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Dietary glycemic index, glycemic load, and intake of carbohydrate and rice in relation to risk of mortality from stroke and its subtypes in Japanese men and women

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Abstract

We assessed the relationship of the dietary glycemic index (GI), glycemic load (GL), and intake of carbohydrate and rice, and risk of mortality from stroke and its subtypes. The cohort consisted of 12 561 men and 15 301 women residing in Takayama, Japan, in 1992. At the baseline, a food frequency questionnaire was administered; and the dietary GI, GL, and intake of carbohydrates and rice were estimated. Deaths from stroke occurring in the cohort were prospectively noted until 1999 with data from the office of the National Vital Statistics. The risk of mortality from stroke was assessed with a Cox proportional hazard model after adjusting for age; body mass index; smoking status; physical activity; history of hypertension; education; and intake of total energy, alcohol, dietary fiber, salt, and total fat. The risk of stroke subtypes was assessed in the age-adjusted model. The hazard ratios of total stroke comparing the highest vs the lowest quartiles of the dietary GI were 0.78 (95% confidence interval [CI], 0.41-1.47) with P_{trend} = .50 in men and 2.09 (95% CI, 1.01-4.31) with P_{trend} = .10 in women. Among women, the association was also significant with the risk of ischemic stroke (hazard ratio = 2.45; 95% CI, 1.01-5.92; P_{trend} = .03); and a significant positive trend was also observed between dietary GL and mortality from hemorrhagic stroke (P_{trend} = .05). The current study implies that diets with a high dietary GI increase the risk of mortality from stroke among Japanese women.

1. Introduction

Stroke is a common condition in Japan, and risk of death due to stroke was about twice of that in the United States and other Western countries from 1950 through 1987 [1]. Mortality from stroke has been declining in following years, but it is still the third leading cause of death in Japan [2]. Prospective epidemiologic studies have provided little information concerning the relationship among the dietary glycemic index (GI), glycemic load (GL), and risk of stroke. A few studies have evaluated the association and suggested that the dietary GL increases the risk of stroke [3-5]. These studies were conducted in Western countries, and no report has yet been published concerning Asian populations. Carbohydrate consumption is high in Japan; and its major source is white rice, which is high in dietary GI. Research into the potential health effects of GI, GL, carbohydrates, and rice is of particular interest in this population.

We therefore conducted a prospective study among Japanese men and women in a community-based cohort to obtain information on the relationship of the dietary GI, GL, intake of carbohydrates and rice, and the risk of stroke. It might be beneficial to study the specific types of stroke because each subtype of stroke has its own risk factors [6,7]. We also assessed the risk of subtypes of stroke in the current study.

2. Materials and methods

2.1. Study participants

The data were provided by the Takayama study in Japan. The details of the Takayama study have been described

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elsewhere [8-10]. Briefly, the study population was men and women residing in Takayama City who were 35 years or older in 1992. At the baseline, a self-administered questionnaire was conducted to the 36 990 residents to collect information on the baseline characteristics of the study cohort such as age, height, weight, and length of education. Physician diagnoses of major diseases including hypertension, cancer, myocardial infarction or angina, stroke, and diabetes were also reported in the questionnaire. Of the participants who responded to the questionnaire, those who did not complete more than 45% of it and those who gave unreliable or inconsistent responses were excluded. Based on the answers to the food frequency questionnaire (FFQ) administered at the same time, subjects who answered only 16 items or fewer, who were regarded to be responded by the other person, who selected the food frequency category of "Never" for all food items, or who selected the food frequency category of "Once a day" or "Two or more times a day" for continuous 40 food items or over were excluded from the study [9]. In addition, subjects who reported to have staple food (any kind of rice, bread, flour, or noodles) 5 times or more, meat 7 times or more, fish 7 times or more, or ethanol 400 mL or more per day were excluded [9].

The final fixed cohort consisted of 31 552 subjects, 14 427 men and 17 125 women, yielding a response rate of 85.3%. From them, the subjects who had cancer, myocardial infarction, angina, or diabetes were excluded from the cohort. Among men, 146 subjects had cancer; 787 subjects had myocardial infarction or angina; 794 subjects had diabetes; 15 subjects had cancer and either myocardial infarction or angina; 18 subjects had cancer and diabetes; 99 subjects had diabetes and either myocardial infarction or stroke; and 7 subjects had cancer, diabetes, and either myocardial infarction or angina. Among women, 476 subjects had cancer; 797 subjects had myocardial infarction or angina; 423 subjects had diabetes; 32 subjects had cancer and either myocardial infarction or angina; 27 subjects had cancer and diabetes; 64 subjects had diabetes and either myocardial infarction or stroke; and 5 subjects had cancer, diabetes, and either myocardial infarction or angina. After the exclusion, the final cohort for the current study consists of 27 862 subjects, 12 561 men and 15 301 women.

