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I am faxing copies of four recent research papers that support the NAS Diet and Health Report conclusions about reduced risk of stroke. I will also send hard copies overnight since these might be hard to read. We look forward to hearing from you.

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

Hiroyasu Iso, MD; Meir J. Stampfer, MD; JoAnn E. Manson, MD; Kathryn Rexrode, MD; Charles H. Hennekens, MD; Graham A. Colditz, MBBS; Frank E. Speizer, MD; Walter C. Willett, MD

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 ≥29 kg/m²	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 ≥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 ≥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 ≥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 >≈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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ORIGINAL CONTRIBUTION

Fruit and Vegetable Intake in Relation to Risk of Ischemic Stroke

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Context Few studies have evaluated the relationship between fruit and vegetable intake and cardiovascular disease.

Objective To examine the associations between fruit and vegetable intake and ischemic stroke.

Design, Setting, and Subjects Prospective cohort studies, including 75 596 women aged 34 to 59 years in the Nurses' Health Study with 14 years of follow-up (1980-1994), and 38 683 men aged 40 to 75 years in the Health Professionals' Follow-up Study with 8 years of follow-up (1986-1994). All individuals were free of cardiovascular disease, cancer, and diabetes at baseline.

Main Outcome Measure Incidence of ischemic stroke by quintile of fruit and vegetable intake.

Results A total of 366 women and 204 men had an ischemic stroke. After controlling for standard cardiovascular risk factors, persons in the highest quintile of fruit and vegetable intake (median of 5.1 servings per day among men and 5.8 servings per day among women) had a relative risk (RR) of 0.69 (95% confidence interval [CI], 0.52-0.92) compared with those in the lowest quintile. An increment of 1 serving per day of fruits or vegetables was associated with a 6% lower risk of ischemic stroke (RR, 0.94; 95% CI, 0.90-0.99; $P = .01$, test for trend). Cruciferous vegetables (RR, 0.68 for an increment of 1 serving per day; 95% CI, 0.49-0.94), green leafy vegetables (RR, 0.79; 95% CI, 0.62- 0.99), citrus fruit including juice (RR, 0.81; 95% CI, 0.68-0.96), and citrus fruit juice (RR, 0.75; 95% CI, 0.61-0.93) contributed most to the apparent protective effect of total fruits and vegetables. Legumes or potatoes were not associated with lower ischemic stroke risk. The multivariate pooled RR for total stroke was 0.96 (95% CI, 0.93-1.00) for each increment of 2 servings per day.

Conclusions These data support a protective relationship between consumption of fruit and vegetables—particularly cruciferous and green leafy vegetables and citrus fruit and juice—and ischemic stroke risk.

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IN SEVERAL ARTICLES, NUTRIENTS IN fruit and vegetables such as dietary fiber, potassium, and antioxidants have been associated with reduced risk of cardiovascular disease (CVD).[1-5] However, the data directly relating fruit and vegetable intake and CVD are sparse, as summarized in a recent review,[6] and the results of studies that specifically examined fruit and vegetables as a group were inconsistent.[5] Furthermore, many studies were small with few end points, dietary assessments were often crude and available only at baseline, and the distinction was often not made between hemorrhagic and ischemic strokes, which have different causes. To understand better the relationship between diet and stroke, we examined intakes of specific fruits and vegetables, as well as overall fruit and vegetable consumption, in relation to the incidence of ischemic stroke in 2 large cohorts of women and men.

METHODS

Study Populations

Data for this analysis were derived from 2 ongoing cohorts, the Nurses' Health Study (NHS)[7] and the Health Professionals' Follow-up Study (HPFS).[1] The 2 studies are similar in design; participants in both cohorts have been completing mailed questionnaires every 2 years to provide information on medical history, health behaviors, and the occurrence of cardiovascular and other outcomes. The NHS enrolled 121 700 female registered nurses aged 30 to 55 years in 1976.

The HPFS study population is composed of 51 529 male health professionals including dentists, veterinarians, pharmacists, optometrists, osteopathic physicians, and podiatrists who were 40 to 75 years of age in 1986.

See also Patient Page.

Population for Analysis

After 4 mailings, 98 462 women returned the 1980 NHS dietary question-

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naire. We excluded those with 10 or more items blank, those with implausible scores for total food intake (<2092 kJ/d or >14 644 kJ/d) (n = 5994), and those with previously diagnosed cancer, diabetes, or CVDs (n = 7254). Among the men, we excluded 6442 participants who reported CVD, cancer, or diabetes prior to the follow-up period. We further excluded 1349 men who reported daily energy intake outside the plausible range of 3360 to 17 640 kJ/d or who left 70 or more of the 131 dietary questions blank. More than 90% of the baseline population, on average, responded to at least 1 follow-up questionnaire, and about 80% completed each of the repeated dietary questionnaires during follow-up in these cohorts. The total number of subjects included in this analysis were 75 596 women and 38 683 men (TABLE 1).

Assessment of Stroke End Points

Participants (or next of kin for the deceased) reporting an incident stroke on a follow-up questionnaire were asked permission to have their medical records reviewed. Using these records, including imaging results recommended by the National Survey of Stroke,[8] we subclassified the strokes into ischemic (embolic or thrombotic), hemorrhagic (subarachnoid or intracerebral), or unknown type. Cases attributed to infections or malignant processes or cases of indeterminate age discovered on computed tomographic or magnetic resonancing imaging scans without acute symptoms were not included. Physicians reviewing the medical records were unaware of the participants' dietary status. Deaths were reported by next of kin or coworkers or were obtained from postal authorities or from the National Death Index. Only strokes confirmed by medical records were included in this analysis. We considered nonresponders who were not listed on the National Death Index as noncases.

Table 1. Description of Age-Standardized Cardiovascular Risk Factors by Baseline Quintiles of Fruit and Vegetable Intake Among 75 596 Women and 38 683 Men*

	Fruit Quintiles			Vegetable Quintiles		
	1	3	5	1	3	5
Women						
Servings per day	0.9	2.3	4.5	1.6	3.3	6.2
Age, y	44.6	46.2	47.4	45.5	45.9	47.0
Current smoker, %	42.8	25.9	19.8	32.1	28.5	25.5
Current estrogen replacement, %†	6.3	6.7	7.1	6.9	6.6	6.6
Regular vigorous activity, %	34.2	46.2	54.2	37.9	44.0	53.5
Body mass index, kg/m²	24.2	24.3	24.3	24.2	24.3	24.4
History at baseline, %						
Hypertension	13.2	14.8	17.1	14.2	15.1	15.9
High cholesterol level	5.1	4.7	5.4	4.4	4.9	5.7
Parents' coronary heart disease history at age ≤65 y, %	20.0	20.5	20.3	19.4	20.0	21.2
Multivitamin supplement use, %	27.6	34.5	38.7	30.8	33.0	37.3
Saturated fat, g/d	26.7	27.3	28.7	24.7	27.6	29.7
Cereal fiber, g/d	2.3	2.7	2.9	2.4	2.7	2.8
Men						
Servings per day	0.7	2.1	4.3	1.4	2.8	5.4
Age, y	51.5	54.1	55.2	53.0	53.7	54.6
Current smoker, %	18.4	8.6	4.9	13.0	10.0	7.0
Physical activity, metabolic equivalent/wk‡	14.1	19.7	26.5	16.0	19.2	24.9
Body mass index, kg/m²	25.7	25.4	25.2	25.5	25.4	25.5
History at baseline, %						
Hypertension	19.3	19.3	19.6	19.0	20.0	20.0
High cholesterol level	9.2	9.7	11.8	9.0	11.0	11.0
Family history of coronary heart disease at age <60 y, %	12.0	12.0	12.0	11.0	12.0	13.0
Multivitamin supplement use, %	41.2	48.4	54.1	45.0	46.0	52.0
Saturated fat, g/d	24.3	24.7	24.9	22.6	25.0	26.1
Cereal fiber, g/d	5.6	7.1	8.1	5.9	7.0	7.9

*Standardized for age (except for age itself) to the cohort age distribution (Nurses' Health Study or Health Professionals' Follow-up Study); values are means unless otherwise specified.
†Among postmenopausal women only.
‡Metabolic equivalent (MET) hours = sum of the average time per week spent in each activity × MET value of each activity

$$\text{MET value} = \frac{\text{caloric need/kg body weight/hour activity}}{\text{caloric need/kg body weight/hour at rest}}$$

Dietary Assessment

In the NHS, diet was assessed in 1980, 1984, 1986, and 1990. A 61-item semiquantitative food frequency questionnaire (FFQ) including 6 fruit and 11 vegetable items, and potatoes was included in 1980. An expanded 116-item FFQ including 15 fruit items, 28 vegetable items, and potatoes were included in 1984; similar questionnaires were repeated in 1986 and 1990. In the HPFS, diet was assessed in 1986 and 1990 using an expanded semiquantitative FFQ similar to that used in the NHS. Further details about the NHS and the HPFS have been described elsewhere.[1,7]

On dietary questionnaires, participants reported their average intake of a specified portion size for each food over the past year. For each food item on the questionnaire, 9 responses were possible, ranging from never or less than once per month to 6 or more times per day. Detailed descriptions of the reproducibility and validity of the FFQ for both men and women have been published previously.[9-11] Validity of the dietary data has been documented by comparisons with multiple weighted dietary records correcting for within-person weekly variation in diet. The correlation coefficients for responses to the 61-item questionnaire in the NHS for fruits and vegetables compared with four 1-week diet records averaged 0.57 (ranging from 0.27-0.93). In the HPFS, Pearson correlations between intake from the questionnaire and the diet records, corrected for within-person weekly variation in diet record, were on average approximately 0.7 for intake of individual fruits and 0.5 for intake of individual vegetables.

Responses to the individual food items were converted to average daily intake of each fruit and vegetable item for each participant. The average daily intakes of individual food items were combined to compute total fruit and vegetable intake, as well as intakes of composite fruit and vegetable groups. The definitions of composite groups were based on a report by Steinmetz et al[12]; the groups were modified to relate to our questionnaires and hypothesis (available on request from the authors). Vitamin C–rich fruits and vegetables included items containing more than 30 mg of vitamin C per serving. For total vegetable intake, we did not include potatoes, tofu and soybeans, dried beans and lentils, or items with small portion sizes such as chili sauce and garlic. Missing individual components were counted as zero intake when aggregating items to compute the composite items.

Data Analyses

We recorded 670 total strokes among women: 366 new cases of ischemic stroke, 198 new cases of hemorrhagic stroke, and 106 of unknown type. There were 317 total strokes among men: 204 ischemic, 64 hemorrhagic, and 49 of unknown type. Due to the relatively small number of cases of hemorrhagic stroke to date and the differences in cause between ischemic and hemorrhagic stroke, this article focuses only on ischemic stroke.

