Prospective Study of Calcium, Potassium, and Magnesium Intake and Risk of Stroke in Women

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Background and Purpose—High intakes of calcium, potassium, and magnesium have been hypothesized to reduce risks of cardiovascular disease, but only a few prospective studies have examined intakes of these cations in relation to risk of stroke.

Methods—In 1980, 85 764 women in the Nurses' Health Study cohort, aged 34 to 59 years and free of diagnosed cardiovascular disease and cancer, completed dietary questionnaires from which we calculated intakes of calcium, potassium, and magnesium. By 1994, after 1.16 million person-years of follow-up, 690 incident strokes (129 subarachnoid hemorrhages, 74 intraparenchymal hemorrhages, 386 ischemic strokes, and 101 strokes of undetermined type) had been documented.

Results—Intakes of calcium, potassium, and magnesium were each inversely associated with age- and smoking-adjusted relative risks of ischemic stroke, excluding embolic infarction of nonatherogenic origin (n=347). Adjustment for other cardiovascular risk factors, including history of hypertension, attenuated these associations, particularly for magnesium intake. In a multivariate analysis, women in the highest quintile of calcium intake had an adjusted relative risk of ischemic stroke of 0.69 (95% CI, 0.50 to 0.95; *P* for trend=0.03) compared with those in the lowest quintile; for potassium intake the corresponding relative risk was 0.72 (95% CI, 0.51 to 1.01; *P* for trend=0.10). Further simultaneous adjustment for calcium and potassium intake suggested an independent association for calcium intake. The association of risk with calcium intake did not appear to be log linear; the increase in risk was limited to the lowest quintile of intake, and intakes $>\approx$600 mg/d did not appear to reduce risk of stroke further. The inverse association with calcium intake was stronger for dairy than for nondairy calcium intake. Intakes of calcium, potassium, and magnesium were not related to risk of other stroke subtypes.

Conclusions—Low calcium intake, and perhaps low potassium intake, may contribute to increased risk of ischemic stroke in middle-aged American women. It remains possible that women in the lowest quintile of calcium intake had unknown characteristics that made them susceptible to ischemic stroke. **(*Stroke*. 1999;30:1772-1779.)**

Key Words: calcium ■ diet ■ magnesium ■ potassium ■ stroke

In observational studies, intakes of calcium,[1,2] potassium,[3] and magnesium[2,4,5] have been inversely associated with blood pressure or risk of hypertension; clinical trials[6–10] have tended to find that potassium had the strongest hypotensive effects. High intake of these cations may prevent stroke because hypertension is a strong risk factor for stroke.[11] Moreover, animal experiments suggest additional mechanisms for these cations in the prevention of stroke.[12–18] Stroke mortality in rats was reduced after supplementation with calcium[19] and potassium,[16] but not with magnesium.[18] Only a few prospective studies have addressed the relation between intake of these cations and risk of stroke, and data in women are sparse.[20,21] An inverse relation between calcium intake and risk of ischemic stroke was reported from a study of Japanese-American men.[20] An inverse relation between potassium intake and stroke risk was reported from studies of American white men and women,[21] Japanese-American men,[22] and US health professional men.[23] We investigated the relation between intake of these cations and the incidence of stroke among US women followed prospectively for 14 years in the Nurses' Health Study.

Subjects and Methods

The Nurses' Health Study began in 1976, when 121 700 female registered nurses (98% white) living in 11 states completed questionnaires about lifestyle factors and medical history, including previous cardiovascular disease, cancer, diabetes, hypertension, and high serum cholesterol levels.[24] Every 2 years, follow-up question-

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naires are sent to these women so that information can be updated and newly diagnosed major illnesses identified.

