Impact of Glucose Tolerance Status on Development of Ischemic Stroke and Coronary Heart Disease in a General Japanese Population

The Hisayama Study

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Background and Purpose—Few studies have shown the association between glucose tolerance status defined by a 75-g oral glucose tolerance test and the development of different types of cardiovascular disease.

Methods—A total of 2421 community-dwelling Japanese subjects aged 40 to 79 years who underwent the oral glucose tolerance test were followed up for 14 years.

Results—In multivariable analysis, the risks of ischemic stroke in both sexes and coronary heart disease (CHD) in women were significantly higher in subjects with diabetes determined by the World Health Organization criteria than in those with normal glucose tolerance even after adjustment for other confounding factors, but such association was not seen for CHD in men (ischemic stroke: adjusted hazard ratio [HR]=2.54, P=0.002 in men; adjusted HR=2.02, P=0.03 in women; CHD: adjusted HR=1.26, P=0.47 in men; adjusted HR=3.46, P=0.002 in women). Similar associations were observed for fasting plasma glucose levels of ≥7.0 mmol/L (ischemic stroke: adjusted HR=2.15, P=0.03 in men; adjusted HR=2.10, P=0.045 in women; CHD: adjusted HR=1.29, P=0.47 in men; adjusted HR=3.83, P=0.003 in women) and for 2-hour postload glucose levels of ≥11.1 mmol/L (ischemic stroke: adjusted HR=2.71, P=0.003 in men; adjusted HR=2.19, P=0.03 in women; CHD: adjusted HR=1.58, P=0.16 in men; adjusted HR=4.44, P<0.001 in women). The age-adjusted incidences of ischemic stroke and CHD did not significantly increase in subjects with impaired fasting glycemia or impaired glucose tolerance in either sex.

Conclusions—Our findings suggest that diabetes is an independent risk factor for ischemic stroke in both sexes and CHD in women in the Japanese population. ***(Stroke.* 2010;41:00-00.)**

Key Words: coronary heart disease ■ diabetes ■ ischemic stroke ■ oral glucose tolerance test ■ prospective study

Cardiovascular disease continues to be a major global public health concern. Investigations into glucose tolerance levels and cardiovascular disease have become increasingly important, because the impact of diabetes on cardiovascular disease is considered to be rising due to the rapid increase in the worldwide prevalence of diabetes mellitus in recent years. A number of epidemiological studies have demonstrated that Type 2 diabetic subjects have approximately 2.0 to 4.0 times higher risk of cardiovascular disease compared with nondiabetic subjects.[1–13] However, most of these studies had important limitations. In many cohort studies used to investigate this issue, the outcomes were evaluated using mortality data.[3–9,11,12] Because nonfatal events were not included in these studies, the results may not have represented the true association between glucose tolerance levels and cardiovascular disease. Thus, prospective studies using incidence data would provide further information for predicting cardiovascular disease. In addition, the methods used to define diabetes have varied among the epidemiological studies, ranging from administration of questionnaires to measurement of casual blood glucose levels or fasting plasma glucose (FPG) alone.[1,2,11,12] Furthermore, many investigators have evaluated cardiovascular generally, rather than by type, and did not separately evaluate sex, although it is well known that the effects of each risk factor are different for each type of cardiovascular disease and sex. Thus, there have been few cohort studies investigating the associations between glucose tolerance levels, defined by a 75-g glucose tolerance test (OGTT), and the risks of developing stroke and coronary heart disease (CHD) in each sex in Asian populations.

The purpose of the present study was to address the association between glucose tolerance levels and the devel-

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opment of ischemic stroke and CHD in a prospective study of a defined community-dwelling Japanese population, all members of which underwent the OGTT.

Materials and Methods

Study Population

In 1988, a screening survey for the present study was performed in the town of Hisayama, a suburb of the Fukuoka metropolitan area in southern Japan.[14] Of a total 3227 residents aged 40 to 79 years on the town registry, 2587 (participation rate, 80.2%) consented to participate in the examination and underwent a comprehensive assessment. After excluding 82 subjects who had already had breakfast, 10 who were on insulin therapy and 15 due to nausea or general fatigue during the ingestion of glucose, a total of 2480 subjects completed the OGTT. From a total of 2490 subjects including 10 on insulin therapy, 68 who had a history of stroke or CHD based on questionnaires and medical records, and one who died before follow-up was started, were excluded. The remaining 2421 (1037 men and 1384 women) were enrolled in this study.

