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Multivitamin Use and Risk of Stroke Incidence and Mortality among Women

Sally Adebamowo^{1,2}, Diane Feskanich³, Meir Stampfer^{2,3,4}, Kathryn Rexrode⁵, and Walter C. Willett^{2,3,4}

¹Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, MD

²Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA

³The Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

⁴Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA

⁵Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA

Abstract

Introduction—Few studies have examined the association between multivitamin use and the risk of stroke incidence and mortality, and the results remain inconclusive as to whether multivitamins are beneficial.

Methods—We prospectively examined the associations between multivitamin use and the risk of incident stroke and stroke mortality among 86,142 women in the Nurses' Health Study, aged 34 to 59 years and free of diagnosed cardiovascular disease at baseline. Multivitamins use and covariates were updated every two years and strokes were documented by review of medical records. Hazard ratios of total, ischemic and hemorrhagic strokes were calculated across categories of multivitamin use (nonuser, past, current user) and duration (years), using Cox proportional hazard models.

Results—During 32 years of follow-up from 1980 to 2012, 3,615 incident strokes were documented, including 758 deaths from stroke. In multivariate analyses, women who were current multivitamin users did not have a lower risk of incident total stroke compared to nonusers (RR 1.02, 95% CI 0.93–1.11), even those with longer durations of 15 or more years of use (RR 1.08, 95% CI 0.97–1.20) or those with a lower quality diet (RR 0.96, 95% CI 0.80–1.15). There was also no indication of benefit from multivitamin use for incident ischemic or hemorrhagic strokes or for total stroke mortality.

Corresponding Author: Sally N. Adebamowo, MD, MSc, ScD, Department of Epidemiology and Public Health, University of Maryland Comprehensive Cancer Center, University of Maryland School of Medicine, 660 West Redwood Street, Howard Hall, Room 119, Baltimore, MD 21201. Phone: (410) 706-7431 | Fax: (410) 706-1944, sadebamowo@som.umaryland.edu.

Declaration of conflicting interests

The Authors declare that there is no conflict of interest

Conclusion—Long-term multivitamin use was not associated with reduced risk of stroke incidence or mortality among women in the study population, even among those with a lower diet quality. We cannot rule out an effect in a less well-nourished population.

Keywords

Stroke; Multivitamins; Incidence; Ischemic; Hemorrhagic; Mortality

Introduction

Multivitamins, a dietary supplement, are a combination of many different vitamins and minerals(1). In the United States, multivitamins are taken regularly by about one-third of adults, with highest use in women, older age groups and non-Hispanic whites (2, 3). The most common reasons cited by US adults for using dietary supplements are to “improve overall health” (45%) and to “maintain health” (33%)(4). Although randomized trial evidence demonstrates a modest reduction in cancer mortality(5), their efficacy for stroke reduction in generally well-nourished populations is uncertain.

Results from previous studies examining the association between multivitamin use and the risk of stroke have been inconsistent. In prospective studies conducted in the US, no association was observed between multivitamin use and the risk of total incident stroke(6–8). In a randomized controlled trial conducted among physicians in the US, taking a daily multivitamin did not reduce risk of stroke in men(9). The results of studies examining the association between multivitamin use and stroke mortality have also been inconsistent. One prospective study conducted in the US reported no association(10), whereas in a Japanese study, death from total stroke was lower among regular multivitamin users, especially among those with low baseline intake of fruits and vegetables(11). A randomized trial conducted in northern Linxian, an area with low diet quality in China, observed a non-significant lower risk of stroke mortality among persons who took a daily multivitamin, compared to those who took placebo(12).

We prospectively examined the associations between use and duration of multivitamin use and the risk of incident stroke and stroke types, including fatal strokes, among women. We examined these associations in the Nurses’ Health Study, which has up to 32 years of follow-up, long duration of exposure and a large number of stroke outcomes. Thus, the present study can be informative regarding the relationship between long-term multivitamin use and stroke risk. We hypothesized that multivitamin use may reduce the risk of incident stroke and stroke mortality among people with low diet quality.

Methods

Study Population

The Nurses’ Health Study (NHS) is a prospective cohort of 121,700 female registered nurses residing in the United States who were 30 to 55 years old at enrollment in 1976(13). All women provided information on their medical history and lifestyle. Every two years, follow-up questionnaires are sent to update this information. Multivitamin use and dietary intake

were first assessed in 1980, which was used as the baseline for this investigation. Participants with prevalent cancer, stroke, or coronary heart disease, implausibly low or high reported energy intakes, or lack of diet information were excluded at baseline, leaving 86,142 women eligible for analysis.

