Carbohydrate Intake, Glycemic Index, Glycemic Load, and Dietary Fiber in Relation to Risk of Stroke in Women

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The associations of dietary carbohydrate, glycemic index, and glycemic load with stroke risk were examined among 78,779 US women who were free of cardiovascular disease and diabetes in 1980 and completed a food frequency questionnaire. During an 18-year follow-up, 1,020 stroke cases were documented (including 515 ischemic and 279 hemorrhagic). In analyses adjusting for nondietary risk factors and cereal fiber, carbohydrate intake was associated with elevated risk of hemorrhagic stroke when the extreme quintiles were compared (relative risk = 2.05, 95% confidence interval: 1.10, 3.83; p_{trend} = 0.02), but not with ischemic stroke. The positive association between carbohydrate intake and stroke risk was most evident among women with a body mass index of ≥25 kg/m². Likewise, dietary glycemic load was positively associated with total stroke among only those women whose body mass index was ≥25 kg/m². Cereal fiber intake was inversely associated with total and hemorrhagic stroke risk; for total stroke, relative risk = 0.66 (95% confidence interval: 0.52, 0.83; p_{trend} = 0.001) and for hemorrhagic stroke, relative risk = 0.51 (95% confidence interval: 0.33, 0.78; p_{trend} = 0.01). Findings suggest that high intake of refined carbohydrate is associated with hemorrhagic stroke risk, particularly among overweight or obese women. In addition, high consumption of cereal fiber was associated with lower risk of total and hemorrhagic stroke.

cerebrovascular accident; dietary carbohydrates; dietary fiber; prospective studies

Abbreviations: BMI, body mass index; CI, confidence interval; RR, relative risk.

High carbohydrate intake has adverse effects on lipid and glucose metabolism, and these changes would be expected to increase risk of cardiovascular disease (1–3). Dietary glycemic index is an indicator of carbohydrate quality that reflects the effect on blood glucose, and the dietary glycemic load is an indicator of both carbohydrate quality and quantity. Dietary glycemic index and glycemic load appear to have increased in recent years because of increases in carbohydrate intake and changes in food processing (4).

Epidemiologic evidence suggests that a diet with a high glycemic load or glycemic index may increase the risk of coronary heart disease (5) and type 2 diabetes (6), whereas overall carbohydrate intake is less strongly related to these diseases. Furthermore, the adverse metabolic effects of high carbohydrate intake or dietary glycemic load are greatly exaggerated in the presence of underlying insulin resistance (1, 2). Greater body mass index (BMI) is strongly associated with insulin resistance, and we have previously reported a stronger positive association between dietary glycemic load and risk of coronary heart disease among overweight and obese women (1, 2, 5). However, the relation of dietary carbohydrate amount and quality to risk of stroke has not been examined in detail.

We hypothesized that high carbohydrate intake, a high glycemic index diet, and a high glycemic load diet increase

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the risk of stroke and that these relations are stronger among those with a higher BMI.

MATERIALS AND METHODS

Population

The Nurses' Health Study was initiated in 1976 when 121,700 female registered nurses aged 30–55 years completed a mailed questionnaire about their lifestyle factors and medical history, including previous cardiovascular disease, cancer, diabetes, hypertension, and high blood cholesterol levels. Every 2 years, follow-up questionnaires have been sent to these women so that information can be updated and newly diagnosed major illness identified.

Ascertainment of diet

In 1980, we collected information on usual diet by using a semiquantitative food frequency questionnaire. For each of 61 food 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 of the item. Nine responses were possible, ranging from "almost never" to "six or more times per day." In 1984, the dietary questionnaire was expanded to include 116 items. Similar questionnaires were used to update dietary information in 1986, 1990, and 1994. The average daily intake of nutrients was calculated by multiplying the frequency of consumption of each item by its nutrient content and summing the nutrient contributions of all foods.

Methods used to assess the glycemic index of individual foods and mixed meals, as well as to measure glycemic load in the Nurses' Health Study cohort, have been reported elsewhere (5, 6). We calculated a food's glycemic load by multiplying the carbohydrate content of each food by its glycemic index value; we then multiplied this value by frequency of consumption and summed over all food items to produce the dietary glycemic load. Each unit of dietary glycemic load represents the glycemic equivalent of 1 g of carbohydrate from white bread. We also created a variable we termed overall glycemic index by dividing the average daily glycemic load by the average daily carbohydrate intake. We excluded women who left 10 or more food items blank on the questionnaire, who had an implausible total energy intake, and who had a history of cardiovascular disease (angina, myocardial infarction, stroke, other cardiovascular disease; $n = 1,645$), cancer ($n = 3,610$), diabetes ($n = 1,410$), or hypercholesterolemia ($n = 4,269$) before June 1980.

Ascertainment of stroke

The endpoint was incident stroke occurring between return of baseline questionnaires in 1980 and June 1, 1998. Women who reported stroke on a follow-up questionnaire were asked for permission to review their medical records. Medical records were available for 74 percent of stroke cases and were reviewed by physicians without knowledge of the participant's exposure status. Cerebrovascular pathology due to infection, trauma, or malignancy was excluded.

