F.　　知的財産権の出願・登録状況
（予定を含む）

1.　　特許取得：なし
2.　　実用新案登録：なし
3.　　その他：なし

G.　　研究協力者

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特定健診・保健指導におけるメタボリックシンドロームの診断・管理のエビデンス創出に関する
横断・縦断研究

分担研究報告書

地域住民における糖尿病発症に対する空腹時および負荷後2時間血糖値とヘモグロビンA1cのカットオフ値の検討：久山町研究

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研究要旨

欧米を中心に空腹時血糖値（FPG）、負荷後2時間血糖値（2hPG）とヘモグロビン（Hb）A1cの糖尿病発症に対するカットオフ値を検討した報告が散見されるが、わが国の地域住民を対象にした研究は極めて少ない。そこで本研究では、75g経口糖負荷試験（OGTT）を受けた福岡県久山町の地域住民を追跡した調査成績をもとに、糖尿病発症に対するFPG、2hPGおよびHbA1cのカットオフ値を検討した。1988年の久山町の循環器健診で、OGTTで糖尿病［2003年米国糖尿病協会（ADA）基準］のないことを確認した40-79歳の住民1,982名を14年間追跡した。追跡期間内に295例の糖尿病発症をみた。FPG、2hPGおよびHbA1cの各レベルの10分位で対象者を10群に分け、糖尿病発症の相対危険を検討した。その結果、第1分位に比べ、糖尿病発症に対する粗相対危険はFPGでは第5分位の97-98mg/dl、2hPGでは第7分位の124-131mg/dl、HbA1cでは第5分位の5.3-5.4%から有意に上昇した。年齢、性、糖尿病家族歴、空腹時インスリン値、body mass index（BMI）、HDLコレステロール、中性脂肪、高血圧、飲酒、喫煙、運動習慣を調整した多変量解析でも、これらの関係はほぼ変わりなかった。次に、receiver operating characteristic解析を用いて、糖尿病発症を予測するうえでFPG、2hPGとHbA1cの最適なカットオフ値を求めると、それぞれ101mg/dl、124mg/dl、5.5%であった。さらに、BMIの4分位別にカットオフ値をみると、FPGではおよそ101mg/dl、HbA1cではおよそ5.5%といずれの群においても変わりなかったが、2hPGではBMIレベルが低くなるとともにカットオフ値は低下した。以上より、日本人では、糖尿病発症に対するカットオフ値はFPGでは101mg/dl、HbA1cでは5.5%で、ADA基準とほぼ一致していたが、2hPGのカットオフ値はimpaired glucose toleranceの基準値である140mg/dlよりも低いレベルにあることが示唆される。

A. 研究目的

Impaired fasting glucose（IFG）のカットオフ値は、2003年に米国糖尿病協会（ADA）によって空腹時血糖値（FPG）110mg/dlから100mg/dlに引き下げられた。さらに、最近、ADAは糖尿病発症の高リスク者を同定するためにヘモグロビン（Hb）A1cを用いることを推奨し、そのカットオフ値を5.7%とした。これらは、主に欧米人における糖尿病発症に対するFPGとHbA1cのカットオフ値を検討した疫学調査の成績により定められた。一方、impaired glucose tolerance（IGT）を定義する負荷後2時間血糖値（2hPG）140mg/dlも、欧米人の研究の成績に基づく。しかし、日本人では糖尿病発症を予測するFPG、2hPGおよびHbA1cの最適なカットオフ値について十分な検討はなされていない。そこで本報告では、福岡県久山町における追跡調査の成績をもとに、糖尿病発症に対するFPG、2hPGおよびHbA1cのカットオフ値を検討した。

B. 研究方法

1988年の福岡県久山町の循環器健診で、75ｇ経

口糖負荷試験(OGTT)を受けた40-79歳の住民のうち、糖尿病者を除いた1,982名(男性807名、女性1,175名)を本研究の対象とした。この集団を14年間追跡し、追跡期間内に295例の糖尿病発症をみた。糖尿病の定義には2003年のADA基準を用い、FPG≧126mg/dlかつ/または2hPG≧200mg/dlかつ/または糖尿病薬治療ありとした。FPG、2hPGおよびHbA1cの各レベルの10分位で対象者を10群に分け、血糖およびHbA1c値が糖尿病発症に与える影響をCox比例ハザードモデルで求めた相対危険で検討した。さらに、receiver operating characteristic (ROC) 曲線を用いて、糖尿病発症を予測する血糖値およびHbA1cの最適なカットオフ値を求めた。

倫理面の配慮

本研究は2省合同の「疫学研究に関する倫理指針」に準拠し、九州大学医学研究院等倫理委員会の承認の元で行われた。本研究は、健診受診者を対象とした疫学調査で、対象者が研究によって不利益を被ることはない。研究者は、対象者の個人情報の漏洩を防ぐうえで細心の注意を払い、その管理に責任を負っている。

C. 研究結果

1. 空腹時血糖値、負荷後2時間血糖値およびヘモグロビンA1cレベルと糖尿病発症の関係

対象者をFPG、2hPGおよびHbA1cの10分位で10群に分けて、糖尿病発症に対する相対危険を求めた。その結果、FPGレベル別の検討では、第1分位を基準にすると糖尿病発症に対する粗の相対危険は第5分位の97-98mg/dlから有意に上昇した(図1)。同様に2hPGレベル別にみると、糖尿病発症の粗相対危険は第7分位の124-131mg/dlから有意に高くなった。HbA1cについては、第5分位の5.3-5.4%のレベルから糖尿病発症の粗相対危険は有意に上昇した。多変量解析で、年齢、性、糖尿病家族歴、空腹時インスリン値、body mass index (BMI)、HDLコレステロール、中性脂肪、高血圧、飲酒、喫煙、運動習慣を調整しても、これらの関係にほぼ変わりはなかった。

2. 糖尿病発症に対する血糖値およびヘモグロビンA1cのカットオフ値

次に、ROC解析を用いて、FPG、2hPGおよびHbA1cの糖尿病発症に対する最適なカットオフ値を求めると、FPGでは101mg/dlが、2hPGでは124mg/dlが、そしてHbA1cでは5.5%が最もよく糖尿病発症を予測した(図2)。

3. 肥満度が血糖値およびヘモグロビンA1cのカットオフ値に及ぼす影響

BMIレベルがFPG、2hPGおよびHbA1cのカットオフ値に及ぼす影響を検討するために、対象者をBMIの4分位(第1分位<20.8、第2分位20.8-22.7、第3分位22.8-24.8、第4分位≧24.9kg/m²)で4群に分け、各群でROC解析によるカットオフ値を算出した。その結果、BMIの4分位の各群においてFPGとHbA1cのカットオフ値は、ROC解析で求めた101mg/dl、5.5%とほとんど変わらなかった(表)。一方、2hPGのカットオフ値は第4分位の136mg/dlから第1分位の120mg/dlへ、BMIレベルが低くなるとともに低下した。

D. 考　察

わが国の地域住民を追跡した本研究の成績では、OGTTで定義された糖尿病発症のリスクは、FPGでは97mg/dlから、2hPGでは124mg/dlから、HbA1cでは5.3%から、他の危険因子を調整しても有意に上昇した。以上の成績は、ROC解析結果とほとんど一致していた。しかし、BMIのレベル別にみると、ROC解析におけるFPGとHbA1cのカットオフ値はBMIレベルの影響を受けなかったが、2hPGのカットオフ値はBMIレベルが低くなるとともに低下した。これらの結果より、わが国の地域住民において、糖尿病発症に対するカットオフ値はFPGでは101mg/dl、HbA1cでは5.5%でADA基準とほぼ一致していたが、2hPGのカットオフ値は、IGTの基準値である140mg/dlよりも低いことが示唆される。