Person-time for each participant was calculated from the date of return of the 1980 questionnaire (in the NHS) or the 1986 questionnaire (in the HPFS) to the earlier of the date of first stroke event, death, or the cutoff date (June 1, 1994, for the NHS, and January 31, 1994, for the HPFS). Participants who reported CVD or cancer or diabetes prior to completion of the baseline dietary questionnaires were excluded. Each participant thus contributed only 1 end point, and the cohort at risk for each follow-up period included only those who remained free from stroke at the beginning of each 2-year follow-up period.

Due to the difference in sex, follow-up time, and the questionnaires in the 2 cohorts, the analyses were performed separately in each cohort and combined to achieve better control of confounding. The risk for ischemic stroke was compared by fruit/vegetable intake using pooled logistic regression methods proposed by Cupples et al[13] and D'Agostino et al,[14] which summarize the relative risk (RR) across all 2-year follow-up periods. Analyses were adjusted for age (5-year categories); smoking (never, former, current: 1-14, 15-24, and ≥25 cigarettes per day); alcohol consumption (5 categories in women, 7 categories in men); family history of myocardial infarction (<65 years of age in women, <60 years of age in men); body mass index (quintiles); multivitamin supplement use; vitamin E use, aspirin use, physical activity (2 categories in women, quintiles in men); and reported hypertension and hypercholesterolemia and time period. Additionally, among the women, we controlled for postmenopausal hormone use. We also controlled for total energy intake.[15,16]

Because of the long follow-up period, exposures and confounders were updated to better represent long-term dietary patterns.[17] In the NHS we used the 1980, 1984, 1986, and 1990 questionnaires, and in the HPFS we used the 1986 and 1990 questionnaires. We computed fruit and vegetable intake for each follow-up period as a cumulative average of intake from all available FFQs up to the start of the 2-year follow-up period in which events were reported. Since intermediate end points may influence diet, in cases in which the participant experienced angina, coronary artery bypass grafting or angioplasty, hypercholesterolemia, hypertension, or diabetes, we stopped updating diet at the beginning of the interval in which they experienced the outcome.

The average daily intake for each composite item was coded into quintiles of intake within each cohort. Each quintile of intake was compared with the lowest quintile of intake. Trends in stroke risk across individual fruits and vegetables and composite items were assessed in logistic models by using a variable for the average number of servings consumed per day. To assess the trend for composite items, we used the median values of intake for each quintile of the composite item to minimize the influence of outliers. The RR for the continuous measures, for both the individual and composite items, indicates the increase or decrease in risk associated with an average increment of 1 serving per day of the standard portion size defined in the questionnaires.

Because a protective effect of fruits and vegetables could be explained by their vitamin content, we also evaluated associations between fruit and vegetables and ischemic stroke separately among multivitamin supplement users and nonusers. Nonusers of multivitamins who took other vitamin supplements at baseline were excluded from these subgroup analyses. Nonusers from the HPFS who took mineral supplements at baseline were also excluded from the subgroup analyses; data on mineral supplements were not available in the NHS in 1980.

We also performed the analyses separately for current smokers and for never or past smokers to determine if smoking influenced the association between intake of fruits and vegetables and ischemic stroke. For the primary analyses, the RR from the (pooled) logistic regres-

Table 2. Multivariate Relative Risks (RRs) of Ischemic Stroke With 95% Confidence Intervals (CIs) by Quintile and per Serving per Day*

	Quintile†					Median Servings per Day§	
Composite Items	2	3	4	5	1 Serving per Day‡	Overall	[Quintile 1, 5]
All fruits and vegetables							
Women	0.89 (0.66-1.20)	0.75 (0.55-1.04)	0.60 (0.42-0.85)	0.74 (0.52-1.05)	0.93 (0.87-1.00)	5.82	[2.93, 10.15]
Men	0.77 (0.49-1.20)	0.70 (0.44-1.10)	1.03 (0.67-1.57)	0.61 (0.37-1.00)	0.96 (0.89-1.03)	5.07	[2.54, 9.15]
Pooled	0.85 (0.66-1.09)	0.73 (0.56-0.95)	0.77 (0.46-1.31)	0.69 (0.52-0.92)	0.94 (0.90-0.99)		
All fruits							
Women	0.88 (0.65-1.20)	0.82 (0.60-1.13)	0.66 (0.47-0.93)	0.69 (0.49-0.98)	0.87 (0.78-0.96)	2.33	[0.86, 4.54]
Men	0.78 (0.50-1.22)	0.84 (0.54-1.31)	0.87 (0.56-1.34)	0.68 (0.42-1.10)	0.93 (0.82-1.05)	2.09	[0.72, 4.33]
Pooled	0.85 (0.66-1.09)	0.83 (0.64-1.07)	0.73 (0.56-0.96)	0.69 (0.52-0.91)	0.89 (0.82-0.97)		
All vegetables							
Women	1.23 (0.92-1.65)	0.88 (0.63-1.22)	0.76 (0.54-1.08)	0.89 (0.63-1.26)	0.95 (0.86-1.06)	3.34	[1.60, 6.21]
Men	0.99 (0.65-1.51)	0.76 (0.49-1.20)	0.81 (0.51-1.26)	0.90 (0.58-1.41)	0.98 (0.88-1.09)	2.83	[1.36, 5.37]
Pooled	1.15 (0.90-1.46)	0.84 (0.64-1.09)	0.78 (0.59-1.03)	0.90 (0.68-1.18)	0.96 (0.89-1.04)		
Total citrus fruits							
Women	0.70 (0.51-0.96)	0.82 (0.60-1.10)	0.72 (0.52-0.98)	0.59 (0.42-0.82)	0.75 (0.62-0.91)	0.85	[0.08, 1.80]
Men	1.24 (0.80-1.92)	0.92 (0.59-1.45)	0.92 (0.59-1.44)	0.92 (0.59-1.44)	0.93 (0.73-1.18)	0.86	[0.08, 1.88]
Pooled	0.91 (0.52-1.60)	0.85 (0.66-1.09)	0.78 (0.60-1.01)	0.72 (0.47-1.11)	0.81 (0.68-0.96)		
Citrus fruit juices							
Women	0.80 (0.58-1.11)	0.77 (0.56-1.05)	0.91 (0.66-1.25)	0.61 (0.45-0.84)	0.73 (0.56-0.95)	0.43	[0.00, 1.00]
Men	0.91 (0.60-1.39)	0.84 (0.54-1.31)	0.85 (0.53-1.37)	0.74 (0.49-1.13)	0.80 (0.57-1.13)	0.43	[0.00, 1.00]
Pooled	0.84 (0.65-1.09)	0.79 (0.61-1.02)	0.89 (0.68-1.16)	0.65 (0.51-0.84)	0.75 (0.61-0.93)		
Cruciferous vegetables							
Women	1.09 (0.80-1.50)	1.04 (0.77-1.42)	0.91 (0.65-1.26)	0.77 (0.54-1.08)	0.69 (0.44-1.08)	0.42	[0.14, 0.95]
Men	0.65 (0.42-0.99)	0.82 (0.54-1.23)	0.69 (0.45-1.05)	0.64 (0.42-0.99)	0.70 (0.43-1.14)	0.04	[0.14, 1.01]
Pooled	0.86 (0.51-1.44)	0.95 (0.74-1.22)	0.82 (0.63-1.06)	0.71 (0.55-0.93)	0.68 (0.49-0.94)		
Green leafy vegetables							
Women	0.65 (0.46-0.91)	0.71 (0.52-0.96)	0.77 (0.56-1.06)	0.76 (0.55-1.05)	0.84 (0.61-1.15)	0.73	[0.16, 1.51]
Men	1.01 (0.67-1.52)	1.08 (0.70-1.67)	0.76 (0.49-1.17)	0.76 (0.48-1.20)	0.73 (0.52-1.03)	0.59	[0.16, 1.36]
Pooled	0.80 (0.51-1.24)	0.85 (0.57-1.27)	0.77 (0.59-0.99)	0.76 (0.58-0.99)	0.79 (0.62-0.99)		
Vitamin C–rich fruits and vegetables							
Women	0.83 (0.62-1.12)	0.73 (0.54-1.00)	0.68 (0.49-0.95)	0.64 (0.46-0.89)	0.80 (0.68-0.93)	1.53	[0.54, 3.08]
Men	0.82 (0.52-1.27)	0.62 (0.39-0.99)	1.00 (0.66-1.51)	0.77 (0.49-1.20)	0.95 (0.80-1.13)	1.42	[0.46, 2.96]
Pooled	0.83 (0.64-1.06)	0.70 (0.54-0.90)	0.81 (0.56-1.17)	0.68 (0.52-0.89)	0.87 (0.73-1.03)		
Legumes							
Women	1.15 (0.83-1.60)	1.01 (0.71-1.44)	1.38 (1.02-1.88)	1.16 (0.83-1.63)	1.65 (0.81-3.40)	0.16	[0.00, 0.43]
Men	0.83 (0.55-1.25)	0.98 (0.62-1.54)	1.07 (0.71-1.62)	0.85 (0.54-1.34)	0.71 (0.33-1.52)	0.22	[0.00, 0.57]
Pooled	1.00 (0.73-1.38)	1.00 (0.75-1.32)	1.26 (0.98-1.62)	1.03 (0.77-1.39)	1.09 (0.47-2.51)		
Potatoes							
Women	0.96 (0.61-1.52)	0.92 (0.61-1.39)	1.12 (0.74-1.72)	1.09 (0.69-1.72)	1.15 (0.69-1.90)	0.43	[0.14, 0.96]
Men	1.11 (0.81-1.52)	1.10 (0.81-1.50)	1.04 (0.74-1.46)	1.23 (0.88-1.72)	1.25 (0.85-1.83)	0.51	[0.14, 1.02]
Pooled	1.06 (0.82-1.37)	1.03 (0.80-1.32)	1.07 (0.82-1.40)	1.18 (0.90-1.54)	1.21 (0.89-1.64)		

*Results in men, women, and pooled data for quintiles of intake compared with the lowest quintile and for an increment of 1 serving per day. Person-years = 581 118 among women and 166 566 among men; cases = 366 among women and 204 among men. Models are adjusted for age (5-year categories), smoking (never, former, current: 1-14, 15-24, ≥25 cigarettes per day), alcohol (7 categories in men, 5 categories in women), family history of myocardial infarction (age <60 y in men and age <65 y in women), body mass index (quintiles), vitamin supplement use, vitamin E use, physical activity, aspirin use, 7 time periods for women, 4 time periods for men, hypertension and hypercholesterolemia, total energy intake, and among women, postmenopausal hormone use.
†*Reference is quintile 1, lowest intake.*
‡Continuous variable for increments of 1 serving per day using median value for the quintile of intake.
§Distribution based on 1986 questionnaires.

sion pooling across 2-year time periods from the 2 cohorts were further combined using the pooling methods proposed by DerSimonian and Laird[18] that weighted the RR in each cohort by the inverse of the SEs. Finally, we examined the adjusted RR for total stroke, using methods similar to those used for ischemic stroke.