2.2. Estimation of nutrient intake, GI, and GL

The FFQ was previously validated and in a semiquantitative format measuring 169 food items [8]. From the FFQ, the total daily calorie intake and intake of each nutrient and food item, including carbohydrates, were estimated according to the *Japanese Standard Tables of Food Composition, Fifth Edition*, published by the Science and Technology Agency of Japan. Fatty-acid food composition was defined based on the data published by Sasaki et al [11]. The amount of rice intake was estimated from the FFQ in grams. Detailed information on the FFQ, including its validity and reproducibility, was previously described [8]. Updated Spearman correlation coefficients for men between the FFQ and 12-day food record were 0.34 for carbohydrate and 0.63 for dietary fiber. For women, they were 0.45 for carbohydrate and 0.60 for dietary fiber. We assigned GI values based on the international table of GI [12] and published data from studies in Japan [13,14]. Whenever there was more than one value, preference was given to data from Japanese studies. The carbohydrate intake after subtracting the dietary fiber intake was used for calculating the GI and GL values [13,14]. We used glucose as the reference. The foods for which only the white rice–based GI was available were transformed into glucose-based GI values by multiplying the white rice–based GI by 0.82 (=100/122) [14,15]. Of the 169 FFQ items, 8 items containing 3.5 g or more carbohydrates per serving had no GI values from the previous data. Because the carbohydrate content of these foods is still low and it is not likely that they will induce a significant rise in blood glucose, we assigned a 0 value to each one of them. The dietary GL was computed by summing the product of the carbohydrate intake from each food by the GI for that food and divided by 100. The dietary GI of each subject was obtained by dividing the dietary GL by the daily intake of total carbohydrate intake and multiplying by 100. The amount of regular physical activity was estimated from the validated questionnaire by ascertaining the average number of hours spent weekly performing various kinds of activities in the past year, and the information was calculated to determine the weekly metabolic equivalent [16].

2.3. Ascertainment of mortality

Deaths in the cohort were recorded between September 1992 and December 1999. In Japan, the underlying cause of death in the death certificates has been determined based on the rules defined by the World Health Organization [17]. After obtaining permission to review the death data from the Ministry of Internal Affairs and Communication, the cause of each death and the date were confirmed with data from the office of the National Vital Statistics. The Statistics and Information Department of the Japanese Ministry of Health and Welfare recorded the cause of death in each case, which was coded according to the International Classification of Diseases (ICD). The major end point of this study was mortality from stroke (ICD-9 codes 430-438 and ICD-10 codes I60-I69) and its subtypes: ischemic stroke (ICD-9 codes 434 and ICD-10 codes I63 and I69.3) and hemorrhagic stroke (ICD-9 codes 430 and 431 and ICD-10 codes I60, I61, I69.0, and I69.1). This study was approved by the Ethics Committee at Gifu University Graduate School of Medicine.

2.4. Data analysis

To assess the magnitude of the association of the dietary GI, GL, and intake of carbohydrates and rice to mortality from stroke, a Cox proportional hazard model was applied to estimate the hazard ratios (HRs) with 95% confidence

Table 1
Baseline characteristics by quartiles of dietary GI in 12 561 men and 15 301 women in the Takayama study, Japan, 1992

Variable[a]	Men					Women				
	Quartiles of dietary GI				Total	Quartiles of dietary GI				Total
	1	2	3	4		1	2	3	4	
	Mean (SD) or %					Mean (SD) or %				
Age (y)	54.4 (12.2)	53.9 (12.2)	53.3 (11.9)	53.0 (12.3)	53.7 (12.1)	54.3 (11.8)	54.4 (12.8)	54.9 (13.2)	56.1 (13.9)	54.9 (13.0)
BMI (kg/m^2)	22.5 (2.8)	22.6 (2.8)	22.4 (2.7)	22.5 (2.7)	22.5 (2.8)	22.0 (2.8)	22.0 (3.0)	22.0 (2.9)	21.8 (2.9)	22.0 (2.9)
Height (cm)	165.0 (6.6)	164.9 (6.9)	164.6 (6.8)	164.5 (7.0)	164.8 (6.8)	152.5 (6.1)	152.4 (6.3)	152.2 (6.3)	151.4 (6.7)	152.1 (6.4)
Exercise, metabolic equivalent (h/wk)	27.5 (42.1)	27.9 (42.4)	26.4 (39.8)	27.4 (42.5)	27.3 (41.7)	19.5 (29.6)	19.7 (30.9)	19.0 (30.1)	17.5 (28.4)	18.9 (29.8)
Current cigarette smokers (%)	57.8	56.7	55.7	51.3	55.4	15.5	13.0	12.1	11.9	13.1
Currently married (%)	91.9	92.0	92.4	89.8	91.5	75.9	76.4	76.5	73.7	75.6
Education ≥12 y (%)	43.5	43.4	43.5	42.5	43.2	37.5	36.5	34.3	28.6	34.2
Aspirin use within 6 mo (%)	4.7	4.1	4.1	3.3	4.0	7.7	7.1	6.6	5.9	6.8
Use of antihypertensive drug within 6 mo (%)	11.2	10.6	11.0	9.6	10.6	11.7	11.2	12.1	12.2	11.8
Current hormone replacement therapy in postmenopausal women (%)						2.7	2.4	1.5	1.6	2.0
Daily food and dietary intake										
GI	58.0 (3.1)	63.3 (1.0)	66.4 (0.9)	70.3 (2.0)	64.5 (4.9)	58.3 (2.9)	63.1 (0.9)	66.1 (0.9)	70.0 (2.0)	64.4 (4.7)
GL	202.8 (79.2)	228.0 (72.7)	233.7 (65.0)	237.2 (61.4)	225.4 (71.2)	183.4 (67.8)	184.7 (65.3)	193.9 (67.3)	201.9 (62.8)	191.0 (66.3)
Carbohydrate (g)	370 (144)	377 (120)	367 (102)	350 (91)	366 (116)	337 (127)	310 (109)	309 (107)	301 (94)	314 (111)
White rice (serving)[b]	2.3 (1.2)	3.2 (1.2)	3.7 (1.1)	4.0 (1.1)	3.3 (1.3)	1.9 (0.9)	2.3 (0.9)	2.7 (1.1)	3.2 (1.2)	2.6 (1.1)
Total energy (kcal)	2902 (1065)	2751 (872)	2537 (725)	2278 (640)	2617 (873)	2435 (907)	2148 (761)	2055 (720)	1884 (616)	2131 (784)
Alcohol (g)	58.5 (47.6)	45.9 (41.5)	36.6 (35.9)	27.6 (32.3)	42.1 (41.4)	10.9 (22.4)	8.5 (17.2)	6.9 (14.1)	5.1 (11.3)	7.8 (16.9)
Salt (g)	17.7 (7.7)	15.4 (6.0)	13.1 (4.8)	10.5 (4.1)	6.4 (1.5)	16.7 (6.9)	13.7 (5.4)	12.2 (4.7)	9.7 (3.9)	13.1 (5.9)
Polyunsaturated fat (g)	19.1 (8.9)	17.5 (7.3)	15.3 (6.1)	12.6 (5.2)	7.4 (2.4)	18.3 (8.0)	15.6 (6.7)	14.2 (6.1)	11.6 (5.0)	14.9 (7.0)
Monounsaturated fat (g)	25.1 (12.3)	22.5 (10.2)	19.4 (8.4)	15.8 (7.4)	10.3 (1.6)	23.6 (10.7)	19.7 (9.1)	17.6 (8.1)	14.0 (6.8)	18.7 (9.5)
Saturated fat (g)	20.8 (10.8)	17.9 (7.9)	15.3 (6.3)	12.3 (5.4)	8.5 (1.5)	20.4 (10.0)	16.1 (7.1)	14.1 (6.2)	11.1 (5.1)	15.4 (8.1)
Cholesterol (mg)	504 (251)	441 (203)	379 (176)	301 (153)	213 (19)	456 (220)	373 (173)	330 (155)	260 (138)	354 (188)
Protein (g)	110.0 (46.2)	99.6 (36.6)	88.5 (30.0)	74.9 (25.7)	37.8 (18.1)	100.9 (39.9)	84.6 (31.7)	77.2 (28.8)	65.4 (24.3)	82.0 (34.2)
Dietary fiber (g)	20.2 (11.6)	17.4 (8.2)	14.8 (6.3)	12.1 (5.0)	8.7 (1.6)	22.1 (11.4)	17.3 (7.9)	15.2 (6.7)	12.1 (5.1)	16.7 (8.9)
Dietary vitamin E (mg)	13.4 (6.8)	11.8 (5.2)	10.0 (4.1)	8.1 (3.4)	5.4 (1.4)	13.6 (6.3)	11.0 (4.9)	9.8 (4.3)	7.8 (3.4)	10.6 (5.3)
Folate (μg)	598 (339)	504 (231)	426 (176)	341 (137)	252 (57)	613 (314)	474 (211)	416 (178)	330 (136)	458 (243)
Fruits (g)	108.4 (115.4)	86.8 (79.7)	70.8 (61.9)	52.8 (46.9)	79.7 (82.7)	150.1 (143.2)	107.0 (88.0)	87.6 (71.9)	62.5 (52.7)	101.8 (100.4)