Nonfatal strokes for which confirmatory information was obtained by telephone or letter but for which no medical records were available were regarded as probable (25 percent). Deaths were ascertained by reports from relatives or postal authorities and a search of the National Death Index (7). They were then documented by medical records and/or death certificates. Mortality follow-up was more than 98 percent complete (7). Fatal strokes for which information was confirmed by telephone, letter, or death certificate but for which no medical records were available were regarded as probable (32 percent).

Incident strokes were confirmed by medical record review by using National Survey of Stroke criteria (8), which require a constellation of neurologic deficits, sudden or rapid in onset, and duration of at least 24 hours or until death. We subclassified the strokes into ischemic (embolic or thrombotic) and hemorrhagic (subarachnoid or intracerebral) according to Perth Community Stroke Study criteria and based on computed tomography, magnetic resonance imaging, or autopsy findings (9).

Statistical analyses

For each study participant, person-years of follow-up were counted from the date of return of the 1980 questionnaire to the date of stroke diagnosis; the date of death; or June 1, 1998, whichever came first. Women were grouped in quintiles of carbohydrate intake, dietary glycemic index, and dietary glycemic load. In multivariate analysis, the estimated relative risks were simultaneously adjusted for potential confounding variables by using Cox proportional hazards regression. To best represent the participants' long-term dietary patterns during follow-up, we used a cumulative average method based on all available measurements of diet up to the beginning of each 2-year interval (10). Other covariates, including age; BMI; smoking; alcohol intake; parental history of myocardial infarction; histories of hypertension, hypercholesterolemia, and diabetes; postmenopausal hormone use; aspirin use; multivitamin use; vitamin E supplement use; physical activity; energy; and cereal fiber intake were updated every 2 years. In addition, when examining the effect of substitution of carbohydrate for protein, we used multivariate nutrient-density models that simultaneously included the percentages of energy derived from carbohydrate, saturated fat, monounsaturated fat, polyunsaturated fat, *trans*-fat, omega-3 fatty acids, and other confounding variables. To control for total energy intake, fiber intake was adjusted for total energy intake by using the residual method (11). We also conducted analyses stratified by BMI. Tests for trends were conducted by assigning the median value to each quintile and modeling these values as a continuous variable. The log-likelihood ratio test was used to assess the significance of interaction terms.

RESULTS

Among the 78,779 women followed for 18 years, we documented 1,020 incident strokes: 515 ischemic strokes and 279 hemorrhagic strokes were confirmed; the remaining stroke cases could not be classified. After adjustment for nondi-

etary and dietary risk factors, smoking and history of hypertension were significant risk factors for both hemorrhagic and ischemic stroke. For current smoking (≥ 25 cigarettes/day vs. never smoked), the relative risks were 3.73 (95 percent confidence interval (CI): 2.46, 5.64) for hemorrhagic stroke and 3.31 (95 percent CI: 2.35, 4.67) for ischemic stroke. For history of hypertension (yes vs. no), the relative risks were 2.04 (95 percent CI: 1.57, 2.64) for hemorrhagic stroke and 2.17 (95 percent CI: 1.80, 2.62) for ischemic stroke. History of diabetes was positively associated with risk of ischemic stroke (relative risk (RR) = 2.11, 95 percent CI: 1.53, 2.90) but not hemorrhagic stroke (RR = 1.05, 95 percent CI: 0.51, 2.16). A family history of myocardial infarction was associated with risk of ischemic stroke (RR = 1.38, 95 percent CI: 1.13, 1.68) but not hemorrhagic stroke (RR = 1.18, 95 percent CI: 0.89, 1.56). BMI was inversely associated with risk of hemorrhagic stroke (RR for ≥ 29 kg/m^2 vs. <22 kg/m^2 = 0.60, 95 percent CI: 0.41, 0.89) and ischemic stroke (RR = 0.85, 95 percent CI: 0.65, 1.12).

Women were grouped in quintiles according to carbohydrate intake and dietary glycemic load (table 1). At baseline in 1980, women with a high carbohydrate intake had a lower prevalence of smoking and consumed less saturated fat, monounsaturated fat, and *trans*-fat, but they had higher intakes of dietary fiber and cereal fiber. A similar pattern was observed with dietary glycemic load.

Total carbohydrate intake was not significantly related to total or ischemic stroke when adjusted for only age and smoking (table 2). However, after adjustment for other nondietary risk factors and cereal fiber intake, carbohydrate intake was related to a significantly greater risk of hemorrhagic stroke. When we further adjusted for different types of fat, so that the relative risks represented the replacement of protein with carbohydrate, carbohydrate intake was more strongly related to risk of hemorrhagic stroke (RR = 2.05, 95 percent CI: 1.10, 3.83; $p_{trend} = 0.02$). We further examined the relations of carbohydrate intake to risk of subtype of stroke. Carbohydrate intake was positively associated with risk of both subarachnoid and intraparenchymal hemorrhage, but these associations were not statistically significant when considered separately (RR = 1.74, 95 percent CI: 0.78, 3.88; $p_{trend} = 0.21$ for subarachnoid hemorrhage and RR = 2.30, 95 percent CI: 0.81, 6.57; $p_{trend} = 0.08$ for intraparenchymal hemorrhage). In addition, there were no significant relations between carbohydrate intake and risks of thrombotic or embolic stroke. Dietary glycemic load was nonsignificantly associated with risk of total stroke and subtype of stroke, and dietary glycemic index had no apparent relation to total or subtype of stroke.