Ascertainment of Diet

In 1980, we collected data on usual dietary intake using a semiquantitative food frequency questionnaire.[25] For each food (61 items), a commonly used unit or portion size was specified, and each woman was asked how often on average during the previous year she had consumed that amount. Nine responses were possible, ranging from "almost never" to "≥6 times per day." The average daily intake of nutrients was calculated by multiplying the frequency of consumption of each item by the nutrient content and totaling the nutrient intake for all food items. Nutrient intake was adjusted for total energy intake with the use of the residual approach.[26] The reproducibility and validity of this questionnaire have been reported elsewhere.[25,27,28] In a validation study among 200 cohort participants conducted in 1986, the correlations between cation intake assessed by the expanded dietary questionnaire used in 1984, 1986, and 1990 and by two 1-week diet records were 0.62 for calcium, 0.61 for potassium, and 0.76 for magnesium after within-person variation in the diet records was taken into account.[29]

A total of 98 462 women returned the 1980 dietary questionnaire. We excluded women who left ≥10 items blank, whose reported total food intakes were implausible, or who had a history of cancer (except nonmelanoma skin cancer), angina, myocardial infarction, stroke, or other cardiovascular diseases; 86 368 women remained for the analyses.

Ascertainment of Stroke

Women who reported a nonfatal stroke on a follow-up questionnaire were asked for permission to review their medical records. The 18.4% of nonfatal strokes for which confirmatory information was obtained by telephone or letter, but for which no medical records were available, were regarded as probable. Fatal strokes were initially ascertained by reports from relatives or postal authorities and a search of the National Death Index[30] and were then documented by medical records and death certificates. Mortality follow-up was >98% complete.[30] The 22.3% of fatal strokes that were confirmed by telephone, letter, or death certificate, but for which no medical records were available, were regarded as probable. Medical records were reviewed by physicians blinded as to dietary and other risk factors.

Strokes were confirmed by medical records according to the criteria of the National Survey of Stroke,[31] which requires a constellation of neurological deficits of sudden or rapid onset lasting ≥24 hours or until death; strokes were categorized as subarachnoid hemorrhages, intraparenchymal hemorrhages, ischemic strokes (thrombotic or embolic), or strokes of undetermined type. For embolic infarction, sources of emboli were recorded. Atherogenic origins of emboli included ulcerating atherosclerotic plaques in the carotid artery, mural thrombi associated with myocardial infarction, and embolic strokes as a consequence of surgery for coronary heart disease. Other sources of emboli, such as valvular heart disease and bacterial endocarditis, were regarded as nonatherogenic origin. Atrial fibrillation also was regarded as largely nonatherogenic origin because the major predisposition to nonvalvular atrial fibrillation is congestive heart failure rather than coronary disease.[32] Strokes were regarded as incident if they occurred after the date of return of the 1980 questionnaire but before June 1, 1994. Only confirmed and probable strokes were considered in the analyses for all stroke. For analyses of ischemic stroke and the other specific stroke types, only confirmed cases were considered.

Statistical Analyses

The analyses were based on the incidence of stroke during 14 years of follow-up (1980–1994). For each woman, person-months of follow-up were allocated according to 1980 exposure variables and were updated according to information on biennial follow-up questionnaires until death or an end point (stroke) was reached or until May 31, 1994. From the 1980 questionnaire, we used information on the intake of calcium, potassium, magnesium, and ω-3 polyunsaturated fatty acids and on regular exercise. We present results based on the 1980 dietary variables without updating because we were most interested in the long-term effects of intake of cations on risk of stroke. Updating of intakes of these nutrients using the 1984, 1986, and 1990 questionnaires yielded generally similar associations with risk of stroke. In the updated analyses, for example, the incidence of stroke during 1980–1984 was related to nutrient intakes reported on the 1980 questionnaire, and the incidence during 1984–1986 was related to nutrient intakes reported on the 1984 questionnaire.

To examine the relation between use of cation supplements and risk of stroke, subsequent dietary questionnaires were used because information on these individual supplements was not available from the 1980 questionnaire; only multivitamin supplement use was taken into account to assess calcium intake in 1980. Data on use of calcium supplements, including dose, were available for 1982, 1984, 1986, and 1990. Data on magnesium supplement use (no data on dose) were obtained in 1984, 1986, and 1990. For calcium and magnesium supplements, the information was updated in the primary analysis. Use of calcium supplements changed markedly during the follow-up (10% in 1982, 26% in 1984, 52% in 1986, and 35% in 1990), whereas magnesium supplement use did not (4% in 1984 and 1986 and 3% in 1990). Information about potassium supplement use (no data on dose) was available only in 1986, and therefore this information was not updated. Analyses of calcium and magnesium supplementation using the 1986 data only were also conducted to be comparable to the analyses of potassium supplements. Height was ascertained in 1976. Data on usual aspirin use were updated in 1982, 1984, and 1988, and those on alcohol intake were updated in 1984, 1986, and 1990. All other exposure variables (ie, body mass index; menopausal status; postmenopausal hormone use; histories of hypertension, diabetes, and high cholesterol levels; and the use of multivitamins and vitamin E supplements) were updated on each follow-up questionnaire.