[a] Number in each column was the same for each baseline characteristic, except for BMI for which it was 11 856 for men and 14 445 for women, height for which it was 12 062 for men and for 14 672 for women, current cigarette smokers for which it was 12 202 for men and 13 728 for women, currently married for which it was 12 438 for men and 15 052 for women, education for which it was 12 405 for men and 15 067 for women, and current hormone replacement therapy for which it was for 8 095 for women.

[b] *One serving* is defined as 67.6 g.

intervals. For each participant, person-years of follow-up were calculated from the study entry to the date of death from stroke, death from any other cause, date on which the person moved out of Takayama City, or the end of the study. We referred to the city residential registers to obtain information on subjects who had moved out. We considered an age-adjusted model to assess the risk or death from total stroke and the subtypes of stroke. A multivariate model with adjusting for possible confounders such as age; body mass index (BMI; in kilograms per square meter, in quintiles and missing values); smoking status (current, past, never smoked, or missing status); physical activity (metabolic equivalent per week); reported history of hypertension; education (12 years or more, or less); and intake of total energy, alcohol, dietary fiber, salt, and total fat was also considered to assess the risk of total stroke. The dietary GI, GL, and intake of carbohydrate and rice in grams were analyzed in quartiles. To test for linear trends across categories, we modeled the median of each category. The dietary GL and intake of carbohydrates, rice, and other nutrients used in the model were adjusted for the total energy intake using the regression analysis proposed by Willett [18]. The dietary GI was left as the crude value. By definition, it represented the quality of consumed carbohydrate, but not the quantity; and hence, it was not likely to be confounded by between-person variation in total energy intake. All the analyses were stratified by sex and then additionally stratified by BMI (<23 and ≥23) only to assess the risk of total stroke. The analysis stratified by BMI was limited to the 11 856 men and 14 445 women who reported both height and weight. The interaction term between sex or BMI and each dietary factor was tested in the model. All the statistical analyses were performed with SAS (SAS Institute, Cary, NC).

3. Results

The characteristics of the study participants at the baseline are presented in Table 1. Participants in higher quartiles of dietary GI were more likely to have lower alcohol consumption and were less likely to be current cigarette smokers. Women in the highest dietary GI were more likely to be older and less likely to be educated. With regard to daily food and dietary intake, participants in higher quartiles of dietary GI were more likely to have lower total calorie intake in line with lowered intakes of carbohydrate and other nutrients.

Table 2 shows the association between each dietary factor of interest and the risk of mortality from total stroke. Among men, the risk of total stroke was not clearly associated with the dietary GI, GL, carbohydrate intake, or rice intake.