RESULTS

Table 1 shows the distribution of the baseline standard cardiovascular risk factors by quintiles of baseline fruit and vegetable intake from the NHS and the HPFS (quintile 5 being the highest intake group). Persons who consumed more fruit and vegetables were older and generally had healthier lifestyles as indicated by lower rates of smoking and higher levels of physical activity. Similar trends were seen with other behavioral variables. Smoking and exercise were more strongly related to fruit intake compared with vegetables. Intakes of protein, cereal fiber, *trans*fatty acids, saturated fat, polyunsaturated fat, and cholesterol increased with increasing fruit and vegetable intake.

Median intakes of total fruits and vegetables in 1986 were 5.8 servings per day for women (2.9 and 10.2 for quintiles 1 and 5, respectively) and 5.1 servings per day for men (2.6 and 9.2 for quintiles 1 and 5, respectively) (TABLE 2). Results from both studies individually, as well as pooled analyses for composite fruit and vegetable items, are presented in Table 2. **Overall fruit and vegetable intake was inversely related to risk of ischemic stroke after adjusting for potential confounders. Those in the top quintile of intake had an RR of 0.69 (95% CI, 0.52-0.92) compared with those in the lowest quintile; the corresponding RR was 0.74 (95% CI, 0.52-1.05) among women and 0.61 (95% CI, 0.37-1.00) among men. Assessed as a continuous trend, an increment of 1 serving per day was associated with a 7% lower risk among women and a 4% lower risk among men; for the combined population there was a 6% lower risk of ischemic stroke ($P = .01$, test for trend).** Similar results were seen for total fruit and for total vegetables separately. Additional control for intakes of *trans*fatty acids, saturated fat, polyunsaturated fat, or cholesterol did not appreciably alter the results. All the composite items except legumes and potatoes were inversely associated with risk of ischemic stroke.

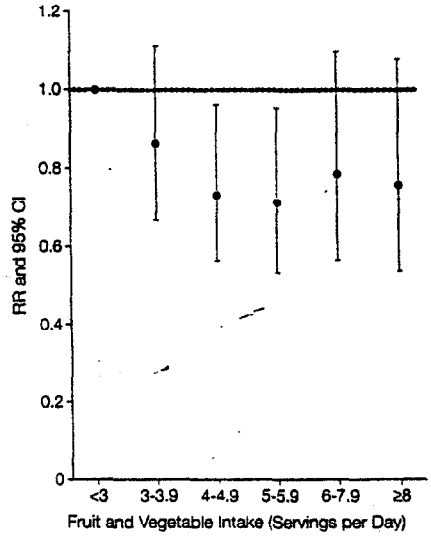
The lowest risks were observed for high consumption of cruciferous vegetables (eg, broccoli, cabbage, cauliflower, brussel sprouts), green leafy vegetables, citrus fruits, and vitamin C–rich fruit and vegetables. The results were similar across both cohorts, especially the measures of trend. Again, additional analyses incorporating nutrients that may be potential confounders including protein, cereal fiber, saturated fat, *trans*fatty acids, polyunsaturated fat and cholesterol intake, or meat intake did not change the results. For example, when meat intake was added to the model, the RR for a 1 serving per day increment of total fruits and vegetables changed from 0.94 (95% CI, 0.90-0.99) to 0.95 (95% CI, 0.90-0.99); addition of *trans*fatty acid quintiles resulted in an RR of 0.94 (95% CI, 0.90-1.0). When we examined total stroke as the outcome, an increment of 1 serving per day of total fruits and vegetables was associated with a 3% lower risk among women and a 5% lower risk among men; the multivariate pooled RR was 0.96 (95% CI, 0.93-1.00). Results for specific fruits and vegetables were in the same direction as for ischemic stroke or null.

The FIGURE shows the multivariate RRs and 95% CIs for ischemic stroke computed for increasing servings per day of intake of fruit and vegetables (pooled for the NHS and the HPFS), suggesting a decreasing risk of ischemic stroke with increasing intake. There was no apparent further reduction in risk beyond 6 servings per day.

Supplement users consumed more fruit and vegetables than nonusers (6.08 servings per day vs 5.64 servings per day among women and 5.40 servings per day vs 4.94 servings per day among men). Similarly, nonsmokers consumed more fruit and vegetables than current smokers (6.00 servings per day vs 5.10 servings per day among women and 5.21 servings per day vs 4.21 servings per day among men). Pooled RRs for an increment of 1 serving per day (linear trend) by multivitamin supplement use or nonuse and by smoking status are presented in TABLE 3. The inverse associations between consumption of fruits, citrus fruit, and cruciferous vegetables and risk of ischemic stroke were somewhat stronger in the nonsupplement group compared with the supplement user group. Although the associations were somewhat weaker and not statistically significant among multiple vitamin users, the number of cases was smaller and the CIs included substantial reductions in risk. No striking differences in associations were seen by smoking status, although the apparent protective effects appeared to be slightly stronger among current smokers than among past and never smokers. The CIs indicate that interactions between intake of fruit and vegetables and smoking (or supplement use) or ischemic stroke are not significant.

Analyses of individual fruit and vegetable items that constituted the composite items did not show any single fruit or vegetable that was strikingly

Figure. Total Fruit and Vegetable Intake and Risk of Ischemic Stroke



Pooled multivariate relative risks (RRs) of ischemic stroke with 95% confidence intervals (CIs) for men and women for increasing intake of total fruits and vegetables. Data are for men and women combined, controlled for the same factors as in Table 2, with none to less than 3 servings per day as the comparison group.

more protective than others. Most items showed null or inverse associations. In general, the findings were consistent with what may be expected from the composite analyses (data not shown).

COMMENT

Overall, these findings support a protective effect between consumption of fruits and vegetables against risk of ischemic stroke in both women and men. Fruit and vegetables—in particular cruciferous and green leafy vegetables, citrus fruits, and citrus fruit juices—were inversely associated with risk of ischemic stroke in both cohorts. Fruit and vegetable intake was associated with behavioral risk factors such as smoking and exercise. However, adjustment for behavioral and other risk factors, including nutrients that were suspected to be confounders, did not explain the apparent benefits of higher fruit and vegetable consumption, although adjustments for these factors did attenuate the observed associations.

These cohorts of health professionals tended to have healthier lifestyles than the general population; for example, the median intake of fruit and vegetables in these cohorts was over the recommended 5 servings per day.[19,20] The existence of a dose-response relationship within these groups, which are relatively homogenous in occupation and education, is particularly notable, as confounding by variables related to socioeconomic status is minimized. We found that intake beyond 6 servings per day provided little further reduction in risk of ischemic stroke compared with intake of 5 to 6 servings per day. These findings lend support to the recommendation of eating 5 servings per day of fruit and vegetables. For specific fruits and vegetables, the RRs for an increment of 1 serving per day should be interpreted in light of the consumption level. For example, the intake of legumes was very low, with only 0.5 servings per day as the median intake in the highest quintile (Tables 2 and 3); hence, our ability to study the effect of higher consumption was limited.

Our results are similar to a study of 832 men from the Framingham cohort. The RR of 0.94 in our study for an increment of 1 serving per day translates to a decremental risk of 0.83 for 3 servings per day, which is reasonably comparable with the RR of 0.75 for ischemic stroke (95% CI, 0.55-1.03) for an increment of 3 servings per day of fruit and vegetables (including potatoes)[21] in the Framingham study. No association between green and yellow vegetables and total stroke was observed among a 16-year follow-up of 265 118 Japanese people,[22] but the study reported on total strokes and the majority of strokes in Japan at that time were likely to be hemorrhagic. In a 5-year follow-up[23] of 1299 Massachusetts nursing home residents, the RR for stroke was 0.40 for carrots (95% CI, 0.17-0.98) and 0.49 for salads (95% CI, 0.31-0.71), comparing 1 or more vs less than 1 serving per day, which is stronger than comparable associations in our study.

The constituents of fruits and vegetables potentially responsible for their apparent beneficial effects on risk of ischemic stroke include potassium, folate, and fiber; the associations between ischemic stroke and these nutrients have been evaluated in other reports.[23-27] Dietary flavonoids (which are present in fruits and vegetables) have also been recently related to decreased risk of ischemic stroke.[28] There is little evidence relating dietary fiber to stroke. The evidence for potassium is limited and most studies were based on a 24-hour recall, which may not be able to adjust for other foods and nutrients that could explain the inverse associations reported.[4,24] However, in a recent report based on the same cohort of men included in these analyses,[25] a significant inverse association was seen (multivariate RR, 0.62; 95% CI, 0.43-0.88 comparing the top and bottom quintile of potassium intake). The evidence for folate is largely indirect through its effect on homocysteine,[26] although in the Framingham Heart Study, an association was observed between low serum concentrations and low intakes of folate and increased risk of extracranial carotid artery stenosis.[27] Hence, the evidence for a protective role of any single constituent of fruits and vegetables is suggestive but inconclusive, and it is important to consider the role of fruits and

Table 3. Multivariate Relative Risks (RRs) and 95% Confidence Intervals (CIs) for Ischemic Stroke for 1 Serving per Day by Multivitamin Use and Smoking Status*

	No Vitamin Supplement (n = 295)	Multivitamin Supplement (n = 216)	Never and Past Smokers (n = 388)	Current Smokers (n = 172)
All fruits and vegetables	0.93 (0.87-0.99)	0.98 (0.91-1.05)	0.96 (0.91-1.02)	0.93 (0.78-1.10)
All fruits	0.90 (0.76-1.05)	0.96 (0.84-1.09)	0.94 (0.85-1.03)	0.86 (0.70-1.06)
All vegetables	0.91 (0.81-1.03)	0.96 (0.85-1.08)	0.97 (0.89-1.06)	0.86 (0.74-1.02)
Total citrus fruits	0.77 (0.62-0.97)	0.86 (0.61-1.23)	0.88 (0.74-1.05)	0.88 (0.48-1.63)
Citrus fruit juices	0.72 (0.53-0.97)	0.90 (0.63-1.26)	0.78 (0.60-1.01)	0.70 (0.47-1.04)
Cruciferous vegetables	0.55 (0.34-0.91)	0.87 (0.52-1.43)	0.66 (0.45-0.98)	0.57 (0.28-1.16)
Green leafy vegetables	0.78 (0.56-1.09)	0.81 (0.56-1.17)	0.74 (0.56-0.98)	0.91 (0.58-1.43)
Vitamin C–rich fruits and vegetables	0.83 (0.66-1.04)	0.89 (0.74-1.08)	0.88 (0.77-1.01)	0.73 (0.58-0.93)
Legumes	1.40 (0.48-4.09)	0.85 (0.36-1.98)	1.05 (0.56-1.98)	1.58 (0.58-4.29)
Potatoes	1.18 (0.72-1.94)	1.12 (0.68-1.85)	1.17 (0.80-1.70)	1.35 (0.79-2.31)
Women				
Person-years	324 869	196 788	449 006	129 324
Cases	214	122	226	139
Men				
Person-years	78 171	69 397	144 125	15 903
Cases	81	94	162	33

*Adjusted for age (5-year categories), smoking (never, former, current: 1-14, 15-24, ≥25 cigarettes per day), alcohol (7 categories in men, 5 categories in women), family history of myocardial infarction (age <60 y in men and age <65 y in women), body mass index (quintiles), vitamin supplement use, vitamin E use, physical activity, aspirin use, 7 time periods for women, 4 time periods for men, hypertension and hypercholesterolemia, total energy intake, and among women, postmenopausal hormone use.

vegetables foods in themselves. Slightly stronger protective associations were seen in the nonusers of supplements, suggesting that constituents of multivitamins may contribute to the apparent protective effect of fruits and vegetables. There was no clear modification of the relation of fruit and vegetable consumption to risk of ischemic stroke by smoking, but current smokers may gain a slightly greater benefit from eating more fruits and vegetables than never or past smokers.