The relative risk of stroke was defined as the incidence rate of stroke among women in various categories for intake of nutrients and foods divided by the corresponding rate among the women in the lowest category of intake. We calculated relative risks with 95% CIs, adjusted for age in 5-year categories and for smoking status in 5 categories (never, former, current 1 to 14/d, current 15 to 24/d, and current ≥25/d), and tested for linear trend across the dietary categories using median variables of each dietary category. To adjust simultaneously for other cardiovascular risk factors, we used pooled logistic regression over the seven 2-year intervals.[33] In multivariate models, potassium and magnesium intakes were not entered into models simultaneously because these 2 variables were highly correlated ($r=0.83$). The correlations between calcium and potassium intake ($r=0.55$) and between calcium and magnesium intake ($r=0.46$) were more moderate.

Results

Among 85 764 women followed for 14 years, we documented 690 incident cases of stroke during 1 164 674 person-years of follow-up. Stroke cases consisted of 129 subarachnoid hemorrhages, 74 intraparenchymal hemorrhages, 386 ischemic strokes, and 101 strokes of undetermined type. Calcium intake was positively associated with history of diabetes, vigorous exercise, use of multivitamin and vitamin E supplements, and intakes of ω-3 polyunsaturated fatty acids and animal protein and was inversely associated with smoking, hypertension, and intakes of alcohol and saturated fat. Intakes of potassium and magnesium had associations with these variables similar to those for calcium intake, except for weak positive correlations with smoking (Table 1).

Table 2 presents age- and smoking-adjusted risk of ischemic stroke according to quintiles of calcium intake (including calcium from multivitamin supplements but not specific

TABLE 1. Baseline Characteristics and Risk Factors in a Cohort of 85 764 Women in 1980, According to Intake of Calcium, Potassium, and Magnesium

	Calcium			Potassium			Magnesium		
	Lowest	Intermediate	Highest	Lowest	Intermediate	Highest	Lowest	Intermediate	Highest
Mean age, y	45.7	46.2	46.2	44.9	46.1	47.3	44.7	46.3	47.3
Women with potential risk indicators, %*									
Current smoking	33.6	27.2	25.9	28.7	28.6	30.5	26.9	28.5	30.8
Hypertension	17.3	15.0	14.8	16.4	15.0	15.9	17.7	15.3	15.1
Diabetes	1.9	2.0	2.8	1.6	2.0	2.6	1.7	2.2	2.4
High cholesterol levels	5.3	5.1	5.1	4.9	4.7	6.2	4.7	4.9	6.2
Body mass index $\geq$29 kg/m^2	14.2	13.4	13.9	15.9	12.9	13.4	16.9	13.2	12.0
Current hormone use in postmenopausal women	35.9	38.9	40.1	38.6	36.6	35.0	38.7	36.6	35.4
Vigorous exercise†	37.9	45.8	48.3	36.4	44.5	52.3	37.0	44.1	52.7
Alcohol intake $\geq$25 g/d	11.7	6.6	3.7	9.2	7.4	5.1	7.0	7.4	7.6
Multivitamin use	26.8	33.4	42.3	29.4	34.0	38.3	28.9	34.2	38.8
Vitamin E use	9.7	12.7	16.8	9.8	12.7	16.5	9.1	12.6	17.5
Aspirin use $\geq$1/wk	39.6	40.8	38.7	39.4	40.8	39.4	39.6	41.1	39.3
Highest quintile of nutrients:									
Saturated fat	25.2	19.0	18.1	32.2	20.0	8.0	33.2	19.5	8.5
ω-3 polyunsaturated fatty acids	12.9	19.3	27.0	5.9	16.5	41.1	6.9	17.0	38.2
Animal protein	13.7	16.0	35.4	10.8	16.5	36.3	13.1	18.4	30.4

*Age-adjusted by the 5-year age categories of the age distribution of the cohort. The women were divided into 5 groups for each cation according to quintiles of dietary intake. "Lowest" denotes the first quintile, "intermediate" the third quintile, and "highest" the fifth quintile.

