Association between intakes of magnesium, potassium, and calcium and risk of stroke: 2 cohorts of US women and updated meta-analyses[1–4]

Sally N Adebamowo, Donna Spiegelman, Walter C Willett, and Kathryn M Rexrode

ABSTRACT

Background: Prospective data on the relation of magnesium, potassium, and calcium intakes with stroke risk are inconsistent, and to our knowledge, the effect of a combined mineral diet score has not been examined.

Objective: We examined associations between intakes of magnesium, potassium, and calcium and risk of incident stroke in 86,149 women in the Nurses' Health Study (NHS) I and 94,715 women in the NHS II.

Design: In this prospective cohort study, we calculated HRs of stroke by quintiles of intake for each mineral and for a combined diet score of all 3 minerals by using multivariate Cox proportional hazard models. In addition, we updated meta-analyses on dietary intakes of these minerals and risk of stroke.

Results: During follow-up (30 y in the NHS I; 22 y in the NHS II) a total of 3780 incident stroke cases were documented. Pooled multivariate RRs of total stroke for women in the highest compared with the lowest quintiles were 0.87 (95% CI: 0.78, 0.97) for total magnesium, 0.89 (95% CI: 0.80, 0.99) for total potassium, and 0.97 (95% CI: 0.87, 1.09) for total calcium intake. Pooled RRs for women in the highest compared with the lowest quintiles of a combined mineral diet score were 0.72 (95% CI: 0.65, 0.81) for total stroke, 0.78 (95% CI: 0.66, 0.92) for ischemic stroke, and 0.80 (95% CI: 0.61, 1.04) for hemorrhagic stroke. In the updated meta-analyses of all prospective studies to date, the combined RR of total stroke was 0.87 (95% CI: 0.83, 0.92) for a 100-mg/d increase in magnesium intake, 0.91 (95% CI: 0.88, 0.94) for a 1000-mg/d increase in potassium intake, and 0.98 (95% CI: 0.94, 1.02) for a 300-mg/d increase in calcium intake.

Conclusions: A combined mineral diet score was inversely associated with risk of stroke. High intakes of magnesium and potassium but not calcium were also significantly associated with reduced risk of stroke in women. *Am J Clin Nutr* 2015;101:1269–77.

Keywords: calcium, magnesium, potassium, stroke, ischemic stroke, hemorrhagic stroke

INTRODUCTION

Magnesium is an essential mineral and cofactor for >300 enzymatic reactions in the body (1). Magnesium is the second most-abundant intracellular cation next to potassium (2). Calcium is the most-abundant mineral in the body. Like magnesium and potassium, calcium is critically involved in cardiovascular functions (3). High dietary intakes of each of these minerals were reported to lower risk of hypertension (4–7), which is the principal modifiable stroke risk factor. However, only a few prospective studies examined the relation between dietary and supplemental intakes of these minerals and risk of stroke in women, and results have been inconsistent. Prospective studies in Europe showed magnesium intake, but not intake of potassium or calcium, was significantly associated with reduced risk of stroke (7, 8). In the United States, intakes of potassium and magnesium, but not of calcium, were associated with reduced stroke risk in men (9), whereas calcium and potassium intakes, but not magnesium intake, were associated with reduced stroke risk in women (10). Also, one study showed no overall association between any of these minerals and risk of stroke (11).

The few prospective observational studies that were conducted did not include follow-up beyond 15 y and had a relatively small number of incident stroke events, and in most studies, the independent effect of each mineral intake from supplements and stroke types was not examined. In this article, we provide evidence on the association of each mineral intake from diet and supplements with risk of total, ischemic, and hemorrhagic incident strokes. In addition, we hypothesized that a combined diet score of all 3 minerals may be associated with reduced stroke risk because these minerals exist together in foods, and intakes are strongly correlated. We addressed these aims in US women who were followed prospectively in the 2 large cohorts the Nurses' Health Study (NHS)[5] I and II.

[1] From the Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA (SNA and KMR); the Departments of Department of Nutrition (SNA, DS, and WCW), Biostatistics (DS), Epidemiology (DS and WCW), and Global Health and Population (DS), Harvard T.H. Chan School of Public Health, Boston, MA; and the Channing Division of Network Medicine, Boston, MA (WCW).

[2] Supported by the NIH (grants UM1CA176726, UM1CA186107, D43TW009106, HL34594, CA87969, and HL088521) and the Bernard Lown Cardiovascular Disease Program (to SNA).

[3] Supplemental Tables 1–9 are available from the "Supplemental data" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

[4] Address correspondence to SN Adebamowo, Department of Nutrition, Harvard T.H. Chan School of Public Health, 677 Huntington Avenue, Boston, MA 02115. E-mail: sallya@mail.harvard.edu.

[5] Abbreviations used: FFQ, food-frequency questionnaire; IHD, ischemic heart disease; NHS, Nurses' Health Study.

Received September 30, 2014. Accepted for publication April 2, 2015.
First published online May 6, 2015; doi: 10.3945/ajcn.114.100354.

METHODS

Study population

The NHS I is a prospective cohort of 121,700 female registered nurses residing in the United States who were 30–55 y old at enrollment in 1976 (12). The NHS II is also a prospective cohort; it was established in 1989 when 116,671 female registered nurses, who were aged 25–42 y and residing in the United States, were enrolled. All women provided information on their medical histories and lifestyles. Every 2 y, follow-up questionnaires were sent to update this information. Detailed dietary intake was assessed by using a semiquantitative food-frequency questionnaire (FFQ) in 1980, 1984, 1986, and every 4 y thereafter in the NHS I and in 1991 and every 4 y thereafter in the NHS II. We excluded participants with prevalent cancer, stroke, or ischemic heart disease (IHD) at baseline, implausibly low or high energy intakes, and lack of diet information. After these exclusions, 86,149 women in the NHS I were eligible and followed up from 1980 until 2010 for stroke incidence, and 94,715 women in the NHS II were eligible and followed up from 1989 until 2011 for stroke incidence.

Ethics

The study was approved by the Committee on the use of Human Subjects in Research at Brigham and Women's Hospital. The return of a questionnaire was considered to imply consent.

Ascertainment of diet

The FFQ asked about average frequency of intake during the previous year of specified portions of 131 foods and use of vitamin and mineral supplements. In addition, we asked about the use of specific supplements of magnesium, potassium, and calcium. The reproducibility and validity of this questionnaire was reported elsewhere (13–15). In a validation study in 200 nurses in NHS I cohort participants conducted in 1986, correlations between mineral intake assessed by the expanded dietary questionnaire and by 2 1-wk diet records were 0.62 for calcium, 0.61 for potassium, and 0.76 for magnesium after the within-person variation in diet records was taken into account (16).

Ascertainment of stroke

The primary endpoint was incident stroke that occurred after the return of the 1980 FFQ but before June 2010 for the NHS I and after the return of the 1989 FFQ but before June 2011 for the NHS II. Participants who reported an incident stroke on a follow-up questionnaire were asked for permission to review their medical records. Medical records were reviewed by study physicians with no knowledge of the self-reported risk-factor status of the participants. Strokes were confirmed if characterized by a typical neurologic defect of sudden or rapid onset that lasted >24 h and was attributable to a cerebrovascular event. Strokes were classified according to the criteria of the National Survey of Stroke as being due to ischemia (embolic or thrombotic), hemorrhage (subarachnoid or intracerebral hemorrhage), or an unknown cause (17). Nonfatal strokes for which confirmatory information was obtained by interview or letter but for which no medical records were available were designated as probable and assigned to a stroke of unspecified type because of the lack of primary data for review. In total, 24% of the women with stroke in NHS I and 32% in NHS II did not give permission to review their medical records, and 6% in the NHS I and 8% in the NHS II gave permission for a review of their medical records, but the records could not be obtained.