These data support a protective effect of higher consumption of fruits and vegetables—in particular cruciferous and green leafy vegetables, citrus fruits, and citrus juice—against risk of ischemic stroke. Our results provide further support for the recommendation to consume at least 5 servings of fruits and vegetables a day.

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Protective Effect of Fruits and Vegetables on Development of Stroke in Men

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Objective.—To examine the effect of fruit and vegetable intake on risk of stroke among middle-aged men over 20 years of follow-up.

Design.—Cohort.

Setting.—The Framingham Study, a population-based longitudinal study.

Participants.—All 832 men, aged 45 through 65 years, who were free of cardiovascular disease at baseline (1966 through 1969).

Measurements and Data Analysis.—The diet of each subject was assessed at baseline by a single 24-hour recall. The estimated total number of servings per day of fruits and vegetables was the exposure variable for this analysis. Using Kaplan-Meier survival analysis, we examined age-adjusted cumulative incidence of stroke by quintile of servings per day. To adjust for multiple covariates, we used proportional hazards regression to calculate the relative risk (RR) of stroke for each increment of three servings per day.

Main Outcome Measure.—Incidence of completed strokes and transient ischemic attacks.

Results.—At baseline, the mean (±SD) number of fruit and vegetable servings per day was 5.1 (±2.8). During follow-up there were 97 incident strokes, including 73 completed strokes and 24 transient ischemic attacks. Age-adjusted risk of stroke decreased across increasing quintile of servings per day (log rank *P* for trend, .01). Age-adjusted RR for all stroke, including transient ischemic attack, was 0.78 (95% confidence interval [CI], 0.62 to 0.98) for each increase of three servings per day. For completed stroke the RR was 0.74 (95% CI, 0.57 to 0.96); for completed stroke of ischemic origin the RR was 0.76 (95% CI, 0.57 to 1.02); and for completed stroke of hemorrhagic origin, 0.49 (95% CI, 0.25 to 0.95). Adjustment for body mass index, cigarette smoking, glucose intolerance, physical activity, blood pressure, serum cholesterol, and intake of energy, ethanol, and fat did not materially change the results.

Conclusion.—Intake of fruits and vegetables may protect against development of stroke in men.

(*JAMA.* 1995;273:1113-1117)

ALTHOUGH stroke mortality rates have decreased in the past several decades, cerebrovascular disease remains the third leading cause of death in the United States.[1] Acute and long-term care for stroke patients and lost productivity consume at least $20 billion annually, and many of the more than 3 million US stroke victims who are alive today suffer severe disability.[1] Because of this substantial morbidity and mortality and the lack of effective therapies, several authors have stressed the potential value of primary prevention.[2-4]

Data from international epidemiologic comparisons suggest that immigrants rapidly take on the stroke incidence rates of their adopted country.[5] Thus, environmental factors, including diet, may be important in the genesis of stroke and in the potential to prevent its occurrence. Despite this, there have been few studies concerning possible dietary determinants of stroke. In addition, most of these studies have focused on selected nutrients rather than on foods themselves. For example, Gey et al[6] demonstrated an increased risk of stroke among Swiss men with low plasma carotene and vitamin C levels, suggesting a protective role for dietary antioxidant vitamins. Preliminary data from the Nurses' Health Study agree with these findings.[7] Khaw and Barrett-Connor[8] reported an inverse association of potassium intake, irrespective of hypertensive status, with stroke mortality in a population-based cohort study in southern California. Some studies have also suggested a protective role for both dietary fat and protein.[9-12] Ethanol intake appears to increase the risk for hemorrhagic, but not ischemic, stroke.[13-15]

Nutritional advice is often easier to understand in the context of foods rather than the nutrients contained in foods. Therefore, linking foods or food groups to outcomes may be at least as important as nutrient-disease relationships. Fruits and vegetables are of particular interest because of their potassium and antioxidant content[17] and because of national programs aimed at increasing intake of these foods.[18] One ecological study suggested an inverse association between fruit and vegetable consumption and stroke,[19] and another related higher consumption of fruits and vegetables with a decrease in mortality from all cardiovascular diseases.[20] However, longitudinal epidemiologic data concerning this subject are scarce. Preliminary data from one study suggested a reduced risk of stroke with consumption of larger amounts of fruits and vegetables,[21] but the data were limited to women. The purpose of this study was to examine the effect of fruit and vegetable consumption on stroke incidence over 20 years of follow-up among middle-aged men participating in the Framingham Study.

METHODS

The Framingham Study, which began in 1948, is a longitudinal study of cardiovascular and other diseases and their risk factors. The original cohort consisted of 5209 men and women, and they have been examined biennially since the study's inception. Fewer than 2% of the original participants have been lost to follow-up for mortality end points. Further details of recruitment, examination procedures,

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and follow-up can be found elsewhere.[22]

From 1966 through 1969, all 865 men aged 45 through 65 years who were seen at examinations 9, 10, and 11 participated in assessment of dietary intake. Women's diets were not assessed. The method of assessment was designed to be comparable to protocols then in use in the Honolulu and Puerto Rico heart studies.[23-25] Trained interviewers elicited information on the individual's previous 24-hour intake. Household measures were used to determine food portion sizes. After completing the interview, study personnel tallied subjects' responses on a precoded food list (the Framingham Composite Table), using standardized protocols that have previously been described in detail.[26] Briefly, each food reported on the 24-hour recall, including the individual components of mixed dishes, was categorized into one of about 100 food items. Categorization was based on similarities in the energy content and macronutrient composition of foods. Estimates of macronutrient intake were calculated by hand, based on estimates of the nutrient composition of foods that were available at that time.[25] The dietary data set currently available for analysis contains subjects' estimated daily intake of the approximately 100 foods or food groups from the Framingham Composite Table, measured in number of servings (serving size is specified for each food). Also available are values for macronutrients in both grams and percentage of total energy. No estimates for micronutrients are available. These dietary data have been used previously to explore relationships between dietary lipids and development of coronary heart disease.[23,27]

For these analyses, we concentrated on the food groups that comprised fruits and vegetables.[26] In the three groups of fruits, a serving size was defined as 120 mL (½ cup). The first group was watery fruit, consisting of fruits for which a single serving contained no more than 59 kcal (247.8 kJ). Examples were peaches, grapes, oranges, and orange juice. Average fruits were those containing 60 to 89 kcal (252.0 to 373.8 kJ) per serving; examples were apples, bananas, and apple juice. The third category was sweet fruit, with at least 90 kcal (378.0 kJ) per serving. These included canned and frozen fruits. There were 10 categories of vegetables, with varying serving sizes. Roots and fruits (serving size 120 mL) included, among others, beets, onions, and winter squash. Examples of raw and green vegetables (120 mL) included lettuce, cucumbers, green peppers, and raw tomatoes. Cooked leafy vegetables (120 mL) included such items as broccoli, carrots, summer squash, and cooked tomatoes. The remaining categories and their serving sizes were as follows: tomato sauce (60 mL), peas and lima beans (120 mL), baked beans (120 mL), corn (120 mL), potatoes (one), sweet potatoes (one), and potato chips (28 g [1 oz]).

At the baseline examination (1966 through 1969), 16 men had had previous strokes and another 17 men had other forms of cardiovascular disease. The current analyses are based on the 832 men who were free of cardiovascular disease at that time. For this analysis subjects were followed up through examination 20, for 18 to 22 years of follow-up on each subject.

At the time of each follow-up visit the examining physician recorded newly developed cardiovascular disease, cancer, and other events. Information about end points was also obtained by surveillance of hospital admissions records and communication with family physicians and relatives. All cardiovascular events, including stroke, were reviewed by a panel of three physician investigators who used a set of established criteria.[22] For stroke outcomes, this panel included at least two experienced neurologists. Minimal criteria for stroke consisted of abrupt onset of a localizing neurological deficit. Stroke was further categorized into ischemic, including atherothrombotic brain infarction and embolus, or hemorrhagic, including subarachnoid and intracerebral. This categorization was initially based on clinical and cerebrospinal fluid findings and, since the late 1970s, on findings of computed tomography as well. Transient ischemic attack (TIA) was designated when a history of a focal neurological deficit was documented to persist for less than 24 hours. For this analysis TIA was considered an incident event; thus, those subjects who had TIA were no longer at risk for completed stroke.

All covariate measurements were performed at the time of the dietary assessment except for 142 measures of glucose intolerance and 148 measures of serum cholesterol level that were performed at the ninth examination in subjects whose dietary assessment was at the 10th examination. Serum total cholesterol was measured by the method of Abell et al.[28] Systolic blood pressure was taken as the first of two measurements made by the examining physician using a standard mercury sphygmomanometer. Glucose intolerance, a dichotomous variable, was considered present if the patient had a diagnosis of diabetes mellitus, exhibited glycosuria at the baseline examination, or had a baseline blood glucose level exceeding 6.66 mmol/L (120.0 mg/dL). Left ventricular hypertrophy, determined electrocardiographically, was coded as none, borderline, or definite. Cigarette smoking was the self-reported number of cigarettes smoked per day. Body mass index was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). The physical activity index was based on a weighted average of the self-reported number of hours spent in the following types of activities: rest, sedentary, light, moderate, and heavy.

We defined the exposure variable to be the total number of daily servings of fruits and vegetables. We pursued three analytic strategies. First, we calculated 20-year age-adjusted cumulative incidence rates by quintile of servings, along with P values for trend by the Mantel-Haenszel method. Second, we calculated Kaplan-Meier survival curves to examine age-adjusted 20-year incidence rates by quintile of servings. We used the stratified log rank test to examine trends over quintiles, and we adjusted for age by direct standardization at each time point, using the age distribution at entry into the study.

To adjust for multiple covariates, we used Cox proportional hazards analysis to obtain relative risks (RRs) and 95% confidence intervals (CIs) of stroke for each increment of three servings. The proportional hazards assumption was found to be appropriate for these data. Because blood pressure or serum cholesterol level might be an intermediate in the biological pathway, we determined the change in the main effect of adding each of these variables singly to the model. Because these single additions did not alter the RRs, we included them together with other covariates in the multivariate models that we present. We also examined the effect of fruits independent of that of vegetables in separate multivariate models. To adjust for energy intake, we first regressed the exposure variable on total energy and then used the residual in the multivariate model.[29]

RESULTS

At baseline the mean (±SD) age of the 832 men was 55.8 (±4.6) years. The mean (±SD) total number of daily servings of fruits and vegetables ("servings") was 5.1 (±2.8), and mean total energy intake was 2613 (±719) kcal (10 975 [±3020] kJ). Table 1 shows characteristics of the subjects by quintile of servings. The number of subjects in each quintile varies because the exposure variable servings could take only integer values. There was little evidence for a strong association between any of these variables and intake of fruits and vegetables, except for cigarette smoking, which was inversely related to fruit and vegetable intake, and energy intake, which was directly related.