①空腹時血糖値のカットオフ値について

IFGの診断基準値は、アジア人に比べBMIレベルの高い欧米人を対象とした成績をもとに、ADAによってFPG100mg/dlに引き下げられた。本研究

の成績では、糖尿病発症の相対危険はおよそ100mg/dlから有意に上昇し、ROC解析でのFPGのカットオフ値も同じ値であった。この結果は、糖尿病発症に対するFPGのカットオフ値を検討した他のアジア人の報告と一致した。これらの成績から、日本人を含むアジア人では、糖尿病発症に対するFPGのカットオフ値は、欧米人と同様100mg/dlと考えられる。さらに本研究の層別解析では、BMIレベルに関わらず、FPGのカットオフ値はほとんど変わらなかった。以上の結果より、糖尿病発症に対するFPGのカットオフ値は、人種や肥満の程度に関わらず100mg/dlで同一であることが示唆される。

②負荷後2時間血糖値のカットオフ値について

アジア人において糖尿病発症に対する2hPGのカットオフ値を検討した前向き研究は極めて少ない。本研究の結果では、糖尿病発症の相対危険は2hPGでは124mg/dlから有意に上昇し、ROC解析によるカットオフ値も同じ値であった。つまり、日本人における2hPGのカットオフ値は、現在のIGTの基準値である140mg/dlよりも低いレベルにあることが示唆される。さらに、本研究の集団では、2hPGのカットオフ値はBMIレベルが低くなるとともに低下した。この理由は明らかでないが、糖負荷に対するインスリン分泌能の違いが関与しているかもしれない。複数の疫学研究において、インスリン分泌の低下はFPGレベルに比べ2hPGレベルと強く関連していることが示されている。さらに、痩せている集団では、インスリン分泌の低下が糖尿病発症の主な役割を担っていることが報告されている。このように、糖尿病のハイリスク者のうち、痩せている集団では著明にインスリン分泌が障害されており、肥満した集団に比べ、2hPGのより低いレベルから糖尿病発症のリスクが増加することが推察される。よって、本研究では、BMIレベルの低下とともに、糖尿病発症に対する2hPGのカットオフ値が低下したと考えられる。さらに、アジア人のインスリン分泌能は、欧米人に比べ低いことが知られている。したがって、日本人を含み相対的に痩せているアジア人における糖尿病発症に対する2hPGのカットオフ値は、欧米人に比べ低い可能性がある。それゆえ、アジア人では糖尿病発症に対する2hPGのカットオフレベルはIGTの診断基準値140mg/dlよりも低いのかもしれない。

③ヘモグロビンA1cのカットオフ値について

アジア人における糖尿病発症に対するHbA1cのカットオフ値を検討した前向き研究はいまだ少ない。本研究の結果では、糖尿病発症の相対危険はHbA1c 5.3%から有意に上昇し、ROC解析によるカットオフ値は5.5%であった。同様に、日本人を対象とした複数の研究でも、糖尿病の発症リスクはHbA1c 5.5%のレベルから上昇することが報告されている。中国人の報告では、ROC解析におけるHbA1cの最適なカットオフ値は5.8%であった。これらの結果から、アジア人における糖尿病発症に対するHbA1cのカットオフ値は5.5-5.8%の範囲にあると考えられ、ADAが提唱したHbA1c 5.7%のカットオフ値はアジア人にも適用できると考えられる。

E. 結　論

わが国の地域一般住民において糖尿病発症に対するカットオフ値はFPGでは101mg/dl、HbA1cでは5.5%であり、ADA基準とほぼ一致していた。一方、2hPGのカットオフ値はIGTの診断基準値である140mg/dlよりも低いレベルにあることが示唆される。

F. 健康危険情報

FPGでは100mg/dlのレベルから、HbA1cでは5.5%のレベルから、糖尿病発症の危険度が増加する。一方、欧米人と比べ、日本人の様なやせた集団では、IGTの診断基準値である140mg/dlよりも低いレベルから、糖尿病発症のリスクが上昇している可能性がある。