Deaths were reported by next of kin, coworkers, postal authorities, or the National Death Index. Fatal strokes were confirmed by medical records or autopsy reports or were considered probable if these were not obtainable, and stroke was listed as the underlying cause on the death certificate.

Covariates

Information was obtained on potential confounding factors, including medical history, other aspects of dietary intake, and lifestyle behaviors that could be associated with intake of these minerals and risk of stroke. These variables were updated biennially and included cigarette smoking (never, past, or current), physical activity (<3, 3 to <9, 9 to <18, 18 to <27, or ≥ 27 metabolic equivalent tasks per week), menopausal status (premenopausal or postmenopausal), postmenopausal hormone therapy use (never, past, or current), parental history of early myocardial infarction (before age 60 y), multivitamin use (yes or no), thiazide use (yes or no), aspirin use at least 2 times/wk (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. BMI (in kg/m^2) was calculated as weight divided by height squared. BMI was divided into 3 categories (i.e., <25, 25 to <30, and ≥ 30). Quintiles were calculated for total energy intake (kcal), and we used alcohol consumption categories of 0, 0 to <5, 5 to <10, 10 to <15, and ≥ 15 g/d.

Statistical analyses

To examine associations between diet and stroke, we used Cox proportional hazards models stratified by age (mo) and follow-up cycle to estimate RRs and 95% CIs. Participants were divided into quintiles of cumulative average intake of magnesium, potassium, and calcium to reduce the within-person variation and best represent long-term intake (18). A combined mineral diet score of magnesium, potassium, and calcium were computed by assigning points to each quintile and summing the points. Participants in the lowest quintile (quintile 1) of magnesium, potassium, or calcium intake received 1 point for each mineral, participants in the next quintile (quintile 2) received 2 points, and so forth. We summed points to create the overall mineral diet score, which ranged from 3 to 15. Cumulative averages were calculated by taking the mean of all reported FFQ intakes up to the beginning of each 2-y follow-up interval. The cumulative average intake was 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 (mo) and calendar time (2-y time intervals) and included intakes of total energy (kcal), alcohol (g/d), cigarette smoking, BMI, physical activity, parental history of early myocardial infarction, postmenopausal hormone therapy use, thiazide use, aspirin use, multivitamin use, and history of diabetes, hypertension, and hypercholesterolemia

TABLE 1
Age-standardized characteristics of 86,149 women in the NHS I in 1994 and 94,715 women in the NHS II in 1995 by quintiles of magnesium, potassium, and calcium intakes[1]

	Magnesium						Potassium						Calcium					
	NHS I			NHS II			NHS I			NHS II			NHS I			NHS II		
	Quintile 1	Quintile 3	Quintile 5	Quintile 1	Quintile 3	Quintile 5	Quintile 1	Quintile 3	Quintile 5	Quintile 1	Quintile 3	Quintile 5	Quintile 1	Quintile 3	Quintile 5	Quintile 1	Quintile 3	Quintile 5
n	14,962	17,543	15,534	22,349	18,811	15,695	14,393	17,271	17,189	21,177	18,369	17,747	27,825	16,002	9134	24,456	18,164	14,491
Age, y	58 ± 7	60 ± 7	62 ± 7	40 ± 5	41 ± 5	41 ± 5	58 ± 7	60 ± 7	62 ± 7	40 ± 5	41 ± 5	42 ± 4	60 ± 7	60 ± 7	62 ± 7	41 ± 5	40 ± 5	41 ± 5
BMI, kg/m^2	26.7 ± 5.5	26.5 ± 5.2	26.0 ± 5.0	26.2 ± 6.5	25.5 ± 5.7	25.3 ± 5.5	26.4 ± 5.5	26.4 ± 5.1	26.5 ± 5.2	26.0 ± 6.5	25.6 ± 5.7	25.6 ± 5.5	26.5 ± 5.3	26.5 ± 5.2	26.1 ± 5.0	26.0 ± 6.1	25.7 ± 5.8	25.4 ± 5.6
Physical activity, METs/wk	14.6 ± 20.7	19.1 ± 22.5	21.4 ± 28.7	14.0 ± 19.11	19.0 ± 22.9	24.9 ± 28.6	14.8 ± 22.0	18.7 ± 22.1	25.2 ± 30.0	14.4 ± 19.7	18.0 ± 21.5	25.0 ± 28.8	15.8 ± 21.7	19.6 ± 24.2	22.6 ± 26.9	16.1 ± 21.5	19.6 ± 23.9	21.3 ± 25.5
Smoking, %																		
Never	48	44	41	69	64	62	47	45	41	71	66	58	42	44	47	63	66	67
Past	35	42	47	18	25	29	36	42	46	18	24	30	37	43	44	22	24	25
Current	17	14	12	13	11	9	17	13	13	11	10	12	21	13	9	15	10	18
Aspirin use, %	20	28	30	6	8	8	23	27	29	7	7	9	21	28	31	11	11	12
Thiazide use, %	6	7	7	2	2	2	5	7	8	2	2	3	6	7	7	7	7	9
Multivitamin, %	22	39	59	26	39	58	30	41	46	33	40	45	20	40	59	26	42	57
PMH therapy, %	29	37	41	8	8	10	31	37	37	8	9	11	26	36	46	8	8	12
Calcium, mg/d	685 ± 245	913 ± 246	1184 ± 348	767 ± 292	1040 ± 339	1334 ± 459	703 ± 266	908 ± 285	1141 ± 339	826 ± 342	1032 ± 366	1225 ± 441	513 ± 80	867 ± 50	1433 ± 234	608 ± 98	1027 ± 58	1722 ± 350
Magnesium, mg/d	226 ± 21	297 ± 8	387 ± 38	240 ± 25	321 ± 9	434 ± 57	238 ± 35	297 ± 34	364 ± 48	256 ± 50	321 ± 48	394 ± 57	258 ± 45	300 ± 46	343 ± 58	274 ± 54	328 ± 58	377 ± 82
Potassium, mg/d	2361 ± 297	2930 ± 271	3452 ± 406	2451 ± 341	3070 ± 330	3521 ± 512	2247 ± 210	2880 ± 69	3590 ± 271	2315 ± 240	2999 ± 70	3261 ± 317	2568 ± 423	2927 ± 406	3222 ± 466	2710 ± 495	3045 ± 469	3266 ± 533
Alcohol, g/d	5.3 ± 10.7	5.3 ± 9.2	4.6 ± 8.1	2.5 ± 5.8	3.7 ± 6.9	3.6 ± 6.6	6.0 ± 11.8	5.1 ± 8.9	4.2 ± 7.4	2.8 ± 6.8	3.6 ± 6.7	3.5 ± 6.0	6.4 ± 11.8	5.1 ± 8.9	3.9 ± 7.3	3.6 ± 7.4	3.4 ± 6.1	2.9 ± 5.8
Diabetes, %	6	6	6	1	1	1	6	6	7	1	1	1	6	7	6	1	1	1
Hypertension, %	39	37	35	7	6	6	37	36	38	7	6	6	39	37	35	7	5	6
High cholesterol, %	47	48	48	12	11	11	47	48	48	12	11	11	45	48	49	12	10	12
Parental history of heart disease, %	20	21	21	18	18	18	19	20	22	18	18	20	20	21	20	19	18	18