As hypothesized, the relation between dietary carbohydrate and risk of stroke differed by BMI category (table 3). Strong positive associations between carbohydrate intake and risks of total and hemorrhagic stroke were found among women with a BMI of ≥ 25 kg/m^2 (RR = 2.13, 95 percent CI: 1.28, 3.53; $p_{trend} = 0.002$ for total stroke and RR = 3.84, 95 percent CI: 1.23, 12.05; $p_{trend} = 0.02$ for hemorrhagic stroke) but not among those with a BMI of <25 kg/m^2 (test of interaction for total stroke, $p = 0.01$). Carbohydrate intake had no clear relation to ischemic stroke regardless of BMI. Among women with a BMI of ≥ 25 kg/m^2, dietary glycemic load was

associated with risk of total stroke (RR = 1.61, 95 percent CI: 1.15, 2.27; $p_{trend} = 0.01$), but associations for type of stroke were not statistically significant. Dietary glycemic index was not related to risks of total stroke and type of stroke within categories of BMI. In previous reports, intakes of fruits and vegetables, or potassium, were associated with lower risk of stroke (12, 13). Therefore, we additionally controlled for fruit and vegetable intake or potassium intake, but the relation between carbohydrate intake and hemorrhagic stroke risk did not change appreciably. The relative risks for extreme quintiles of carbohydrate intake were 2.05 (95 percent CI: 1.10, 3.84; $p_{trend} = 0.02$) when additionally adjusted for fruit and vegetable intakes and 2.02 (95 percent CI: 1.08, 3.78; $p_{trend} = 0.02$) when additionally adjusted for potassium intake. The relative risks for extreme quintiles of carbohydrate intake among women with a BMI of ≥ 25 kg/m^2 were 3.78 (95 percent CI: 1.20, 11.92; $p_{trend} = 0.03$) when additionally adjusted for fruit and vegetable intake and 4.00 (95 percent CI: 1.27, 12.66; $p_{trend} = 0.02$) when additionally adjusted for potassium intake.

The relation between fiber and risk of stroke is shown in table 4. Total fiber intake was weakly related to lower risk of total stroke. Among the different sources of fiber, cereal fiber intake was associated with reduced risk of total stroke (RR = 0.66, 95 percent CI: 0.52, 0.83; $p_{trend} = 0.001$) and hemorrhagic stroke (RR = 0.51, 95 percent CI: 0.33, 0.78; $p_{trend} = 0.01$) but was not associated with ischemic stroke. Intake of fiber from fruits and vegetables was not associated with risks of total stroke or type of stroke.

DISCUSSION

In this prospective study, high carbohydrate intake was positively associated with risk of hemorrhagic stroke, independent of other dietary factors and cardiovascular risk factors. This positive association appeared to be stronger among women with a higher BMI.

Many studies have suggested detrimental effects of high carbohydrate intake on lipid metabolism (1, 2, 14), but, to our knowledge, the relation between carbohydrate intake and risk of stroke has not been examined in detail. In our cohort studies, dietary glycemic index and dietary glycemic load have been more strongly related to coronary heart disease and diabetes than carbohydrate intake (5, 6). Contrary to the results of our previous coronary heart disease and diabetes studies (5, 6), total carbohydrate intake was more strongly associated with risk of total and hemorrhagic stroke than dietary glycemic index or dietary glycemic load, which takes into account the quality of carbohydrate.

Our findings are consistent with results of ecologic studies; stroke has been a principal cause of death in eastern Asian countries, which have traditionally had a high carbohydrate and a low fat intake. In a study of Chinese Americans, participants consumed a high-carbohydrate and low-fat diet, and they had lower high density lipoprotein and total cholesterol concentrations compared with elderly Whites. These characteristics were similar to those of urban populations in mainland China, where hemorrhagic stroke is the major cause of cardiovascular disease (15). In Japan, the incidence of hemorrhagic stroke declined in parallel with a

TABLE 1. Age-adjusted baseline characteristics of 78,779 US female nurses according to quintiles of energy-adjusted carbohydrate intake and dietary glycemic load in 1980