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H. 知的所有権の取得状況

1. 特許取得　　なし
2. 実用新案登録　なし

I. 研究協力者

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向井直子（九州大学大学院医学研究院環境医学）

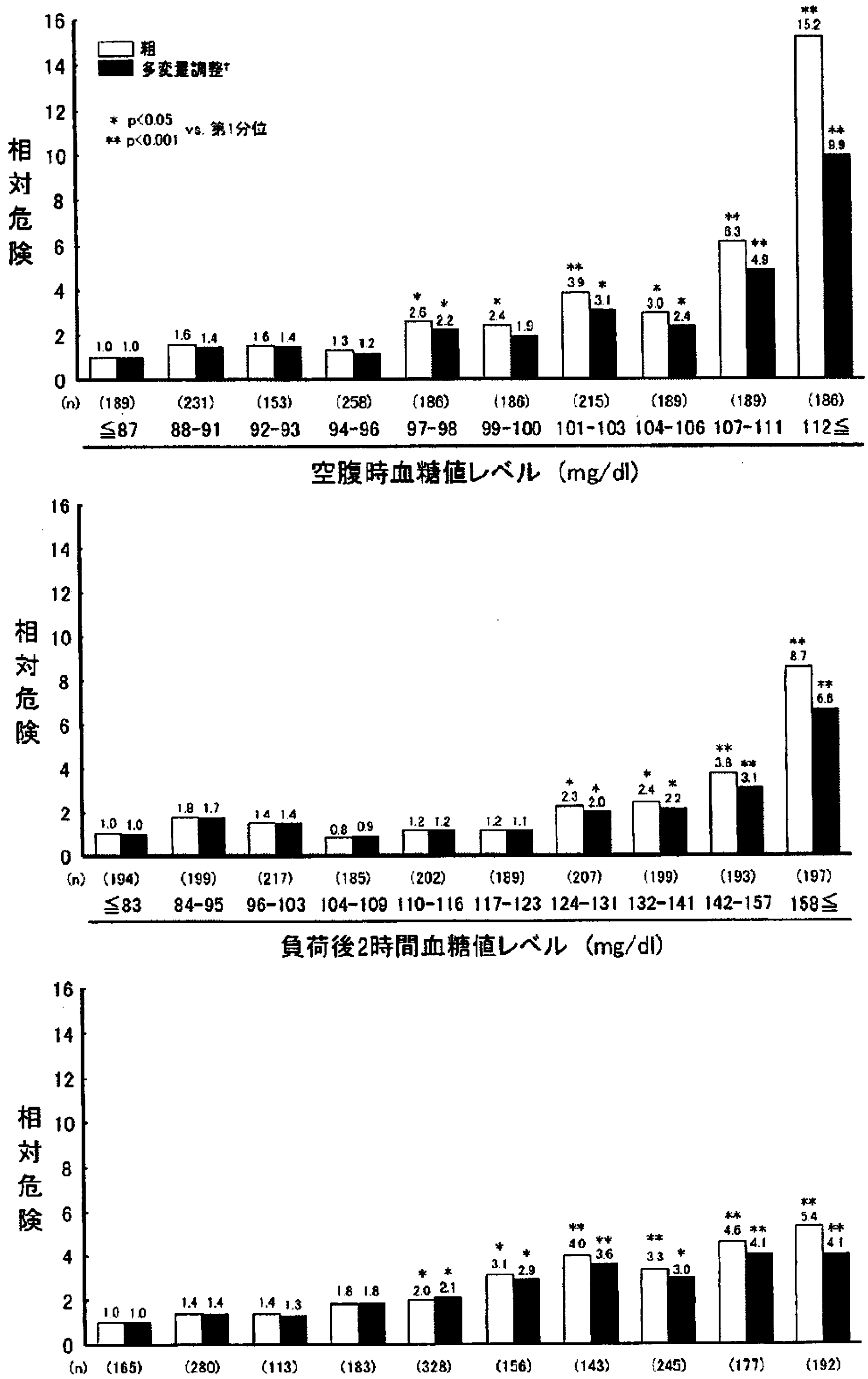

図1.血糖値およびヘモグロビンA1cレベルの10分位別にみた糖尿病発症の相対危険

久山町第3集団 1,982名, 40-79歳, 1988-2002年

†年齢, 性, 糖尿病家族歴, 空腹時インスリン値, BMI, HDLコレステロール, 中性脂肪, 高血圧, 喫煙, 飲酒, 運動で調整.

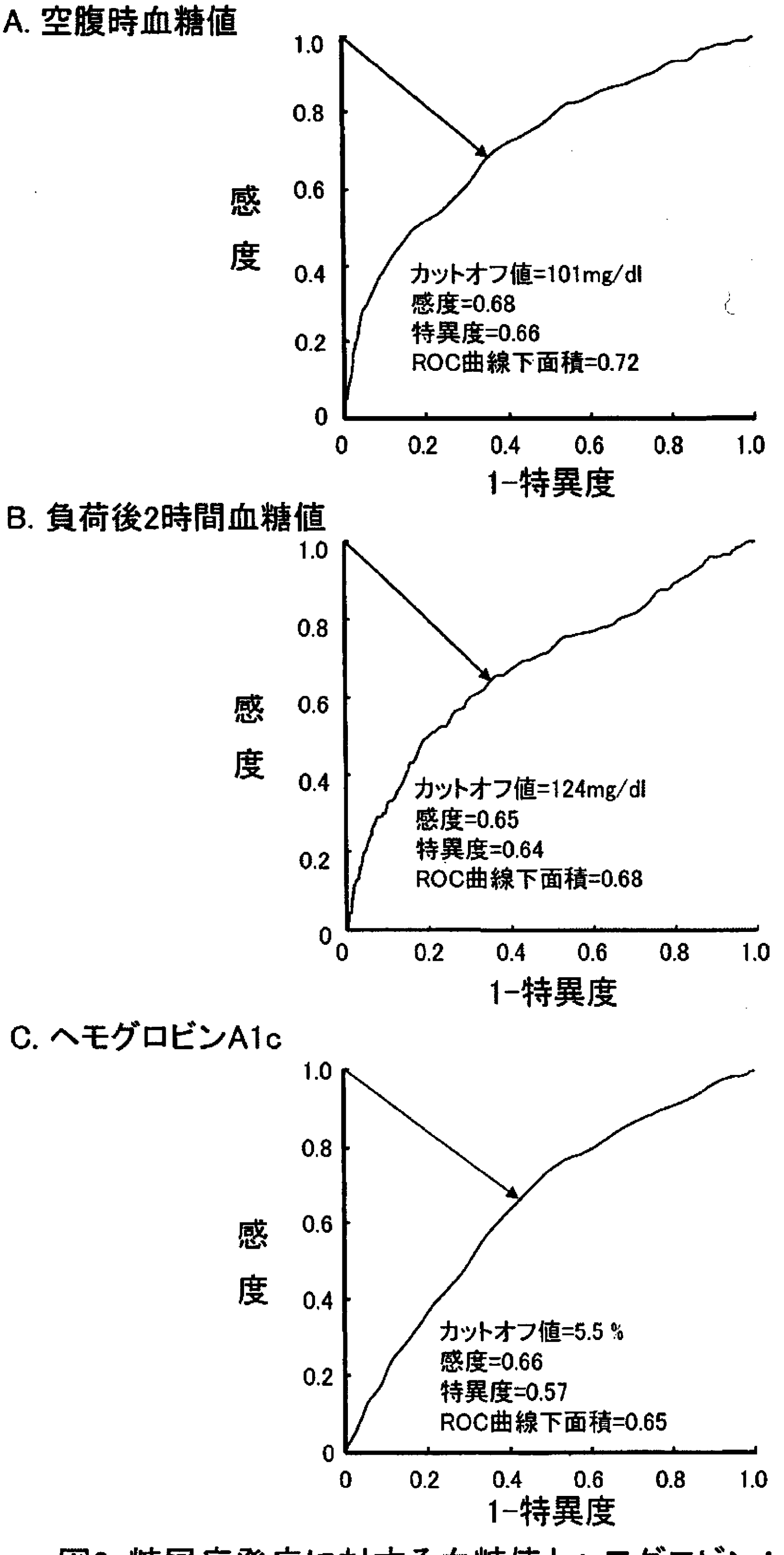

図2. 糖尿病発症に対する血糖値とヘモグロビンA1cのカットオフ値

久山町第3集団　1,982名, 40-79歳, 1988-2002年

表. BMIレベル別にみた糖尿病発症に対する血糖値とヘモグロビンA1cのカットオフ値
久山町住民 1,982名, 40-79歳, 1988-2002年

BMI レベル	対象者数	発症者数	カットオフ値		
			空腹時血糖値	負荷後 2 時間血糖値	ヘモグロビン A1c
(kg/m^2)	(n)	(n)	(mg/dl)	(mg/dl)	(%)
<20.8	495	44	101	120	5.5
20.8-22.7	496	58	101	123	5.6
22.8-24.8	496	70	103	131	5.5
≥24.9	495	123	101	136	5.5

BMI: body mass index
カットオフ値はROC曲線を用いて求めた.

別紙4

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
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原著論文

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Hata J et al.	The effect of metabolic syndrome defined by various criteria on the development of ischemic stroke subtypes in a general Japanese population.	Atherosclerosis	210	249-255	2010
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The effect of metabolic syndrome defined by various criteria on the development of ischemic stroke subtypes in a general Japanese population

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ABSTRACT

Objective: We evaluated the impact of metabolic syndrome (MetS) defined by various criteria on the occurrence of ischemic stroke subtypes in a general Japanese population.
Methods: A total of 2452 residents of a Japanese community, Hisayama, aged 40 years or older, were followed up for 14 years. To define MetS, we used the original Japanese criteria, the modified Japanese criteria, the International Diabetes Federation (IDF) criteria, the original National Cholesterol Education Program's Adult Treatment Panel III (NCEP) criteria, and the modified NCEP criteria. We substituted a waist circumference of ≥90 cm in men and ≥80 cm in women for the values of ≥85 cm and ≥90 cm, respectively, in the modified Japanese criteria and for >102 cm and >88 cm, respectively, in the modified NCEP criteria.
Results: Only MetS defined by the modified Japanese criteria showed a significant association with the development of lacunar infarction, and its hazard ratios (HRs) for the development of atherothrombotic and cardioembolic infarction were significant and greater than those of MetS defined by the other criteria: adjusted HRs for lacunar, atherothrombotic and cardioembolic infarction were 1.94 (95% confidence interval (CI), 1.13–3.32; $P = 0.02$), 2.55 (95% CI, 1.25–5.18; $P = 0.01$) and 3.94 (95% CI, 1.89–8.22, $P < 0.001$), respectively, after adjustment for confounding factors.
Conclusion: Our findings suggest that MetS defined by the Japanese criteria with the modification of a waist circumference of ≥90 cm in men and ≥80 cm in women is a better predictor of each ischemic stroke subtype in the Japanese population.