†Sweat-producing exercise at least once a week.

calcium supplements), dietary potassium, and dietary magnesium intake. Calcium intake was inversely associated with risk of ischemic stroke, and the association was stronger when we excluded nonatherogenic embolic infarctions (n=39). A reduction in risk was found in the second quintile, and further small reductions were observed in higher quintiles, but there was no strong linear trend. There was no clear relation between calcium intake and risk of subarachnoid hemorrhage, but a suggestion of a decreased risk of intraparenchymal hemorrhage was noted. Intakes of potassium and magnesium were not related to risk of intraparenchymal hemorrhage or subarachnoid hemorrhage.

Table 3 shows multivariate adjusted relative risks of ischemic stroke (excluding nonatherogenic embolic infarctions) according to quintile of calcium, potassium, and magnesium intakes. The inverse association between calcium intake remained statistically significant after adjustment for history of hypertension and after further adjustment for other cardiovascular risk factors. Further adjustment for potassium or magnesium intake attenuated the association slightly. The inverse association between potassium intake and risk was attenuated after adjustment for history of hypertension and other cardiovascular risk factors. Further adjustment for calcium intake, however, substantially attenuated the association, which was no longer statistically significant. The inverse association with magnesium intake also was no longer significant after adjustment for history of hypertension. The trend for reduction in risk of intraparenchymal hemorrhage associated with calcium intake remained statistically nonsignificant after multivariate adjustment for cardiovascular risk factors; the multivariate relative risk in the highest versus lowest quintiles of calcium intake was 0.62 (95% CI, 0.27 to 1.39; P for trend=0.11).

There was no clear dose-response association between calcium supplement use and stroke risk, but women who took supplements containing $\geq$400 mg/d tended to have lower risk: the multivariate relative risk adjusted for age, smoking, other cardiovascular risk factors, and dietary calcium was 0.88 (95% CI, 0.66 to 1.18; P=0.39) when we compared calcium supplement users with nonusers (updated information). The multivariate relative risk based on the 1986 data only was 0.75 (95% CI, 0.56 to 1.01; P=0.05) for calcium supplement users compared with nonusers. Potassium supplementation was not associated with risk of ischemic stroke; the multivariate relative risk was 1.03 (95% CI, 0.63 to 1.68; P=0.91). We observed no reduction in risk of ischemic stroke among magnesium supplement users with or without updating of use; the multivariate relative risk was 1.47 (95% CI, 0.73 to 2.93; P=0.28) with updating and 1.46 (95% CI, 0.76 to 2.81; P=0.26) without updating.

Dietary calcium intake (excluding multivitamin supplements) was also inversely associated with the risk of ischemic stroke (Table 4). The inverse association was stronger for dairy calcium than for nondairy calcium, but the CIs broadly overlapped. The age- and smoking-adjusted relative risk of ischemic stroke in the highest versus the lowest quintile was 0.68 (95% CI, 0.50 to 0.94) for dairy calcium (P for trend=0.05) and 0.82 (95% CI, 0.58 to 1.16) for nondairy

TABLE 2. Age- and Smoking-Adjusted Relative Risk (95% CI) of Ischemic Stroke in a Cohort of 85 764 Women Followed During 1980–1994, According to Quintile Group for Calorie-Adjusted Calcium, Potassium, and Magnesium Intake in 1980*

