was assigned to a random date between questionnaires without and with hypertension. Women were censored if they developed CVD during follow-up to avoid possible impact of BP control. The validity of self-reported SBP (r = 0.72) and DBP (r = 0.60) and hypertension that was confirmed with medical record review in a subsample of women and men [27, 28] among health professionals has been estimated to be moderately high [28, 29]. Moreover, in a random sample of women from WHS, self-reported incident hypertension was confirmed in 48 of 50 (96%) women and absence of hypertension was confirmed in 45 of 50 (90%) women by telephone interview with the participant. BP changes after 10 years (after the intervention period) and 18 years (after the observational period) were also calculated. BP was reported at baseline in categories whereas open-ended questions for SBP and DBP were used at the 10-year and 18-year follow-ups. To be able to model BP change as a continuous variable we assigned following SBP values 100, 115, 125, and 135 mm Hg to baseline categories of <110, 110–119, 120–129, and 130–139 mm Hg, respectively. For DBP we assigned 60, 70, 80, and 87 mm Hg to categories of <65, 65–74, 75–84, and 85–89 mmHg, respectively.

Statistical analyses

All statistical analyses were performed with SAS 9.3 (SAS Institute Inc., Cary, NC, USA). Women were categorized into no or current use of multivitamins at baseline and at each follow-up time-point. We further categorized women according to the frequency (<6 pills/week, or ≥6 pills/week) and duration of multivitamin use (no use, <10 years use, or ≥10 years use). In sensitivity analyses, women were also categorized into no supplement use, use of multivitamin supplements only, and use of multivitamins with other individual vitamin/mineral supplements. Age-standardized mean values for continuous variables and percentages for categorical variables were calculated and compared between groups of multivitamin use. The Cox proportional hazard model was used to calculate hazard ratios (HR), with 95 percent confidence intervals (CI) [30] using the PHREG procedure. All HRs were adjusted for age at baseline (years, continuous), BMI (kg/m^2, continuous), smoking status (never, past, current), physical activity (energy expenditure in MET-hours per week), postmenopausal status (no, yes, biologically uncertain, or unclear), hormone replacement therapy use (never, past or current), alcohol consumption (rarely/never, 1–3 drinks/month, 1–6 drinks/week, or ≥1 drinks/day), and intakes of fiber (g/day, continuous), saturated fatty acids (g/day, continuous), and omega-3 fatty acids (g/day, continuous), family history of myocardial infarction, diabetes history, hypercholesterolemia history. In a second set of models, we additionally adjusted for intakes of whole grains, fruits, and vegetables.

We next investigated whether the association between multivitamin use and incident hypertension was modified by potential risk factors by stratifying analysis by categories of age (<55, 55–<65, ≥65 years), body mass index (<25, ≥25 kg/m^2), smoking status (never, past, current), fruit and vegetable intake (<4, 4–<7, ≥7 servings/day), and baseline SBP/DBP (<120/80, ≥120/80 mm Hg). Multiplicative interactions were tested using Wald chi^2-tests.

To investigate the time-varying association between multivitamin supplement use and incident hypertension, a Cox model was constructed using information on current multivitamin use that was updated at each follow-up time. In these analyses, the most recently reported multivitamin use was included in the model to estimate the risk of hypertension in the following time period. If data were missing at a given time point, the last observation was carried forward.

The proportional hazards assumption was tested by adding the product of baseline multivitamin use and the natural logarithm of time in the model; we did find evidence of violation of this assumption. To investigate whether any observed association could be due to cardiovascular symptoms leading to changes in baseline multivitamin use, we also performed sensitivity analyses by excluding hypertension cases that occurred in the first three years of follow-up.

RESULTS

In the WHS, 10,759 of 28,157 women (38%) were taking a multivitamin supplement at baseline in September 1992 to May 1995. In Table 1, baseline characteristics according to baseline multivitamin use are presented. Women reporting current use of multivitamins were less likely to smoke, more physically active, and more likely to be current users of hormone replacement therapy compared to women not taking multivitamins. Age, BMI, alcohol use, history of diabetes, hypercholesterolemia, intakes of whole grains, fruits and vegetables were not different with regard to whether or not women were taking multivitamin.