1. Introduction

Stroke is a major cause of mortality and disability in Japan and other developed countries [1]. Ischemic stroke is the most common type of stroke and can be further divided into three subtypes based on the size and location of the affected arteries and their pathogenesis: lacunar infarction (LI), atherothrombotic infarction (ATI), and cardioembolic infarction (CEI) [2]. The Japanese population is characterized by a higher frequency of LI among the ischemic stroke subtypes [3]. The impact of risk factors on the occurrence of ischemic stroke differs among the subtypes [4].

Metabolic syndrome (MetS) is a constellation of abdominal obesity, dyslipidemia, impaired glucose tolerance and elevated blood pressure [5–7], and individuals with this condition have an elevated risk of cardiovascular disease [8–10]. Several institutions have proposed various definitions of MetS. Among these, the MetS criteria of the National Cholesterol Education Program's Adult Treatment Panel III (NCEP) [5] and those of the International Diabetes Federation (IDF) [6] have been used most frequently in epidemiological studies. Recently, the Committee to Evaluate Diagnostic Standards for Metabolic Syndrome in Japan released a new definition of MetS for Japanese individuals (the Japanese criteria) [7]. Some epidemiological studies have reported that MetS is associated with high risk for the development of ischemic stroke [8–15]. However, to our knowledge, no epidemiological studies have prospectively evaluated the relationship between MetS and ischemic stroke subtype. Furthermore, it remains unclear which of these MetS criteria are better for predicting the risks of ischemic stroke and its subtypes.

The aim of this study was to evaluate the impact of MetS defined by the various criteria on the development of ischemic stroke and its subtypes in a prospective cohort study of a general Japanese population.

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2. Methods

2.1. Study population

The Hisayama Study is a population-based prospective cohort study of cerebro-cardiovascular diseases established in 1961 in the town of Hisayama, a suburb of the Fukuoka metropolitan area in Kyushu Island of Japan [16]. Based on data from the national census, the age and occupational distributions in Hisayama have been almost identical to those in Japan from 1961 to the present. In 1988, a screening examination for the present study was performed in the town. A detailed description of this examination was published previously [8,9]. Briefly, a total of 2736 residents aged 40 years or over (80.7% of the total population of this age range) participated in the examination. After the exclusion of 102 subjects who had a history of stroke or coronary heart disease, 121 subjects with no fasting blood samples and 61 subjects for whom waist circumference was not measured, the remaining 2452 subjects (1050 men and 1402 women) were enrolled in the present study.

This study was conducted with the approval of the Ethics Committee of the Faculty of Medicine, Kyushu University, and written informed consent was obtained from the study participants.

2.2. Risk factor measurements

At the baseline examination, each participant completed a self-administered questionnaire covering medical history, medical treatment for hypertension and diabetes, smoking habits, alcohol intake and leisure time activity. We asked whether subjects were receiving antihypertensive agents, oral hypoglycemic agents and/or insulin. We investigated the number of cigarettes smoked per day and the frequency of alcohol intake over the last year and the kinds and amounts of alcoholic beverages. Smoking habits were classified into currently habitual ($\geq$1 cigarette per day) or not. Alcohol intake was classified into customary drinking of alcoholic beverage at least once a month or not. Subjects engaging in sports or other form of exertion $\geq$3 times a week during their leisure time made up the regular exercise group.

Blood pressure was measured three times on one occasion using a standard mercury sphygmomanometer in the sitting position after rest for at least five minutes. The mean of the three measurements was used for the analysis. Hypertension was defined as blood pressure $\geq$140/90 mmHg and/or current use of antihypertensive agents. The waist circumference was measured at the umbilical level in the standing position by a trained staff member. Electrocardiogram abnormalities were defined as left ventricular hypertrophy (Minnesota code, 3-1) and/or ST depression (Minnesota code, 4-1, 2 or 3).

At the baseline examination, blood samples were collected once from an antecubital vein after an overnight fast of at least 12 h for the determination of lipid and glucose levels. Serum total cholesterol, high-density lipoprotein cholesterol and triglyceride concentrations were determined enzymatically. Fasting plasma glucose levels were measured by the glucose oxidase method. Diabetes was defined as fasting plasma glucose $\geq$7.0 mmol/L and/or current use of insulin or oral medication for diabetes. Fresh voided urine samples were collected at the examination, and proteinuria was defined as a value of 1+ or more using a reagent strip.

2.3. Definitions of metabolic syndrome

Table 1 shows the various MetS criteria used in the present study. We used the original Japanese [7], the IDF [6] and the original NCEP [5] criteria and created two additional criteria sets, the modified Japanese and the modified NCEP criteria, which substituted the waist circumference of the IDF criteria for Asians, $\geq$90 cm in men and $\geq$80 cm in women, for the original cutoff values in the definitions of abdominal obesity.

2.4. Follow-up survey

The subjects were followed up prospectively from December 1988 to November 2002 by repeated health examinations. Health status was checked yearly by mail or telephone for any subjects who did not undergo a regular examination or who had moved out of the town. We also established a daily monitoring system among the study team and local physicians or members of the Health and Welfare Office of the town. When a subject died, an autopsy was performed at the Departments of Pathology of Kyushu University. During the follow-up period, 479 subjects died, of whom 362 (75.6%) underwent autopsy. Only one subject was lost to follow-up.

2.5. Definition of ischemic stroke subtypes

The diagnosis of stroke was determined on the basis of clinical information including computed tomography (CT) and magnetic resonance imaging (MRI) of the brain, cerebral angiography, echocardiography, carotid ultrasonography and autopsy findings. In principle, ischemic stroke was defined as a sudden onset of nonconvulsive and focal neurological deficit due to brain ischemia persisting for over 24 h. Ischemic stroke was further divided into clinical subtypes: LI, ATI and CEI on the basis of the Classification of Cerebrovascular Disease III proposed by the National Institute of Neurological Disorders and Stroke of the United States [2].

A detailed method of classifying ischemic stroke has been published previously [4]. Briefly, LI was diagnosed as the presence of a relevant brainstem, basal ganglia, or subcortical hemispheric lesion with a diameter of <1.5 cm demonstrated on brain imaging or autopsy and no evidence of cerebral cortical or cerebellar impairment. ATI was diagnosed when the subjects had significant stenosis (>50%) or occlusion of a major cerebral artery with infarct size $\geq$1.5 cm on brain imaging or autopsy. The diagnosis of CEI was made on the basis of primary and secondary clinical features suggestive of CEI as reported by the Cerebral Embolism Task Force [17].

During the follow-up period, LI, ATI and CEI developed in 72, 40, and 33 subjects, respectively. Among them, all subjects underwent brain CT and/or MRI studies, and autopsies were performed on 70 subjects (71%) of 98 deceased cases until June 31, 2008. When sufficient clinical and morphologic information was obtained, a diagnosis of ischemic stroke subtype was defined as "definite". When the amount of either type of information was insufficient, the diagnostic level was defined as "probable". Diagnostic levels were defined as definite in 138 subjects and as probable in 7 subjects. In this study, we present the data regarding definite and probable stroke cases together, since these combined data were almost identical to that for definite cases only.