	No. of Cases and Relative Risk by Quintile of Cation Intake					
	1 (Low)	2	3	4	5 (High)	*P* for Trend
Calcium						
Median, mg/d	395	546	675	837	1145	
All stroke						
Cases, n	165	132	117	142	134	
Relative risk (95% CI)	1.0	0.79 (0.63–1.00)	0.71 (0.56–0.90)	0.87 (0.70–1.09)	0.83 (0.66–1.04)	0.34
Subarachnoid hemorrhage						
Cases, n	28	20	15	32	34	
Relative risk (95% CI)	1.0	0.72 (0.40–1.27)	0.58 (0.32–1.06)	1.20 (0.73–1.98)	1.33 (0.82–2.16)	0.03
Intraparenchymal hemorrhage						
Cases, n	16	21	15	13	9	
Relative risk (95% CI)	1.0	1.32 (0.69–2.53)	0.93 (0.46–1.90)	0.80 (0.38–1.69)	0.56 (0.24–1.30)	0.07
Ischemic stroke						
Cases, n	99	77	71	67	72	
Relative risk (95% CI)	1.0	0.76 (0.56–1.03)	0.72 (0.53–0.97)	0.68 (0.50–0.93)	0.72 (0.53–0.98)	0.04
Ischemic stroke excluding nonatherogenic embolic infarction†						
Cases, n	95	70	62	58	62	
Relative risk (95% CI)	1.0	0.72 (0.53–0.99)	0.66 (0.48–0.91)	0.62 (0.45–0.86)	0.65 (0.47–0.90)	0.01
Potassium						
Median, mg/d	2017	2412	2708	3030	3555	
All stroke						
Cases, n	147	117	146	134	146	
Relative risk (95% CI)	1.0	0.75 (0.59–0.95)	0.90 (0.72–1.14)	0.80 (0.63–1.01)	0.83 (0.66–1.04)	0.19
Subarachnoid hemorrhage						
Cases, n	31	22	21	24	31	
Relative risk (95% CI)	1.0	0.70 (0.40–1.20)	0.64 (0.37–1.11)	0.70 (0.41–1.21)	0.96 (0.59–1.56)	0.90
Intraparenchymal hemorrhage						
Cases, n	14	10	18	16	16	
Relative risk (95% CI)	1.0	0.67 (0.30–1.53)	1.15 (0.57–2.32)	1.00 (0.49–2.05)	0.99 (0.49–2.02)	0.81
Ischemic stroke						
Cases, n	87	64	82	74	79	
Relative risk (95% CI)	1.0	0.68 (0.49–0.94)	0.85 (0.63–1.15)	0.73 (0.53–1.00)	0.71 (0.52–0.96)	0.07
Ischemic stroke excluding nonatherogenic embolic infarction†						
Cases, n	81	58	74	66	68	
Relative risk (95% CI)	1.0	0.66 (0.47–0.93)	0.82 (0.60–1.13)	0.70 (0.50–0.97)	0.66 (0.47–0.91)	0.03
Magnesium						
Median, mg/d	211	254	287	323	381	
All stroke						
Cases, n	136	132	136	146	140	
Relative risk (95% CI)	1.0	0.89 (0.70–1.13)	0.86 (0.68–1.09)	0.91 (0.72–1.14)	0.80 (0.63–1.01)	0.11
Subarachnoid hemorrhage						
Cases, n	26	21	25	29	28	
Relative risk (95% CI)	1.0	0.76 (0.43–1.35)	0.86 (0.50–1.49)	0.98 (0.58–1.66)	0.92 (0.54–1.57)	0.90
Intraparenchymal hemorrhage						
Cases, n	15	14	9	23	13	
Relative risk (95% CI)	1.0	0.86 (0.42–1.76)	0.49 (0.21–1.13)	1.33 (0.71–2.49)	0.64 (0.30–1.37)	0.76

TABLE 2. Continued

	No. of Cases and Relative Risk by Quintile of Cation Intake					
	1 (Low)	2	3	4	5 (High)	*P* for Trend
Ischemic stroke						
Cases, n	78	74	83	72	79	
Relative risk (95% CI)	1.0	0.85 (0.62–1.17)	0.90 (0.66–1.23)	0.75 (0.55–1.03)	0.74 (0.54–1.02)	0.06
Ischemic stroke excluding nonatherogenic embolic infarction†						
Cases, n	73	64	74	64	72	
Relative risk (95% CI)	1.0	0.79 (0.56–1.11)	0.85 (0.62–1.18)	0.72 (0.53–1.00)	0.73 (0.52–1.01)	0.06

*Calcium intake was estimated from diet and multivitamin supplements; potassium and magnesium intake was estimated from diet only.