Follow-Up Survey

The subjects were followed up prospectively for 14 years, from December 1988 to November 2002, by repeated health examinations. The health status was checked yearly by mail or telephone for subjects who did not undergo a regular examination or who had moved from town. We also established a daily monitoring system among the study team, local physicians, and members of the town's health and welfare office. Using this system, we gathered information on new events of cardiovascular disease, including suspected cases. When stroke or CHD occurred or was suspected, physicians in the study team examined the subject and evaluated his or her detailed clinical information. The clinical diagnosis of stroke or CHD was based on the patient's history, physical and neurological examinations, and ancillary laboratory examinations. Additionally, when a subject died, an autopsy was performed at the Departments of Pathology of Kyushu University. During the follow-up period, one subject was lost to follow-up and 418 subjects died, of whom 312 (74.6%) underwent autopsy.

Definition of Cardiovascular Events

In principle, stroke was defined as a sudden onset of nonconvulsive and focal neurological deficit persisting for ≥24 hours. The diagnosis and classification of stroke were determined on the basis of clinical information, including brain CT and MRI, cerebral angiography, echocardiography, carotid duplex imaging, or autopsy findings. Ischemic stroke was classified as either lacunar or nonlacunar infarction based on the Classification of Cerebrovascular Disease III criteria proposed by the National Institute of Neurological Disorders and Stroke.[15] In brief, lacunar infarction was diagnosed as the presence of a relevant brain stem, basal ganglia, or subcortical hemispheric lesion with a diameter <1.5 cm demonstrated on brain imaging and no evidence of cerebral cortical or cerebellar impairment. Patients who had typical clinical findings of lacunar infarction and a negative imaging were also categorized as cases of lacunar infarction. The other ischemic strokes were defined as cases of nonlacunar infarction.

CHD included acute myocardial infarction, silent myocardial infarction, sudden cardiac death within 1 hour after the onset of acute illness, and coronary artery disease treated by coronary artery bypass surgery or angioplasty. Acute myocardial infarction was diagnosed when a subject met at least 2 of the following criteria: (1) typical symptoms, including prolonged severe anterior chest pain; (2) evolving diagnostic electrocardiographic changes; (3) cardiac enzyme levels more than twice the upper limit of normal range; and (4) morphological changes, including local asynergy of cardiac wall motion on echocardiography, persistent perfusion defect on cardiac scintigraphy, or myocardial necrosis or scars ≥1 cm long accompanied by coronary atherosclerosis at autopsy. Silent myocardial infarction was defined as myocardial scarring without any historical indication of clinical symptoms or abnormal cardiac enzyme changes.

During the follow-up, we identified 132 cases of ischemic stroke (for men, 61 total, or 27 lacunar and 34 nonlacunar infarctions; for women, 71 total, or 42 lacunar and 29 nonlacunar infarctions) and 112 CHD events (75 men and 37 women). All of the ischemic stroke cases underwent brain imaging.

Risk Factors

At the baseline examination, we performed the OGTT after at least a 12-hour overnight fast. Plasma glucose levels were determined by the glucose-oxidase method. FPG and 2-hour postload glucose (PG) levels were divided into 4 categories: for FPG: <5.6, 5.6 to 6.0, 6.1 to 6.9, and ≥7.0 mmol/L; for 2-hour PG: <6.7, 6.7 to 7.7, 7.8 to 11.0, and ≥11.1 mmol/L. Glucose tolerance status was also defined by the 1998 World Health Organization criteria[16]; namely, for normal glucose tolerance (NGT), FPG <6.1 and 2-hour PG <7.8; for hyperglycemia, FPG ≥6.1 and/or 2-hour PG ≥7.8; for impaired fasting glycemia (IFG), FPG 6.1 to 6.9 and 2-hour PG <7.8; for impaired glucose tolerance (IGT), FPG <7.0 and 2-hour PG 7.8 to 11.0; and for diabetes mellitus, FPG ≥7.0 mmol/L and/or 2-hour PG ≥11.1 mmol/L. Total and high-density lipoprotein cholesterol levels were determined enzymatically.

Blood pressure was measured 3 times using a sphygmomanometer after at least 5 minutes of rest; the average of 3 measurements was used for the analysis. Hypertension was defined as blood pressure levels of ≥140/90 mm Hg or current treatment with antihypertensive agents. Body mass index (kg/m^2) was used as an indicator of obesity. Electrocardiographic abnormalities were defined as left ventricular hypertrophy (Minnesota Code 3 to 1) or ST depression (4 to 1, 4 to 2, or 4 to 3). Each participant completed a self-administered questionnaire covering medical history, antidiabetic and antihypertensive treatments, smoking habits, alcohol intake, and leisure time activity. Smoking habits and alcohol intake were classified as either current use or not. Those subjects engaging in sports or other forms of exertion ≥3 times a week during their leisure time made up a regular exercise group.