Table 2
Hazard ratio of death from stroke according to quartiles of dietary GI, energy-adjusted dietary GL, total carbohydrate intake, and rice intake among 12 561 men and 15 301 women in the Takayama study, Japan

	Men					Women					
	Quartile				*P* for trend	Quartile				*P* for trend	
	1	2	3	4		1	2	3	4		
GI											
No. of cases	33	32	30	25		12	31	33	51		
Age adjusted	1	0.96 (0.59-1.56)	1.02 (0.62-1.67)	0.82 (0.49-1.37)	.53	1	2.00 (1.03-3.91)	1.85 (0.95-3.59)	2.46 (1.30-4.63)	.01	
Multivariate[a]	1	0.97 (0.59-1.60)	0.96 (0.56-1.64)	0.78 (0.41-1.47)	.50	1	1.90 (0.97-3.74)	1.66 (0.83-3.31)	2.09 (1.01-4.31)	.10	
P interaction with sex[a]											.12
Energy-adjusted GL											
No. of cases	42	25	24	29		16	31	43	37		
Age adjusted	1	0.55 (0.34-0.91)	0.68 (0.41-1.13)	0.86 (0.54-1.38)	.41	1	1.49 (0.81-2.72)	1.80 (1.01-3.20)	1.71 (0.95-3.07)	.08	
Multivariate[a]	1	0.61 (0.36-1.02)	0.81 (0.44-1.49)	1.00 (0.47-2.15)	.66	1	1.36 (0.73-2.53)	1.57 (0.83-2.97)	1.17 (0.51-2.68)	.60	
P interaction with sex[a]											.40
Carbohydrate intake											
No. of cases	34	28	27	31		25	24	35	43		
Age adjusted	1	0.72 (0.43-1.18)	0.76 (0.46-1.25)	0.93 (0.57-1.51)	.72	1	0.73 (0.42-1.28)	0.95 (0.57-1.59)	1.10 (0.67-1.80)	.42	
Multivariate[a]	1	0.79 (0.47-1.36)	0.95 (0.51-1.78)	1.17 (0.52-2.62)	.87	1	0.71 (0.39-1.27)	0.88 (0.48-1.60)	0.88 (0.39-2.01)	.85	
P interaction with sex[a]											.78
Rice intake											
No. of cases	36	43	13	28		14	32	47	34		
Age adjusted	1	1.06 (0.68-1.65)	0.54 (0.29-1.03)	0.92 (0.56-1.51)	.33	1	1.57 (0.84-2.95)	1.42 (0.78-2.60)	1.92 (1.03-3.57)	.06	
Multivariate[a]	1	0.95 (0.59-1.52)	0.53 (0.26-1.04)	0.84 (0.43-1.62)	.28	1	1.47 (0.78-2.79)	1.22 (0.62-2.37)	1.37 (0.64-2.94)	.62	
P interaction with sex[a]											.66

[a] Adjusted for age; BMI (in quintiles and missing values); smoking status (current, past, never smoker, or status missing); physical activity (metabolic equivalent per week); reported history of hypertension; education (12 years or longer, or not); and intake of total energy, alcohol, dietary fiber, salt, and total fat.

Among women, a high dietary GI was significantly associated with an increased risk of mortality from total stroke. The interaction between each dietary factor and sex was not significant in each model, but the term with dietary GI had a relatively small *P* value. Table 3 shows the association between each dietary factor of interest and the risk of mortality from hemorrhagic stroke. Among men, the risk was not significantly associated with any of the dietary variables. Among women, dietary GL and rice intake were significantly associated with the increased risk of hemorrhagic stroke. A positive trend for dietary GI was also observed, but the association failed to reach significance. We found a statistically significant interaction between intake of rice and sex on the risk of hemorrhagic stroke. Table 4 shows the association between each dietary factor and the risk of mortality from ischemic stroke. Among men, the risk or mortality from ischemic stroke was not significantly associated with the dietary GI, GL, carbohydrate intake, or rice intake. Among women, the risk of death from ischemic stroke increased with higher dietary GI. There was no significant interaction between sex and each dietary factor.

To separate the effect of the dietary GI from the effect of rice intake, we roughly estimated GI sourcing from all foods except for rice. The dietary GI not sourcing from rice was not associated with total stroke or hemorrhagic stroke among men and among women, and not associated with ischemic stroke among women. It was inversely associated with the risk of ischemic stroke among men (HR for comparing highest to the lowest quartiles was 0.36 [95% confidence interval, 0.15-0.83]).

Table 5 summarizes the analyses stratified by BMI. Among women with BMI less than 23 kg/m^2, higher dietary GI was significantly associated with an increased risk of mortality from total stroke. However, the interaction term between BMI and dietary GI was not significant. No other associations clearly varied by BMI.

4. Discussion

To our knowledge, the current study is the first prospective cohort study that suggests an association between the dietary GI and the risk of stroke. Among Japanese women in this population, the dietary GI was significantly associated with an increasing risk of mortality from stroke. Such association was not observed among men.

In previous studies, diets high in GI have been linked with an increased risk of diabetes and glucose intolerance [19-22]. The association of the dietary GI to the risk of diabetes may explain the increased risk of stroke observed in the current study. Subjects who reported a history of diabetes were excluded in the current study, but prediabetes or developed diabetes during the follow-up in association with a high dietary GI may have increased the risk of stroke. Many epidemiologic studies suggested that type 2 diabetes mellitus has been an important risk factor for stroke [23-27]. In addition, previous studies showed a significantly greater risk in women with diabetes developing stroke than in men with diabetes [25,27-29], indicating that women are more susceptible to diabetes or glucose intolerance and subsequent

Table 3
Hazard ratio of death from hemorrhagic stroke according to quartiles of dietary GI, energy-adjusted dietary GL, total carbohydrate intake, and rice intake among 12 561 men and 15 301 women in the Takayama study, Japan