2.6. Statistical analysis

The SAS software version 9.2 was used to perform statistical analyses. Serum triglycerides were transformed into logarithms to improve skewed distributions. The prevalence of MetS in men and women were compared with the use of the χ^2 test. The hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using the Cox proportional hazards model. $P<0.05$ was considered statistically significant.

3. Results

Table 2 shows the baseline characteristics of the study population by sex. The mean age was 58 years for men and 59 years for

Table 1
Metabolic syndrome criteria used in the present study.

	A. Original Japanese	B. Modified Japanese	C. IDF for Asians	D. Original NCEP	E. Modified NCEP
Definition of metabolic syndrome	(1)+ any two or more of the following	(1)+ any two or more of the following	(1)+ any two or more of the following	Three or more of the following	Three or more of the following
Components					
Abdominal obesity (waist circumference)	(1) ≥85 cm (men), ≥90 cm (women)	(1) ≥90 cm (men), ≥80 cm (women)	(1) ≥90 cm (men), ≥80 cm (women)	(1) >102 cm (men), >88 cm (women)	(1) ≥90 cm (men), ≥80 cm (women)
High blood pressure	(2) ≥130/85 mmHg and/or antihypertensive medication	(2) Same as A	(2) Same as A	(2) Same as A	(2) Same as A
Hyperglycemia (fasting plasma glucose)	(3) ≥6.1 mmol/L and/or antidiabetic medication	(3) Same as A	(3) ≥5.6 mmol/L and/or antidiabetic medication	(3) ≥6.1 mmol/L and/or antidiabetic medication	(3) Same as D
Dyslipidemia	(4) Triglycerides ≥1.7 mmol/L and/or HDLC <1.03 mmol/L	(4) Same as A	(4) Triglycerides ≥1.7 mmol/L	(4) Same as C	(4) Same as C
			(5) HDLC <1.03 mmol/L (men), <1.29 mmol/L (women)	(5) Same as C	(5) Same as C

IDF, International Diabetes Federation; NCEP, National Cholesterol Education Program; HDLC, high-density lipoprotein cholesterol.

women, and mean waist circumference was 82.0 cm and 81.1 cm, respectively. The frequencies of hypertension, diabetes, proteinuria, electrocardiogram abnormalities, smoking habits and alcohol intake and mean values of triglycerides were higher in men than in women, while mean values of total and high-density lipoprotein cholesterols were higher in women.

The prevalence of MetS was 13.8% (21.4% in men and 8.1% in women) as defined by the original Japanese criteria, 14.9% (10.0% in men and 18.5% in women) by the modified Japanese criteria, 25.5% (13.4% in men and 34.5% in women) by the IDF criteria, 19.9% (16.8% in men and 22.3% in women) by the original NCEP criteria and 27.2% (21.6% in men and 31.3% in women) by the modified NCEP criteria. The prevalence of MetS by the original Japanese criteria was significantly higher in men than in women ($P < 0.001$), while the prevalence of MetS defined by the other four criteria was higher in women than in men ($P < 0.001$ for all).

Table 3 presents the age-adjusted HRs for the development of ischemic stroke according to the status of each component of the five MetS criterias by sex. In men, abdominal obesity defined by waist circumference of ≥90 cm was significantly associated with the development of ischemic stroke, while abdominal obesity defined by various waist circumferences was not a significant risk factor for ischemic stroke in women. High blood pressure defined by blood pressure ≥130/85 mmHg and/or use of antihypertensive agents was a significant predictor of ischemic stroke only in women. The definition of hyperglycemia in the Japanese and the NCEP criteria (≥6.1 mmol/L) was superior to that in the IDF criteria (≥5.6 mmol/L) for the prediction of the ischemic stroke in women. Hyperlipidemia of various definitions was not associated with the development of ischemic stroke in either sex.

Multivariate-adjusted HRs of the five MetS criteria for the development of ischemic stroke were estimated after adjustment for age, sex, serum cholesterol, proteinuria, electrocardiogram abnormalities, smoking habits, alcohol intake and regular exercise (Table 4). In men, MetS defined by the modified Japanese and the IDF criteria was an independent and significant risk factor for the occurrence of ischemic stroke, while MetS defined by all five criteria significantly increased the risk of ischemic stroke in women. In both sexes, HR was greater in the modified Japanese criteria than in the other criteria.

Finally, similar analyses were performed for each ischemic stroke subtype (Table 5). Only MetS defined by the modified Japanese criteria was significantly associated with the development of LI. MetS defined by the modified Japanese and the IDF criteria was a significant risk factor for ATI occurrence. MetS defined by the modified Japanese, the IDF or the modified NCEP criteria significantly increased the risk of CEI. For each ischemic stroke subtype, the HR was greater in the modified Japanese criteria than in the other criteria.

Table 2
Clinical characteristics of the study population by sex.

Variables	Men (n = 1050)	Women (n = 1402)
Age (years)	58 ± 11	59 ± 11
Waist circumference (cm)	82.0 ± 8.2	81.1 ± 10.1
Body mass index (kg/m^2)	22.8 ± 2.9	23.0 ± 3.2
Systolic blood pressure (mmHg)	134 ± 20	132 ± 21
Diastolic blood pressure (mmHg)	81 ± 11	76 ± 11
Hypertension (%)	44.2	37.0
Fasting plasma glucose (mmol/L)	5.9 ± 1.3	5.7 ± 1.3
Diabetes mellitus (%)	11.3	7.3
Total cholesterol (mmol/L)	5.11 ± 1.07	5.56 ± 1.07
High-density lipoprotein cholesterol (mmol/L)	1.26 ± 0.31	1.34 ± 0.29
Triglycerides (mmol/L)	1.32 (0.41–4.22)	1.06 (0.41–2.72)
Proteinuria (%)	7.9	4.1
Electrocardiogram abnormalities (%)	19.0	13.1
Smoking habits (%)	50.4	6.7
Alcohol intake (%)	61.5	8.9
Regular exercise (%)	11.5	9.2

Values are means ± SD or percentage. Geometric means and 95% prediction intervals of triglycerides are shown due to the skewed distribution.

Table 3
Age-adjusted hazard ratios for the development of ischemic stroke according to status of each component of various metabolic syndrome criteria by sex.

Components	Status	Men			Women		
		Number of events/population at risk	Hazard ratio (95% confidence interval)	P	Number of events/population at risk	Hazard ratio (95% confidence interval)	P
Abdominal obesity (waist circumference)							
≥85 cm (men), ≥90 cm (women)[a]	No	35/621	1.00		60/1113	1.00	
	Yes	31/429	1.53 (0.94–2.50)	0.09	19/289	1.13 (0.68–1.90)	0.63
≥90 cm (men), ≥80 cm (women)[b,c,d]	No	48/873	1.00		30/601	1.00	
	Yes	18/177	2.39 (1.38–4.14)	0.002	49/801	1.16 (0.73–1.82)	0.53
>102 cm (men), >88 cm (women)[e]	No	66/1042	1.00		57/1069	1.00	
	Yes	0/8	0.00	0.99	22/333	1.16 (0.71–1.90)	0.55
High blood pressure							
≥130/85 mmHg and/or use of antihypertensive agents [a,b,c,d,e]	No	21/420	1.00		16/678	1.00	
	Yes	45/630	1.25 (0.74–2.12)	0.40	63/724	2.36 (1.33–4.17)	0.003
Hyperglycemia (fasting plasma glucose)							
≥6.1 mmol/L and/or use of antidiabetic medication[a,b,d,e]	No	43/764	1.00		52/1151	1.00	
	Yes	23/286	1.34 (0.81–2.23)	0.26	27/251	2.05 (1.28–3.26)	0.003
≥5.6 mmol/L and/or use of antidiabetic medication[c]	No	28/448	1.00		31/766	1.00	
	Yes	38/602	0.95 (0.59–1.56)	0.85	48/636	1.60 (1.02–2.52)	0.04
Hyperlipidemia							
Triglycerides ≥1.7 mmol/L and/or HDLC <1.03 mmol/L[a,b]	No	45/625	1.00		52/1072	1.00	
	Yes	21/425	0.80 (0.48–1.35)	0.40	27/330	1.41 (0.88–2.24)	0.15
Triglycerides ≥1.7 mmol/L[c,d,e]	No	51/742	1.00		58/1172	1.00	
	Yes	15/308	0.87 (0.49–1.56)	0.65	21/230	1.56 (0.94–2.57)	0.08
HDLC <1.03 mmol/L men), <1.29 mmol/L women)[c,d,e]	No	55/812	1.00		37/746	1.00	
	Yes	11/238	0.70 (0.37–1.33)	0.28	42/656	1.19 (0.76–1.85)	0.44