The study was approved by the Committee on the use of Human Subjects in Research at Brigham and Women's Hospital.

Ascertainment of Multivitamin use and Diet

At baseline in 1980, participants were asked to report whether they currently used multivitamins, and if so, their total years of multivitamin use. On every subsequent biennial questionnaire, participants were asked if they currently took a multivitamin (no/yes). Status (nonuser, past user, current user) and duration of multivitamin use were determined and updated at each follow-up cycle. Nonusers were defined as participants who never reported multivitamin use on the current or any previous questionnaire. Duration of multivitamin use was classified into predetermined categories: < 5, 5 years for past users, and < 5, 5 – 9, 10–14, 15 years for current users.

Detailed dietary intake was assessed with a semi-quantitative food-frequency questionnaire (FFQ) in 1980, 1984, 1986, and at 4-year intervals thereafter. The FFQ ascertains average frequency of intake of specified portions of approximately 130 foods during the previous year. The reproducibility and validity of this questionnaire has been reported elsewhere(14–16).

Ascertainment of Stroke

The primary endpoints were incident stroke or death from stroke. Strokes were confirmed if characterized by a typical neurological defect of sudden or rapid onset, lasting more than 24 hours and attributable to a cerebrovascular event. Strokes were classified according to the criteria of the National Survey of Stroke as due to ischemia (embolic or thrombotic), hemorrhage (subarachnoid hemorrhage or intracerebral hemorrhage) or unknown cause(17). Participants reporting an incident stroke on a follow-up questionnaire were asked for additional details and permission to review their medical records. Study physicians with no knowledge of the participants' self-reported risk factor status reviewed the medical records. Medical records were available for 70% (2540/3615) of the reported stroke cases. Of strokes confirmed by medical record review, 1,889 were ischemic and 576 were hemorrhagic strokes, with 75 of undetermined type. Strokes that were confirmed by the participant but those for which medical records were inadequate or unavailable for review (30%, 1075/3615) were classified as stroke of undetermined type. Stroke deaths were reported by next of kin, coworkers, postal authorities, or the National Death Index. Medical records, autopsy reports or death certificates were used to ascertain fatal strokes.

Covariates

Information was obtained on potential confounding factors, including medical history and lifestyle behaviors that could be associated with intake of multivitamins and the risk of stroke. These variables were updated biennially and included cigarette smoking (never, past,

current), physical activity (< 3, 3 – < 9, 9 – < 18, 18 – < 27, or ≥ 27 metabolic equivalent hours/week), menopausal status (pre- or post-menopausal), postmenopausal hormone therapy (never, past, current), parental history of early myocardial infarction (before age 60 years), aspirin use at least twice per week (yes or no), and history of hypertension, diabetes or hypercholesterolemia (yes or no). Height and weight were self-reported at baseline, and weight was updated from follow-up questionnaire responses. Body mass index (BMI) was calculated as weight (kg)/height² (m) and divided into 10 categories. Quintiles were calculated for total energy intake (kcal) and we used alcohol consumption categories of 0, 0 – < 5, 5 – < 10, 10 – < 15, or ≥ 15 g/d g/day. We calculated the Alternate Healthy Eating Index (aHEI) as an overall measure of diet quality using FFQ data(18), without the multivitamin component. Low diet quality was defined as aHEI below the 25th percentile for the population of women in the study.

Statistical Analyses

Person-years of follow-up were calculated from the return of the baseline FFQ to the date of reported first stroke event, death or June 1, 2012, whichever came first. To examine associations between multivitamin intake and stroke, we used Cox proportional hazards models stratified by age (in months) and follow-up cycle to estimate relative risks (RRs) and 95% confidence intervals (CIs). Participants were divided into categories of multivitamin use. Cumulative averages of dietary variables were calculated by taking the mean of all reported FFQ intakes up to the beginning of each 2-year follow-up interval. The cumulative average intake was then used to predict stroke incidence from the time of the last returned questionnaire until the next follow-up cycle. Multivariate models were adjusted for age, calendar time, intakes of total energy (kcal), alcohol (g/day), cigarette smoking, BMI, physical activity, parental history of early myocardial infarction, post-menopausal hormone therapy use, aHEI, aspirin use, history of diabetes, hypertension, and hypercholesterolemia. To test for linear trend in duration of use, we used the duration of multivitamin use for past and current users and modeled this variable as a continuous variable. To examine potential effect modification of the association between multivitamin use and stroke risk, the multivariate models were stratified on age (<60 versus ≥ 60 years), hypertension (yes versus no), diabetes (yes versus no), smoking (never, former, current), fruit and vegetable consumption (< 3 servings/day versus ≥ 3 servings/day), folate intake (< 25th percentile versus ≥ 25th percentile), and pre- and post-implementation of mandatory fortification of enriched cereal grain products with folic acid in the United States (strokes occurring on or before 1994 versus strokes occurring after 1994). Given that mandatory fortification of foods in the US was authorized in 1996 and fully implemented in 1998(19), we used 1994 as the cutpoint to assess the effect of fortification, to avoid including any stroke cases that may have occurred after fortification was authorized or implemented. To test the hypothesis that long-term multivitamin use may reduce the risk of incident stroke and stroke mortality among women with low diet quality, the multivariate models were stratified on aHEI (< 25th percentile versus ≥ 25th percentile). All *P* values are 2-sided and the analyses were conducted using SAS 9.2 (SAS Institute Inc, Cary, NC).