[1]Means ± SDs are given for continuous variables, and percentages of population are given for dichotomous variables. Nutrients except alcohol were calorie-adjusted. MET, metabolic equivalent task; NHS, Nurses' Health Study; PMH, postmenopausal hormone.

at baseline. To test for a linear trend, we assigned each quintile the median value and modeled this variable as a continuous variable. We examined the potential deviation from linearity by using a likelihood ratio test for comparison of a model with the linear term with a model including the linear term plus restricted cubic spline transformations (19). We also conducted analyses that included all 3 minerals simultaneously. Magnesium and potassium intakes were highly correlated ($r = 0.79$ in the NHS I; $r = 0.73$ in the NHS II), and correlations between calcium and potassium intakes ($r = 0.49$ in the NHS I; $r = 0.41$ in the NHS II), whereas between calcium and magnesium intakes ($r = 0.54$ in the NHS I; $r = 0.56$ in the NHS II) were moderate. The Q test was used to test for the heterogeneity between the NHS I and NHS II. RRs (±SEs) for each quintile from each cohort were pooled in fixed-effects models to calculate summary estimates (20). Similarly, the updated meta-analysis followed standard practice (20) of testing for heterogeneity by using the Q test and using fixed effects model to produce summary estimates when no between-studies heterogeneity was evident; otherwise a random-effects model was used.

To examine the potential effect modification of the association between dietary minerals and stroke risk by age, hypertension, and diabetes, we stratified our multivariate model on age (<60 compared with ≥60 y), hypertension (yes compared with no), and diabetes (yes compared with no) and separately tested the significance of an interaction by using a likelihood ratio test for the comparison of the model with interaction terms to the model with only main effects. All *P* values were 2-sided, and analyses were conducted with SAS 9.2 software (SAS Institute Inc.).

RESULTS

During 30 y of follow-up from 1980 through 2010 in the NHS I and 22 y of follow-up from 1989 through 2011 in the NHS II, a total of 3780 incident stroke cases were ascertained. Of these cases, 3237 incident strokes were documented in the NHS I (including 1664 ischemic, 544 hemorrhagic, and 1029 unspecified strokes), and 543 incident strokes were documented in the NHS II (including 186 ischemic, 92 hemorrhagic, and 265 unspecified strokes). Age-standardized characteristics of study participants at midpoint during follow-up in 1994 for the NHS I and in 1995 for the NHS II are shown in **Table 1**. Women with higher mineral intake were more likely to use aspirin, multivitamins, and postmenopausal hormone therapy, more physically active, less likely to be current smokers than were women with lower mineral intake. Data for women in the NHS I and NHS II were combined because we did not observe a significant between-study heterogeneity (Q-statistic $P > 0.05$).

TABLE 2
Pooled RRs (95% CIs) of total, ischemic, and hemorrhagic strokes by quintiles of total and dietary magnesium intake in 86,149 women in the NHS I and 94,715 women in the NHS II[1]

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P*-linear trend
Total magnesium intake						
Total stroke	662	679	735	836	868	—
Age-adjusted model	1.0 (reference)	0.84 (0.75, 0.93)	0.82 (0.73, 0.91)	0.83 (0.75, 0.92)	0.77 (0.70, 0.86)	<0.001
Multivariate model 1	1.0 (reference)	0.87 (0.78, 0.97)	0.88 (0.79, 0.98)	0.91 (0.82, 1.01)	0.87 (0.78, 0.97)	0.07
Multivariate model 2	1.0 (reference)	0.89 (0.79, 1.01)	0.92 (0.80, 1.05)	0.97 (0.84, 1.11)	0.93 (0.79, 1.08)	0.69
Ischemic stroke	299	341	379	404	427	—
Age-adjusted model	1.0 (reference)	0.91 (0.78, 1.06)	0.91 (0.78, 1.07)	0.87 (0.75, 1.06)	0.83 (0.71, 0.96)	0.01
Multivariate model 1	1.0 (reference)	0.90 (0.77, 1.06)	0.93 (0.80, 1.09)	0.90 (0.77, 1.05)	0.87 (0.75, 1.02)	0.13
Multivariate model 2	1.0 (reference)	0.94 (0.79, 1.12)	1.00 (0.82, 1.21)	0.99 (0.81, 1.22)	0.99 (0.79, 1.25)	0.85
Hemorrhagic stroke	129	116	122	134	135	—
Age-adjusted model	1.0 (reference)	0.79 (0.61, 1.02)	0.78 (0.60, 1.00)	0.81 (0.63, 1.03)	0.75 (0.58, 0.96)	0.06
Multivariate model 1	1.0 (reference)	0.81 (0.63, 1.05)	0.81 (0.63, 1.05)	0.85 (0.66, 1.09)	0.80 (0.62, 1.03)	0.15
Multivariate model 2	1.0 (reference)	0.84 (0.63, 1.12)	0.88 (0.65, 1.21)	0.94 (0.67, 1.31)	0.84 (0.58, 1.22)	0.51
Dietary magnesium intake						
Total stroke	718	709	733	839	781	—
Age-adjusted model	1.0 (reference)	0.81 (0.73, 0.90)	0.76 (0.69, 0.84)	0.81 (0.73, 0.90)	0.72 (0.65, 0.80)	<0.001
Multivariate model 1	1.0 (reference)	0.85 (0.77, 0.95)	0.82 (0.74, 0.91)	0.89 (0.81, 0.99)	0.81 (0.73, 0.90)	0.001
Multivariate model 2	1.0 (reference)	0.85 (0.75, 0.96)	0.83 (0.72, 0.95)	0.92 (0.79, 1.06)	0.82 (0.69, 0.97)	0.08
Ischemic stroke	329	354	357	429	381	—
Age-adjusted model	1.0 (reference)	0.87 (0.75, 1.01)	0.79 (0.68, 0.92)	0.89 (0.77, 1.02)	0.75 (0.64, 0.87)	<0.001
Multivariate model 1	1.0 (reference)	0.88 (0.76, 1.03)	0.82 (0.70, 0.95)	0.94 (0.81, 1.08)	0.81 (0.69, 0.94)	0.03
Multivariate model 2	1.0 (reference)	0.91 (0.76, 1.08)	0.87 (0.71, 1.06)	1.03 (0.83, 1.28)	0.91 (0.71, 1.15)	0.71
Hemorrhagic stroke	134	112	131	126	133	—
Age-adjusted model	1.0 (reference)	0.74 (0.57, 0.95)	0.80 (0.63, 1.02)	0.74 (0.58, 0.95)	0.75 (0.59, 0.96)	0.05
Multivariate model 1	1.0 (reference)	0.76 (0.59, 0.98)	0.83 (0.65, 1.06)	0.78 (0.60, 1.00)	0.79 (0.61, 1.01)	0.11
Multivariate model 2	1.0 (reference)	0.78 (0.59, 1.04)	0.91 (0.66, 1.25)	0.88 (0.62, 1.25)	0.87 (0.59, 1.29)	0.69