†Embolic infarction due to nonvalvular atrial fibrillation, valvular heart disease, cardiomyopathy, bacterial endocarditis, and other nonatherogenic embolic origins were excluded.

calcium (*P* for trend=0.08). Further adjustment for other cardiovascular risk factors attenuated the associations, but they continued to be stronger for dairy than for nondairy calcium.

We further explored the relation between specific food sources of dairy calcium and the risk of ischemic stroke. We observed an inverse relation between yogurt intake and the age- and smoking-adjusted risk of ischemic stroke; the relative risk among women who ate yogurt ≥5 times per week compared with those who almost never ate it was 0.69 (95% CI, 0.34 to 1.40; *P* for trend=0.06). Similar inverse trends were seen for hard cheese (the relative risk compared with women who almost never ate it was 0.63 [95% CI, 0.40 to 0.99] for women who ate cheese ≥1 times per day; *P* for trend=0.20), ice cream (0.70 [95% CI, 0.42 to 1.17] for women who ate ≥5 times per week; *P* for trend=0.14), and milk (0.74 [95% CI, 0.51 to 1.06] for women who ate ≥2 times per day; *P* for trend=0.44), but less so for cottage cheese (0.94 [95% CI, 0.60 to 1.47] for women who ate ≥5 times per week; *P* for trend=0.71).

Discussion

We observed that intakes of calcium, potassium, and magnesium were each inversely associated with the age- and smoking-adjusted risk of ischemic stroke, excluding embolic infarction of nonatherogenic origin. After adjustment for history of hypertension and other cardiovascular risk factors, the association with calcium remained statistically significant, and that with potassium was of borderline significance. Further simultaneous adjustment of calcium and potassium intake more strongly supported an independent association of ischemic stroke with calcium intake.

TABLE 3. Multivariate Relative Risk (95% CI) of Ischemic Stroke* in a Cohort of 85 764 Women Followed During 1980–1994, According to Quintile Group for Calorie-Adjusted Calcium, Potassium, and Magnesium Intake in 1980

	Adjusted Relative Risk by Quintile of Cation Intake					
	1 (Low)	2	3	4	5 (High)	*P* for Trend
Calcium	1.0	0.75 (0.55–1.03)†	0.68 (0.49–0.94)	0.64 (0.46–0.89)	0.69 (0.50–0.95)	0.02
	1.0	0.76 (0.56–1.04)‡	0.69 (0.50–0.96)	0.66 (0.47–0.92)	0.69 (0.50–0.95)	0.03
	1.0	0.78 (0.57–1.07)§	0.71 (0.51–1.00)	0.68 (0.47–0.97)	0.72 (0.49–1.05)	0.11
	1.0	0.76 (0.55–1.05)‖	0.69 (0.49–0.96)	0.65 (0.46–0.93)	0.68 (0.47–0.97)	0.05
Potassium	1.0	0.69 (0.49–0.97)†	0.85 (0.62–1.16)	0.71 (0.52–0.99)	0.69 (0.50–0.95)	0.04
	1.0	0.72 (0.51–1.01)‡	0.90 (0.66–1.25)	0.75 (0.54–1.05)	0.72 (0.51–1.01)	0.10
	1.0	0.78 (0.55–1.10)¶	1.03 (0.73–1.44)	0.89 (0.62–1.27)	0.87 (0.58–1.30)	0.67
Magnesium	1.0	0.83 (0.59–1.16)†	0.90 (0.65–1.24)	0.75 (0.54–1.05)	0.79 (0.57–1.10)	0.15
	1.0	0.86 (0.61–1.20)‡	0.94 (0.68–1.31)	0.80 (0.57–1.13)	0.84 (0.60–1.19)	0.31
	1.0	0.93 (0.66–1.31)¶	1.08 (0.77–1.52)	0.95 (0.66–1.36)	1.04 (0.71–1.52)	0.83

*Embolic infarction due to nonvalvular atrial fibrillation, valvular heart disease, cardiomyopathy, bacterial endocarditis, and other nonatherogenic embolic origins were excluded.