During the 20-year follow-up period there were 97 incident cerebrovascular events, of which 24 were categorized as TIAs and 73 as completed strokes. Of the

Table 1.—Baseline Characteristics of Subjects by Quintile of Fruit and Vegetable Intake*

Baseline Characteristic	Quintile 1 (n=144)	2 (n=225)	3 (n=135)	4 (n=180)	5 (n=148)	P for Trend
Fruit and vegetable intake, servings per day, range (mean)	0-2 (1.3)	3-4 (3.6)	5	6-7 (6.4)	8-19 (9.6)	...
			Mean			
Age, y	55.5	55.6	55.8	56.3	56.1	.04
Systolic blood pressure, mm Hg	136.6	134.9	138.4	136.2	136.6	.29
Serum cholesterol, mmol/L (mg/dL)	5.80 (222.7)	5.90 (228.4)	5.80 (224.1)	5.70 (219.4)	5.75 (222.2)	.10
Physical activity index	34.9	35.0	36.0	36.3	34.8	.50
Body mass index, kg/m^2	26.5	26.8	26.9	26.6	27.7	.04
No. of cigarettes smoked per day	13.9	10.3	10.4	8.6	8.0	<.001
Energy intake, kcal (kJ)	2373 (9967)	2508 (10 534)	2635 (11 067)	2742 (11 516)	2831 (11 890)	<.001
Ethanol intake, mL per week	195	156	186	183	177	.96
Fat intake, % energy	38.5	40.7	38.4	39.2	37.3	.02
Protein intake, % energy	15.7	15.8	15.6	15.8	15.6	.99
			No. (%) of Subjects			
Glucose intolerance	13 (9.0)	33 (14.7)	14 (10.4)	24 (13.3)	14 (9.5)	.84
Borderline or definite LVH†	4 (2.8)	7 (3.1)	5 (3.7)	4 (2.2)	3 (2.0)	.88

*Data from 832 men, aged 45 through 65 years, from the Framingham Study.
†LVH indicates electrocardiographic left ventricular hypertrophy.

Table 2.—Age-Adjusted Stroke Cumulative Incidence Rates per 1000 Subjects, by Quintile of Fruit and Vegetable Intake*

Quintile	Type of Stroke (No. of Events): All, Including Transient Ischemic Attack (97)	Completed (73)	Ischemic (61)	Hemorrhagic (14)
1	191.7	148.9	121.3	42.4
2	100.9	84.2	66.2	18.0
3	121.8	83.1	67.4	15.3
4	107.7	63.8	63.8	0
5	78.7	63.7	51.4	12.3
P for trend	.01	.01	.05	.02

*Twenty-year follow-up data from 832 men, aged 45 through 65 years at baseline, from the Framingham Study.

completed strokes, 61 were ischemic and 14 hemorrhagic (two subjects had both types). Table 2 shows age-adjusted cumulative incidence rates per 1000 subjects by type of stroke, according to fruit and vegetable intake. For all stroke (including TIA) and for completed stroke, both ischemic and hemorrhagic, there was a substantial decrease in risk with increasing quintile of fruit and vegetable servings.

Age-adjusted cumulative incidence for all stroke (including TIA), calculated by using Kaplan-Meier survival analysis, is shown in the Figure. There was a substantial trend of protection against stroke from lowest (first quintile) to highest (fifth quintile) fruit and vegetable intake (log rank P for trend, .01). We observed the same trend of protection across quintiles for completed stroke (log rank P for trend, .009; data not shown).

The Cox proportional hazards results appear in Table 3. For each increment of three daily servings of fruits and vegetables, there was a 22% decrease in the risk of all stroke, including TIA (age-adjusted RR, 0.78; 95% CI, 0.62 to 0.98). Relative risks for completed stroke and for completed stroke of ischemic origin were similar (RR, 0.74; 95% CI, 0.57 to 0.96; and RR, 0.76; 95% CI, 0.57 to 1.02, respectively). The RR for hemorrhagic stroke was 0.49, but with few events, the 95% CI was wide (0.25 to 0.95).

Except for hemorrhagic stroke, adjustment for covariates made little difference in the estimated amount of protection afforded by increasing servings. For example, for all stroke, adjustment for cigarette smoking, glucose intolerance, body mass index, left ventricular hypertrophy, physical activity index, serum cholesterol level, systolic blood pressure, and intake of total energy, ethanol, and fat in addition to age did not materially alter the effect estimate (RR adjusted for all covariates, 0.77; 95% CI, 0.60 to 0.98). We observed the same pattern of little change in overall effect with multivariate adjustment for completed stroke, including those of ischemic origin (Table 3).

Inferences about hemorrhagic stroke were limited by the small number of events, but in contrast to the results for ischemic stroke, adjustment for multiple covariates did moderate the protective effect (multivariate RR, 0.64; 95% CI, 0.31 to 1.30). None of the difference between the age-adjusted and multivariate RRs for hemorrhagic stroke, however, was due to adjustment for systolic blood pressure. This reflects the fact that although systolic blood pressure is a strong predictor of hemorrhagic stroke, it was not related to fruit and vegetable consumption in our data (Table 1).

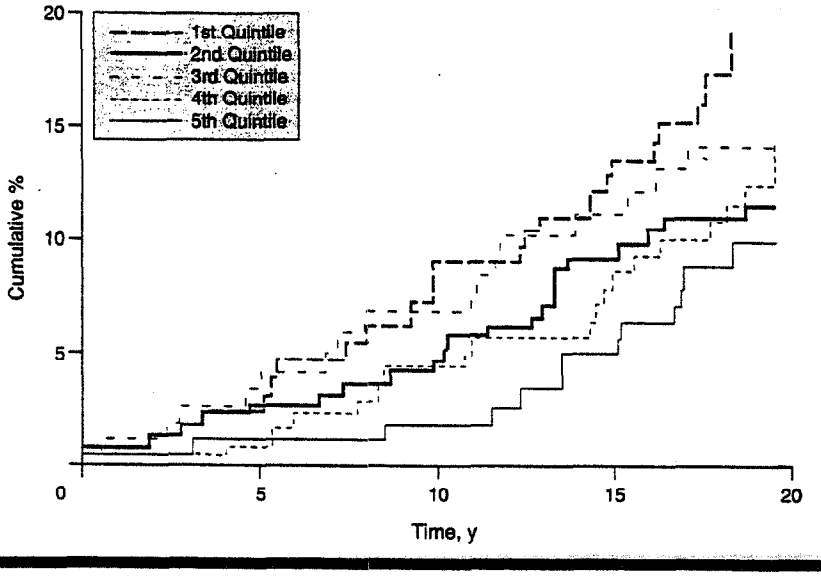
We also examined the effect of fruits separate from that of vegetables. The mean number of servings of fruit per day was 1.8, and the mean number of vegetable servings was 3.3. The multivariate RR of all stroke for an increment of three daily servings of fruit was 0.81 (95% CI, 0.56 to 1.19). For vegetables, the corresponding RR was 0.74 (95% CI, 0.54 to 1.02). The numbers of servings of specific fruit and vegetable categories were too small to assess their individual effects.

The results presented herein concern stroke incidence. We also observed a reduced risk for stroke mortality, but there were only 14 cases of death due to stroke. For each increment of three daily servings of fruits and vegetables per day, the age-adjusted RR was 0.55 (95% CI, 0.29 to 1.05). Adjustment for multiple covariates moderated the effect estimate slightly (multivariate RR, 0.62; 95% CI, 0.30 to 1.28).

COMMENT

In this 20-year follow-up study of middle-aged men from the Framingham Study, we observed an inverse association between fruit and vegetable intake and the development of stroke. For each increment of three servings per day, there was a 22% decrease in the risk of all stroke. We observed similar results for both ischemic and hemorrhagic stroke, although the CIs were wide for hemorrhagic stroke because of the small number of events. The findings were not substantially altered by adjustment for several covariates, including blood pressure, serum cholesterol level, other cardiovascular risk factors, and intake of total energy, ethanol, and fat.

We considered two alternative hypotheses for a causal association for our findings. The first is that an increase in fruit and vegetable intake was associated with a decrease in some other harmful dietary constituent. The question arises, however, as to the identity of that constituent. Although increased fat intake may be associated with coronary heart disease, some human and animal studies of dietary fat and stroke suggest an inverse



Twenty-year follow-up data from 832 men from the Framingham Study, aged 45 through 65 years at baseline, demonstrating cumulative incidence of all stroke, including transient ischemic attack, by quintile of fruit and vegetable intake, as calculated by age-adjusted Kaplan-Meier analysis. First quintile is the lowest intake, fifth quintile the highest. Log rank *P* for trend across quintiles, .01.

Table 3.—Relative Risk of Stroke for Each Increment of Three Servings per Day of Fruits and Vegetables as Determined by Cox Proportional Hazards Analysis*

	Adjusted for			
	Age Only		All Covariates†	
Type of Stroke	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval
All, including transient ischemic attack	0.78	0.62-0.98	0.77	0.60-0.98
Completed	0.74	0.57-0.96	0.75	0.57-1.00
Ischemic	0.76	0.57-1.02	0.75	0.55-1.03
Hemorrhagic	0.49	0.25-0.95	0.64	0.31-1.30

*Twenty-year follow-up data from 832 men, aged 45 through 65 years at baseline, from the Framingham Study.
†Systolic blood pressure, serum cholesterol, cigarette smoking, glucose intolerance, body mass index, physical activity index, left ventricular hypertrophy, energy intake, and consumption of ethanol and fat.

association.[10,30,31] Even so, we adjusted for fat intake in our multivariate model and observed no change in the overall effect estimate. Intake of ethanol may be a risk factor only for hemorrhagic, not ischemic, stroke,[13-16] and was not a confounder of the protective effect of fruits and vegetables in our data. Dietary sodium may confer risk for stroke through its association with elevated blood pressure,[32] but adjustment for systolic blood pressure did not alter our main findings. Thus, it is difficult to implicate competing deleterious dietary factors to explain our findings.

A second possibility may be termed a healthy lifestyle bias. In this scenario, people who eat more fruits and vegetables have other healthy habits that protect them from developing a stroke. This type of bias, a potential problem in many observational studies of diet and disease,[33] is difficult to exclude. However, adjustment for body mass index, cigarette smoking, and physical activity—"lifestyle variables"—did not alter our results.