Statistical Analysis

The SAS software package Version 9.2 (SAS Institute Inc, Cary, NC) was used to perform all statistical analyses. Incidence was calculated by a person-year method and was adjusted for age by the direct method using 10-year age groupings. The age- and multivariable-adjusted hazard ratios (HRs) and their 95% CIs were estimated using the Cox proportional hazards model.

Ethical Considerations

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

Results

The baseline characteristics of the subjects are summarized by sex in Table 1. Mean values of age and body mass index did not differ between the sexes. The means of FPG, 2-hour PG, and systolic and diastolic blood pressures and frequencies of diabetes, hypertension, electrocardiographic abnormalities, smoking habits, alcohol intake, and regular exercise were higher in men than in women, whereas women had higher concentrations of total and high-density lipoprotein cholesterol.

The age-adjusted incidences and age-adjusted and multivariable-adjusted HRs of ischemic stroke and CHD according to FPG levels are shown in Table 2. The age-adjusted incidences of ischemic stroke and CHD did not differ between subjects with FPG levels of <5.6 mmol/L and those with FPG levels of 5.6 to 6.0 mmol/L in either sex. In women, the age-

Table 1. Characteristics of Subjects by Sex, 1988

	Men (n=1037)	Women (n=1384)
Age, years	57 (10)	58 (10)
Fasting plasma glucose, mmol/L	5.9 (1.3)	5.7 (1.3)
2-hour PG, mmol/L	7.7 (4.0)	7.4 (3.3)
Diabetes, %	15.1	9.7
Systolic blood pressure, mm Hg	134 (20)	131 (20)
Diastolic blood pressure, mm Hg	81 (11)	76 (11)
Hypertension, %*	43.3	34.8
Electrocardiographic abnormalities, %†	19.6	12.6
Body mass index, kg/m^2	22.9 (2.9)	23.0 (3.2)
Total cholesterol, mmol/L	5.07 (1.07)	5.51 (1.05)
High density lipoprotein cholesterol, mmol/L	1.25 (0.31)	1.33 (0.29)
Current smoking, %	50.1	6.7
Current alcohol use, %	62.2	9.0
Regular exercise, %	11.2	9.0

All values are given as the mean (SD) or as a percent.
*Blood pressure ≥140/90 mm Hg or current use of antihypertensive agents.
†Minnesota Codes 3–1, 4–1, 4–2, or 4–3.

adjusted incidence and HR of ischemic stroke were significantly higher in subjects with FPG levels of 6.1 to 6.9 mmol/L than in those with the FPG levels of <5.6 mmol/L; however, this association was attenuated after adjustment for the following confounding factors: age, systolic blood pressure, electrocardiographic abnormalities, body mass index, total and high-density lipoprotein cholesterol, smoking habits, alcohol intake, and regular exercise. An FPG level of ≥7.0 mmol/L was a significant risk factor for ischemic stroke in both sexes and for CHD in women, even after adjustment for the previously mentioned confounding factors (ischemic stroke: multivariable-adjusted HR=2.15, 95% CI, 1.07 to 4.31, P=0.03 in men; multivariable-adjusted HR=2.10, 95% CI, 1.02 to 4.35, P=0.045 in women; CHD: multivariable-adjusted HR=3.83, 95% CI, 1.59 to 9.25, P=0.003 in women).

Table 3 presents data of the analyses for ischemic stroke and CHD according to 2-hour PG levels. Compared with subjects with 2-hour PG levels of <6.7 mmol/L, the age-adjusted incidences and multivariable-adjusted HRs of ischemic stroke in both sexes and CHD in women were significantly higher in those with glucose levels of ≥11.1 mmol/L (ischemic stroke: multivariable-adjusted HR=2.71, 95% CI, 1.41 to 5.20, P=0.003 in men; multivariable-adjusted HR=2.19, 95% CI, 1.07 to 4.48, P=0.03 in women; CHD: multivariable-adjusted HR=4.44, 95% CI, 1.85 to 10.6, P<0.001 in women). Subjects with a prediabetic range of 2-hour PG levels did not have an increased risk of either ischemic stroke or CHD.