	1 (lowest)	2	3	4	5 (highest)
Quintiles of carbohydrate intake					
Mean (% of energy from carbohydrate)	30 (5)*	39 (1)	44 (1)	48 (1)	55 (5)
Age (years)	46 (7)	46 (7)	46 (7)	46 (7)	46 (7)
Body mass index (kg/m²)	24 (4)	24 (4)	24 (4)	24 (5)	24 (4)
Current smoker (%)	33	27	24	24	25
Physical activity (hours/week)	3.8 (2.9)	4.0 (2.9)	4.0 (2.9)	3.9 (2.9)	4.0 (2.9)
History of high blood pressure (%)	14	13	13	14	14
Parental history of myocardial infarction at age ≤65 years (%)	20	20	20	20	20
Hormone use in postmenopausal women (%)	16	16	16	17	17
Aspirin use (%)	41	41	40	40	37
Multivitamin use (%)	33	33	34	35	34
Dietary intake (g)					
Glycemic index	72 (7)	74 (6)	74 (6)	75 (6)	77 (6)
Glycemic load†	93 (21)	123 (15)	138 (17)	152 (20)	181 (33)
Polyunsaturated fat	10 (3)	10 (3)	9 (3)	9 (3)	8 (3)
Monounsaturated fat	34 (6)	28 (4)	26 (4)	24 (4)	20 (4)
Saturated fat	32 (6)	28 (4)	26 (4)	24 (4)	20 (4)
Trans-fat	4.2 (1.3)	4.1 (1.3)	3.9 (1.3)	3.8 (1.3)	3.4 (1.3)
Marine omega-3 fatty acids	0.09 (0.07)	0.08 (0.06)	0.08 (0.06)	0.08 (0.06)	0.07 (0.06)
Dietary fiber	11.5 (3.5)	13.8 (3.8)	14.8 (4.3)	15.6 (4.8)	17.4 (6.8)
Cereal fiber	1.9 (1.1)	2.6 (1.3)	2.9 (1.5)	3.1 (1.7)	3.3 (2.1)
Vegetable fiber	4.6 (2.5)	4.9 (2.6)	5.0 (2.8)	5.1 (3.0)	5.4 (4.0)
Fruit fiber	3.0 (2.1)	4.2 (2.6)	4.9 (3.0)	5.4 (3.5)	6.8 (4.9)
Quintiles of glycemic load					
Mean†	89 (17)	118 (5)	133 (4)	147 (4)	181 (26)
Age (years)	46 (7)	46 (7)	46 (7)	46 (7)	45 (7)
Body mass index (kg/m²)	24 (4)	24 (4)	24 (4)	24 (4)	24 (5)
Current smoker (%)	32	27	24	26	27
Physical activity (hours/week)	3.9 (2.9)	4.0 (2.9)	4.0 (2.9)	3.9 (2.9)	3.8 (2.8)
History of high blood pressure (%)	14	13	14	14	15
Parental history of myocardial infarction at age ≤65 years (%)	20	20	20	20	19
Hormone use in postmenopausal women (%)	16	16	17	16	15
Aspirin use (%)	40	41	40	41	39
Multivitamin use (%)	34	33	34	34	33
Dietary intake (g)					
Glycemic index	70 (7)	73 (5)	75 (5)	76 (5)	79 (5)
Carbohydrate	122 (24)	155 (16)	169 (16)	181 (17)	205 (25)
Polyunsaturated fat	10 (3)	10 (3)	9 (3)	9 (3)	9 (3)
Monounsaturated fat	33 (7)	29 (5)	27 (5)	25 (5)	23 (5)
Saturated fat	32 (6)	28 (5)	27 (5)	25 (5)	22 (5)
Trans-fat	4.1 (1.3)	4.1 (1.3)	4.1 (1.3)	4.0 (1.3)	3.7 (1.4)
Marine omega-3 fatty acids	0.09 (0.07)	0.08 (0.06)	0.08 (0.06)	0.07 (0.06)	0.07 (0.05)
Dietary fiber	11.9 (3.9)	13.9 (4.1)	14.7 (4.5)	15.0 (4.8)	15.4 (6.2)
Cereal fiber	1.9 (1.2)	2.6 (1.4)	2.9 (1.6)	3.0 (1.6)	2.9 (1.8)
Vegetable fiber	4.8 (2.6)	5.0 (2.7)	5.0 (2.8)	5.0 (2.8)	5.0 (3.5)
Fruit fiber	3.3 (2.4)	4.4 (2.9)	4.8 (3.2)	5.0 (3.5)	5.4 (4.3)

* Numbers in parentheses, standard deviation.
† Each unit represents the glycemic equivalent of 1 g of carbohydrate from white bread.

decrease in carbohydrate intake and increased fat and protein intake (16). In addition, in the Honolulu Heart Program (17),

carbohydrate intake (percentage of energy intake) in Japanese men in Japan was higher than in Japanese migrants to

TABLE 2.   Relative risks of stroke according to quintiles of total carbohydrate intake, dietary glycemic index, and dietary glycemic load among 78,779 US female nurses from 1980 to 1998