Results

During 2,342,979 person-years of follow-up from 1980 through 2012, we documented 3,615 incident cases of total stroke, of which 758 were fatal. About 27% of the women reported multivitamin use at baseline (1980); usage increased to 41% by the midpoint of follow-up (1994). The age-standardized characteristics of the study participants at the midpoint of follow-up in 1994 are shown in Table 1. On average, current multivitamin users were more likely to use aspirin and post-menopausal hormone therapy, were more physically active, had a lower BMI and were less likely to be current smokers, compared to nonusers of multivitamins.

Table 2 shows the age and multivariate adjusted RRs of incident total, ischemic and hemorrhagic stroke according to status and duration of multivitamin use. Overall, we observed no significant association between multivitamin use and total stroke risk for either current or past multivitamin users. The results were similarly null for ischemic stroke. For hemorrhagic stroke, there was a suggestion of an increased risk among current multivitamin users (RR 1.21 [95% CI: 0.98, 1.50]), however there was no evidence of a linear trend in increasing risk with longer durations (p for trend=0.81).

We also observed no significant associations for stroke mortality after adjusting for all covariates (Table 3). In the age-adjusted models, women who were current multivitamin users had a 19% lower risk of mortality from total stroke (RR 0.81 [95% CI: 0.67, 0.97], p for trend=0.04). However, in the multivariate model, the association was no longer inverse or significant (RR 1.06 [95% CI: 0.88, 1.29]). No significant increased or decreased risk of total, ischemic or hemorrhagic stroke were observed in any categories of duration of use. However, contrary to our hypothesis, there was a significant trend across duration of multivitamin use with total stroke ($p=0.01$) and ischemic stroke ($p=0.001$) among current multivitamin users.

Our results did not support our hypothesis of lower risk of incident stroke among multivitamin users with low diet quality (Table 4). Among women with low diet quality (below the 25th percentile of the aHEI for the sample population), the RR of total incident stroke was 0.95 (95% CI: 0.80, 1.15) for current multivitamin users compared to nonusers. Similarly, among women who were below the 25th percentile of folate intake for the sample population, the RR of total incident stroke was 0.95 (0.79, 1.14) for current multivitamin users compared to nonusers. We observed significant interactions in analyses stratified by age ($p=0.02$, lower risk for current users in younger women) and diabetes ($p=0.02$, higher risk in those with diabetes) for stroke incidence. Associations did not differ when stratified by smoking status, fruit and vegetable intake, or stroke diagnosis before or after 1994. In stratified analyses examining for stroke mortality (Table 5), we found a significant interaction with age ($p=0.04$, lower risk for current users in younger women) but not for any of the other stratifying factors.

Discussion

In these analyses of multivitamin use from a large prospective study of women with more than 3,600 incident stroke cases, we did not observe an overall association between multivitamin use and the risk of stroke. There were also no indication that a longer duration of multivitamin use was associated with lower risk of total, ischemic or hemorrhagic strokes and death from total stroke. In addition, we did not confirm the hypothesis that multivitamin use may reduce the risk of incident stroke and stroke mortality among individuals with low diet quality.

Consistent with our findings, previous studies conducted in the US(6–9) did not observe a significant association between multivitamin use and the risk of incident stroke. Use of vitamins has been shown to reduce the risk of stroke in some studies(20, 21), but benefits were not seen in other studies(22–25). Many vitamins are highly correlated and their independent effects are difficult to separate. Given that multivitamins are a combination of several different vitamins, it remains possible that the beneficial effect of some are counter-balanced by adverse effects of others. Perhaps more importantly, a beneficial effect of a nutritional supplement may not be seen in a population in which intake is already adequate for most persons.