[1]Values are the *n* of cases. Cox proportional hazards models were used to estimate RRs and 95% CIs. Model 1 was adjusted for age, calendar year, total calories (quintiles of kcal), BMI (in kg/m^2; <25, 25 to <30, or ≥30), parental history of heart disease (aged ≤60 y), alcohol intake (0, 0 to <5, 5 to <10, 10 to <15, or ≥15 g/d), physical activity (<3, 3 to <9, 9 to<18, 18 to <27, or ≥27 metabolic equivalent tasks/wk), smoking, postmenopausal hormone therapy, oral contraceptive use (never, past, or current), menopausal status (premenopausal or postmenopausal), aspirin (0 to <2 or ≥2 pills/wk), multivitamin, history of hypertension, hypercholesterolemia, diabetes at baseline, and thiazide use (yes or no). Model 2 was adjusted as for model 1 and for intakes of potassium and calcium (quintiles of g/d). NHS, Nurses' Health Study.

In the multivariate analyses, total and dietary magnesium intakes were inversely associated with risk of total but ischemic or hemorrhagic stroke (**Table 2**). The pooled multivariate RR for total stroke was 0.87 (95% CI: 0.78, 0.97; *P*-trend = 0.07) for the comparison of women in the highest with lowest quintiles of total magnesium intake; whereas the pooled multivariate RR for the comparison of highest with lowest quintiles of dietary magnesium intake was 0.81 (95% CI: 0.69, 0.94; *P*-trend = 0.001) for total stroke. Total potassium intake was inversely associated with risk of total but not ischemic or hemorrhagic stroke (**Table 3**). For comparison of women in the highest with lowest quintiles of total potassium intake, the pooled multivariate RR for total stroke was 0.89 (95% CI: 0.80, 0.99; *P*-trend = 0.01). Multivariate RRs for both magnesium and potassium were attenuated when all 3 minerals were included in the models simultaneously (multivariate model 2). There was no significant association between total or dietary calcium intake and total, ischemic, or hemorrhagic stroke (**Table 4**). Multivariate RRs for total magnesium (**Supplemental Table 1**), total potassium (**Supplemental Table 2**), total calcium (**Supplemental Table 3**), dietary magnesium (**Supplemental Table 4**), dietary potassium (**Supplemental Table 5**), and dietary calcium (**Supplemental Table 6**) and risk of total, ischemic, and hemorrhagic strokes for each cohort separately are shown in the supplemental material.

Because of the relatively high degree of correlation between these minerals, we also examined a combined magnesium, potassium, and calcium diet score (**Table 5**). For comparison of women in the highest with lowest quintiles of combined magnesium, potassium, and calcium diet score, the pooled multivariate RR for total stroke was 0.81 (95% CI: 0.72, 0.91; *P*-trend = 0.003). Findings were similar for ischemic but not hemorrhagic stroke.

We examined separately the relation between intakes of magnesium, potassium, and calcium from supplements and risk of stroke. There was no significant association between supplemental magnesium or calcium intake and risk of total, ischemic, or hemorrhagic stroke in the pooled analyses. We observed a significant inverse association between supplemental potassium intake and risk of ischemic but not total or hemorrhagic stroke. The pooled multivariate RR for comparison of highest with lowest quintiles of supplemental potassium intake was 0.71 (95% CI: 0.56, 0.89, *P*-trend $<$ 0.01) for ischemic stroke. Pooled multivariate RRs for supplemental magnesium (**Supplemental Table 7**), supplemental potassium (**Supplemental Table 8**), and supplemental calcium (**Supplemental**

TABLE 3
Pooled RRs (95% CIs) of total, ischemic, and hemorrhagic strokes by quintiles of total and dietary potassium intake in 86,149 women in the NHS I and 94,715 women in the NHS II[1]

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P*-linear trend
Total potassium intake						
Total stroke	647	723	732	795	883	—
Age-adjusted model	1.0 (reference)	0.92 (0.83, 1.02)	0.84 (0.75, 0.93)	0.82 (0.74, 0.92)	0.83 (0.75, 0.93)	0.0003
Multivariate model 1	1.0 (reference)	0.97 (0.87, 1.08)	0.89 (0.80, 0.99)	0.89 (0.80, 0.99)	0.89 (0.80, 0.99)	0.01
Multivariate model 2	1.0 (reference)	1.00 (0.89, 1.12)	0.92 (0.81, 1.05)	0.91 (0.79, 1.05)	0.91 (0.78, 1.06)	0.16
Ischemic stroke	298	349	381	384	438	—
Age-adjusted model	1.0 (reference)	0.95 (0.81, 1.11)	0.93 (0.80, 1.08)	0.85 (0.73, 0.99)	0.87 (0.75, 1.01)	0.03
Multivariate model 1	1.0 (reference)	0.96 (0.82, 1.12)	0.93 (0.80, 1.09)	0.86 (0.73, 1.00)	0.87 (0.75, 1.02)	0.04
Multivariate model 2	1.0 (reference)	0.98 (0.82, 1.16)	0.95 (0.79, 1.15)	0.87 (0.71, 1.07)	0.89 (0.72, 1.11)	0.23
Hemorrhagic stroke	128	135	114	117	142	—
Age-adjusted model	1.0 (reference)	0.94 (0.73, 1.19)	0.74 (0.57, 0.95)	0.71 (0.55, 0.91)	0.80 (0.63, 1.02)	0.02
Multivariate model 1	1.0 (reference)	0.97 (0.76, 1.24)	0.79 (0.61, 1.02)	0.76 (0.59, 0.98)	0.85 (0.67, 1.10)	0.08
Multivariate model 2	1.0 (reference)	0.99 (0.76, 1.30)	0.79 (0.58, 1.07)	0.74 (0.53, 1.03)	0.81 (0.56, 1.16)	0.16
Dietary potassium intake						
Total stroke	666	736	746	782	850	—
Age-adjusted model	1.0 (reference)	0.91 (0.82, 1.02)	0.84 (0.76, 0.94)	0.80 (0.72, 0.89)	0.81 (0.73, 0.90)	$<$0.001
Multivariate model 1	1.0 (reference)	0.96 (0.87, 1.07)	0.90 (0.81, 1.00)	0.87 (0.78, 0.96)	0.88 (0.79, 0.98)	0.006
Multivariate model 2	1.0 (reference)	1.05 (0.93, 1.18)	1.01 (0.88, 1.16)	0.96 (0.82, 1.12)	1.00 (0.84, 1.18)	0.76
Ischemic stroke	311	354	384	383	418	—
Age-adjusted model	1.0 (reference)	0.93 (0.80, 1.08)	0.91 (0.78, 1.06)	0.82 (0.71, 1.96)	0.83 (0.71, 0.96)	0.004
Multivariate model 1	1.0 (reference)	0.94 (0.81, 1.10)	0.92 (0.79, 1.07)	0.84 (0.72, 0.98)	0.86 (0.74, 1.00)	0.02
Multivariate model 2	1.0 (reference)	1.00 (0.84, 1.19)	1.00 (0.82, 1.21)	0.88 (0.71, 1.10)	0.92 (0.72, 1.18)	0.38
Hemorrhagic stroke	130	132	122	114	138	—
Age-adjusted model	1.0 (reference)	0.90 (0.70, 1.14)	0.78 (0.61, 1.00)	0.68 (0.53, 0.88)	0.78 (0.61, 1.00)	0.01
Multivariate model 1	1.0 (reference)	0.93 (0.73, 1.19)	0.84 (0.65, 1.08)	0.73 (0.56, 0.94)	0.84 (0.66, 1.08)	0.06
Multivariate model 2	1.0 (reference)	0.98 (0.74, 1.30)	0.86 (0.62, 1.19)	0.73 (0.51, 1.05)	0.82 (0.55, 1.22)	0.22