HDLC, High-density lipoprotein cholesterol.
[a] Original Japanese criteria.
[b] Modified Japanese criteria.
[c] International Diabetes Federation criteria for Asians.
[d] Modified NCEP criteria.
[e] Original National Cholesterol Education Program (NCEP) criteria.

Table 4
Multivariate-adjusted hazard ratios for the development of ischemic stroke according to MetS statuses by various definitions by sex.

Criteria	Men			Women		
	Number of events/population at risk	Hazard ratio (95% confidence interval)	P	Number of events/population at risk	Hazard ratio (95% confidence interval)	P
Original Japanese						
MetS(−)	48/825	1.00		65/1289	1.00	
MetS(+)	18/225	1.32 (0.76–2.30)	0.33	14/113	2.09 (1.17–3.75)	0.01
Modified Japanese						
MetS(−)	51/945	1.00		48/1142	1.00	
MetS(+)	15/105	3.07 (1.68–5.61)	<0.001	31/260	2.21 (1.39–3.51)	<0.001
IDF						
MetS(−)	50/909	1.00		38/918	1.00	
MetS(+)	16/141	2.66 (1.47–4.81)	0.001	41/484	1.74 (1.11–2.73)	0.02
Original NCEP						
MetS(−)	54/874	1.00		49/1090	1.00	
MetS(+)	12/176	1.10 (0.58–2.07)	0.77	30/312	1.73 (1.09–2.76)	0.02
Modified NCEP						
MetS(−)	46/823	1.00		39/963	1.00	
MetS(+)	20/227	1.59 (0.93–2.74)	0.09	40/439	1.73 (1.10–2.71)	0.02

Adjusted for age, total cholesterol, proteinuria, electrocardiogram abnormalities, smoking habits, alcohol intake and regular exercise. MetS, Metabolic syndrome; IDF, International Diabetes Federation; NCEP, National Cholesterol Education Program.

4. Discussion

In a long-term prospective study of a general Japanese population, we demonstrated that MetS was an independent and significant risk factor for all of ischemic stroke subtypes when the modified Japanese criteria, in which a waist circumference of ≥90 cm in men and ≥80 cm in women was substituted for the original cutoff values, was used.

Several prospective studies [10–15] including ours [8], have investigated significant associations between MetS defined by the NCEP criteria or their modification and the risk of ischemic stroke. In these studies, however, ischemic stroke was not classified into clinical subtypes. Only a few studies have reported the relationship between MetS and ischemic stroke subtypes. In a hospital-based case–control study of elderly Greek subjects, the prevalence of MetS was higher in the non-embolic stroke group including LI and ATI than in the control group [18]. A case–control study for Japanese ischemic stroke patients [19] demonstrated that MetS was significantly related to ATI but not to LI and CEI. Another clinical study in Japan [20] revealed that the prevalence of MetS defined by the original Japanese criteria was highest among patients with CEI followed by those with LI. To our knowledge, the present study is the first population-based prospective cohort study to investigate the association between MetS and the development of each ischemic stroke subtype.

Among the several MetS criteria, the cutoff values of waist circumference to define abdominal obesity are largely different. Because the cutoff values of waist circumference in the original NCEP criteria (>102 cm in men and >88 cm in women) were created for American subjects [5], these values seem to be unsuitable for the Japanese population. The original Japanese criteria used the cutoff values of ≥85 cm in men and ≥90 cm in women based on correlations with visceral fat mass [7]. However, the IDF has claimed that using these values produces "odd results" in relation to cardiovascular risk and recommends the use of cutoff values of ≥90 cm in men and ≥80 cm in women for Asian populations including Japanese [6]. In our previous study, we compared the ability to predict cardiovascular disease at each published cutoff level of waist circumference among the MetS criteria and demonstrated that the optimal cutoff point of waist circumference was 90 cm in men and 80 cm in women [9]. In the present study, we observed a similar result for the risk of ischemic stroke in men (Table 3). Therefore, we created the modified Japanese and the modified NCEP criteria, which substitute waist circumference cutoff values of ≥90 cm in men and ≥80 cm in women for the original values. Among these five criteria, we found that the modified Japanese criteria were the best at predicting the risk of ischemic stroke and its subtypes. These findings are concordant with those of our previous study [9], in which MetS defined by the modified Japanese criteria was a better predictor for the development of cardiovascular disease.

In this study, the risks of ischemic stroke and all subtypes were higher for the modified Japanese MetS criteria than for the IDF or the modified NCEP criteria despite the identical cutoff values of waist circumference. One reason for this is the difference in the definition of hyperglycemia: the definition of hyperglycemia in the modified Japanese criteria (≥6.1 mmol/L) was superior to that in the IDF criteria (≥5.6 mmol/L) for the prediction of ischemic stroke in our subjects (Table 3). Another reason seems to be that abdominal obesity is an essential component for the modified Japanese criteria, but not for the NCEP criteria. These findings support the opinion that abdominal obesity should be an essential component for the diagnosis of MetS though there has been controversy over the necessity of abdominal obesity.

Our study demonstrated that MetS defined by the modified Japanese criteria appears to be a significant risk factor for the development of LI. Very few studies have examined the relationship between MetS and LI. A cross-sectional study recently demonstrated a significant association between MetS and silent LI [21]. LI develops due mainly to arteriolosclerosis such as lipohyalinosis, fibrinoid necrosis or microatheroma in penetrating arteries of the brain [22]. Some disorders in secretion of adipocytokines have been observed in the MetS status. For example, it was reported that plasma concentrations of adiponectin decreased in subjects with abdominal obesity [23], and lower adiponection levels were associated with impaired endothelial function [24]. It has also been demonstrated that the plasma concentration of plasminogen activator inhibitor-1 (PAI-1) increased in subjects with abdominal obesity [25], and overexpression of PAI-1 was associated with subendocardial myocardial infarction as a result of perivascular fibrosis and thrombosis in penetrating coronary arteries in PAI-1 transgenic mice [26]. It is reasonably considered that similar arteriosclerotic lesions may also occur in penetrating brain arteries. Therefore, adipocytokine disorders may be related to endothelial

Table 5
Multivariate-adjusted hazard ratios for the development of ischemic stroke subtypes according to MetS status by various definitions.