If intake of fruits and vegetables truly protects against the risk of stroke, what is the mechanism? One possibility concerns blood pressure, a major determinant of stroke risk.[1] Previous studies have shown that a vegetarian diet is associated with lower blood pressure,[34] and some studies have indicated that dietary fiber, a constituent of many fruits and vegetables, may also lower blood pressure.[35] In our study, although systolic blood pressure was a strong predictor of stroke incidence, it was not related to intake of fruits and vegetables (Table 1). Thus, the addition of systolic blood pressure to the multivariate model did not alter the RR estimates. This finding argues against the intermediate role of blood pressure, but these data are limited by the fact that only a single measurement of blood pressure was used. Further, in the 8% of subjects who were taking antihypertensive medications, mean intake of fruits and vegetables was not different from intake in the other 92% of subjects. Therefore, treatment for hypertension was not a confounding factor.

It is less likely that any beneficial effect of fruits and vegetables is mediated through effects on serum cholesterol. First, although dietary soluble fiber may lower serum cholesterol concentration, the magnitude of its effect is probably small,[36] and there is little evidence that there are other cholesterol-lowering constituents of fruits and vegetables. Second, serum cholesterol is a relatively minor risk factor for stroke. Although serum cholesterol is a major determinant of atherosclerosis, only about 10% of strokes are related to large-vessel disease.[37] In epidemiologic studies, serum cholesterol level is variably related to stroke, although studies that separate types of stroke tend to demonstrate a direct association with ischemic stroke (and an inverse relationship with hemorrhagic stroke).[38] Further, a recent meta-analysis of cholesterol-lowering trials showed no beneficial effect on stroke mortality.[39] In our data, adjustment for serum cholesterol did not alter the overall findings, confirming skepticism of its role in the biological pathway.

One leading possibility to explain the protective effect we observed is dietary potassium, which is contained in many fruits and vegetables. Although increased potassium intake may lower blood pressure, animal studies indicate that dietary potassium may decrease the risk of stroke independent of its effects on blood pressure level.[40] Antioxidant vitamins are another potential mediator of the beneficial effects of fruits and vegetables. However, one of the main benefits of antioxidant vitamins is their effect on atherosclerosis, chiefly through reduction of the amount of oxidized low-density lipoprotein available to be incorporated into lesions.[33] This hypothesis may apply more to coronary heart disease than to stroke, the majority of which is not associated with large-vessel atherosclerosis. In our data, intake of fruits and vegetables was not associated with risk of coronary heart disease (data not shown). One other possibly beneficial nutrient contained in fruits and vegetables is folate. There have been several recent studies relating plasma homocysteine levels with risk of stroke and coronary heart disease.[41-45] Dietary folate is a determinant of plasma homocysteine level.[46] A reduction in stroke risk is therefore possible if fruit and vegetable intake, through provision of adequate dietary folate, moderates plasma homocysteine levels.

In our analyses that examined the effects of fruits separate from those of vegetables, we found decreased RRs for both

The protection afforded from vegetables, however, appeared somewhat greater than that from fruits. We could not draw conclusions concerning specific varieties of vegetables because of the small amount of each type consumed. The data set in use in the mid 1960s, when the dietary assessment for this study was done, contains no information about micronutrients. Therefore, we were unable to examine directly the effects of dietary sodium, potassium, antioxidants, and folate. Also, the data set in use for this study did not separate the food groups into distinct categories—such as cruciferous vegetables or citrus fruits—now thought to contain potentially beneficial nutrients. Although these considerations hampered our ability to examine the biological pathways involved, they do not diminish the potential recommendations to the public to increase intake of fruits and vegetables.[18]

This study has several attributes that lend confidence to its results. The first is a relatively long follow-up period, allowing for accrual of a considerable number of outcome events. In addition, a detailed clinical assessment of each stroke outcome was made by a panel of experienced neurologist-investigators. Further, we obtained direct information on a large number of potentially confounding variables. A limitation of our study was that the dietary assessment was by means of a single 24-hour recall, and thus individuals' usual intakes were undoubtedly estimated with poor precision. The implication of this, however, is that use of a more precise assessment method would have revealed a stronger association. Also, the dietary assessment was limited to middle-aged men, but preliminary data from a similar follow-up study in women indicate that the protective effect of fruits and vegetables may not be sex specific.[21]

In conclusion, intake of fruits and vegetables appears to protect against the risk of stroke in men. In this study, the association was present for both ischemic and hemorrhagic strokes, and the protective effect was apparently not mediated through effects on blood pressure. These results provide support to programs aimed at widespread increases in the consumption of fruits and vegetables. If successful, such programs may have beneficial effects on the incidence of stroke as well as other chronic diseases that constitute the leading causes of morbidity and mortality in Western societies.[47]

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Intake of Potassium, Magnesium, Calcium, and Fiber and Risk of Stroke Among US Men

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Background—Animal experiments and epidemiological studies have suggested that high potassium intake may reduce the risk of stroke, but the evidence is inconclusive, and the role of other nutrients in potassium-rich foods remains unknown.

Methods and Results—We examined the association of potassium and related nutrients with risk of stroke among 43 738 US men, 40 to 75 years old, without diagnosed cardiovascular diseases or diabetes, who completed a semiquantitative food frequency questionnaire in 1986. During 8 years of follow-up, 328 strokes (210 ischemic, 70 hemorrhagic, 48 unspecified) were documented. The multivariate relative risk of stroke of any type for men in the top fifth of potassium intake (median intake, 4.3 g/d) versus those in the bottom (median, 2.4 g/d) was 0.62 (95% CI, 0.43, 0.88; P for trend=0.007). Results for ischemic stroke alone were similar. Intakes of cereal fiber and magnesium, but not of calcium, were also inversely associated with risk of total stroke. These inverse associations were all stronger in hypertensive than normotensive men and were not materially altered by adjustment for blood pressure levels. Use of potassium supplements was also inversely related to risk of stroke, particularly among men taking diuretics (relative risk, 0.36; 95% CI, 0.18, 0.72).

Conclusions—Although these data do not prove a causal relationship, they are consistent with the hypothesis that diets rich in potassium, magnesium, and cereal fiber reduce the risk of stroke, particularly among hypertensive men. Potassium supplements may also be beneficial, but because of potential risks, use should be carefully monitored and restricted to men taking potassium-losing diuretics. (***Circulation*. 1998;98:1198-1204.**)

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

A role for potassium in determining risk of stroke is suggested by epidemiological studies[1-4] and animal experiments.[5] A beneficial effect of potassium intake could be due to its hypotensive effect,[6,7] but this is small, and neither in rats[5] nor in humans[1,4] could it explain the reduced risk of stroke. Other mechanisms that have been suggested include inhibition of free radical formation,[8] vascular smooth muscle proliferation,[9] and arterial thrombosis.[10]

However, the overall evidence is unconvincing. Small size and inadequate dietary assessment are among the limitations of the previous epidemiological studies, because diet based on a single 24-hour recall was used to predict stroke incidence over a 12-,[1] 16-,[2] or 20-year period.[4] This dietary assessment reduces the ability to adjust for consumption of other foods or nutrients that may explain the inverse associations reported.[11] To overcome this limitation, we addressed the hypothesis that high potassium intake reduces the risk of stroke in a large cohort of men who completed a detailed and validated semiquantitative food frequency questionnaire at baseline and were followed up for 8 years. In addition, we examined the associations between risk of stroke and intakes of dietary fiber, magnesium, and calcium, which are correlated with intake of potassium and may be related to risk of stroke.

Methods

Population

The Health Professionals Follow-up Study began in 1986, when 51 529 health professionals 40 to 75 years old[12] completed a 131-item food-frequency questionnaire and provided information about medical history and lifestyle. Follow-up questionnaires were sent every 2 years to update information on potential risk factors and to identify newly diagnosed cases of stroke and other diseases. We excluded from analysis 1595 men who did not satisfy the a priori criteria of daily caloric intake between 800 and 4200 kcal and <70 blanks out of 131 total listed food items. In addition, we excluded men with prior diagnosis of myocardial infarction, angina, coronary artery surgery, stroke, transient ischemic attack, peripheral arterial disease, or diabetes. We followed up the 43 738 eligible men for stroke incidence during the subsequent 8 years. The average response rate for the 2-year follow-up cycles was >94%. Nonresponding participants not matched to the National Death Index were assumed to be alive.

Assessment of Diet and Other Exposure Variables

The 1986 questionnaire asked about average frequency of intake during the previous year of specified portions of 131 foods and use

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of vitamin and mineral supplements. Nutrient calculations took into account the specific brand of breakfast cereal and multivitamins reported by each subject. We also asked about use of specific supplements of potassium and magnesium (apart from multivitamins). We assumed the amount of potassium in these specific supplements to be 1 g/d and that of magnesium 0.3 g/d, because details on doses were not asked in the questionnaire. We assessed the validity of the questionnaire in a random sample of 127 men who completed two 1-week diet records.[13] The correlations between the 2 assessments of intake, energy-adjusted and corrected for within-person variation in the diet records, were 0.65 for potassium, 0.64 for dietary fiber, 0.66 for magnesium, and 0.53 for calcium. In addition to diet, in 1986, participants were asked to report their usual systolic and diastolic blood pressure and whether or not they had physician-diagnosed hypertension. The validity of these variables has been documented previously.[14]

Cases

End points were fatal and nonfatal strokes occurring between the return of the baseline questionnaire and January 31, 1994. Participants reporting an incident stroke on a follow-up questionnaire were asked for permission to review medical records. Strokes were confirmed if characterized by a typical neurological defect of sudden or rapid onset, lasting ≥24 hours and attributable to a cerebrovascular event. Strokes caused by infection or neoplasia were excluded. Reviews were conducted by physicians with no knowledge of the subjects' risk factor status. Strokes were subclassified according to the criteria of the National Survey of Stroke as due to ischemia (embolism or thrombosis), subarachnoid hemorrhage, intracerebral hemorrhage, or unknown cause.[15] If no records could be obtained, strokes were considered probable if they required hospitalization and were corroborated by additional information provided by letter or interview.

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.

Statistical Analysis

Participants contributed follow-up time from the return of the 1986 questionnaire up to the occurrence of a confirmed stroke, death, or January 31, 1994. The occurrence of nonfatal cardiovascular events, such as myocardial infarction or coronary surgery, was not a reason for censoring. Intakes of potassium and other nutrients were energy-adjusted to 2000 kcal/d.[16] Relative risks (RR) were calculated by dividing the incidence of stroke among men in each fifth of energy-adjusted potassium intake at baseline by the incidence among men in the lowest fifth of intake. Similar calculations were done for the other nutrients. We adjusted RRs for age (5-year categories)[17] and used the Mantel extension test[18] to test for linear trends. To adjust for other risk factors, we used pooled logistic regression with 2-year intervals. When the probability of an event within an interval is small, this method is equivalent to a Cox proportional-hazards analysis.[19] Multivariate models included as covariates calendar time (2-year intervals), total energy intake (continuous variable), smoking (current, past, and 1 to 14, 15 to 24, and ≥25 cigarettes/d), alcohol consumption (<5, 5 to 9, 10 to 14, 15 to 29, and ≥30 g/d), history of hypertension, history of hypercholesterolemia, parental history of myocardial infarction before age 65 years, profession, and quintiles of body mass index and physical activity. In these models, we evaluated monotonic trends by using the median value of each category and modeling this as a continuous variable. All P values are 2-sided. Covariates were not updated during the follow-up.