†Adjusted for age (5-year category), smoking status (5 categories), time interval, and a history of hypertension (yes vs no).

‡Adjusted for factors cited above and for body mass index (5 categories), alcohol intake (4 categories), menopausal status and postmenopausal hormone use, vigorous exercise (yes vs no), usual aspirin use (<1/wk, 1–2/wk, 3–6/wk, 7–14/wk, and ≥15/wk), multivitamin use (yes vs no), vitamin E use (yes vs no), ω-3 fatty acid intake (quintile), and histories of diabetes and high cholesterol levels (yes vs no).

§Adjusted for factors cited above and for potassium intake.

‖Adjusted for factors cited above and for magnesium intake.

¶Adjusted for factors cited above and for calcium intake.

TABLE 4. Relative Risk (95% CI) of Ischemic Stroke* in a Cohort of 85 764 Women Followed During 1980–1994, According to Quintile Group for Calorie-Adjusted Dairy and Nondairy Calcium Intake

	No. of Cases and Relative Risk by Quintile of Cation Intake					
	1 (Low)	2	3	4	5 (High)	*P* for Trend
Dietary calcium (without supplement)						
Median, g/d	393	543	670	829	1128	
Cases, n	91	73	62	57	64	
Relative risk (95% CI)†	1.0	0.79 (0.58–1.08)†	0.68 (0.49–0.95)	0.63 (0.45–0.88)	0.70 (0.51–0.97)	0.02
Relative risk (95% CI)‡	1.0	0.83 (0.61–1.13)‡	0.73 (0.53–1.01)	0.67 (0.48–0.94)	0.73 (0.53–1.01)	0.04
Dairy calcium						
Median, g/d	108	244	374	535	844	
Cases, n	100	53	76	53	65	
Relative risk (95% CI)†	1.0	0.55 (0.40–0.77)†	0.80 (0.59–1.08)	0.57 (0.40–0.79)	0.68 (0.50–0.94)	0.05
Relative risk (95% CI)‡	1.0	0.56 (0.40–0.79)‡	0.83 (0.62–1.12)	0.59 (0.42–0.83)	0.70 (0.51–0.97)	0.08
Nondairy calcium						
Median, g/d	199	247	284	324	391	
Cases, n	65	84	63	70	65	
Relative risk (95% CI)†	1.0	1.24 (0.90–1.71)†	0.89 (0.63–1.26)	0.95 (0.68–1.33)	0.82 (0.58–1.16)	0.08
Relative risk (95% CI)‡	1.0	1.31 (0.95–1.82)‡	0.95 (0.67–1.35)	1.03 (0.73–1.45)	0.91 (0.64–1.29)	0.25

*Embolic infarction due to nonvalvular atrial fibrillation, valvular atrial fibrillation, valvular heart disease, cardiomyopathy, bacterial endocarditis, and other nonatherogenic embolic origins were excluded.

†Adjusted for age (5-year categories), smoking status (5 categories), and time interval.

‡Adjusted for factors cited above and for body mass index (5 categories), alcohol intake (4 categories), menopausal status and postmenopausal hormone use, vigorous exercise (yes vs no), usual aspirin use (<1/wk, 1–2/wk, 3–6/wk, 7–14/wk and ≥15/wk), multivitamin use (yes vs no), vitamin E use (yes vs no), ω-3 fatty acid intake (quintile), and histories of hypertension, diabetes, and high cholesterol levels (yes vs no).

A prospective study of Japanese Americans living in Honolulu, Hawaii, showed an inverse relation between calcium intake and risk of ischemic stroke,[20] an association restricted to dairy calcium intake and specifically to milk consumption. In our study, however, the inverse association with dairy calcium intake was not restricted to milk but was also observed for yogurt, hard cheese, and ice cream. This discrepancy is not surprising because milk is a dominant source of dairy calcium for Japanese Americans, but in the present study population, milk accounted for ≈60% of dairy calcium, and yogurt, cheese, and ice cream accounted for ≈40%. Median intake of calcium was 406 mg/d for the Japanese-American men[20] and 675 mg/d for our population of women, with dairy calcium accounting for most of the difference between the 2 populations.