[1]Values are the *n* of cases. Cox proportional hazards models were used to estimate RRs and 95% CIs. Model 1 was adjusted for age, calendar year, total calories (quintiles of kcal), BMI (in kg/m^2; $<$25, 25 to $<$30, or $\geq$30), parental history of heart disease (aged $\leq$60 y), alcohol intake (0, 0 to $<$5, 5 to $<$10, 10 to $<$15, or $\geq$15 g/d), physical activity ($<$3, 3 to $<$9, 9 to$<$18, 18 to $<$27, or $\geq$27 metabolic equivalent tasks/wk), smoking, postmenopausal hormone therapy, oral contraceptive use (never, past, or current), menopausal status (premenopausal or postmenopausal), aspirin (0 to $<$2 or $\geq$2 pills/wk), multivitamin, history of hypertension, hypercholesterolemia, diabetes at baseline, and thiazide use (yes or no). Model 2 was adjusted as for model 1 and for intakes of magnesium and calcium (quintiles of g/d). NHS, Nurses' Health Study.

TABLE 4
Pooled RRs (95% CIs) of total, ischemic, and hemorrhagic strokes by quintiles of total and dietary calcium intake in 86,149 women in the NHS I and 94,715 women in the NHS II[1]

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P*-linear trend
Total calcium intake						
Total stroke	646	710	728	789	907	—
Age-adjusted model	1.0 (reference)	0.94 (0.84, 1.05)	0.89 (0.79, 0.99)	0.86 (0.77, 0.95)	0.82 (0.74, 0.92)	<0.001
Multivariate model 1	1.0 (reference)	1.01 (0.90, 1.12)	0.97 (0.87, 1.08)	0.97 (0.87, 1.08)	0.97 (0.87, 1.09)	0.57
Multivariate model 2	1.0 (reference)	1.04 (0.93, 1.16)	1.02 (0.91, 1.14)	1.03 (0.91, 1.15)	1.04 (0.92, 1.17)	0.67
Ischemic stroke	307	347	354	408	434	—
Age-adjusted model	1.0 (reference)	0.96 (0.82, 1.12)	0.89 (0.76, 1.04)	0.92 (0.79, 1.07)	0.82 (0.71, 0.95)	0.01
Multivariate model 1	1.0 (reference)	0.98 (0.84, 1.15)	0.90 (0.77, 1.06)	0.94 (0.80, 1.10)	0.86 (0.74, 1.01)	0.08
Multivariate model 2	1.0 (reference)	1.00 (0.85, 1.17)	0.93 (0.79, 1.10)	0.97 (0.82, 1.15)	0.90 (0.76, 1.08)	0.30
Hemorrhagic stroke	118	119	124	131	144	—
Age-adjusted model	1.0 (reference)	0.94 (0.72, 1.21)	0.95 (0.74, 1.23)	0.95 (0.73, 1.22)	0.93 (0.72, 1.20)	0.66
Multivariate model 1	1.0 (reference)	1.03 (0.79, 1.33)	1.07 (0.83, 1.39)	1.11 (0.85, 1.44)	1.12 (0.86, 1.46)	0.34
Multivariate model 2	1.0 (reference)	1.11 (0.85, 1.45)	1.20 (0.91, 1.57)	1.27 (0.95, 1.68)	1.31 (0.98, 1.76)	0.06
Dietary calcium intake						
Total stroke	754	780	688	799	759	—
Age-adjusted model	1.0 (reference)	0.93 (0.84, 1.03)	0.78 (0.70, 0.87)	0.89 (0.81, 0.99)	0.85 (0.76, 0.94)	0.006
Multivariate model 1	1.0 (reference)	0.99 (0.90, 1.10)	0.85 (0.77, 0.95)	0.98 (0.88, 1.08)	0.92 (0.83, 1.02)	0.20
Multivariate model 2	1.0 (reference)	1.03 (0.93, 1.14)	0.90 (0.80, 1.00)	1.04 (0.93, 1.17)	0.99 (0.88, 1.12)	0.75
Ischemic stroke	367	390	338	394	361	—
Age-adjusted model	1.0 (reference)	0.95 (0.82, 1.10)	0.79 (0.68, 0.91)	0.91 (0.78, 1.05)	0.82 (0.71, 0.95)	0.01
Multivariate model 1	1.0 (reference)	0.98 (0.85, 1.13)	0.83 (0.71, 0.96)	0.95 (0.82, 1.10)	0.86 (0.74, 1.00)	0.06
Multivariate model 2	1.0 (reference)	1.01 (0.87, 1.17)	0.86 (0.74, 1.01)	1.00 (0.85, 1.17)	0.92 (0.77, 1.10)	0.47
Hemorrhagic stroke	130	126	121	132	127	—
Age-adjusted model	1.0 (reference)	0.92 (0.72, 1.18)	0.87 (0.68, 1.11)	0.94 (0.73, 1.20)	0.89 (0.70, 1.14)	0.50
Multivariate model 1	1.0 (reference)	0.99 (0.77, 1.27)	0.96 (0.75, 1.24)	1.05 (0.82, 1.35)	0.99 (0.77, 1.27)	0.95
Multivariate model 2	1.0 (reference)	1.06 (0.82, 1.37)	1.07 (0.82, 1.40)	1.20 (0.92, 1.58)	1.15 (0.86, 1.54)	0.27

[1]Values are the *n* of cases. Cox proportional hazards models were used to estimate RRs and 95% CIs. Model 1 was adjusted for age, calendar year, total calories (quintiles of kcal), BMI (in kg/m^2; <25, 25 to <30, or ≥30), parental history of heart disease (aged ≤60 y), alcohol intake (0, 0 to <5, 5 to <10, 10 to <15, or ≥15 g/d), physical activity (<3, 3 to <9, 9 to<18, 18 to <27, or ≥27 metabolic equivalent tasks/wk), smoking, postmenopausal hormone therapy, oral contraceptive use (never, past, or current), menopausal status (premenopausal or postmenopausal), aspirin (0 to <2 or ≥2 pills/wk), multivitamin, history of hypertension, hypercholesterolemia, diabetes at baseline, and thiazide use (yes or no). Model 2 was adjusted as for model 1 and for intakes of potassium and magnesium (quintiles of g/d). NHS, Nurses' Health Study.

Table 9) and risk of total, ischemic, and hemorrhagic strokes are shown in the supplemental material.

We examined total and dietary intakes of each mineral and risk of stroke to determine any potential nonlinear association by using restricted cubic splines; however, no significant deviation from linearity was observed. In addition, we explored the potential effect modification by age, hypertension, or diabetes on the relation between total intake of all 3 minerals and risk of total stroke. No significant effect modification was observed by these factors.