	Men					Women					
	Quartile				*P* for trend	Quartile				*P* for trend	
	1	2	3	4		1	2	3	4		
GI											
No. of cases	14	9	13	12		6	9	15	16		
Age adjusted	1	0.64 (0.28-1.49)	0.97 (0.46-2.06)	0.90 (0.42-1.94)	.94	1	1.38 (0.49-3.88)	2.15 (0.83-5.57)	2.10 (0.82-5.39)	.08	
P interaction with sex[a]											.35
Energy-adjusted GL											
No. of cases	18	8	8	14		6	9	15	16		
Age adjusted	1	0.44 (0.19-1.00)	0.48 (0.21-1.11)	0.86 (0.43-1.73)	.47	1	1.33 (0.47-3.73)	2.08 (0.80-5.37)	2.30 (0.90-5.88)	.05	
P interaction with sex[a]											.13
Carbohydrate intake											
No. of cases	17	9	8	14		7	10	11	18		
Age adjusted	1	0.51 (0.23-1.14)	0.47 (0.20-1.08)	0.84 (0.42-1.71)	.46	1	1.22 (0.47-3.22)	1.27 (0.49-3.29)	1.96 (0.82-4.70)	.11	
P interaction with sex[a]											.13
Rice intake											
No. of cases	17	13	6	12		6	7	17	16		
Age adjusted	1	0.73 (0.35-1.50)	0.39 (0.15-1.00)	0.71 (0.34-1.49)	.15	1	0.98 (0.33-2.91)	1.81 (0.71-4.66)	2.36 (0.92-6.03)	.02	
P interaction with sex[a]											.03

[a] Adjusted for age, sex, and the single dietary factor of the interaction term.

Table 4
Hazard ratio of death from ischemic stroke according to quartiles of dietary GI, energy-adjusted dietary GL, total carbohydrate intake, and rice intake among 12 561 men and 15 301 women in the Takayama study, Japan

	Men					Women					
	Quartile				*P* for trend	Quartile				*P* for trend	
	1	2	3	4		1	2	3	4		
GI											
No. of cases	15	16	16	13		6	15	13	32		
Age adjusted	1	1.00 (0.50-2.03)	1.22 (0.60-2.46)	0.91 (0.43-1.92)	.96	1	1.67 (0.64-4.31)	1.18 (0.44-3.12)	2.45 (1.01-5.92)	.03	
P interaction with sex[a]											.29
Energy-adjusted GL											
No. of cases	20	13	13	14		8	16	23	19		
Age adjusted	1	0.56 (0.28-1.12)	0.77 (0.38-1.55)	0.92 (0.47-1.83)	.77	1	1.42 (0.61-3.32)	1.63 (0.72-3.66)	1.59 (0.70-3.65)	.27	
P interaction with sex[a]											.73
Carbohydrate intake											
No. of cases	16	13	16	15		15	9	20	22		
Age adjusted	1	0.62 (0.30-1.30)	0.90 (0.45-1.80)	0.91 (0.45-1.85)	.97	1	0.43 (0.19-0.98)	0.80 (0.41-1.57)	0.86 (0.44-1.65)	.85	
P interaction with sex[a]											.78
Rice intake											
No. of cases	18	21	5	16		7	18	25	16		
Age adjusted	1	0.97 (0.51-1.82)	0.52 (0.19-1.41)	1.21 (0.61-2.37)	.97	1	1.53 (0.64-3.68)	1.14 (0.49-2.67)	1.67 (0.69-4.07)	.39	
P interaction with sex[a]											.37

[a] Adjusted for age, sex, and the single dietary factor of the interaction term.

stroke than men. That may also support that a significant risk increase of stroke with high dietary GI was only observed among women in the current study. Previously, the intake of carbohydrates was generally not found to predict the risk of diabetes [20-28]. The studies may support the findings of the current study because no clear association was observed between carbohydrate intake and the risk of total stroke.

Dietary GI may have influence on factors other than diabetes, such as others that lead to the increased risk of stroke. It was reported that low-GI diets increased body fat loss among overweight or obese young adults in an intervention study, and progression of atherosclerosis was accelerated with high carbohydrate intake from high-GI sources among women with coronary heart disease in a 3-year prospective study [30,31]. These results may be supported by the studies that indicated the inflammatory reactions with hyperglycemia [32,33]. In the current study, however, subjects with high dietary GI were likely to consume low level of dietary fat; and the effect of dietary GI on lipid profile, if it existed, could be overridden.

Findings from previous prospective cohort studies implied that dietary GL was positively associated with the risk of stroke [3-5], whereas the association between dietary GL and the risk of total stroke was not clear in the current study. This could be attributed to the fact that the subjects in the current study population were relatively slim. Two of the studies found associations between the dietary GL and stroke among overweight women but not among those who were not overweight [3,4]. Alternatively, our results may indicate that, although large amounts of carbohydrates were regularly consumed among Japanese population, the quality of carbohydrates (represented by dietary GI) is more important than its quantity (partially represented by dietary GL).