Criteria	Lacunar infarction			Atherothrombotic infarction			Cardioembolic infarction		
	Number of events/population at risk	Hazard ratio (95% confidence interval)	P	Number of events/population at risk	Hazard ratio (95% confidence interval)	P	Number of events/population at risk	Hazard ratio (95% confidence interval)	P
Original Japanese									
MetS(−)	57/2114	1.00		31/2114	1.00		25/2114	1.00	
MetS(+)	15/338	1.50 (0.82–2.72)	0.19	9/338	1.61 (0.76–3.43)	0.22	8/338	1.96 (0.87–4.45)	0.11
Modified Japanese									
MetS(−)	51/2,087	1.00		28/2087	1.00		20/2087	1.00	
MetS(+)	21/365	1.94 (1.13–3.32)	0.02	12/365	2.55 (1.25–5.18)	0.01	13/365	3.94 (1.89–8.22)	<0.001
IDF									
MetS(−)	44/1,827	1.00		25/1827	1.00		19/1827	1.00	
MetS(+)	28/625	1.65 (0.98–2.78)	0.06	15/625	2.15 (1.06–4.34)	0.03	14/625	2.69 (1.27–5.68)	0.01
Original NCEP									
MetS(−)	50/1964	1.00		29/1964	1.00		24/1964	1.00	
MetS(+)	22/488	1.48 (0.88–2.47)	0.14	11/488	1.37 (0.67–2.79)	0.38	9/488	1.47 (0.67–3.21)	0.34
Modified NCEP									
MetS(−)	44/1,786	1.00		23/1786	1.00		18/1786	1.00	
MetS(+)	28/666	1.35 (0.83–2.22)	0.23	17/666	1.90 (0.99–3.63)	0.05	15/666	2.20 (1.08–4.45)	0.03

Adjusted for age, total cholesterol, proteinuria, electrocardiogram abnormalities, smoking habits, alcohol intake and regular exercise. MetS, Metabolic syndrome; IDF, International Diabetes Federation; NCEP, National Cholesterol Education Program.

dysfunction and induce arteriolosclerotic lesions in the brain leading to the development of LI.

In our subjects, MetS defined by the modified Japanese or IDF criteria was also clearly associated with the occurrence of ATI. ATI is caused by atherosclerosis in extracranial or intracranial arteries. There have been several other studies demonstrating associations between MetS and atherosclerotic lesions in extracranial or intracranial arteries [27,28].

In this study, MetS defined by the modified Japanese, IDF or modified NCEP criteria was associated with the development of CEI. CEI occurs due to thromboembolism from the heart to the arteries of the brain as a result of cardiac diseases such as atrial fibrillation, valvular heart diseases and myocardial infarction [17]. It was recently shown in a cohort study that MetS was a significant risk factor for the development of atrial fibrillation [29], which is the most common embolic source of CEI. In our study, the prevalence of atrial fibrillation at baseline was significantly higher in the subjects with CEI than in those without CEI (21.2% vs. 0.9%, $P<0.001$). Consequently, it is considered that atrial fibrillation occurs on the pathway between MetS and CEI.

The strengths of our study include accurate measurement of MetS components including waist circumference at baseline, longitudinal population-based study design, long duration of follow-up, perfect follow-up of subjects and accuracy for diagnosis of stroke including ischemic stroke subtypes. One limitation of our study is that the diagnosis of MetS and other risk factors was based on a single measurement at baseline, as has been the case in other epidemiological studies. During the follow-up, risk factor levels could be changed due to modifications in lifestyle or medication; hence, misclassification of MetS is possible. This would weaken the association found in this study, biasing the results toward the null hypothesis. Therefore, the true association may be stronger than that shown in our study.

In conclusion, we have shown that MetS defined by the modified Japanese criteria is an independent and significant risk factor for the development of all ischemic stroke subtypes. In these criteria, the impact of MetS on the occurrence of CEI was largest, followed by those of ATI and LI. Because the prevalence of metabolic disorders has shown a steep increase during the past several decades in the overall Japanese population [3], our findings indicate that correction of MetS is important for prevention of all ischemic stroke subtypes in Japan.

Conflict of interest

No authors have any conflict of interest.

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Trends in the prevalence of chronic kidney disease and its risk factors in a general Japanese population: The Hisayama Study

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Abstract

Background. Chronic kidney disease (CKD) is increasingly recognized as a leading public health issue. However, there are limited data assessing secular trends in the prevalence of CKD in general Asian communities.

Methods. We performed three repeated cross-sectional surveys of residents aged ≥40 years in 1974 [2118 subjects (participation rate, 81.2%)], 1988 [2741 subjects (80.9%)] and 2002 [3297 subjects (77.6%)] in a Japanese community. We compared the prevalence of CKD [one or both of proteinuria and estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2] and potential risk factors among the three surveys.

Results. The prevalence of CKD increased significantly with time in men (13.8% [95% confidence interval (95% CI), 11.4–16.2%] in 1974, 15.9% [95% CI, 13.6–18.2%] in 1988 and 22.1% [95% CI, 19.6–24.6%] in 2002; P for trend < 0.001), but not in women (14.3% [95% CI, 12.2–16.4%], 12.6% [95% CI, 10.9–14.3%] and 15.3% [95% CI, 13.4–17.2%]; P for trend = 0.97). The frequencies of individuals with CKD Stages 3–5 (eGFR < 60 mL/min/1.73 m^2) increased over the three decades in both sexes. Despite the widespread use of antihypertensive agents, the proportions of individuals with CKD who reached blood pressure of <130/80 mmHg were only 27.0% in men and 47.5% in women. The frequency of metabolic disorders including diabetes, hypercholesterolaemia and obesity increased over the three decades in both sexes.

Conclusions. The prevalence of CKD increased significantly in men, but not in women over the last three decades in a general Japanese population. Our findings support the requirement for a comprehensive treatment for hypertension and metabolic disorders to reduce the burden of CKD.

Keywords: chronic kidney disease; general population; hypertension; metabolic disorder; prevalence

Introduction

Chronic kidney disease (CKD), most commonly defined by a reduction in kidney function or the presence of proteinuria [1,2], is increasingly recognized as a leading public health issue. The number of patients with end-stage kidney disease has been expanding rapidly and is predicted to exceed 2 million worldwide by the year 2010 [3]. Furthermore, it has been established that CKD is a risk factor not only for progressive kidney failure, but also for cardiovascular morbidity and mortality [4–6].

Several cross-sectional studies have demonstrated that CKD affects 10–15% of the adult population in developed Western countries [7–9]. Recent epidemiological studies have suggested that CKD may be more prevalent in Asian countries than in developed Western countries [10,11]. Furthermore, it has been reported that the number of patients undergoing dialysis in Asian countries such as Malaysia and Japan has been increasing [12,13]. It is likely that the prevalence of CKD would increase over time as a consequence of the accumulation of risk factors such as hypertension, glucose intolerance, obesity and hypercholesterolaemia, probably owing to the westernization of the lifestyle in these Asian countries. However, there are limited data assessing secular trends in the prevalence of CKD in general Asian communities to date. A better understanding of the past and current prevalence of CKD and its potential risk factors may provide useful information for the development of management strategies for CKD.

The Hisayama Study is a community-based cohort study that has been underway since 1961, with a goal of estimating the effects of the remarkable lifestyle changes on the burden of cardiovascular diseases in Japan [14–17]. The aim of the present study is to assess trends in the prevalence of CKD and its risk factors over the last three decades and to examine their relationships.