	1 (lowest)	2		3		4		5 (highest)		*p* for trend
		RR*	95% CI*	RR	95% CI	RR	95% CI	RR	95% CI	
Carbohydrate intake										
Median (% of energy)	32.6	39.6		43.8		47.6		52.9		
Total stroke (*n* = 1,020)										
Age, smoking adjusted	1	0.89	0.72, 1.10	0.87	0.70, 1.07	0.90	0.73, 1.11	0.98	0.80, 1.20	1.00
Multivariate†	1	0.99	0.80, 1.23	1.03	0.82, 1.29	1.12	0.89, 1.40	1.22	0.97, 1.53	0.05
Multivariate‡	1	1.00	0.80, 1.26	1.04	0.80, 1.35	1.11	0.84, 1.48	1.25	0.91, 1.73	0.16
Ischemic stroke (*n* = 515)										
Age, smoking adjusted	1	0.89	0.66, 1.20	0.89	0.66, 1.19	0.82	0.61, 1.10	0.94	0.70, 1.25	0.63
Multivariate†	1	0.88	0.64, 1.20	0.88	0.64, 1.21	0.82	0.59, 1.14	0.94	0.68, 1.32	0.78
Multivariate‡	1	0.84	0.60, 1.16	0.81	0.56, 1.17	0.72	0.48, 1.09	0.86	0.54, 1.36	0.46
Hemorrhagic stroke (*n* = 279)										
Age, smoking adjusted	1	1.20	0.82, 1.76	1.15	0.78, 1.71	1.19	0.80, 1.78	1.17	0.79, 1.76	0.48
Multivariate†	1	1.48	1.00, 2.18	1.55	1.02, 2.34	1.67	1.09, 2.56	1.61	1.04, 2.50	0.03
Multivariate‡	1	1.60	1.05, 2.43	1.77	1.09, 2.88	1.99	1.16, 3.43	2.05	1.10, 3.83	0.02
Glycemic index										
Median	68.0	72.2		74.6		77.0		80.3		
Total stroke (*n* = 1,020)										
Age, smoking adjusted	1	0.82	0.67, 0.99	0.84	0.69, 1.02	0.88	0.73, 1.07	1.00	0.82, 1.21	0.93
Multivariate†	1	0.85	0.70, 1.04	0.88	0.72, 1.07	0.91	0.74, 1.11	0.98	0.80, 1.20	0.98
Ischemic stroke (*n* = 515)										
Age, smoking adjusted	1	0.89	0.67, 1.18	1.02	0.77, 1.34	1.01	0.76, 1.33	1.12	0.85, 1.48	0.31
Multivariate†	1	0.87	0.66, 1.16	0.98	0.74, 1.30	0.96	0.72, 1.27	1.05	0.78, 1.40	0.62
Hemorrhagic stroke (*n* = 279)										
Age, smoking adjusted	1	0.84	0.58, 1.21	0.78	0.54, 1.14	0.80	0.55, 1.16	1.01	0.71, 1.44	0.89
Multivariate†	1	0.92	0.63, 1.33	0.87	0.59, 1.27	0.88	0.60, 1.29	1.06	0.73, 1.53	0.87
Glycemic load										
Median	96.4	119.0		133.0		146.3		166.8		
Total stroke (*n* = 1,020)										
Age, smoking adjusted	1	1.02	0.83, 1.24	0.79	0.64, 0.98	0.94	0.77, 1.16	1.07	0.87, 1.31	0.61
Multivariate†	1	1.14	0.92, 1.40	0.93	0.74, 1.17	1.12	0.90, 1.41	1.23	0.98, 1.53	0.08
Ischemic stroke (*n* = 515)										
Age, smoking adjusted	1	1.11	0.83, 1.48	0.86	0.63, 1.16	0.90	0.67, 1.21	1.12	0.84, 1.49	0.74
Multivariate†	1	1.12	0.83, 1.51	0.87	0.63, 1.20	0.91	0.66, 1.26	1.12	0.81, 1.54	0.71
Hemorrhagic stroke (*n* = 279)										
Age, smoking adjusted	1	1.15	0.80, 1.67	1.01	0.68, 1.49	1.17	0.80, 1.71	1.01	0.68, 1.50	0.93
Multivariate†	1	1.40	0.95, 2.03	1.31	0.86, 1.97	1.53	1.01, 2.31	1.23	0.81, 1.89	0.31

* RR, relative risk; CI, confidence interval.

† Adjusted for age (5-year categories); body mass index (five categories); smoking (never, past, current 1–14, 15–24, ≥25 cigarettes/day); alcohol intake (four categories); parental history of myocardial infarction; history of hypertension, hypercholesterolemia, and diabetes; menopausal status and postmenopausal hormone use; aspirin use (five categories); multivitamin use; vitamin E supplement use; physical activity (hours/week, five categories); energy; and cereal fiber (quintiles).

‡ Additionally adjusted for saturated fat, monounsaturated fat, polyunsaturated fat, *trans*-fat, and omega-3 fatty acids (quintiles).

the United States, while fat and protein intakes were lower. The prevalence of stroke in Japanese men in Japan was higher than that of Japanese migrants to the United States, suggesting that higher carbohydrate intake may be related to risk of stroke.