Differences in the association between dietary GI and stroke subtypes were not clear in the current study. Among women, the risk of mortality from ischemic stroke was increased among the subjects with the highest level of dietary GI; and a similar pattern of risk increase for hemorrhagic stroke was also observed, although the association was not significant. Previous studies consistently reported that diabetes increased the risk of ischemic stroke [23,24,28], whereas the risk of hemorrhagic stroke does not seem to increase among people with diabetes [7,24,34]. However, in the current study, the dietary GL and rice intake significantly increased the risk of hemorrhagic stroke; but the associations were not significant with the risk of ischemic stroke among women in the current study. The large consumption of rice and the dietary GL may have been linked to the Japanese-style diet [35]. It was reported in the Honolulu Heart Program that a Western-type diet, compared with an Oriental-style diet, tended to be inversely associated with thromboembolic and hemorrhagic stroke. However, a recent cohort study in Japan reported that the Japanese dietary pattern was associated with a decreased risk of total stroke mortality [36]. The dietary GI sourcing from food items other than rice was not associated with the risk of total stroke or hemorrhagic stroke in the current study, and the inverse association was observed with the risk of ischemic stroke among men. Nonetheless, there is still a possibility that

Table 5
Hazard ratio of death from stroke according to quartiles of dietary GI, energy-adjusted dietary GL, total carbohydrate intake, and rice intake among 6970 men and 9747 women whose BMI was less than 23 and 4886 men and 4698 women whose BMI was 23 or over in Takayama study, Japan

	Men						Women					
	Quartile				*P* for trend	*P* for interaction with BMI[a]	Quartile				*P* for trend	*P* for interaction with BMI[a]
	1	2	3	4			1	2	3	4		
GI												
BMI <23 kg/m^2												
No. of cases	19	17	20	17			5	19	21	36		
Age-adjusted HR	1	0.84 (0.44-1.62)	1.09 (0.58-2.05)	0.93 (0.49-1.80)	.99		1	2.92 (1.09-7.84)	2.55 (0.96-6.81)	3.86 (1.51-9.90)	.01	
BMI ≥23 kg/m^2												
No. of cases	8	8	4	5			6	7	8	8		
Age-adjusted HR	1	1.21 (0.45-3.23)	0.68 (0.21-2.26)	0.82 (0.27-2.50)	.57		1	1.00 (0.33-2.97)	1.06 (0.36-3.08)	0.94 (0.32-2.76)	.94	
						.94						.21
Energy-adjusted GL												
BMI <23 kg/m^2												
No. of cases	23	17	16	17			9	21	26	25		
Age-adjusted HR	1	0.65 (0.35-1.22)	0.79 (0.42-1.49)	0.90 (0.48-1.69)	.71		1	1.86 (0.85-4.06)	1.87 (0.87-4.01)	1.92 (0.90-4.13)	.15	
BMI ≥23 kg/m^2												
No. of cases	11	3	4	7			6	6	9	8		
Age-adjusted HR	1	0.27 (0.08-0.98)	0.48 (0.15-1.50)	0.85 (0.33-2.20)	.56		1	0.81 (0.26-2.52)	1.17 (0.42-3.31)	1.16 (0.40-3.35)	.64	
						.46						.73
Carbohydrate intake												
BMI <23 kg/m^2												
No. of cases	18	19	17	19			17	14	23	27		
Age-adjusted HR	1	0.96 (0.51-1.84)	0.94 (0.48-1.81)	1.14 (0.60-2.17)	.90		1	0.59 (0.29-1.20)	0.87 (0.46-1.62)	0.88 (0.48-1.62)	.93	
BMI ≥23 kg/m^2												
No. of cases	9	3	4	9			7	6	5	11		
Age-adjusted HR	1	0.27 (0.07-0.99)	0.40 (0.12-1.30)	0.96 (0.38-2.41)	.90		1	0.84 (0.28-2.49)	0.59 (0.19-1.86)	1.27 (0.49-3.28)	.64	
						.70						.65
Rice intake												
BMI <23 kg/m^2												
No. of cases	21	26	10	16			7	24	29	21		
Age-adjusted HR	1	1.09 (0.62-1.94)	0.67 (0.31-1.42)	0.87 (0.45-1.67)	.44		1	2.02 (0.87-4.72)	1.48 (0.64-3.42)	2.10 (0.89-4.94)	.22	
BMI ≥23 kg/m^2												
No. of cases	8	8	2	7			7	5	9	8		
Age-adjusted HR	1	0.91 (0.34-2.44)	0.50 (0.10-2.41)	1.10 (0.40-3.05)	.93		1	0.56 (0.18-1.78)	0.79 (0.29-2.14)	0.98 (0.36-2.73)	.77	
						.45						.87

[a] Adjusted for age, BMI, and the single dietary factor of the interaction term.

nutrients or food items typical in Japanese-style diet could have played a role as confounders in the association between the dietary variables and stroke or its subtypes. Further evaluation of the consumption of rice in relation to risk of stroke and its subtypes in a larger study is warranted.

The dietary GI may have been associated with risk factors of stroke subtypes, other than diabetes. Several studies reported that a low dietary GI was associated with a high concentration of serum high-density lipoprotein cholesterol [37,38]. Low serum cholesterol levels with a condition of high blood pressure are reported risk factors of hemorrhagic stroke [39,40]. If the prevalence of uncontrolled high blood pressure was high in the group with a high dietary GI, GL, or rice consumption, such a condition with a lowered level of high-density lipoprotein cholesterol might explain the increased the risk of hemorrhagic stroke observed among women.

In the current study, stratified analysis by BMI showed that dietary GI and dietary GL were significantly associated with increased risk of death from total stroke among women with BMI less than 23. The interaction terms between BMI and the dietary factors were not significant. The results contradicted previous studies reporting the association between dietary GL and total stroke, or the association between dietary GL and cardiovascular disease among overweight or obese women [3,4]. There were a limited number of events available in the current study, and they may be too few to draw a conclusion after the stratification.