We identified 16,316 cases of incident hypertension during a mean follow-up of 11.5 years (323,414 person-years). In Table 2, we present age-and multivariable-adjusted HRs of hypertension according to baseline and time-varying multivitamin use. Baseline multivitamin use was not associated with the risk of hypertension, neither in the age (HR: 1.00, 95% CI: 0.97, 1.03) - nor the multivariable-adjusted analyses (HR: 1.03, 95% CI: 1.00, 1.07). Adding dietary factors to the multivariable-adjusted model did not change the results (HR: 1.03, 95% CI: 0.98, 1.07). When investigating the time-varying association between multivitamin use and risk of hypertension we observed a modest lower risk in age-adjusted analyses (HR: 0.94, 95% CI: 0.91, 0.97). Adding other lifestyle, clinical, and dietary factors attenuated the association (HR: 0.97, 95% CI: 0.94–1.00) Moreover, longer duration of multivitamin use (≥10 years) as compared to no use showed no association (HR: 1.02, 95% CI: 0.97, 1.07) in the fully adjusted model (Table 3).

In sensitivity analyses, we excluded hypertension cases that occurred in the first three years of follow-up as cardiovascular symptoms may lead to changes in multivitamin use. Similar results were observed among multivitamin users compared to non-users (HR: 1.02, 95% CI: 0.99, 1.06). We further investigated the associations for using multivitamins only (HR: 1.02, 95% CI: 0.97, 1.07) or multivitamins with other supplements (HR: 1.04, 95% CI: 1.00, 1.08) at baseline as compared to not using any supplements, and no statistically significant associations were observed.

We further investigated whether multivitamin use was associated with uncontrolled hypertension by defining uncontrolled hypertension as SBP ≥140 mm Hg or DBP ≥90 mm Hg. In the multivariable-adjusted analysis, we observed that baseline multivitamin use was associated with 4% (95% CI: 1–8%) increased risk of uncontrolled hypertension whereas time-varying multivitamin use showed no association.

We also investigated whether the association between multivitamin use and hypertension was modified by other potential hypertension risk factors such as age, BMI, smoking, fruit and vegetable intake, and baseline BP (Table 4). Among women with baseline SBP/DBP ≥120/80 mm Hg, multivitamin use appeared to be associated with 8% (95% CI: 1 – 15%) higher risk of hypertension; whereas for women with baseline SBP/DBP <120/80 mm Hg; no statistically significant association was observed (P for interaction = 0.06).

We next investigated SBP and DBP change from baseline to the end of the intervention period (10 years) as well as the end of the observation period (18 years) (Table 5). There were no statistically significant associations of baseline multivitamin use with BP changes during either follow-up period.

DISCUSSION

In this prospective cohort of middle-aged and elderly women, baseline multivitamin use was not associated with risk of hypertension and the null association was consistent across categories of potential risk factors for hypertension. Neither was taking multivitamins ≥10 years at baseline associated with incident hypertension. When updating multivitamin use over the course of the study, we also observed no association for short-term risk of hypertension. Thus, our results suggest that multivitamins may not be recommended as a preventive strategy to reduce the risk of developing hypertension among women who have no history of hypertension, CVD, and cancer at baseline.

To the best of our knowledge, this is the first prospective cohort study investigating multivitamin use and the short- and long-term risk of developing hypertension. The lack of association suggests that multivitamins should not be considered for the prevention of hypertension in a normotensive population. The role of baseline nutritional status warrants further investigation, as the female health professionals in our study may be less prone to nutritional insufficiencies than the general population.

We are aware of two trials that have tested multivitamin supplements with a wide-spectrum of vitamins and minerals at low doses on hypertension or blood pressure change as secondary endpoints in highly selective populations. In the Linxian trial, a multivitamin supplement was tested among 3,318 women and men diagnosed with esophageal dysplasia and having micronutrient-poor diet, and reported reduced the risk of hypertension among men but not among women after 6 years of follow-up [20]. Another trial including 128 obese women with increased risk of CVD, reported significant reduction in SBP and DBP in the multivitamin arm after 26-weeks of follow-up [21]. However, in line with our observations, the Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) trial that tested a low-dose supplement including 5 antioxidant nutrients reported no effect

on hypertension risk [31]. The recently initiated COcoa Supplement and Multivitamin Outcomes Study (COSMOS) will recruit 18,000 women and men and test a wide-spectrum, low-dose multivitamin in the prevention of CVD and cancer (ClinicalTrials.gov Identifier: NCT02422745). COSMOS trial will provide unique opportunities to examine if a multivitamin supplement has any effects on incident hypertension or changes in BP.