Results

During 323 394 person-years of follow-up, we documented 328 cases of cerebrovascular accidents (50 fatal), including 210 ischemic, 70 hemorrhagic, and 48 unclassified strokes.

TABLE 1. Age-Standardized Relation of Intake of Potassium to Selected Variables at Baseline

	Quintile of Energy-Adjusted Potassium Intake	
	1	5
Mean potassium intake, g/d	2.5	4.5
Use of potassium supplements, %	6.5	29.2
Currently smoking, %	13.5	7.6
Mean alcohol consumption, g/d	15.2	8.6
History at baseline of		
Hypertension, %	18.5	24.6
High cholesterol, %	9.0	12.6
Mean systolic blood pressure*	131	129
Mean diastolic blood pressure*	82	81
Mean physical activity, METs/wk	15.3	25.6
Use of aspirin, %	25	28
Mean daily intake of		
Total fat, % of energy	34.4	28.1
Saturated fat, % of energy	12.0	9.4
Protein, g/d	81	96
Cholesterol, mg/d	303	279
Dietary fiber, g/d	15	26
Magnesium, mg/d	277	432
Sodium, g/d	3.0	3.0
Calcium, g/d	0.7	1.1
Vitamin C, mg/d	295	617
Vitamin E, IU/d	68	147
Carotene, IU/d	5978	15 677
Folic acid, μg/d	364	615
Servings/d, mean		
Fish	0.27	0.52
Vegetables	2.3	5.2
Fruit	1.4	3.7
Cereal products	3.2	3.2
Red meat	1.2	0.7
Chicken	0.3	0.4
Low-fat dairy	0.4	1.6
High-fat dairy	1.4	1.0

*Based on 38 726 men, including men with history of hypertension, who reported their systolic and diastolic blood pressure at baseline.

Men in the top fifth of potassium intake (including potassium from supplements) were less likely to smoke, were more physically active, and consumed less alcohol, less fat, more protein, and more micronutrients than men in the bottom fifth (Table 1). Similar relations were found for magnesium, fiber, and calcium (data not shown). The age-adjusted RR of total stroke for men in the top fifth of potassium intake compared with those in the bottom fifth was 0.59 (Table 2). This RR was slightly attenuated by adjustment for nondietary risk factors (RR=0.62) and by further adjustment for intakes of magnesium and dietary fiber (RR=0.69). The corresponding associations with ischemic stroke were similar, whereas no significant associations were observed for hemorrhagic stroke

TABLE 2. RR of Stroke According to Intake of Potassium, Total Fiber, Magnesium, and Calcium Adjusted by Energy

Variable	Quintile 1	2	3	4	5	χ for Trend	P
Potassium							
Median intake, g/d	2.4	3.0	3.3	3.6	4.3		
Person-years	67 605	67 003	65 826	63 708	59 253		
Total stroke							
No. of cases	76	65	62	64	61		
Age-adjusted	1.0	0.80	0.71	0.68	0.59	−2.91	0.004
Multivariate*	1.0	0.85 (0.61, 1.18)	0.78 (0.55, 1.10)	0.76 (0.54, 1.07)	0.62 (0.43, 0.88)	−2.69	0.007
Further adjusted for fiber and magnesium intake	1.0	0.86 (0.61, 1.23)	0.82 (0.56, 1.20)	0.83 (0.56, 1.24)	0.69 (0.45, 1.07)	−1.58	0.110
Total fiber							
Median intake, g/d	12.4	16.6	19.7	23.0	28.9		
Person-years	67 534	65 935	65 299	63 636	60 990		
Total stroke							
No. of cases	81	66	68	54	59		
Age-adjusted	1.0	0.77	0.75	0.53	0.57	−3.87	<0.001
Multivariate*	1.0	0.85 (0.61, 1.19)	0.85 (0.61, 1.19)	0.65 (0.45, 0.93)	0.70 (0.48, 1.00)	−2.20	0.028
Further adjusted for fiber and magnesium intake	1.0	0.87 (0.62, 1.22)	0.89 (0.63, 1.27)	0.71 (0.48, 1.07)	0.86 (0.55, 1.32)	−0.89	0.370
Magnesium							
Median intake, mg/d	243	298	337	376	452		
Person-years	66 457	66 088	64 991	63 500	62 359		
Total stroke							
No. of cases	74	79	58	65	52		
Age-adjusted	1.0	1.03	0.73	0.79	0.62	−3.15	0.002
Multivariate*	1.0	1.09 (0.79, 1.50)	0.81 (0.57, 1.15)	0.90 (0.64, 1.26)	0.70 (0.49, 1.01)	−2.21	0.027
Further adjusted for potassium and fiber intake	1.0	1.23 (0.87, 1.74)	0.98 (0.66, 1.45)	1.15 (0.76, 1.73)	0.92 (0.58, 1.46)	−0.48	0.630
Calcium							
Median intake, g/d	0.5	0.7	0.8	1.0	1.4		
Person-years	64 728	65 534	64 596	64 425	64 112		
Total stroke							
No. of cases	75	69	51	63	70		
Age-adjusted	1.0	0.89	0.64	0.78	0.78	−1.66	0.100
Multivariate*	1.0	0.95 (0.68, 1.32)	0.72 (0.50, 1.03)	0.84 (0.60, 1.19)	0.88 (0.63, 1.23)		
Further adjusted for potassium and fiber intake	1.0	0.99 (0.71, 1.39)	0.78 (0.54, 1.13)	0.94 (0.66, 1.35)	1.05 (0.72, 1.53)		

*Model includes age (5-year categories), total energy intake (continuous variable), smoking (current, past, and 1–14, 15–24, and ≥25 cigarettes/d), alcohol consumption (<5, 5–9, 10–14, 15–29, ≥30 g/d), history of hypertension, history of hypercholesterolemia, parental history of myocardial infarction before age 65 years, profession, and quintiles of body mass index and physical activity.

(data not shown). Further adjustment for intakes of total fat, protein, saturated fat, vitamin C, vitamin E, carotene, or folic acid did not materially change the association between potassium intake and risk of total stroke, nor did adjustment for baseline systolic and diastolic blood pressure or addition to the model of an interaction term between age and hypertension.

Intakes of dietary fiber and magnesium were both inversely associated with risk of total stroke in age-adjusted analyses (Table 2). These associations were only moderately attenuated by adjustment for nondietary risk factors, but they were substantially weakened in regression models that simultaneously included potassium, magnesium, and dietary fiber because of the positive correlations between intakes of these nutrients (Pearson correlation coefficients were 0.65 for magnesium and potassium, 0.62 for magnesium and fiber, and 0.58 for potassium and fiber).

Neither calcium nor sodium intake (data not shown) was significantly associated with risk of total, ischemic, or hemorrhagic stroke. Sodium intake was also unrelated to intake of potassium (Pearson correlation = −0.02) and was not analyzed further. Because in a previous investigation an inverse

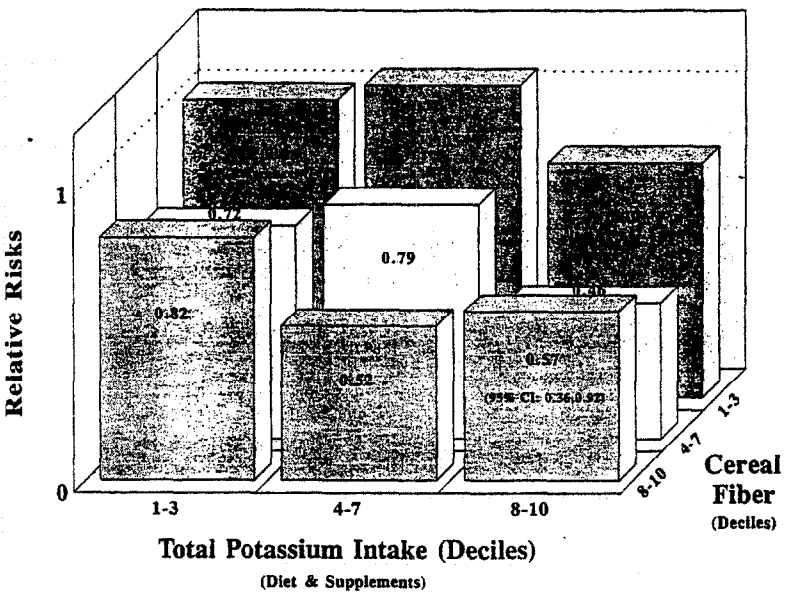


Figure 1. RR of stroke by intake of potassium and cereal fiber.

association was reported between calcium from dairy sources and risk of stroke,[20] we examined this relationship in our cohort. The multivariate risk for the top compared with the bottom quintile of dairy calcium intake was 0.83 (95% CI, 0.59, 1.17) for total (Table 2), 0.90 (95% CI, 0.59, 1.37) for ischemic, and 0.73 (95% CI, 0.36, 1.51) for hemorrhagic stroke; the lowest incidence of each outcome was observed in the middle quintile of intake. Also, we examined whether the risk of stroke was lower among men who reported using calcium supplements at baseline. The RR for men who took ≥400 mg/d of supplemental calcium compared with nonusers was 0.88 for total stroke (95% CI, 0.60, 1.27) and 0.83 for ischemic stroke (95% CI, 0.52, 1.34).

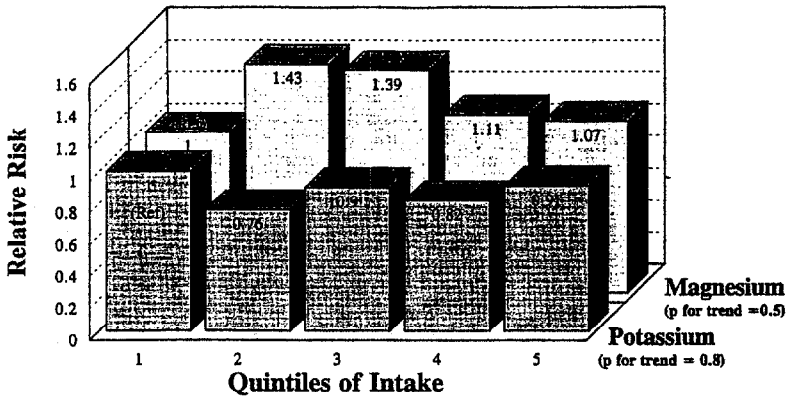
When intakes of dietary fiber from different sources were considered separately, only cereal fiber was inversely associated with risk of stroke. This association remained after adjustment for potassium, magnesium, and fiber from other sources; both potassium and cereal fiber intake appeared to be independently inversely associated with risk of total stroke (Figure 1). Intakes of fruits, vegetables, and cereal products were each inversely associated with risk of total stroke, but none of these associations were significant. The multivariate RR for an increase of 1 serving per day was 0.96 (95% CI, 0.89, 1.03; P for trend=0.26) for fruits, 0.96 (95% CI, 0.91, 1.02; P for trend=0.18) for vegetables, and 0.94 (95% CI, 0.87, 1.02; P for trend=0.11) for cereal. Results for ischemic stroke were similar.