Our results on stroke mortality are consistent with those of the Cancer Prevention II study, a cohort of 1,063,023 American adults with 122 deaths from stroke during 7 years of follow-up, which reported that there was no risk reduction in stroke mortality among persons who used multivitamins(9). However, results from other regions, which may have different baseline dietary intake, specifically Asia, suggest that multivitamin use may reduce the risk of stroke mortality. In the Nutrition Intervention Trials in Linxian, China, a randomized controlled trial of 3318 men and women with esophageal dysplasia, a non-significant lower risk of stroke mortality was observed among persons taking a daily multivitamin compared to those who took placebo (HR, 0.62; 95% CI, 0.37 – 1.06)(12). A recent randomized trial conducted among hypertensive adults in an area of China with low folate intake compared enalapril (10 mg) and folic acid (0.8 mg) daily with enalapril alone, and demonstrated a 21% reduced the risk of first stroke(26).

In a prospective study of Japanese adults, the Japan Collaborative Cohort (JACC) study, there was an inverse relationship (HR, 0.87; 95% CI, 0.76–1.01) between multivitamin use and the risk of death from total stroke(11). Also, among people with lower intake of fruits and vegetables (< 3 times/day) in the JACC study, daily multivitamin intake appeared to confer some protection against stroke mortality(11). In the present study, we did not observe an association between current multivitamin use and total stroke mortality. Furthermore, in stratified analyses, the risk of death from stroke was not significantly reduced among multivitamin users who had lower fruit and vegetable consumption. However, dietary intake patterns and fortification practices differ in China, Japan and US.

This study has several strengths. The NHS is a very large female prospective cohort study, which reduces recall bias. Detailed data were collected on numerous exposures using validated questionnaires, which also collected data on duration of multivitamin use.

Physicians who adjudicated strokes were not aware of the participants' exposure status, thus minimizing differential misclassification. The long duration of follow-up and large number of stroke events allowed us to examine the long-term effect of multivitamin use on the risk of stroke and stroke types. However, the total number of strokes in the cohort may have been underestimated due to self-reporting. Although we controlled for possible confounding factors in this non-interventional study and used repeated dietary measurements during follow-up, we cannot rule out the possibility of residual confounding or measurement error. Given that medical records were inadequate or unavailable for review in about a third of the stroke cases, this study did not have sufficient power to examine the relation between multivitamin use and stroke subtypes. We also did not have sufficient power to examine the relation between multivitamin use and fatal stroke types because of the relatively small number of deaths due to stroke. Furthermore, the NHS is a cohort of mostly Caucasian women in the United States; the results may not be generalizable to other populations. Since populations at highest risk of nutritional deficiency who may benefit from multivitamin use are least likely to take them(27), this study should be replicated in populations where nutritional inadequacies persist and variation of multivitamin use is high.

In conclusion, duration of multivitamin use was not associated with reduced risk of incident total, ischemic or hemorrhagic stroke or total stroke mortality in a generally well-nourished population of women.

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References

1. Supplements NIOHOD. Multivitamin/mineral Supplements [cited 2017 May 2017] Available from: <https://ods.od.nih.gov/factsheets/MVMS-Consumer/>
2. Gahche J, Bailey R, Burt V, Hughes J, Yetley E, Dwyer J, et al. Dietary supplement use among U.S. adults has increased since NHANES III 1988–1994. NCHS data brief. 2011; (61):1–8.
3. Bailey RL, Gahche JJ, Lentino CV, Dwyer JT, Engel JS, Thomas PR, et al. Dietary supplement use in the United States, 2003–2006. The Journal of nutrition. 2011; 141(2):261–6. [PubMed: 21178089]
4. Bailey RL, Gahche JJ, Miller PE, Thomas PR, Dwyer JT. Why US adults use dietary supplements. JAMA Intern Med. 2013; 173(5):355–61. [PubMed: 23381623]
5. Gaziano JM, Sesso HD, Christen WG, Bubes V, Smith JP, MacFadyen J, et al. Multivitamins in the prevention of cancer in men: the Physicians' Health Study II randomized controlled trial. JAMA. 2012; 308(18):1871–80. [PubMed: 23162860]
6. Neuhauser ML, Wassertheil-Smoller S, Thomson C, Aragaki A, Anderson GL, Manson JE, et al. Multivitamin use and risk of cancer and cardiovascular disease in the Women's Health Initiative cohorts. Archives of internal medicine. 2009; 169(3):294–304. [PubMed: 19204221]
7. Rautiainen S, Lee IM, Rist PM, Gaziano JM, Manson JE, Buring JE, et al. Multivitamin use and cardiovascular disease in a prospective study of women. The American journal of clinical nutrition. 2015; 101(1):144–52. [PubMed: 25527758]
8. Rautiainen S, Rist PM, Glynn RJ, Buring JE, Gaziano JM, Sesso HD. Multivitamin Use and the Risk of Cardiovascular Disease in Men. The Journal of nutrition. 2016
9. Sesso HD, Christen WG, Bubes V, Smith JP, MacFadyen J, Schvartz M, et al. Multivitamins in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. JAMA. 2012; 308(17):1751–60. [PubMed: 23117775]