The mechanisms by which carbohydrate intake could increase risk of hemorrhagic stroke are not well elucidated; however, several pathways may be involved. Diets relatively high in carbohydrate may decrease total, low density lipoprotein, and high density lipoprotein concentrations, and these changes may contribute to higher risk of hemorrhagic stroke by weakening of arterial wall and subsequent rupturing of intracerebral arteries (18, 19). Serum total cholesterol concentrations have been inversely related to risk

TABLE 3. Relative risks of stroke according to body mass index and total carbohydrate intake, dietary glycemic index, and dietary glycemic load among 78,779 US female nurses from 1980 to 1998

	1 (lowest)	2		3		4		5 (highest)		p for trend
		RR*	95% CI*	RR	95% CI	RR	95% CI	RR	95% CI	
Carbohydrate intake†										
Total stroke (n = 1,020)										
<25 kg/m² (n = 528)	1	0.94	0.70, 1.27	0.80	0.57, 1.14	0.89	0.61, 1.29	0.89	0.58, 1.36	0.54
≥25 kg/m² (n = 492)	1	1.15	0.80, 1.66	1.50	1.00, 2.25	1.63	1.04, 2.55	2.13	1.28, 3.53	0.002
Ischemic stroke (n = 515)										
<25 kg/m² (n = 259)	1	0.84	0.55, 1.29	0.53	0.32, 0.88	0.54	0.31, 0.94	0.58	0.32, 1.07	0.05
≥25 kg/m² (n = 256)	1	0.92	0.55, 1.54	1.39	0.80, 2.42	1.20	0.64, 2.26	1.61	0.79, 3.28	0.16
Hemorrhagic stroke (n = 279)										
<25 kg/m² (n = 178)	1	1.36	0.82, 2.25	1.71	0.96, 3.05	1.54	0.79, 3.00	1.57	0.74, 3.35	0.20
≥25 kg/m² (n = 101)	1	2.37	1.07, 5.26	2.17	0.86, 5.44	3.50	1.30, 9.42	3.84	1.23, 12.05	0.02
Glycemic index‡										
Total stroke (n = 1,021)										
<25 kg/m² (n = 528)	1	0.80	0.61, 1.04	0.77	0.58, 1.01	0.76	0.58, 1.01	0.90	0.67, 1.18	0.37
≥25 kg/m² (n = 492)	1	0.94	0.70, 1.25	1.03	0.77, 1.37	1.11	0.83, 1.49	1.12	0.83, 1.52	0.26
Ischemic stroke (n = 515)										
<25 kg/m² (n = 259)	1	0.73	0.49, 1.09	0.94	0.64, 1.37	0.73	0.49, 1.10	0.84	0.56, 1.26	0.42
≥25 kg/m² (n = 256)	1	1.09	0.72, 1.65	1.06	0.69, 1.62	1.29	0.85, 1.94	1.39	0.91, 2.12	0.09
Hemorrhagic stroke (n = 279)										
<25 kg/m² (n = 178)	1	0.72	0.45, 1.14	0.53	0.32, 0.89	0.71	0.44, 1.14	0.98	0.64, 1.51	0.87
≥25 kg/m² (n = 101)	1	1.53	0.80, 2.93	1.89	1.00, 3.57	1.41	0.71, 2.81	1.27	0.62, 2.60	0.54
Glycemic load‡										
Total stroke (n = 1,020)										
<25 kg/m² (n = 528)	1	1.04	0.79, 1.37	0.81	0.59, 1.11	0.97	0.71, 1.31	1.03	0.76, 1.38	0.93
≥25 kg/m² (n = 492)	1	1.33	0.96, 1.85	1.15	0.81, 1.62	1.42	1.01, 1.99	1.61	1.15, 2.27	0.01
Ischemic stroke (n = 515)										
<25 kg/m² (n = 259)	1	1.00	0.67, 1.49	0.73	0.47, 1.14	0.72	0.45, 1.13	0.88	0.57, 1.36	0.42
≥25 kg/m² (n = 256)	1	1.37	0.86, 2.17	1.13	0.70, 1.84	1.27	0.78, 2.06	1.56	0.96, 2.54	0.11
Hemorrhagic stroke (n = 279)										
<25 kg/m² (n = 178)	1	1.36	0.86, 2.15	1.20	0.72, 1.99	1.35	0.81, 2.26	1.07	0.64, 1.81	0.81
≥25 kg/m² (n = 101)	1	1.49	0.74, 2.98	1.57	0.76, 3.22	2.00	0.98, 4.08	1.69	0.81, 3.56	0.13

* RR, relative risk; CI, confidence interval.

† Adjusted for age (5-year categories); body mass index (five categories); smoking (never, past, current 1–14, 15–24, ≥25 cigarettes/day); alcohol intake (four categories); parental history of myocardial infarction; history of hypertension, hypercholesterolemia, and diabetes; menopausal status and postmenopausal hormone use; aspirin use (five categories); multivitamin use; vitamin E supplement use; physical activity (hours/week, five categories); energy; and cereal fiber (quintiles). Also adjusted for saturated fat, monounsaturated fat, polyunsaturated fat, *trans*-fat, and omega-3 fatty acids (quintiles).