We updated the meta-analyses of prospective studies of dietary magnesium (21), potassium (22), and calcium (23) intakes and risk of stroke. Previous meta-analyses included results from previous analyses in the NHS (10); these results were replaced by the results in the current study. In addition, the literature was searched, and recent prospective studies (8, 24) were included in these updated meta-analyses. No between-studies heterogeneity was observed for any of the 3 minerals. The combined RR of total stroke was 0.87 (95% CI: 0.83, 0.92) for a 100-mg/d increase of magnesium intake, 0.91 (95% CI: 0.88, 0.94) for a 1000-mg/d increase of potassium intake, and 0.98 (95% CI: 0.94, 1.02) for a 300-mg/d increase of calcium intake.

DISCUSSION

In these analyses of mineral intakes from 2 large prospective cohort studies of women, we showed higher dietary and total intakes of magnesium and potassium were inversely associated with risk of total stroke. A higher combined mineral diet score of magnesium, potassium, and calcium intakes was associated with ~20% reduced risk of total stroke.

To our knowledge, this is the first study to examine the association between a combined magnesium, potassium, and calcium diet score and stroke risk. Foods sources rich in these minerals include green leafy vegetables, whole grains, legumes, fruits, nuts, and milk. Diets such as the Dietary Approaches to Stop Hypertension diet and Mediterranean diet, which have high content of these minerals, have been reported to be associated with reduced risk of stroke (25, 26), hypertension (27, 28), and diabetes (29–32). Moreover, some prospective studies reported an inverse association between moderate consumption of coffee, a rich source of magnesium, and risk of stroke (33, 34). A prudent dietary pattern characterized by higher intakes of fruits, vegetables, legumes, fish, and whole grains, was previously shown to be associated with reduced stroke risk in women in this study population (35).

The inverse association between magnesium intake and risk of stroke is consistent with findings from several prospective studies

TABLE 5
RRs (95% CI) of total, ischemic, and hemorrhagic strokes by quintiles of combined diet scores for magnesium, potassium, and calcium intakes in 86,149 women in the NHS I and 94,715 women in the NHS II[1]

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P*-linear trend
Median combined diet score						
NHS I	3	6	9	11	14	—
NHS II	3	6	9	11	14	—
Total stroke						
Age-adjusted model						
NHS I	1.0 (reference)	0.81 (0.71, 0.91)	0.76 (0.67, 0.86)	0.87 (0.67, 0.87)	0.72 (0.64, 0.82)	<0.001
NHS II	1.0 (reference)	0.75 (0.56, 0.99)	0.82 (0.61, 1.09)	0.75 (0.57, 0.98)	0.71 (0.53, 0.94)	0.05
Pooled	1.0 (reference)	0.80 (0.71, 0.89)	0.77 (0.69, 0.87)	0.77 (0.69, 0.86)	0.72 (0.65, 0.81)	<0.001
Multivariate model						
NHS I	1.0 (reference)	0.85 (0.75, 0.96)	0.83 (0.73, 0.94)	0.86 (0.76, 0.96)	0.81 (0.72, 0.92)	0.007
NHS II	1.0 (reference)	0.78 (0.59, 1.04)	0.88 (0.66, 1.18)	0.83 (0.63, 1.09)	0.78 (0.58, 1.05)	0.25
Pooled	1.0 (reference)	0.84 (0.75, 0.94)	0.84 (0.74, 0.94)	0.85 (0.76, 0.95)	0.81 (0.72, 0.91)	0.003
Ischemic stroke						
Age-adjusted model						
NHS I	1.0 (reference)	0.81 (0.68, 0.96)	0.81 (0.67, 0.96)	0.80 (0.68, 0.95)	0.74 (0.62, 0.87)	0.002
NHS II	1.0 (reference)	0.74 (0.46, 1.19)	0.75 (0.46, 1.24)	0.69 (0.44, 1.08)	0.66 (0.41, 1.08)	0.12
Pooled	1.0 (reference)	0.80 (0.68, 0.94)	0.80 (0.68, 0.95)	0.79 (0.69, 0.92)	0.73 (0.62, 0.85)	<0.001
Multivariate model						
NHS I	1.0 (reference)	0.83 (0.70, 0.99)	0.83 (0.69, 0.99)	0.85 (0.72, 1.00)	0.78 (0.66, 0.93)	0.03
NHS II	1.0 (reference)	0.79 (0.49, 1.28)	0.82 (0.49, 1.36)	0.77 (0.48, 1.25)	0.75 (0.45, 1.25)	0.34
Pooled	1.0 (reference)	0.83 (0.71, 0.97)	0.83 (0.70, 0.98)	0.84 (0.72, 0.98)	0.78 (0.66, 0.92)	0.01
Hemorrhagic stroke						
Age-adjusted model						
NHS I	1.0 (reference)	0.76 (0.57, 1.00)	0.71 (0.53, 0.96)	0.69 (0.53, 0.91)	0.73 (0.55, 0.96)	0.04
NHS II	1.0 (reference)	0.90 (0.44, 1.81)	1.03 (0.50, 2.11)	0.92 (0.47, 1.81)	0.74 (0.36, 1.56)	0.50
Pooled	1.0 (reference)	0.78 (0.60, 1.01)	0.75 (0.57, 0.99)	0.72 (0.56, 0.93)	0.73 (0.56, 0.95)	0.03
Multivariate model						
NHS I	1.0 (reference)	0.93 (0.71, 1.22)	0.69 (0.51, 0.94)	0.86 (0.64, 1.14)	0.69 (0.52, 0.91)	0.25
NHS II	1.0 (reference)	0.83 (0.41, 1.68)	0.95 (0.46, 1.97)	0.83 (0.41, 1.65)	0.66 (0.31, 1.39)	0.35
Pooled	1.0 (reference)	0.81 (0.62, 1.05)	0.61 (0.61, 1.06)	0.77 (0.60, 1.00)	0.80 (0.61, 1.04)	0.15

[1]Cox proportional hazards models were used to estimate RRs and 95% CIs. The multivariate model was adjusted for age, calendar year, total calories (quintiles of kcal), BMI (in kg/m^2; <25, 25 to <30, or ≥30), parental history of heart disease (aged ≤60 y), alcohol intake (0, 0 to <5, 5 to <10, 10 to <15, or ≥15 g/d), physical activity (<3, 3 to <9, 9 to<18, 18 to <27, or ≥27 metabolic equivalent tasks/wk), smoking, postmenopausal hormone therapy, oral contraceptive use (never, past, or current), menopausal status (premenopausal or postmenopausal), aspirin (0 to <2 or ≥2 pills/wk), multivitamin, history of hypertension, hypercholesterolemia, diabetes at baseline, and thiazide use (yes or no). NHS, Nurses' Health Study.

(7–10, 36). The updated meta-analysis of prospective studies also supported the finding of significant 13% reduced risk of stroke associated with each 100-mg/d increase in magnesium intake. Total potassium intake was inversely associated with risk of total stroke in the current study. These results are consistent with the results from the NHANES I Epidemiologic Follow-up Study (37). In some (9, 10) but not all (8) prospective studies, there was an inverse association between potassium intake and stroke risk. The updated meta-analysis of prospective cohort studies showed that a 1000-mg/d increase of dietary potassium intake was associated with 8% reduced risk of total stroke.