10. Watkins ML, Erickson JD, Thun MJ, Mulinare J, Heath CW Jr. Multivitamin use and mortality in a large prospective study. *American journal of epidemiology*. 2000; 152(2):149–62. [PubMed: 10909952]
11. Dong JY, Iso H, Kitamura A, Tamakoshi A. Multivitamin Use and Risk of Stroke Mortality: The Japan Collaborative Cohort Study. *Stroke*. 2015
12. Li JY, Taylor PR, Li B, Dawsey S, Wang GQ, Ershow AG, et al. Nutrition intervention trials in Linxian, China: multiple vitamin/mineral supplementation, cancer incidence, and disease-specific mortality among adults with esophageal dysplasia. *J Natl Cancer Inst*. 1993; 85(18):1492–8. [PubMed: 8360932]
13. Colditz GA, Stampfer MJ, Willett WC, Rosner B, Speizer FE, Hennekens CH. A prospective study of parental history of myocardial infarction and coronary heart disease in women. *American journal of epidemiology*. 1986; 123(1):48–58. [PubMed: 3940442]
14. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. *American journal of epidemiology*. 1985; 122(1):51–65. [PubMed: 4014201]
15. Willett WC, Sampson L, Browne ML, Stampfer MJ, Rosner B, Hennekens CH, et al. The use of a self-administered questionnaire to assess diet four years in the past. *American journal of epidemiology*. 1988; 127(1):188–99. [PubMed: 3337073]
16. Salvini S, Hunter DJ, Sampson L, Stampfer MJ, Colditz GA, Rosner B, et al. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. *International journal of epidemiology*. 1989; 18(4):858–67. [PubMed: 2621022]
17. Walker AE, Robins M, Weinfeld FD. The National Survey of Stroke. Clinical findings. *Stroke*. 1981; 12(2 Pt 2 Suppl 1):I13–44. [PubMed: 7222164]
18. McCullough ML, Willett WC. Evaluating adherence to recommended diets in adults: the Alternate Healthy Eating Index. *Public health nutrition*. 2006; 9(1A):152–7. [PubMed: 16512963]
19. Administration FaD. Food standards: amendment of standards of identity for enriched grain products to require addition of folic acid. Final Rule 21 CFR Parts 136, 137, and 139 Federal Register. 1996; (61):8781–9.
20. Chen GC, Lu DB, Pang Z, Liu QF. Vitamin C intake, circulating vitamin C and risk of stroke: a meta-analysis of prospective studies. *J Am Heart Assoc*. 2013; 2(6):e000329. [PubMed: 24284213]
21. Sun Q, Pan A, Hu FB, Manson JE, Rexrode KM. 25-Hydroxyvitamin D levels and the risk of stroke: a prospective study and meta-analysis. *Stroke*. 2012; 43(6):1470–7. [PubMed: 22442173]
22. Zhang C, Chi FL, Xie TH, Zhou YH. Effect of B-vitamin supplementation on stroke: a meta-analysis of randomized controlled trials. *PLoS One*. 2013; 8(11):e81577. [PubMed: 24282609]
23. Schurks M, Glynn RJ, Rist PM, Tzourio C, Kurth T. Effects of vitamin E on stroke subtypes: meta-analysis of randomised controlled trials. *BMJ*. 2010; 341:c5702. [PubMed: 21051774]
24. Sesso HD, Buring JE, Christen WG, Kurth T, Belanger C, MacFadyen J, et al. Vitamins E and C in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. *JAMA*. 2008; 300(18):2123–33. [PubMed: 18997197]
25. Al-Delaimy WK, Rexrode KM, Hu FB, Albert CM, Stampfer MJ, Willett WC, et al. Folate intake and risk of stroke among women. *Stroke*. 2004; 35(6):1259–63. [PubMed: 15105514]
26. Huo Y, Li J, Qin X, Huang Y, Wang X, Gottesman RF, et al. Efficacy of folic acid therapy in primary prevention of stroke among adults with hypertension in China: the CSPPT randomized clinical trial. *JAMA*. 2015; 313(13):1325–35. [PubMed: 25771069]
27. National Institutes of Health State-of-the-Science P. National Institutes of Health State-of-the-Science Conference Statement: multivitamin/mineral supplements and chronic disease prevention. *The American journal of clinical nutrition*. 2007; 85(1):257S–64S. [PubMed: 17209206]

