厚生労働科学研究費
循環器疾患等生活習慣病対策総合研究事業

循環器リスクと耐糖能障害の効率的な
健診マーカーの探索

平成21年度　総括研究報告書

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【１】総括研究報告

厚生労働省科学研究費補助金（循環器疾患等生活習慣病対策総合研究事業）
総括研究報告書

循環器リスクと耐糖能障害の効率的な健診マーカーの探索

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研究要旨
２型糖尿病は軽症段階や予備軍であっても心血管イベントの重要リスクとなることが明らかとなっている。前年度の成績から、日本人の耐糖能異常は60% が非肥満であり、境界型の段階から肥満の有無を問わず、インスリン分泌の初期反応が低下していることが確認された。空腹時血糖が正常である「かくれ糖尿病」を効率的に検出する基準を模索した結果、耐糖能異常の検出においては、メタボ健診で用いられる空腹時血糖値よりも HbA1c 5.5% の方が優れていることを明らかにした。現在、メタボ健診で汎用されているウエスト周囲径は肥満の BMI 基準に比して耐糖能異常の検出感度が低いことも明らかとなり、健診の基準設定の見直しが必要と考えられた。また、耐糖能異常の生活リスクとして喫煙状況を解析し、喫煙者の糖尿病リスクのみならず、受動喫煙の配偶者においても IGT リスクが増大し、背景としてインスリン分泌能が低下する可能性を提示し、禁煙を指導の重要項目として挙げた。

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A. 研究目的

耐糖能異常は軽症段階の糖尿病や境界型（予備軍）であっても心血管イベントの重要リスクである。しかし、耐糖能異常も循環器疾患も共に不均一な病態なので、効率的な予防を行なうには、日本人の病態とリンクした健診項目の設定と個々の体質や生活特性に配慮した保健指導が必要である。

平成15-17年度に、脳梗塞多発地域である東濃の恵那保健所管区で、健診でHbA1c 5.5以上であった住民162人を対象として糖負荷試験(GTT)を実施し、耐糖能異常について６ヶ月間の保健師による生活指導介入を行なった。その結果、大半において耐糖能の改善が認められ、その効果は１年後も継続した。そこで同研究を拡大し、感受性素因と不応素因を選別して健診項目と指導内容に反映させる

ことを考案した。

本研究では、GTTで明確に判定された耐糖能に従って、糖尿病型、境界型、正常型の3群を設定すると共に、生化学検査、健康・生活に関する質問票調査を実施する。2－3年後にフォローアップ解析し、耐糖能の変化と関連する血中因子や生活因子を特定する。本年度は生活習慣の内で、喫煙について耐糖能との関連に焦点を当てた。

当初は、日本人の心筋梗塞と有意に関連する約30種類の遺伝子多型マーカー(N Engl J Med. 347:1916-23, 2002)と関係因子の関連解析を行ない、感受性体質に基づいたテイラーメイド指導を可能とする健診マーカーを開発する計画であった。しかし、中間評価において審査員から遺伝子研究は本研究から除外するように指導を受けたので、以降は同項目の実施は試みなかった。

B. 研究方法

(糖代謝異常の早期検出の検討)

初年度にGTTの結果に基づいて、正常型、境界型、糖尿病型に分類し、HOMA-RとInsulinogenic indexを算定してインスリン抵抗性とインスリン初期分泌能を評価した。その結果、日本人の耐糖能異常は肥満の有無を問わず、初期の追加分泌から障害されることが明らかとなった。空腹時血糖が正常あるいは正常高値に留まり、負荷後の血糖値が上昇するいわゆる「かくれ糖尿病」が相当部分を占めることが判明した。そこで、GTTの適応者を選別するために感度と特異度を考慮したHbA1cと空腹時血糖値の基準設定を試みた。

特定健診で測定されるウエスト周囲径と従来から使用されているBMI肥満基準との耐糖能検出感度の比較も行った。

(生活状況調査)

初年度に自記式質問票（36ページ）を作成し、アンケート調査を実施した。本質問票により、性別、生年月日、家庭環境、職業等の背景、既往歴、20歳時からの体重の増減、健康状態、睡眠時間、喫煙習慣と受動喫煙、歯の衛生、家族の人数と既往歴、糖尿病の知識（24問）、ストレステスト(12問)、食習慣と食事内容、健康食品、嗜好品、運動習慣、QOL-26、女性の妊娠・出産歴・閉経などの情報収集を行ない、コンピュータ入力を完了した。諸項目の解析を逐次進行させているが、2年度は喫煙に関する調査の解析が先行して終了した。

喫煙は心血管イベントの強力なリスク習慣であり、糖尿病発症においてもリスクであると示唆されている。本研究では、喫煙者のリスクに加えて受動喫煙に関してもリスクになるかどうかの評価を試みた。

岐阜県は糖尿病対策活動が活発で、岐阜大は研究面で主導する立場にある。本解析は、一連の研究課題の1つで、喫煙と糖尿病、特に環境たばこ煙 (ETS；environmental tobacco smoke) にさらされる女性に焦点を当て、糖尿病発症との関係を明らかにすることを目的に行われた。

本研究は、岐阜県内 の男性452人、女性648人を対象に断面調査を行った。調査では、75g糖負荷試験の2時間値や身長、体重、女性自身と配偶者の喫煙の状況、身体状況、飲酒歴、親の糖尿病歴などを解析した。

<u>倫理面への配慮</u>

全ての実験はヘルシンキ宣言と3省庁合同指針を遵守して行われる。本計画は医学部の疫学研究と臨床研究に関する倫理審査委員会の承認を受けている。臨床上の個人情報を含めて、研究ソースはすべて本研究に関わらない秘守義務を負う識別管理者（研究機関が指定）が管理する。