‡ Adjusted for age (5-year categories); body mass index (five categories); smoking (never, past, current 1–14, 15–24, ≥25 cigarettes/day); alcohol intake (four categories); parental history of myocardial infarction; history of hypertension, hypercholesterolemia, and diabetes; menopausal status and postmenopausal hormone use; aspirin use (five categories); multivitamin use; vitamin E supplement use; physical activity (hours/week, five categories); energy; and cereal fiber (quintiles).

of intracerebral hemorrhage (20, 21). Furthermore, our findings suggest that some of the apparent harmful effects of high carbohydrate intake may be due to benefits of protein intake because the associations were strongest when all types of fat were included in multivariate models. In this cohort and Japanese populations (22, 23), low intake of protein (particularly animal protein) was associated with increased risk of hemorrhagic stroke. Another possible mechanism is that diets high in carbohydrate and low in protein may increase blood pressure (24), a strong risk factor for stroke.

In the Multiple Risk Factor Intervention Trial (25), protein intake was inversely associated with blood pressure, while starch intake was positively associated with blood pressure. In our analyses, we controlled for history of hypertension, but we may not have fully accounted for residual effects of diet on blood pressure. In addition, high carbohydrate intake has been associated with increased C-reactive protein (a marker of inflammation) (26), probably representing an exacerbation of insulin resistance, which may be related to higher risk of stroke (27).

TABLE 4. Relative risks* of stroke according to quintiles of fiber intake among 78,779 US female nurses from 1980 to 1998

	1 (lowest)	2 RR†	95% CI†	3 RR	95% CI	4 RR	95% CI	5 (highest) RR	95% CI	p for trend
				Total fiber						
Median (g)	10.0	12.8		14.9		17.1		21.0		
Total stroke (*n* = 1,020)										
Age, smoking adjusted	1	0.91	0.74, 1.12	0.83	0.67, 1.02	0.81	0.66, 1.00	0.79	0.64, 0.97	0.02
Multivariate	1	0.97	0.79, 1.19	0.89	0.71, 1.10	0.86	0.69, 1.07	0.83	0.66, 1.04	0.07
Ischemic stroke (*n* = 515)										
Age, smoking adjusted	1	0.95	0.71, 1.28	0.86	0.64, 1.16	0.76	0.56, 1.03	0.80	0.60, 1.07	0.07
Multivariate	1	0.95	0.70, 1.28	0.86	0.63, 1.17	0.74	0.54, 1.02	0.78	0.56, 1.09	0.09
Hemorrhagic stroke (*n* = 279)										
Age, smoking adjusted	1	1.07	0.74, 1.53	0.87	0.59, 1.28	0.95	0.65, 1.40	0.83	0.55, 1.24	0.28
Multivariate	1	1.10	0.76, 1.60	0.90	0.61, 1.35	0.98	0.65, 1.48	0.84	0.54, 1.30	0.34
				Cereal fiber						
Median (g)	1.4	2.4		3.2		4.1		5.7		
Total stroke (*n* = 1,020)										
Age, smoking adjusted	1	0.80	0.65, 0.98	0.75	0.61, 0.92	0.74	0.60, 0.91	0.62	0.50, 0.76	<0.0001
Multivariate	1	0.84	0.68, 1.03	0.79	0.63, 0.98	0.79	0.64, 0.98	0.66	0.52, 0.83	0.001
Ischemic stroke (*n* = 515)										
Age, smoking adjusted	1	0.89	0.65, 1.22	0.98	0.73, 1.32	0.96	0.71, 1.30	0.81	0.60, 1.10	0.20
Multivariate	1	0.88	0.64, 1.21	0.95	0.69, 1.31	0.94	0.68, 1.30	0.80	0.57, 1.12	0.23
Hemorrhagic stroke (*n* = 279)										
Age, smoking adjusted	1	0.66	0.46, 0.94	0.58	0.40, 0.84	0.62	0.43, 0.90	0.50	0.34, 0.74	0.002
Multivariate	1	0.67	0.47, 0.96	0.58	0.40, 0.86	0.63	0.42, 0.93	0.51	0.33, 0.78	0.01
				Vegetable fiber						
Median (g)	2.9	4.2		5.2		6.4		8.5		
Total stroke (*n* = 1,020)										
Age, smoking adjusted	1	1.10	0.90, 1.35	0.96	0.78, 1.18	0.97	0.79, 1.19	0.88	0.71, 1.08	0.06
Multivariate	1	1.16	0.95, 1.43	1.02	0.83, 1.26	1.03	0.84, 1.27	0.92	0.74, 1.14	0.14
Ischemic stroke (*n* = 515)										
Age, smoking adjusted	1	1.26	0.93, 1.71	1.13	0.83, 1.53	1.12	0.83, 1.52	1.02	0.75, 1.39	0.53
Multivariate	1	1.25	0.92, 1.69	1.11	0.82, 1.51	1.09	0.80, 1.49	1.01	0.74, 1.38	0.48
Hemorrhagic stroke (*n* = 279)										
Age, smoking adjusted	1	0.95	0.66, 1.36	0.76	0.52, 1.11	0.88	0.61, 1.28	0.71	0.48, 1.05	0.09
Multivariate	1	1.00	0.70, 1.44	0.82	0.56, 1.21	0.96	0.66, 1.40	0.76	0.51, 1.13	0.18
				Fruit fiber						
Median (g)	1.3	2.5		3.6		4.9		7.3		
Total stroke (*n* = 1,020)										
Age, smoking adjusted	1	0.89	0.73, 1.09	0.88	0.72, 1.07	0.89	0.73, 1.08	0.88	0.72, 1.08	0.35
Multivariate	1	0.93	0.76, 1.13	0.90	0.73, 1.11	0.91	0.74, 1.12	0.87	0.70, 1.09	0.28
Ischemic stroke (*n* = 515)										
Age, smoking adjusted	1	1.02	0.77, 1.35	1.05	0.80, 1.39	0.86	0.64, 1.16	0.85	0.63, 1.14	0.13
Multivariate	1	1.03	0.77, 1.37	1.06	0.79, 1.42	0.88	0.65, 1.19	0.87	0.63, 1.21	0.22
Hemorrhagic stroke (*n* = 279)										
Age, smoking adjusted	1	0.93	0.65, 1.32	0.63	0.42, 0.94	0.99	0.69, 1.42	0.91	0.62, 1.32	0.85
Multivariate	1	0.95	0.66, 1.36	0.63	0.42, 0.95	0.99	0.68, 1.44	0.86	0.57, 1.29	0.64