Some epidemiologic studies have suggested that high calcium intake may reduce risk of stroke, but the evidence has been inconsistent. Although several prospective studies reported no association between dietary calcium intake and risk of stroke (7, 9, 11), other prospective studies showed an inverse association with ischemic stroke risk (10, 38, 39), and no between-study heterogeneity was evident for this association in the meta-analysis. In the updated meta-analysis of prospective studies, the association between calcium intake and risk of total stroke was minimal and NS.

Mechanisms for effects of magnesium, potassium, and calcium on stroke risk have not been well elucidated. The antihypertensive effects of these minerals may be a potential mechanism. In previous prospective studies of the association between dietary magnesium intake and risk of hypertension, results have been inconsistent (9, 40). In a previous randomized trial within the NHS II, potassium supplements reduced blood pressure, but supplements of calcium and magnesium did not (41). Meta-analyses of randomized trials that assessed the blood pressure response to changes in mineral intake reported a modest reduction in blood pressure with magnesium (42) and potassium (43). Also, intake of calcium was inversely associated with risk of hypertension in middle-aged and older women in a randomized trial (40). Meta-analyses of randomized trials that assessed the blood pressure response to changes in calcium intake should be conducted. Other possible mechanisms by which these minerals may reduce risk of stroke include the inverse association between magnesium supplementation and endothelial dysfunction (44), dietary potassium and the formation of free radicals (45), and dietary calcium and the inhibition of fatty acid synthesis and activation of lipolysis (34) in humans.

The relation between intakes of magnesium, potassium, and calcium and risk of stroke shown in the current study is similar to the relation between intake of these minerals and risk of IHD. In prospective studies, dietary intake of magnesium and potassium

were inversely associated with risk of IHD (46, 47), but there was no relation with calcium intake and risk of IHD in women (48). Also, intakes of magnesium and calcium but not potassium were associated with lower risk of CVD mortality in some (24, 46, 49) but not all (50) studies.

Our study has several strengths and limitations. The prospective design reduced the possibility of recall and selection biases, and the high rate of retention reduced bias because of a loss to follow-up. Diet was assessed multiple times during follow-up, which took into account changes in eating behaviors and reduced measurement error; however, some error was inevitable. Although strokes were self-reported, study physicians, with no knowledge of the self-reported risk factor status of participants, reviewed participants' medical records to confirm the stroke diagnosis and classify the stroke type. However, because 24% of women with stroke in the NHS I and 32% in the NHS II did not give permission to review their medical records, we were unable to classify all strokes as ischemic or hemorrhagic; therefore, the numbers of stroke types were reduced. Nonetheless, the large number of participants and the long duration of follow-up provided sufficient power to detect clinically relevant differences in risks of total stroke and stroke types. In addition, the updated meta-analyses provided support for our findings on dietary intakes of magnesium, potassium, and calcium and risk of total stroke. A major limitation of the current study was the inability to separate the independent effects of the 3 minerals with much certainty because of the high correlations between them. Also, because the study population predominantly consisted of Caucasian women (12), the results of the current study may not be generalizable to men or ethnically diverse populations.

In conclusion, results from these 2 large prospective studies provide strong evidence to support an inverse association between combined intakes of magnesium, potassium, and calcium from diet and stroke risk. The independent role of each mineral in the reduction of stroke risk is difficult to define. In addition, the effect of these minerals on risk of stroke independent of food sources is difficult to define. This study supports the recommendations of the Dietary Approaches to Stop Hypertension, Optimal Macronutrient Intake Trial to Prevent Heart Disease, and Mediterranean diets, which promote high dietary intake of these minerals.

The authors' responsibilities were as follows—SNA: performed statistical analyses and wrote the manuscript; DS, WCW, and KMR: provided critical feedback of the manuscript; and all authors: read and approved the final manuscript. None of the authors reported a conflict of interest related to the study.

REFERENCES

1. Elin RJ. Magnesium: the fifth but forgotten electrolyte. Am J Clin Pathol 1994;102:616–22.
2. Wacker WE, Parisi AF. Magnesium metabolism. N Engl J Med 1968; 278:658–63.
3. Morgan JP, Morgan KG. Calcium and cardiovascular function. Intracellular calcium levels during contraction and relaxation of mammalian cardiac and vascular smooth muscle as detected with aequorin. Am J Med 1984;77:33–46.
4. Cutler JA, Brittain E. Calcium and blood pressure. An epidemiologic perspective. Am J Hypertens 1990;3:137S–46S.
5. Whelton PK, Klag MJ. Magnesium and blood pressure: review of the epidemiologic and clinical trial experience. Am J Cardiol 1989;63:26G–30G.
6. Ascherio A, Rimm EB, Giovannucci EL, Colditz GA, Rosner B, Willett WC, Sacks F, Stampfer MJ. A prospective study of nutritional factors and hypertension among US men. Circulation 1992;86: 1475–84.
7. Joffres MR, Reed DM, Yano K. Relationship of magnesium intake and other dietary factors to blood pressure: the Honolulu heart study. Am J Clin Nutr 1987;45:469–75.
8. Sluijs I, Czernichow S, Beulens JW, Boer JM, van der Schouw YT, Verschuren WM, Grobbee DE. Intakes of potassium, magnesium, and calcium and risk of stroke. Stroke 2014;45:1148–50.
9. Peacock JM, Folsom AR, Arnett DK, Eckfeldt JH, Szklo M. Relationship of serum and dietary magnesium to incident hypertension: the Atherosclerosis Risk in Communities (ARIC) Study. Ann Epidemiol 1999;9:159–65.
10. Kao WH, Folsom AR, Nieto FJ, Mo JP, Watson RL, Brancati FL. Serum and dietary magnesium and the risk for type 2 diabetes mellitus: the Atherosclerosis Risk in Communities Study. Arch Intern Med 1999; 159:2151–9.
11. Pai JK, Pischon T, Ma J, Manson JE, Hankinson SE, Joshipura K, Curhan GC, Rifai N, Cannuscio CC, Stampfer MJ, et al. Inflammatory markers and the risk of coronary heart disease in men and women. N Engl J Med 2004;351:2599–610.
12. 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. Am J Epidemiol 1986;123:48–58.
13. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, Hennekens CH, Speizer FE. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985;122: 51–65.
14. Willett WC, Sampson L, Browne ML, Stampfer MJ, Rosner B, Hennekens CH, Speizer FE. The use of a self-administered questionnaire to assess diet four years in the past. Am J Epidemiol 1988; 127:188–99.
15. Salvini S, Hunter DJ, Sampson L, Stampfer MJ, Colditz GA, Rosner B, Willett WC. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. Int J Epidemiol 1989;18:858–67.
16. Ascherio A, Hennekens C, Willett WC, Sacks F, Rosner B, Manson J, Witteman J, Stampfer MJ. Prospective study of nutritional factors, blood pressure, and hypertension among US women. Hypertension 1996;27:1065–72.
17. Walker AE, Robins M, Weinfeld FD. The National Survey of Stroke. Clinical findings. Stroke 1981;12(2 Pt 2 Suppl 1):I13–44.
18. Hu FB, Stampfer MJ, Rimm E, Ascherio A, Rosner BA, Spiegelman D, Willett WC. Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. Am J Epidemiol 1999;149:531–40.
19. Govindarajulu US, Spiegelman D, Thurston SW, Ganguli B, Eisen EA. Comparing smoothing techniques in Cox models for exposure-response relationships. Stat Med 2007;26:3735–52.
20. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
21. Guerrero-Romero F, Rodriguez-Moran M. The effect of lowering blood pressure by magnesium supplementation in diabetic hypertensive adults with low serum magnesium levels: a randomized, double-blind, placebo-controlled clinical trial. J Hum Hypertens 2009;23: 245–51.
22. Larsson SC, Orsini N, Wolk A. Dietary potassium intake and risk of stroke: a dose-response meta-analysis of prospective studies. Stroke 2011;42:2746–50.
23. Larsson SC, Orsini N, Wolk A. Dietary calcium intake and risk of stroke: a dose-response meta-analysis. Am J Clin Nutr 2013;97: 951–7.
24. Zhang W, Iso H, Ohira T, Date C, Tamakoshi A, Group JS. Associations of dietary magnesium intake with mortality from cardiovascular disease: the JACC study. Atherosclerosis 2012;221:587–95.
25. Fung TT, Chiuve SE, McCullough ML, Rexrode KM, Logroscino G, Hu FB. Adherence to a DASH-style diet and risk of coronary heart disease and stroke in women. Arch Intern Med 2008;168: 713–20.
26. Fung TT, Rexrode KM, Mantzoros CS, Manson JE, Willett WC, Hu FB. Mediterranean diet and incidence of and mortality from coronary heart disease and stroke in women. Circulation 2009;119: 1093–100.
27. Moore TJ, Conlin PR, Ard J, Svetkey LP. DASH (Dietary Approaches to Stop Hypertension) diet is effective treatment for stage 1 isolated systolic hypertension. Hypertension 2001;38:155–8.