Age-Standardized Characteristics of the Population by Duration of Multivitamin Use in 1994 (Midpoint of Follow-up)

TABLE 1

	Multivitamin Use, years						
	Non user		Past user		Current user		
	< 5	5	< 5	5 – 9	10 – 14	15	
Participants (n)	24,169	8,619	6,895	7,471	7,138	10,022	
Mean age (years)	60 ± 7	60 ± 7	60 ± 7	60 ± 7	61 ± 7	62 ± 7	
BMI, kg/m ²	27 ± 5	26 ± 5	26 ± 5	26 ± 5	26 ± 5	26 ± 5	
Physical activity, M/wk	18 ± 23	20 ± 23	19 ± 22	20 ± 25	21 ± 27	22 ± 26	
Smoking, %							
Never	44	44	44	45	45	46	
Past	40	44	44	43	43	42	
Current	16	12	12	12	12	12	
PMH therapy use, %	32	39	38	41	43	44	
Aspirin use, %	24	29	31	32	34	36	
aHEI	39 ± 17	44 ± 10	45 ± 12	44 ± 11	45 ± 11	46 ± 11	
Folate, ug/day	270 ± 79	324 ± 108	442 ± 178	397 ± 136	498 ± 185	593 ± 201	
Alcohol, g/day	5.1 ± 9	4.8 ± 9	5.1 ± 9	4.9 ± 9	4.5 ± 8	5.1 ± 9	
Total calories, g/day	1683 ± 452	1700 ± 440	1701 ± 435	1699 ± 431	1707 ± 430	1734 ± 437	
Diabetes, %	6	6	6	6	6	5	
Hypertension, %	36	38	36	36	36	36	
High cholesterol, %	47	51	49	50	51	49	
Family history of HD, %	20	20	20	20	21	20	

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

M/wk = Metabolic Equivalent of Task/Week; PMH = Current use of post-menopausal hormone therapy; HD = Heart Disease; aHEI = Alternative Healthy Eating Index, ranges from 0 to 100, a higher score indicates healthier diet. n = number of participants.

TABLE 2
Multivariable Association Between Status, Duration of Multivitamin Use and Incidence of Total, Ischemic and Hemorrhagic Stroke

	Total Stroke			Ischemic Stroke			Hemorrhagic Stroke		
	Cases	Model 1	Model 2	Cases	Model 1	Model 2	Cases	Model 1	Model 2
Nonusers	925	1.00 (Ref)	1.00 (Ref)	483	1.00 (Ref)	1.00 (Ref)	576	1.00 (Ref)	1.00 (Ref)
Past Users All	731	1.01 (0.91, 1.11)	1.04 (0.93, 1.15)	386	1.04 (0.91, 1.20)	1.01 (0.88, 1.16)	102	0.95 (0.73, 1.23)	1.07 (0.83, 1.40)
< 5 years	331	0.96 (0.84, 1.09)	0.99 (0.87, 1.13)	178	1.00 (0.84, 1.19)	0.97 (0.81, 1.15)	56	1.03 (0.76, 1.41)	1.19 (0.87, 1.64)
5 years	400	1.05 (0.93, 1.18)	1.08 (0.95, 1.23)	208	1.08 (0.92, 1.28)	1.06 (0.89, 1.26)	46	0.86 (0.61, 1.21)	0.96 (0.68, 1.36)
P for trend		0.24	0.18		0.73	0.77		0.97	0.99
Current users All	1,959	0.93 (0.85, 1.01)	1.02 (0.93, 1.11)	1,020	0.96 (0.85, 1.07)	0.99 (0.88, 1.12)	303	1.03 (0.84, 1.26)	1.21 (0.98, 1.50)
< 5 years	299	0.92 (0.81, 1.05)	0.99 (0.86, 1.13)	169	1.01 (0.84, 1.21)	1.01 (0.85, 1.22)	48	0.85 (0.61, 1.17)	0.98 (0.70, 1.35)
5 – 9 years	410	0.96 (0.85, 1.08)	1.05 (0.93, 1.19)	203	0.92 (0.78, 1.09)	0.95 (0.80, 1.12)	82	1.29 (0.98, 1.70)	1.51 (1.14, 1.99)
10 – 14 years	321	0.84 (0.73, 0.96)	0.91 (0.80, 1.05)	170	0.87 (0.73, 1.04)	0.89 (0.74, 1.06)	58	1.10 (0.80, 1.50)	1.29 (0.94, 1.77)
15 years	929	0.96 (0.87, 1.06)	1.08 (0.97, 1.20)	478	1.00 (0.87, 1.15)	1.06 (0.91, 1.22)	115	0.95 (0.73, 1.23)	1.13 (0.86, 1.49)
P for trend		0.36	0.12		0.46	0.21		0.87	0.81

Cases=number of stroke events

Model 1 = Adjusted for age and follow-up cycle.