This study has several limitations. The FFQ in this study was not specifically designed to derive dietary GI values, as in many other studies; and thus, no validation data for the estimation of the dietary GI or GL exist. The data we collected for food and nutrient intake and estimated dietary GL may have been overestimated by the FFQ. However, our questionnaire was designed to measure the relative intake of food and nutrients rather than the absolute value. Correlation coefficients between the value from the FFQ and that from the food record for carbohydrate intake were relatively low; and attenuation of association, if the association existed, may have occurred. It was suggested that the correlation needs to be at least 0.3 or 0.4 to detect associations between diet and disease [41], and our FFQ may have minimal validity for the assessment of carbohydrate intake. The diagnoses of outcome were based on death certificates; and the possibility of misdiagnosis, especially for the subtypes of stroke, cannot be ruled out for the findings of the current study. High dissemination of computerized tomography in Japan, however, may warrant sufficient accuracy for the use of death certificate in the current study [42,43]. The information in deaths was not able to be updated after 1999, and the number of deaths from the subtypes of stroke was not enough to control for the potential risk factors. The impact of initial exclusion of the subjects on the study results is unknown; but the fairly high participation rates reduce concern of bias from nonparticipation, and its systematic effect, if it exists, may be minimal. We repeatedly performed statistical tests, so the results should be interpreted with caution.

5. Summary

In conclusion, we found a positive relationship between the dietary GI and risk of mortality from stroke among women in a community-based cohort in Japan, where a high risk of stroke is still observed. The results of the study also suggest that the risk of mortality from ischemic stroke is increased with increased level of the dietary GI among women, and a positive trend is also suggested between dietary GL and mortality from hemorrhagic stroke among women. Conducting further studies that precisely investigate the biomarkers for glucose metabolism in relation to the dietary GI and the risk of stroke would be desirable, and further investigation of the risk factors of stroke subtypes in response to the dietary GI with a specific focus on male-female differences is recommended.

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References

[1] Thom TJ, Epstein FH, Feldman JJ, Leaverton PE, Wolz M. Total mortality and mortality from heart disease, cancer, and stroke from 1950 to 1987 in 27 countries. Washington DC: National Institutes of Health; 1992 (NIH publication 92-3088).

[2] Health and Welfare Statistics Association, editor. Journal of Health and Welfare Statistics (2007 Kokumin-Eisei-no-Doko). Tokyo: Health and Welfare Statistics Association; 2007. (in Japanese).

[3] Oh K, Hu FB, Cho E, Rexrode KM, Stampfer MJ, Manson JE, et al. Carbohydrate intake, glycemic index, glycemic load, and dietary fiber in relation to risk of stroke in women. Am J Epidemiol 2005;161: 161-9.

[4] Beulens JW, de Bruijne LM, Stolk RP, Peeters PH, Bots ML, Grobbee DE, et al. High dietary glycemic load and glycemic index increase risk of cardiovascular disease among middle-aged women: a population-based follow-up study. J Am Coll Cardiol 2007;50:14-21.

[5] Levitan EB, Mittleman MA, Håkansson N, Wolk A. Dietary glycemic index, dietary glycemic load, and cardiovascular disease in middle-aged and older Swedish men. Am J Clin Nutr 2007;85:1521-6.

[6] Iso H, Jacobs Jr DR, Wentworth D, Neaton JD, Cohen JD. Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. N Engl J Med 1989;320:904-10.

[7] Neaton JD, Wentworth DN, Cutler J, Stamler J, Kuller L. Risk factors for death from different types of stroke. Multiple Risk Factor Intervention Trial Research Group. Ann Epidemiol 1993;3:493-9.

[8] Shimizu H, Ohwaki A, Kurisu Y, Takatsuka N, Ido M, Kawakami N, et al. Validity and reproducibility of a quantitative food frequency questionnaire for a cohort study in Japan. Jpn J Clin Oncol 1999;29: 38-44.

[9] Shimizu H. The basic report on Takayama study. Gifu: Department of Public Health, Gifu University School of Medicine; 1996.

[10] Oba S, Shimizu N, Nagata C, Shimizu H, Kametani M, Takeyama N, et al. The relationship between the consumption of meat, fat, and