We further examined separately the associations of potassium and magnesium from supplements with risk of stroke. Neither use of potassium supplements (RR=0.78; 95% CI, 0.69 to 1.22) nor use of magnesium supplements (RR=0.85; 95% CI, 0.55 to 1.32) was associated with risk of total or ischemic stroke in analyses adjusted for age only, but use of potassium supplements became strongly inversely associated after adjustment for history of hypertension (RR=0.55; 95% CI, 0.35 to 0.86). History of hypertension was a strong independent risk factor for stroke (RR=2.8; 95% CI, 2.1, 3.7) and was associated with use of potassium supplements (46% of the 1248 supplement users were hypertensives, compared with 19% of nonusers). The inverse association between use of potassium supplements and risk of stroke in multivariate analyses was independent of dietary intakes of nutrients, including potassium, magnesium, and fiber, and was stronger among men with low dietary intake of potassium, magnesium, and cereal fiber. The RR comparing the top with the bottom quintile of potassium intake was 0.39 in the lowest tertile of a dietary score, including the 3 nutrients, 0.57 in the middle, and 0.86 in the highest tertile. To further test the hypothesis that use of potassium supplements reduces the risk of stroke, we compared men who reported using supplements both in 1986 and 1988 with men who never used supplements. During the 6 remaining years of follow-up, the multivariate RR of total stroke among supplement users was 0.31 (95% CI, 0.12, 0.85; P=0.02); the risk of stroke was also reduced among men who reported using potassium supplements only in 1986 (0.46; 95% CI, 0.22, 0.98; P=0.05) but not among men who started taking supplements in 1988 (1.07; 95% CI, 0.55, 2.11).

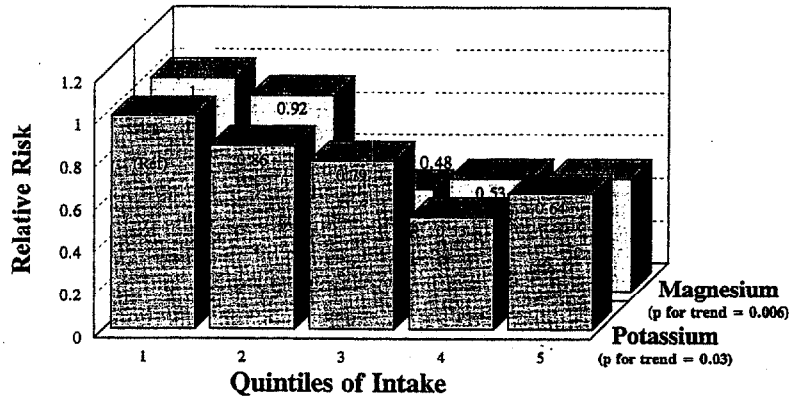
Because of the importance of hypertension as a risk factor for stroke, we conducted analyses stratified by history of hypertension at baseline. Inverse associations between nutrient intakes and risk of stroke were observed only among hypertensive men (Figures 2 and 3). In analyses restricted to men taking diuretics at baseline, alone or in combination with other antihypertensive drugs, the RR of stroke for users of potassium supplements compared with nonusers was 0.36 (95% CI, 0.18, 0.72; P=0.004). Both fiber and cereal fiber were significantly inversely associated with risk of stroke among hypertensive (RRs for a 10-g increase in intake were 0.59 and 0.33, respectively) but not among normotensive (RRs were 0.88 for both) men.

Discussion

In this large prospective study, we found that men with diets higher in potassium, cereal fiber, and magnesium had a substantially reduced risk of stroke. These inverse associa-



No History of Hypertension



History of Hypertension

Figure 2. Multivariate RR of total stroke according to intake of dietary potassium and magnesium. Top, Men without history of hypertension; bottom, men with history of hypertension.

tions were only partly explained by nondietary risk factors but were strong and significant only among men with diagnosed hypertension. No significant associations were found between intakes of sodium and calcium and risk of stroke.

A protective effect of potassium intake on risk of stroke would be consistent with the reduced risk that we observed among hypertensive men taking potassium supplements in the present study and with the findings of a previous epidemiological investigation[1] and experiments with hypertensive rats.[5,21] In a separate cohort among Japanese men in Hawaii, potassium intake was inversely related to risk of fatal thromboembolic stroke (RR for the top versus the bottom quintile of intake=0.3, P for trend=0.002) but not with risk of nonfatal thromboembolic stroke (RR=0.87, P for trend=0.12).[2] The weak association with nonfatal events is not inconsistent with a protective effect, which may have been diluted by error in the single 24-hour recall– based dietary assessment. In randomized trials, high potassium intake has caused modest reduction in blood pressure, especially among hypertensive subjects.[6,7] This effect, however, is small and could only partially explain the strong inverse association observed in this study. In addition, adjustment for baseline blood pressure levels had little effect on the estimated RRs relating potassium intake to stroke incidence, and potassium intake was not a significant predictor of risk of hypertension within this cohort.[14] Alternative mechanisms proposed include the inhibition of free radical formation, vascular smooth muscle proliferation, and arterial thrombosis.[22] However, these effects were produced by experimental increases in serum potassium concentrations in animals, and their relevance to humans is uncertain. High potassium intake may increase serum concentrations, particularly when intake is low or sodium intake is high,[22] and could therefore reduce the risk of hypokalemia among men at high risk because of diuretic treatment. Diuretic-induced hypokalemia may increase the risk of ventricular dysrhythmia.[23,24] Although no increased mortality from cardiovascular disease or other causes was found among men with low serum potassium in 2 previous studies,[25,26] neither was large enough to detect a specific association between serum potassium and risk of stroke.

Intakes of magnesium and fiber were also inversely associated with risk of stroke, but their correlation with intake of potassium and measurement errors reduced the ability of multivariate analyses to discriminate between them. This difficulty is compounded by the fact that some previous epidemiological evidence and biological plausibility can be invoked for a beneficial effect of any of these nutrients, although only potassium has been shown to directly reduce risk of stroke in animal models. In a cross-sectional study, magnesium intake has been found to be inversely associated with carotid artery thickness in women but not in men.[27] Also, there are reports that magnesium deficiency increases suscep-

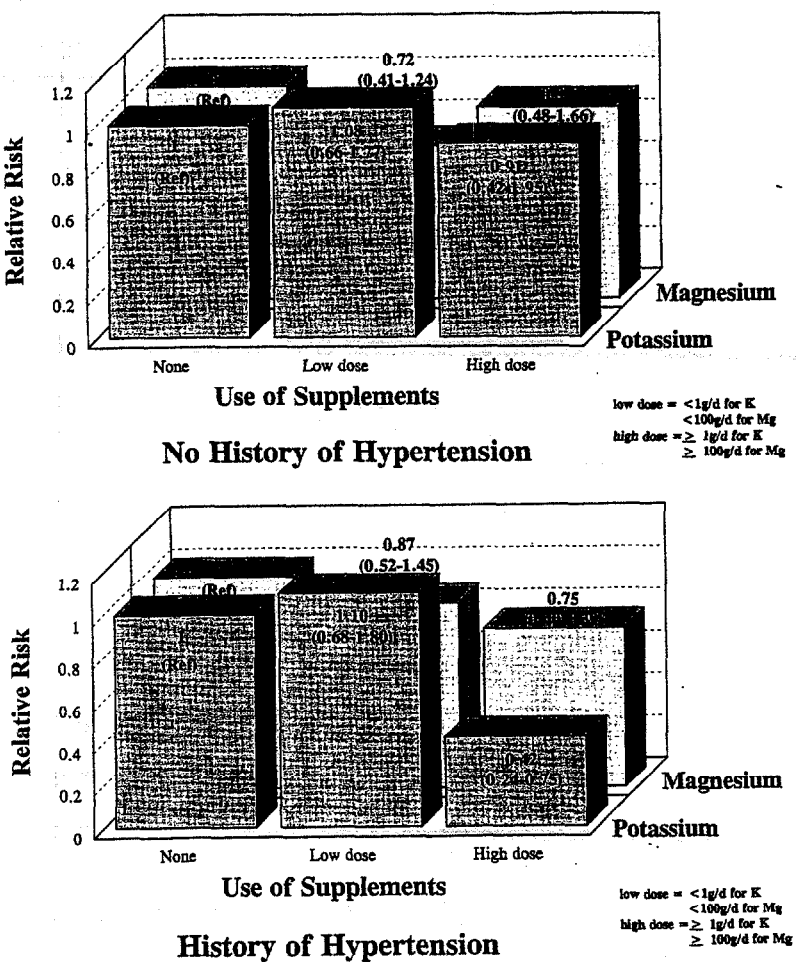


Figure 3. Multivariate RR of total stroke according to intake of potassium and magnesium supplements. Top, Men without history of hypertension; bottom, men with history of hypertension.

tibility of lipoproteins to peroxidation in rats.[28] Conversely, magnesium supplementation failed to reduce blood pressure in randomized trials among normotensive subjects,[7,29] and high-magnesium diets have been reported to increase rather than decrease the risk of stroke in hypertensive rats.[30] In a randomized trial in China, a multiple vitamin/mineral supplement containing 200 mg of magnesium reduced the risk of stroke among men, but this effect may have been due to 1 of the several other micronutrients included in the supplement.[31] Intake of fiber, particularly cereal fiber, has been shown to be inversely related to risk of coronary heart disease in most prospective investigations.[32–34] These results strongly suggest that high fiber intake inhibits the development of atherosclerosis or thrombosis and indirectly support a preventive effect of fiber on risk of ischemic stroke. Mechanisms for these beneficial effects, however, remain largely elusive.[33]

The lack of association between sodium intake and risk of stroke in our study may be due to the difficulty in measuring sodium intake accurately and to the scarcity of men with low or very high intake and does not in itself contradict the hypothesis that substantial reductions in intake decrease risk.[35–38] Although measurement error also may have affected the results on calcium, our data do not support the previously reported inverse association between calcium consumption and risk of stroke.[20] In hypertensive rats, high calcium intake provided partial protection against salt-induced stroke, decreasing lesion size but increasing lesion number,[39] whereas in rabbits it prolonged clotting time and reduced the severity of atherosclerosis.[40] The relevance of these observations to humans, however, remains to be established.

In conclusion, although these data do not prove a causal relationship, they provide strong support for a preventive effect of diets rich in potassium, magnesium, and cereal fiber on stroke, particularly among men with high blood pressure. Increased intake of potassium alone may decrease the risk of stroke, and perhaps potassium supplements for hypertensives should be more broadly considered. However, evidence is inadequate to support an indiscriminate use of potassium supplements, which can be harmful.[41] Rather, potassium intake should be increased by substituting fruits, vegetables, and their natural juices for low-potassium processed foods and sodas.

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