Model 2 = Model 1 + total calories, smoking, BMI, parental history of heart disease, alcohol intake, physical activity, aspirin, post-menopausal therapy use, Alternate Healthy Eating Index, history of hypertension, hypercholesterolemia and diabetes.

P for trend is for linear trend in duration and does not include nonusers.

TABLE 3
Multivariable Association Between Status, Duration of Multivitamin Use and Stroke Mortality

	Total Stroke			Ischemic Stroke			Hemorrhagic Stroke		
	Cases	Model 1	Model 2	Cases	Model 1	Model 2	Cases	Model 1	Model 2
Nonusers	195	1.00 (Ref)	1.00 (Ref)	33	1.00 (Ref)	1.00 (Ref)	90	1.00 (Ref)	1.00 (Ref)
Past Users All	158	0.96 (0.77, 1.20)	1.16 (0.92, 1.45)	40	1.12 (0.69, 1.82)	1.38 (0.83, 2.29)	47	0.81 (0.56, 1.17)	1.03 (0.70, 1.51)
< 5 years	64	0.88 (0.66, 1.18)	1.07 (0.80, 1.44)	16	1.13 (0.61, 2.09)	1.45 (0.76, 2.73)	26	0.91 (0.58, 1.43)	1.19 (0.75, 1.89)
5 years	94	1.06 (0.81, 1.37)	1.28 (0.98, 1.67)	24	1.15 (0.66, 2.00)	1.41 (0.79, 2.52)	21	0.71 (0.43, 1.17)	0.89 (0.54, 1.48)
P for trend		0.26	0.24		0.44	0.45		0.94	0.88
Current users All	405	0.81 (0.67, 0.97)	1.06 (0.88, 1.29)	99	0.86 (0.56, 1.32)	1.17 (0.74, 1.84)	144	0.86 (0.64, 1.55)	1.15 (0.85, 1.55)
< 5 years	45	0.65 (0.47, 0.90)	0.80 (0.57, 1.12)	9	0.74 (0.35, 1.55)	0.92 (0.43, 1.97)	21	0.67 (0.41, 1.08)	0.87 (0.53, 1.41)
5 – 9 years	86	0.90 (0.69, 1.17)	1.16 (0.89, 1.52)	15	0.69 (0.36, 1.31)	0.94 (0.48, 1.83)	36	1.04 (0.69, 1.55)	1.33 (0.89, 2.01)
10 – 14 years	68	0.79 (0.59, 1.06)	1.03 (0.77, 1.39)	12	0.60 (0.30, 1.20)	0.79 (0.39, 1.61)	32	1.11 (0.72, 1.69)	1.50 (0.97, 2.31)
15 years	206	0.85 (0.68, 1.06)	1.18 (0.94, 1.48)	63	1.07 (0.67, 1.70)	1.54 (0.94, 2.53)	55	0.76 (0.52, 1.10)	1.05 (0.71, 1.55)
P for trend		0.04	0.01		0.003	0.001		0.92	0.86

Cases=number of stroke events

Model 1 = Adjusted for age and follow-up cycle.

Model 2 = Model 1 + total calories, smoking, BMI, parental history of heart disease, alcohol intake, physical activity, aspirin, post-menopausal therapy use, Alternate Healthy Eating Index, history of hypertension, hypercholesterolemia and diabetes.

P for trend is for linear trend in duration and does not include nonusers.

TABLE 4
Multivariable Association Between Multivitamin Use and Total Stroke Incidence, Stratified by Key Risk Factors