coffee and the risk of colon cancer: a prospective study in Japan. Cancer Lett 2006;244:260-7.
[11] Sasaki S, Kobayashi M, Tsugane S. Development of substituted fatty acid composition table for the use in nutritional epidemiologic studies for Japanese populations: its methodological backgrounds and the evaluation. J Epidemiol 1999;9:190-207.
[12] Atkinson FS, Foster-Powell K, Brand-Miller JC. International tables of glycemic index and glycemic load values: 2008. Diabetes Care 2008; 31:2281-3.
[13] Murakami K, Sasaki S, Takahashi Y, Okubo H, Hosoi Y, Horiguchi H, et al. Dietary glycemic index and load in relation to metabolic risk factors in Japanese female farmers with traditional dietary habits. Am J Clin Nutr 2006;83:1161-9.
[14] Sugiyama M, Wakaki Y, Nakamoto N, Koyama W, Mitsuhashi F, Inoue M, et al. The study of rice and glycemic index. J Jpn Soc Nutr Care Manage 2003;3:1-15 (in Japanese with English abstract).
[15] Sugiyama M, Tang AC, Wakaki Y, Koyama W. Glycemic index of single and mixed meal foods among common Japanese foods with white rice as a reference food. Eur J Clin Nutr 2003;57:743-52.
[16] Suzuki I, Kawakami N, Shimizu H. Reliability and validity of a questionnaire for assessment of energy expenditure and physical activity in epidemiological studies. J Epidemiol 1998;8:152-9 Supplemental material published in J Epidemiol 2002;12:54.
[17] The Statistics and Information Department. Minister's secretariat plans. Manual to fill in death certificate, birth certificate and stillbirth certificate (in Japanese). Tokyo: Health and Welfare Statistics Association; 1995.
[18] Willett WC. Implications of total energy intake for epidemiologic analyses. In: Willett WC, editor. Nutritional epidemiology. New York: Oxford University Press; 1990. p. 245-71.
[19] Villegas R, Liu S, Gao YT, Yang G, Li H, Zheng W, et al. Prospective study of dietary carbohydrates, glycemic index, glycemic load, and incidence of type 2 diabetes mellitus in middle-aged Chinese women. Arch Intern Med 2007;167:2310-6.
[20] Salmerón J, Manson JE, Stampfer MJ, Colditz GA, Wing AL, Willett WC. Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. JAMA 1997;277:472-7.
[21] Salmerón J, Ascherio A, Rimm EB, Colditz GA, Spiegelman D, Jenkins DJ, et al. Dietary fiber, glycemic load, and risk of NIDDM in men. Diabetes Care 1997;20:545-50.
[22] Hodge AM, English DR, O'Dea K, Giles GG. Glycemic index and dietary fiber and the risk of type 2 diabetes. Diabetes Care 2004;27: 2701-6.
[23] Iso H, Imano H, Kitamura A, Sato S, Naito Y, Tanigawa T, et al. Type 2 diabetes and risk of non-embolic ischaemic stroke in Japanese men and women. Diabetologia 2004;47:2137-44.
[24] Janghorbani M, Hu FB, Willett WC, Li TY, Manson JE, Logroscino G, et al. Prospective study of type 1 and type 2 diabetes and risk of stroke subtypes: the Nurses' Health Study. Diabetes Care 2007;30:1730-5.
[25] Wannamethee SG, Perry IJ, Shaper AG. Nonfasting serum glucose and insulin concentrations and the risk of stroke. Stroke 1999;30: 1780-6.
[26] Hart CL, Hole DJ, Smith GD. Comparison of risk factors for stroke incidence and stroke mortality in 20 years of follow-up in men and women in the Renfrew/Paisley Study in Scotland. Stroke 2000;31: 1893-6.
[27] Tuomilehto J, Rastenyte D, Jousilahti P, Sarti C, Vartiainen E. Diabetes mellitus as a risk factor for death from stroke. Prospective study of the middle-aged Finnish population. Stroke 1996;27:210-5.
[28] Tanizaki Y, Kiyohara Y, Kato I, Iwamoto H, Nakayama K, Shinohara N, et al. Incidence and risk factors for subtypes of cerebral infarction in a general population: the Hisayama study. Stroke 2000;31:2616-22.
[29] Toeller M, Buyken AE, Heitkamp G, Cathelineau G, Ferriss B, Michel G, EURODIAB IDDM Complications Study Group. Nutrient intakes as predictors of body weight in European people with type 1 diabetes. Int J Obes Relat Metab Disord 2001;25:1815-22.
[30] McMillan-Price J, Petocz P, Atkinson F, O'neill K, Samman S, Steinbeck K, et al. Comparison of 4 diets of varying glycemic load on weight loss and cardiovascular risk reduction in overweight and obese young adults: a randomized controlled trial. Arch Intern Med 2006; 166:1466-75.
[31] Mozaffarian D, Rimm EB, Herrington DM. Dietary fats, carbohydrate, and progression of coronary atherosclerosis in postmenopausal women. Am J Clin Nutr 2004;80:1175-84.
[32] Dickinson S, Brand-Miller J. Glycemic index, postprandial glycemia and cardiovascular disease. Curr Opin Lipidol 2005;16:69-75.
[33] Liu S, Manson JE, Buring JE, Stampfer MJ, Willett WC, Ridker PM. Relation between a diet with a high glycemic load and plasma concentrations of high-sensitivity C-reactive protein in middle-aged women. Am J Clin Nutr 2002;75:492-8.
[34] Njølstad I, Arnesen E, Lund-Larsen PG. Body height, cardiovascular risk factors, and risk of stroke in middle-aged men and women. A 14-year follow-up of the Finnmark Study. Circulation 1996;94: 2877-82.
[35] Reed DM. The paradox of high risk of stroke in populations with low risk of coronary heart disease. Am J Epidemiol 1990;131:579-88.
[36] Shimazu T, Kuriyama S, Hozawa A, Ohmori K, Sato Y, Nakaya N, et al. Dietary patterns and cardiovascular disease mortality in Japan: a prospective cohort study. Int J Epidemiol 2007;36:600-9.
[37] Amano Y, Kawakubo K, Lee JS, Tang AC, Sugiyama M, Mori K. Correlation between dietary glycemic index and cardiovascular disease risk factors among Japanese women. Eur J Clin Nutr 2004;58:1472-8.
[38] Frost G, Leeds AA, Doré CJ, Madeiros S, Brading S, Dornhorst A. Glycaemic index as a determinant of serum HDL-cholesterol concentration. Lancet 1999;353:1045-8.
[39] Ebrahim S, Sung J, Song YM, Ferrer RL, Lawlor DA, Davey Smith G. Serum cholesterol, haemorrhagic stroke, ischaemic stroke, and myocardial infarction: Korean national health system prospective cohort study. BMJ 2006;333:22.
[40] Prospective Studies Collaboration, Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet 2007;370:1829-39.
[41] Cade J, Thompson R, Burley V, Warm D. Development, validation and utilisation of food-frequency questionnaires - a review. Public Health Nutr 2002;5:567-87.
[42] Anderson GF, Poullier JP. Health spending, access, and outcomes: trends in industrialized countries. Health Aff 1999;18:178-92.
[43] Iso H, Jacobs Jr DR, Goldman L. Accuracy of death certificate diagnosis of intracranial hemorrhage and nonhemorrhagic stroke. The Minnesota Heart Survey. Am J Epidemiol 1990;132:993-8.