C. 結果

（耐糖能異常の早期検出の検討）

岐阜市民 1,029 人を対象として、糖尿病型と境界型について、HbA1c と空腹時血糖の検出能の感度と特異度を ROC 解析により検定した。

HnA1c については、糖尿病型では 5.5%において感度 81.6&、特異度 70.9%、境界型では 5.3%において感度 73.0%、特異度 52.5%であった。60 歳以下に限定すれば、感度 83.2&、特異度 79.5%と高まった。BMI,23 以下とすれば、同じく感度 81.8&、特異度 78.7%と高まった。

空腹時血糖については、糖尿病型では 96mg/dl において感度 71.4&、特異度 74.6%、境界型では 92mg/dl において感度 67.2%、特異度 64.9%であった。年齢や肥満度で区分しても、HbA1c のようには感度と特異度の双方は共に 80%程度には上昇しなかった。

ウエスト周囲径と BMI による耐糖能異常の検出能は、基準が厳格すぎるとされる女性(90cm)でほぼ同定度であったが、男性(85cm)においては IRI と HOMA-R は同程度であったが、空腹時血糖値、2 時間値、HbA1c において BMI に比してウエスト周囲径は感度が有意に低かった。Insulinogenic index では両マーカーとも有意な検出力を認めなかったので、日本人においては肥満度と関連しない遺伝的体質が規定していると考えられた。

（喫煙と糖尿病発症との関連の解析）

まず、非喫煙者の女性で夫が喫煙している場合、家庭内で何日ぐらい環境たばこ煙（ETS）にさらされているのか調べたところ、1週間のうち7日が55%近くで最も多かった（n=138）。一方、非喫煙者の女性で夫が喫煙しない場合は、1週間のうち0日が58%近くで最も多かった（n=358）。次に非喫煙者の女性で夫が喫煙している場合で、家庭内でタバコを吸う人を調べたところ、配偶者が68%で最も多く、訪問者が15%、友人らが3%、配偶者 以外の家族らが2%などだった。まったく環境たばこ煙にさらされていないのは15%に過ぎなかった。

糖尿病との関連では、糖尿病になるオッズ比（95%信頼区間）を求めたところ、非喫煙者を1.00とした場合、喫煙経験者が 1.05（0.55-2.01）、喫煙者2.62（1.41-4.90）だった。IGTでは、非喫煙者を1.00とした場合、喫煙経験者が 0.91（0.61-1.36）、喫煙者1.32（0.83-2.12）だった。

男性だけで見ると、糖尿病のオッズ比（95%信頼区 間）は、非喫煙者を1.00とした場合、喫煙経験者が0.82（0.34-1.95）、喫煙者1.94（0.81-4.69）だった。IGTでは、非喫煙者を1.00とした場合、喫煙経験者が1.11（0.60-2.03）、喫煙者1.20（0.59-2.47）だった。一方、女性（584 人）では、糖尿病のオッズ比（95%信頼区間）は、自身が非喫煙者で夫が喫煙しない場合（オッズ比1.00）に対し、自身が非喫煙者で夫が喫煙する場合が 0.55（0.15-1.98）、自身が喫煙経験者の場合が0.61（0.08-4.79）、自身が喫煙者の場合が2.72（0.71-10.46）だっ た。

耐糖能異常(IGT)のオッズ比は、自身が非喫煙者で夫が喫煙しない場合（オッズ比1.00）に対し、自身が非喫煙者で夫が喫煙する場合が1.78（1.06-2.98）、自身が喫煙経験者の場合は0.76（0.29-1.97）、自身が喫煙者では2.94（1.28-6.76）だっ た。

D. 考察

前年度の我々の成績から、日本人では糖尿病や心血管病には分泌不全を基盤として、軽度のインスリン抵抗性が関与する図式が確認されている。耐糖能異常に肥満が占める割合は約40%であったことから、腹囲を必須項目として空腹時血糖を測定するメタボ健診では、重要リスクである食後血糖の高値を示す「かくれ糖尿病」を高率に見逃す危険性が考えられる。従って、随時血糖値やHbA1cを

併用した健診に改善することが必要と考えられた。

従来の論文で示されているように、喫煙は糖尿病の発症に関与することが日本人でも確認された。女性喫煙者、あるいは非喫煙者の女性で夫が喫煙者の場合、自身が非喫煙者で夫が喫煙しない場合に対して、IGTになりやすいことが新たに明らかになった。 さらに、非喫煙者の女性で夫が喫煙者の場合、自身が非喫煙者で夫が喫煙しない場合に対して、膵β細胞の機能が低いことも判明した。

E. 結論

日本人で多くを占めるインスリン分泌不全型の耐糖能異常を早期に健診で検出するには、空腹時血糖ではなく、HbA1c を併用した健診に見直すことがより効果的である。

生活習慣の改善項目としては、禁煙の励行と喫煙場所の制限が喫煙者自身のみならず配偶者の糖尿病の予防のために重要と示唆された。

F 健康危険情報

なし

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H　知的財産権の出願・登録

1　特許取得　　なし
2　実用新案登録　　なし
3　その他　　なし

【２】研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表雑誌名	巻	ページ	出版年
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C, Nagata.	Factors to consider in the association between soy isoflavone intake and breast cancer risk.	Journal of Epidemiology	20	83-89	2009
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S. Oba, et al.	Consumption of coffee, green tea, oolong tea, black tea, chocolate snacks and the caffeine content in relation to	British Journal of Nutrition	103	453-459	2010

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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.