Hypertension is a major risk factor for CVD and is characterized by multiple pathophysiologic pathways such as endothelial dysfunction, vascular inflammation, increased arterial stiffness [2]. Salt reduction is considered as one of the most important dietary advises in the prevention of hypertension [32]. However, besides salt reduction, there are other dietary preventive strategies shown to be of importance in both hypertension prevention and BP reduction as well as lowering subsequent risk of CVD [33]. The Dietary Approaches to Stop Hypertension (DASH) diet has been pointed out as a promising dietary intervention [33]. The DASH diet is rich in fruits, vegetables, whole grains, and low-fat dairy products providing adequate intakes of several essential vitamins and minerals [4].

Multivitamin supplements typically aim to mirror the combination of low-dose essential vitamins and minerals that would be obtained through a healthy diet e.g. the DASH diet. Several vitamins and minerals have been suggested to have important roles in the mechanistic pathways in hypertension development. Nutrients with antioxidant properties may inhibit oxidative stress caused by increased reactive oxygen/nitrogen species, which is involved in the pathophysiology of hypertension [34]. Vitamin D inhibits the expression of renin gene, which reduces activity of the renin-angiotensin-aldosterone system, leading to favourable effects on volume homeostasis and BP reduction [35]. Magnesium may have BP lowering effects as a calcium channel blocker. Magnesium also regulates intracellular calcium, sodium, and potassium; low magnesium levels have been linked to insufficient amounts of prostaglandin E_1, which leads to vasoconstriction and increases BP [36]. Potassium promotes vasodilation through stimuli of the sodium pump lowering cystolic calcium [33]. Moreover, a Cochrane review of randomized trials testing potassium supplementation reported nonsignificant BP lowering effects however, there was heterogeneity between trials [37].

This observational study of women has several strengths including the large prospective cohort design, a high follow-up rate, and high-quality information on various lifestyle, clinical, and dietary factors. Moreover, we had updated measures of multivitamin use and important confounders. However, our study also has limitations. Women in our study are health professionals who may have on average better baseline nutritional status than the general population thus, our results may not therefore, be generalizable to other populations. We did not collect information on season variability in multivitamin use. In addition, we cannot exclude the possibility that our results are biased by measurement error in self-reported multivitamin use. However, previous studies have demonstrated reasonable validity and reproducibility of multivitamin use [25].

In conclusion, in this prospective study of middle-aged and elderly women who were apparently healthy at baseline, we observed that baseline multivitamin use was not associated with incident hypertension. We also observed no association with updated

information on multivitamin use over the course of the study. Future randomized controlled trials and observational studies are needed to confirm or refute our findings.

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Table 1

Baseline characteristics according to baseline use of multivitamins (n=28,157).

	Baseline use of multivitamin supplements	
	No (n=17,398)	**Yes (n=10,759)**
Age, years[a]	53.6 (6.5)	53.9 (6.7)
Baseline body mass index, kg/m^2	25.4 (4.6)	25.0 (4.3)
Current smokers, %	15	12
≥ 1 alcohol drink/month, %	57	57
Postmenopausal, %	48	48
Physical activity, total metabolic equivalent hrs/week	14.2 (18.3)	16.7 (20.0)
Current use of postmenopausal hormones, %	39	45
History of diabetes, %	1	1
History of high cholesterol, %	23	24
Fruit and vegetable intake, servings/day	5.9 (3.7)	6.2 (3.6)
Whole grain intake, servings/day	1.4 (1.2)	1.5 (1.3)

Values are means (SD) or percentages and are standardized to the age distribution of the study population.

[a]Value is not age adjusted

Table 2

Baseline and time-varying multivitamin use and risk of hypertension (N=28,157).

	No use (n = 17,398)	Baseline multivitamin use (n = 10,759)	Time-varying multivitamin use
Cases	10,084	6232	
Age-adjusted HR (95% CI)	1.00 (ref)	1.00 (0.97, 1.03)	0.94 (0.91, 0.98)
+ Lifestyle factors[a]	1.00 (ref)	1.03 (1.00, 1.07)	0.97 (0.93, 1.00)
+ Lifestyle, clinical, dietary factors[b]	1.00 (ref)	1.03 (1.00, 1.07)	0.97 (0.94, 1.00)

HR, hazard ratio; CI, confidence interval. All statistical tests were conducted by using Cox proportional hazards regression models.

[a]Additionally adjusted for body mass index, smoking, physical activity, postmenopausal status, randomized treatment assignment, diabetes history, hypercholesterolemia history, alcohol consumption

[b]Additionally adjusted for intakes of fruits and vegetables, and whole grains.

Table 3

Duration of baseline multivitamin use and risk of hypertension.