The present study also suggested an inverse association between nondairy calcium intake and risk of ischemic stroke, although the relation was not as strong as for dairy calcium, perhaps in part because of the smaller range of calcium intake from nondairy (a 3-fold difference in medians of extreme quintiles) compared with dairy foods (a 10-fold difference) (Table 4). The weaker association may also be due to lower bioavailability of nondairy calcium than dairy calcium.[34] The relation between calcium supplements and reduced risk of ischemic stroke was stronger when the variable of calcium supplementation was not updated, suggesting a long-term protective effect of calcium supplementation on ischemic stroke. These results suggest that calcium intake per se may reduce risk of ischemic stroke.

The mechanisms by which calcium intake could reduce risk of ischemic stroke are not well elucidated. A recent meta-analysis of randomized clinical trials concludes that calcium supplementation may slightly reduce systolic blood pressure, by −0.9 to −1.3 mm Hg, but not diastolic blood pressure.[6,7] In the Nurses' Health Study,[2] dietary calcium estimated from the 1980 dietary questionnaire had an independent and significant inverse association with risk of development of hypertension during 1980–1984. However, the analysis of dietary calcium and risk of hypertension during 1984–1988 using the 1984 dietary questionnaire did not yield a significant association.[29] These results suggest that a hypotensive effect of calcium intake, if any, is small and unlikely to explain any substantial part of the inverse relation between calcium intake and risk of ischemic stroke. This interpretation is supported by our finding that the inverse association was only slightly attenuated in multivariate analyses after adjustment for history of hypertension. In addition to a hypotensive effect, increased calcium intake reduced platelet aggregation in animal and human studies,[35,36] providing another mechanism that may lead to reduction of risk of

ischemic stroke. In animal studies[35,37] and human trials of hypercholesterolemic persons,[38,39] calcium supplementation has reduced serum total cholesterol, which may also contribute to reduce the risk of ischemic stroke.[40]

Dietary potassium intake also was associated with reduced risk of ischemic stroke, but the relation was far from statistically significant after simultaneous adjustment for calcium intake. However, we cannot rule out a modest independent effect of dietary potassium on risk. We found no association between potassium supplement use and risk of ischemic stroke. A meta-analysis of randomized clinical trials found that potassium supplementation reduces both systolic (−5.9 mm Hg) and diastolic blood pressure (−3.4 mm Hg).[8] Hypertensive rats given a high-potassium diet had decreased vascular smooth muscle cell proliferation that may contribute to a reduced risk of stroke.[16] A prospective study of American white men and women showed a significant inverse association between potassium intake and stroke-associated mortality.[21] However, the number of end points was small (n=24) and relied solely on the death certificate diagnoses, which did not allow analyses of specific stroke subtype. A study of Japanese persons living in Honolulu showed an inverse association between potassium intake and risk of fatal ischemic stroke (n=33), but not of nonfatal ischemic stroke (n=221).[22] A recent study of US health professional men indicated an inverse association between potassium intake and risk of all stroke and ischemic stroke, particularly among hypertensive men.[23]

As in the study of US men,[23] in the present study we found no independent association between magnesium intake and risk of stroke, but we cannot exclude a modest effect of this cation on risk of ischemic stroke. A weak inverse trend was found in the age- and smoking-adjusted analysis. Attenuation of the association after further adjustment for history of hypertension was consistent with the finding that magnesium intake was associated with reduced risk of development of hypertension in this cohort.[2] Several randomized trials have tested whether magnesium supplementation reduces blood pressure, but the results have been inconsistent.[3,9,10]

In conclusion, dietary intake of calcium was inversely associated with risk of ischemic stroke in middle-aged American women. The shape of this inverse association was not log linear; the increase in risk was limited to the lowest quintile of intake, and intakes $>\approx$600 mg/d did not appear to reduce risk of stroke further. Although the mechanisms to account for this relation are not clear, the present study suggests that avoiding low intakes of calcium and possibly potassium may be beneficial for prevention of ischemic stroke. However, it also remains possible that women in the lowest quintile of calcium intake had unknown characteristics that made them susceptible to ischemic stroke. Further studies of intake of cations and risk of stroke are warranted.

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