28. Núñez-Córdoba JM, Valencia-Serrano F, Toledo E, Alonso A, Martinez-Gonzalez MA. The Mediterranean diet and incidence of hypertension: the Seguimiento Universidad de Navarra (SUN) Study. Am J Epidemiol 2009;169:339–46.
29. Liese AD, Nichols M, Sun X, D'Agostino RB Jr., Haffner SM. Adherence to the DASH Diet is inversely associated with incidence of type 2 diabetes: the insulin resistance atherosclerosis study. Diabetes Care 2009;32:1434–6.
30. Salas-Salvadó J, Bullo M, Estruch R, Ros E, Covas MI, Ibarrola-Jurado N, Corella D, Aros F, Gomez-Gracia E, Ruiz-Gutierrez V, et al. Prevention of diabetes with Mediterranean diets: a subgroup analysis of a randomized trial. Ann Intern Med 2014;160:1–10.
31. Mitka M. Mediterranean diet may reduce stroke risk in individuals with genetic predisposition to diabetes. JAMA 2013; 310:1013.
32. Esposito K, Giugliano D. Mediterranean diet and type 2 diabetes. Diabetes Metab Res Rev 2014;30(Suppl 1):34–40.
33. Kokubo Y, Iso H, Saito I, Yamagishi K, Yatsuya H, Ishihara J, Inoue M, Tsugane S. The impact of green tea and coffee consumption on the reduced risk of stroke incidence in Japanese population: the Japan public health center-based study cohort. Stroke 2013;44: 1369–74.
34. Zemel MB. Calcium modulation of hypertension and obesity: mechanisms and implications. J Am Coll Nutr 2001;20(5 Suppl): 428S–35S.
35. Fung TT, Stampfer MJ, Manson JE, Rexrode KM, Willett WC, Hu FB. Prospective study of major dietary patterns and stroke risk in women. Stroke 2004;35:2014–9.
36. Ohira T, Peacock JM, Iso H, Chambless LE, Rosamond WD, Folsom AR. Serum and dietary magnesium and risk of ischemic stroke: the Atherosclerosis Risk in Communities Study. Am J Epidemiol 2009; 169:1437–44.
37. Bazzano LA, He J, Ogden LG, Loria C, Vupputuri S, Myers L, Whelton PK. Dietary potassium intake and risk of stroke in US men and women: National Health and Nutrition Examination Survey I epidemiologic follow-up study. Stroke 2001;32:1473–80.
38. Umesawa M, Iso H, Ishihara J, Saito I, Kokubo Y, Inoue M, Tsugane S. Dietary calcium intake and risks of stroke, its subtypes, and coronary heart disease in Japanese: the JPHC Study Cohort I. Stroke 2008;39: 2449–56.
39. Abbott RD, Curb JD, Rodriguez BL, Sharp DS, Burchfiel CM, Yano K. Effect of dietary calcium and milk consumption on risk of thromboembolic stroke in older middle-aged men. The Honolulu Heart Program. Stroke 1996;27:813–8.
40. Wang L, Manson JE, Buring JE, Lee IM, Sesso HD. Dietary intake of dairy products, calcium, and vitamin D and the risk of hypertension in middle-aged and older women. Hypertension 2008;51:1073–9.
41. Sacks FM, Willett WC, Smith A, Brown LE, Rosner B, Moore TJ. Effect on blood pressure of potassium, calcium, and magnesium in women with low habitual intake. Hypertension 1998;31:131–8.
42. Dickinson HO, Nicolson DJ, Campbell F, Cook JV, Beyer FR, Ford GA, Mason J. Magnesium supplementation for the management of essential hypertension in adults. Cochrane Database Syst Rev 2006;3: CD004640.
43. Geleijnse JM, Kok FJ, Grobbee DE. Blood pressure response to changes in sodium and potassium intake: a metaregression analysis of randomised trials. J Hum Hypertens 2003;17:471–80.
44. Song Y, Ridker PM, Manson JE, Cook NR, Buring JE, Liu S. Magnesium intake, C-reactive protein, and the prevalence of metabolic syndrome in middle-aged and older U.S. women. Diabetes Care 2005;28:1438–44.
45. McCabe RD, Bakarich MA, Srivastava K, Young DB. Potassium inhibits free radical formation. Hypertension 1994;24:77–82.
46. Hruby A, O'Donnell CJ, Jacques PF, Meigs JB, Hoffmann U, McKeown NM. Magnesium intake is inversely associated with coronary artery calcification: the Framingham Heart Study. JACC Cardiovasc Imaging 2014;7:59–69.
47. D'Elia L, Barba G, Cappuccio FP, Strazzullo P. Potassium intake, stroke, and cardiovascular disease a meta-analysis of prospective studies. J Am Coll Cardiol 2011;57:1210–9.
48. Paik JM, Curhan GC, Sun Q, Rexrode KM, Manson JE, Rimm EB, Taylor EN. Calcium supplement intake and risk of cardiovascular disease in women. Osteoporos Int 2014;25:2047–56.
49. Geleijnse JM, Witteman JC, Stijnen T, Kloos MW, Hofman A, Grobbee DE. Sodium and potassium intake and risk of cardiovascular events and all-cause mortality: the Rotterdam Study. Eur J Epidemiol 2007;22:763–70.
50. Xiao Q, Murphy RA, Houston DK, Harris TB, Chow WH, Park Y. Dietary and supplemental calcium intake and cardiovascular disease mortality: the National Institutes of Health-AARP diet and health study. JAMA Intern Med 2013;173:639–46.