	No use (n=17,398)	<10 years (n=7210)	≥10 years (n=1690)
Cases	10,084	4176	1690
Age-adjusted HR (95% CI)	1.00 (ref)	1.01 (0.98, 1.05)	0.96 (0.91, 1.01)
+ Lifestyle factors[a]	1.00 (ref)	1.04 (1.00, 1.07)	1.02 (0.96, 1.07)
+ Lifestyle, clinical, dietary factors[b]	1.00 (ref)	1.04 (1.00, 1.08)	1.02 (0.97, 1.07)

HR, hazard ratio; CI, confidence interval. All statistical tests were conducted by using Cox proportional hazards regression models.

[a]Additionally adjusted for body mass index, smoking, physical activity, postmenopausal status, randomized treatment assignment, diabetes history, hypercholesterolemia history, alcohol consumption

[b]Additionally adjusted for intakes of fruits and vegetables, and whole grains.

Table 4

Multivitamin supplement use and hypertension events by subgroups of individuals.

	No. of events		Multivariate HR[a] (95% CI)	
	No use	Multivitamin use	Multivitamin use versus no use	P for interaction
Age				
<55 years	6234	3748	1.03 (0.98, 1.07)	
55–<65 years	2986	1881	1.06 (1.00, 1.12)	
≥65 years	864	603	1.03 (0.92, 1.14)	0.67
Body mass index				
<25 kg/m^2	4937	3269	1.03 (0.99, 1.08)	
≥25 kg/m^2	5147	2963	1.02 (0.98, 1.07)	0.78
Smoking				
Current smokers	1444	723	0.96 (0.88, 1.06)	
Past smokers	3663	2312	1.05 (1.00, 1.11)	
Never smokers	4977	3197	1.04 (1.00, 1.09)	0.26
Fruit and vegetables				
<4 servings/day	2937	1662	1.03 (0.97, 1.10)	
4–<7 servings/day	4206	2551	1.02 (0.97, 1.07)	
≥7 servings per day	2941	2019	1.06 (1.00, 1.12)	0.74
Baseline systolic/diastolic BP				
<120/80 mm Hg	7594	4777	1.03 (1.00, 1.07)	
≥120/80 mm Hg	2490	1455	1.08 (1.01, 1.15)	0.06
High cholesterol				
No	7419	4487	1.03 (1.00, 1.07)	
Yes	2665	1745	1.04 (0.98, 1.10)	0.80
Diabetes				
No	9904	6141	1.03 (1.00, 1.07)	
Yes	180	91	0.95 (0.73, 1.25)	0.79
High CVD risk profile[b]				
No	6621	4205	1.03 (0.99, 1.07)	
Yes	3463	2027	1.05 (1.00, 1.11)	0.37

HR, hazard ratio; CI, confidence interval. All statistical tests were conducted by using Cox proportional hazards regression models. Interaction test were done using the Wald's statistics.

[a]Multivariable models were adjusted for age, body mass index, smoking, physical activity, postmenopausal status, randomized treatment assignment, diabetes history, hypercholesterolemia history, alcohol consumption, intakes of fruits and vegetables, and whole grains.

[b]A high CVD risk profile is defined as having at least two of the following factors: currently smoking, body mass index ≥25 kg/m^2, baseline BP ≥120/80 mm Hg, high cholesterol, or diabetes.

Table 5

Baseline multivitamin use and mean blood pressure changes.

	No use	Baseline multivitamin use	P value
Through the intervention period (10 years)			
N	13,828	8577	
SBP			
Age-adjusted mean (SD)	5.19 (0.56)	5.17 (0.57)	0.91
+ Lifestyle, clinical, dietary factors[a]	5.52 (0.58)	5.56 (0.59)	0.85
DBP			
Age-adjusted mean (SD)	0.24 (0.42)	0.24 (0.43)	0.99
+ Lifestyle, clinical, dietary factors	0.66 (0.44)	0.62 (0.44)	0.76
Through the observational follow-up period (18 years)			
N	5715	3487	
SBP			
Age-adjusted mean (SD)	5.33 (1.06)	5.19 (1.07)	0.63
+ Lifestyle, clinical, dietary factors	5.56 (1.08)	5.34 (1.09)	0.42
DBP			
Age-adjusted mean (SD)	−1.10 (0.84)	−0.87 (0.85)	0.30
+ Lifestyle, clinical, dietary factors	−1.00 (0.85)	−0.91 (0.86)	0.69

SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure

[a]Additionally adjusted for body mass index, smoking, physical activity, postmenopausal status, randomized treatment assignment, diabetes history, hypercholesterolemia history, alcohol consumption, intakes of fruits and vegetables, and whole grains.