Subjects and methods

Study population

The town of Hisayama is a suburban community adjacent to Fukuoka City, a metropolitan area on Kyushu Island in southern Japan. The population of the town has been stable for 50 years and was approximately 8000 in 2008. The age and occupational distributions of the Hisayama population are almost identical to those of Japan as a whole. Full community surveys of the residents have been repeated from the initiation of the study to date. The study design and characteristics of the subject population have been described in detail elsewhere [14–18]. Briefly, four study cohorts composed of Hisayama residents aged ≥40 years were established in 1961, 1974, 1988 and 2002. For this study, we used data from the cross-sectional surveys conducted at baseline in the latter three cohorts, which included available data on serum creatinine and proteinuria. The full community surveys were conducted as follows. In 1974, we invited all 2629 residents in that age group in the town registry to participate in the survey by the assistance of the town office, and of those, 2135 (participation rate, 81.2%) consented to participate in the health examination. After excluding 17 subjects for whom blood samples were unavailable, 2118 subjects (911 men, 1207 women) were enrolled in this study. In the same manner, 2741 subjects from 2742 participants (participation rate, 80.9%) in 1988 and 3297 subjects from 3298 participants (participation rate, 77.6%) in 2002 were enrolled in the study. A total of 3059 (38%) subjects participated in two or more of the three surveys.

Definition of CKD

Details of the measurement of risk factors in each survey were described previously [15,16,18,19]. Freshly voided urine samples were tested by the dipstick method in all surveys. Proteinuria was defined as 1+ or more. Serum creatinine was measured by the non-compensated Jaffé method in 1974 and 1988 and the enzymatic method in 2002. Serum samples were assayed using a Technicon autoanalyser (Technicon Instruments, Tarrytown, NY) in 1974, a TBA-80S autoanalyser (Toshiba Inc., Tokyo, Japan) in 1988 and an AU-800 autoanalyser (Olympus Corporation, Tokyo, Japan) in 2002. The difference between the serum creatinine levels by the Jaffé method and those by the enzymatic method was calibrated by using 98 serum samples standardized by CRC Corporation (Fukuoka, Japan). The range of creatinine levels in the samples was 0.5 to 15.2 mg/dl by the Jaffé method. The conversion equation was estimated by using a simple linear regression model. The correlation coefficient of this equation was 0.996. The Jaffé method value was converted to an enzymatic method value by using the following equation:

$$\text{Serum creatinine (enzymatic method [mg/dl])} = 0.9754 \times \text{serum creatinine(Jaff amethod[mg/dl])} - 0.2802.$$

The estimated glomerular filtration rate (eGFR) was calculated using the isotope dilution mass spectrometry–traceable creatinine-based four-variable Modification of Diet in Renal Disease (MDRD) Study equation with the Japanese Society of Nephrology Chronic Kidney Disease Initiatives coefficient of 0.741 [20]. eGFR was derived using the following equation:

$$\begin{aligned} \text{eGFR}(\text{mL/min/1.73 m}^2) &= 0.741 \times 175 \\ &\times \text{serum creatinine(enzymatic method[mg/dl])}^{-1.154} \\ &\times \text{age(years)}^{-0.203} \\ &\times 0.742(\text{if female}) \end{aligned}$$

CKD was defined as either the presence of proteinuria or eGFR < 60 mL/min/1.73 m². The clinical stages of CKD were classified according to the recommendations of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines [1]: Stage 1 or 2 (eGFR ≥ 60 mL/min/1.73 m² and the presence of proteinuria), Stage 3 (eGFR 30–59 mL/min/1.73 m²) and Stage 4 or 5 (eGFR < 30 mL/min/1.73 m²).

Risk factors

In each survey, blood pressures were measured three times in a sitting position after at least 5 min of rest, and the mean of the three measurements was used for the analysis. Hypertension was defined as a mean systolic blood pressure ≥140 mmHg or a mean diastolic blood pressure ≥90 mmHg or a current use of antihypertensive agents. Subjects with hypertension were classified as treated or untreated based on whether or not they were currently using antihypertensive agents. Diabetes was defined by fasting glucose concentrations ≥126 mg/dl (7.0 mmol/L) or postprandial glucose concentrations ≥200 mg/dl (11.1 mmol/L) in addition to medical history of diabetes in 1974 and by those methods and a 75-g oral glucose tolerance test in 1988 and 2002. Diabetes was regarded as treated when the subject was under therapy with insulin or hypoglycaemic agents in 1988 and 2002, but the designation of treated or untreated diabetes was not made in 1974 due to an absence of information on treatment status. Serum total cholesterol levels were determined by the Zurkowski method in 1974 and by the enzymatic method in 1988 and 2002. Hypercholesterolaemia was defined as serum total cholesterol ≥220 mg/dl (5.7 mmol/L) or current use of a lipid-modifying agent. Treated hypercholesterolaemia was defined as current use of lipid-modifying agents only in 2002 because information on anti-lipidaemic agents was not available in 1974 and 1988. Body height and weight were measured in light clothing without shoes, and the body mass index (in kilogrammes per square metre) was calculated. Obesity was defined as a body mass index ≥25 kg/m². Metabolic syndrome was defined by using criteria recommended in a joint interim statement of five major scientific organizations [21]. Information on medical history, medical treatment, alcohol intake and smoking habits was obtained through a standard questionnaire by trained interviewers. Alcohol intake and smoking habits were classified as either current habitual use or not.

Statistical analysis

The prevalences of CKD and each risk factor were adjusted for the age distribution of the world standard population in 1998 by using the direct method. The age-adjusted mean values of risk factors were calculated using the analysis of covariance method with age included as a continuous variable. Trends in the prevalence or mean values of each factor across survey years were assessed by fitting the logistic or linear regression model with evenly spaced numeric codes for the survey year, respectively. The age-adjusted relative risk (RR) and its 95% confidence interval (95% CI) for CKD were estimated by using Poisson regression analysis [22]. The SAS software package, release 9.2 (SAS Institute, Cary, NC), was used to perform all statistical analyses. A two-tailed value of P < 0.05 was considered statistically significant.

Results

We compared the age-adjusted prevalence and mean values of risk factors among the three surveys by sex, as shown in Table 1. The prevalence of hypertension was constant in men, but decreased in women from 1974 to 2002. The prevalence of treated hypertension increased over time, whereas the prevalence of untreated hypertension decreased in both sexes. Consequently, mean blood pressure levels decreased over the last three decades. The frequencies of diabetes, hypercholesterolaemia, obesity, metabolic syndrome and alcohol intake increased with time, whereas the frequency of smoking habits decreased in both sexes. The prevalence of diabetes, especially untreated diabetes, increased with time in both sexes.

Figure 1 presents the age-adjusted prevalence of CKD in the three surveys by sex. The age-adjusted prevalence of CKD increased significantly with time in men (13.8% in 1974, 15.9% in 1988 and 22.1% in 2002; P for trend < 0.001), but not in women (14.3%, 12.6% and 15.3%, respectively; P for trend = 0.9). The prevalence of CKD Stages 3–5 increased 3-fold over time in men (4.8%, 9.4% and 15.7%; P for trend < 0.001) and doubled in women (5.8%, 9.9% and 11.7%; P for trend < 0.001). Conversely, the prevalence of CKD Stages 1–2 decreased to two-thirds in men (9.0%, 6.5% and 6.4%; P for trend = 0.02) and by half in women (8.5%, 2.7% and 3.4%; P for trend < 0.001). Similar trends in the prevalence of CKD across the three surveys were also observed in middle-aged and elderly populations in either sex (Figure 2). There was a comparable relationship for the prevalence of