* Adjusted for age; body mass index; smoking; alcohol intake; parental history of myocardial infarction; history of hypertension, hypercholesterolemia, and diabetes; menopausal status and postmenopausal hormone use; aspirin use; multivitamin use; vitamin E supplement use; physical activity; energy; and carbohydrate intake.

† RR, relative risk; CI, confidence interval.

Jeppesen et al. (2) have shown that, in women, the adverse metabolic response to a high-carbohydrate diet, including low high density lipoprotein cholesterol and hyperinsulinemia, is exaggerated in the presence of underlying insulin resistance, which is strongly influenced by adiposity. When fed a high-carbohydrate diet (55 percent of energy), overweight men also had a greater rise in fasting hyperglycemia, hyperinsulinemia, and triglyceride concentration than did lean men (28), and obese adolescents had a significantly greater increase in fasting insulin level than nonobese adolescents after 2 weeks of carbohydrate overfeeding (29). In a cross-sectional analysis in this cohort, the adverse metabolic response to a high carbohydrate intake was also much greater in overweight and obese women (30). In the Honolulu Heart Program (31), hyperinsulinemia appeared to predict increased risk of hemorrhagic and thromboembolic stroke. In our analyses stratified by BMI, high carbohydrate intake and dietary glycemic load were most strongly associated with risk of stroke among women with a high BMI ($\geq$25 kg/m^2). This result was consistent with a previous study in this cohort in which the association between dietary glycemic load and coronary heart disease risk was much stronger among women with a BMI of $\geq$23 kg/m^2 (5).

High fiber intake may decrease the risk of chronic diseases by improving the postprandial glycemic response and insulin concentration, and the type of fiber could be differentially related to risk of the diseases (6, 32). Micronutrients that accompany fiber in whole-grain cereal products could also contribute to lower risk of stroke. In a study on risk of stroke in US men, among different sources of fiber only cereal fiber was inversely associated with risk of stroke (12), consistent with the results of this study.

The study included 279 hemorrhagic strokes during 18 years of follow-up, and diets were assessed prospectively by repeated questionnaires that take into account possible changes in diet over time and reduce random variation. In addition, many known or suspected risk factors for stroke, including other dietary factors, BMI, smoking, alcohol consumption, aspirin use, and history of hypertension and diabetes, were well controlled. However, the possibility of residual confounding by unknown risk factors could not be excluded. Although we used repeated measurements of diet by validated questionnaires, some error in assessing dietary intake is inevitable. In general, these errors will tend to result in underestimation of associations. Another limitation is that we did not measure blood lipid levels, which could be useful to clarify the related mechanisms.

In summary, our results provide evidence that high intake of refined carbohydrate may increase risk of hemorrhagic stroke in women and that the deleterious effect is stronger among those who are overweight or obese. In addition, our data support a benefit of cereal fiber in preventing hemorrhagic stroke. These findings suggest that replacing sugar and refined starches with whole-grain, high-fiber forms of carbohydrate may reduce hemorrhagic stroke, particularly among women who are overweight or obese. Furthermore, our results may have implications for preventing hemorrhagic stroke in Asian countries with a higher rate of hemorrhagic stroke and a higher intake of carbohydrate.

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