Risk Factors	Multivitamin User					P-interaction
	Cases	Nonuser	Cases	Past User	Current User	
Age						0.02
< 60 years	314	1.0	120	1.01 (0.80, 1.26)	0.86 (0.71, 1.03)	
60 years	611	1.0	611	1.05 (0.93, 1.18)	1.06 (0.96, 1.17)	
Hypertension						0.56
No	355	1.0	222	1.01 (0.85, 1.21)	1.00 (0.86, 1.15)	
Yes	570	1.0	509	1.04 (0.92, 1.19)	1.04 (0.93, 1.16)	
Diabetes						0.02
No	757	1.0	566	0.99 (0.88, 1.11)	1.02 (0.92, 1.12)	
Yes	168	1.0	165	1.23 (0.97, 1.57)	1.05 (0.85, 1.31)	
Smoking						0.14
Never	320	1.0	289	1.11 (0.93, 1.31)	1.05 (0.91, 1.21)	
Former	314	1.0	301	1.03 (0.87, 1.21)	1.06 (0.92, 1.23)	
Current	291	1.0	141	1.01 (0.81, 1.26)	0.88 (0.73, 1.06)	
aHEI						0.42
< 25 th Percentile	228	1.0	173	1.05 (0.85, 1.30)	0.95 (0.80, 1.15)	
25 th Percentile	697	1.0	558	1.02 (0.91, 1.15)	1.03 (0.93, 1.13)	
Folate intake						0.71
< 25 th Percentile	387	1.0	113	0.97 (0.79, 1.20)	0.95 (0.79, 1.14)	
25 th Percentile	538	1.0	598	1.07 (0.95, 1.21)	1.05 (0.94, 1.17)	
Fruit & vegetable intake						0.30
< 3 servings/day	343	1.0	140	1.04 (0.92, 1.17)	1.06 (0.96, 1.17)	
3 servings/day	583	1.0	591	1.05 (0.84, 1.31)	0.89 (0.74, 1.07)	
Strokes occurring						0.18
On/before 1994	531	1.0	231	1.02 (0.86, 1.20)	0.95 (0.83, 1.09)	
After 1994	394	1.0	500	1.04 (0.91, 1.20)	1.04 (0.93, 1.17)	

Cases=number of stroke events

aHEI = Alternative Healthy Eating Index

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Models are adjusted for age, follow-up cycle, total calories, smoking, BMI, parental history of heart disease, alcohol intake, physical activity, aspirin and post-menopausal therapy use, Alternate Healthy Eating Index, history of hypertension, hypercholesterolemia and diabetes.

TABLE 5
Multivariable Association Between Multivitamin Use and Total Stroke Mortality, Stratified by Key Risk Factors

Risk Factors	Multivitamin User					P-interaction
	Cases	Nonuser	Cases	Past User	Current User	
Age						0.04
< 60 years	77	1.0	19	0.99 (0.58, 1.72)	0.74 (0.49, 1.12)	
60 years	118	1.0	139	1.19 (0.91, 1.54)	1.12 (0.89, 1.41)	
Hypertension						0.66
No	83	1.0	50	1.19 (0.81, 1.75)	0.95 (0.69, 1.31)	
Yes	112	1.0	108	1.17 (0.88, 1.57)	1.16 (0.91, 1.49)	
Diabetes						0.31
No	165	1.0	119	1.05 (0.82, 1.36)	1.05 (0.85, 1.30)	
Yes	30	1.0	39	1.67 (0.95, 2.91)	1.15 (0.70, 1.90)	
Smoking						0.71
Never	64	1.0	57	1.08 (0.73, 1.59)	1.05 (0.75, 1.46)	
Former	67	1.0	73	1.12 (0.78, 1.60)	1.01 (0.74, 1.38)	
Current	64	1.0	28	1.24 (0.75, 2.05)	0.99 (0.67, 1.48)	
aHEI						0.87
< 25 th Percentile	41	1.0	36	1.12 (0.68, 1.83)	1.06 (0.69, 1.63)	
25 th Percentile	154	1.0	122	1.06 (0.82, 1.37)	0.97 (0.78, 1.21)	
Folate intake						
< 25 th Percentile	77	1.0	27	1.12 (0.69, 1.84)	1.15 (0.77, 1.73)	0.59
25 th Percentile	118	1.0	131	1.15 (0.88, 1.51)	1.02 (0.80, 1.29)	
Fruit & vegetable intake						0.50
< 3 servings/day	74	1.0	33	1.13 (0.87, 1.48)	1.11 (0.88, 1.39)	
3 servings/day	121	1.0	125	1.40 (0.88, 2.24)	0.93 (0.63, 1.39)	
Strokes occurring						0.06
On/before 1994	115	1.0	33	0.90 (0.59, 1.35)	0.87 (0.63, 1.18)	
After 1994	80	1.0	125	1.29 (0.96, 1.74)	1.18 (0.90, 1.53)	

Cases=number of stroke events

aHEI = Alternative Healthy Eating Index

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Models are adjusted for age, follow-up cycle, total calories, smoking, BMI, parental history of heart disease, alcohol intake, physical activity, aspirin and post-menopausal therapy use, Alternate Healthy Eating Index, history of hypertension, hypercholesterolemia and diabetes.