Finally, the relationships between glucose tolerance levels defined by the World Health Organization criteria and the risks of ischemic stroke and CHD are displayed in Table 4. Compared with those in women with NGT, the age-adjusted incidences and HRs of ischemic stroke and CHD were significantly increased in women with hyperglycemia, but these associations disappeared after adjustment for other confounding factors. In regard to subtypes of hyperglycemia, the age-adjusted incidences and HRs of ischemic stroke and CHD did not significantly increase in those with IFG or IGT

Table 2. Age-Adjusted Incidence and Age- and Multivariable-Adjusted HRs and Their 95% CIs for the Development of Cardiovascular Diseases According to FPG Levels

	FPG Level, mmol/L	Person-Years	No. of Events	Age-Adjusted Incidence per 1000 Person-Years	Age-Adjusted HR (95% CI)	P	Multivariable-Adjusted HR (95% CI)	P
Ischemic stroke								
Men	<5.6	5391	26	5.4	1 (referent)		1 (referent)	
	5.6 to 6.0	3791	13	4.0	0.70 (0.36 to 1.36)	0.29	0.66 (0.33 to 1.29)	0.22
	6.1 to 6.9	1909	9	4.7	0.85 (0.40 to 1.82)	0.68	0.68 (0.30 to 1.54)	0.36
	≥7.0	1170	13	11.7	2.06 (1.06 to 4.00)	0.03	2.15 (1.07 to 4.31)	0.03
Women	<5.6	9707	28	3.4	1 (referent)		1 (referent)	
	5.6 to 6.0	4821	18	3.9	1.11 (0.61 to 2.00)	0.74	0.98 (0.54 to 1.79)	0.95
	6.1 to 6.9	1733	14	7.1	2.01 (1.05 to 3.84)	0.03	1.59 (0.80 to 3.13)	0.18
	≥7.0	1107	11	9.6	2.47 (1.22 to 4.97)	0.01	2.10 (1.02 to 4.35)	0.045
CHD								
Men	<5.6	5450	33	7.0	1 (referent)		1 (referent)	
	5.6 to 6.0	3808	16	4.7	0.68 (0.38 to 1.24)	0.21	0.67 (0.37 to 1.23)	0.20
	6.1 to 6.9	1942	14	7.3	1.01 (0.54 to 1.90)	0.97	0.80 (0.42 to 1.54)	0.50
	≥7.0	1195	12	9.9	1.50 (0.77 to 2.90)	0.23	1.29 (0.65 to 2.58)	0.47
Women	<5.6	9844	12	1.4	1 (referent)		1 (referent)	
	5.6 to 6.0	4893	9	1.8	1.31 (0.55 to 3.10)	0.55	1.13 (0.47 to 2.71)	0.78
	6.1 to 6.9	1815	6	2.5	1.99 (0.74 to 5.36)	0.17	1.36 (0.49 to 3.81)	0.56
	≥7.0	1138	10	7.0	5.30 (2.28 to 12.35)	<0.001	3.83 (1.59 to 9.25)	0.003

Multivariable adjustment was made for age, systolic blood pressure, electrocardiogram abnormalities, body mass index, total and high-density lipoprotein cholesterol, smoking habits, alcohol intake, and regular exercise.

Table 3. Age-Adjusted Incidence and Age- and Multivariable-Adjusted HRs and Their 95% CIs for the Development of Cardiovascular Diseases According to 2-Hour PG Levels

	Two-Hour PG Levels, mmol/L	Person-Years	No. of Events	Age-Adjusted Incidence per 1000 Person-Years	Age-Adjusted HR (95% CI)	*P*	Multivariable-Adjusted HR (95% CI)	*P*
Ischemic stroke								
Men	<6.7	6253	25	4.4	1 (referent)		1 (referent)	
	6.7 to 7.7	2246	7	3.5	0.81 (0.35 to 1.87)	0.61	0.84 (0.36 to 1.96)	0.68
	7.8 to 11.0	2363	13	5.5	1.22 (0.62 to 2.38)	0.57	1.05 (0.52 to 2.13)	0.89
	≥11.1	1399	16	10.9	2.66 (1.42 to 4.98)	0.002	2.71 (1.41 to 5.20)	0.003
Women	<6.7	8728	25	3.3	1 (referent)		1 (referent)	
	6.7 to 7.7	3982	17	5.3	1.51 (0.82 to 2.80)	0.19	1.29 (0.69 to 2.44)	0.43
	7.8 to 11.0	3374	15	3.8	1.18 (0.62 to 2.24)	0.62	0.99 (0.51 to 1.92)	0.96
	≥11.1	1284	14	10.3	2.80 (1.45 to 5.40)	0.002	2.19 (1.07 to 4.48)	0.03
CHD								
Men	<6.7	6239	33	6.0	1 (referent)		1 (referent)	
	6.7 to 7.7	2277	9	4.7	0.78 (0.37 to 1.63)	0.50	0.73 (0.34 to 1.55)	0.41
	7.8 to 11.0	2430	18	7.3	1.20 (0.67 to 2.13)	0.54	0.97 (0.53 to 1.77)	0.93
	≥11.1	1449	15	11.5	1.82 (0.99 to 3.34)	0.06	1.58 (0.83 to 3.00)	0.16
Women	<6.7	8858	11	1.4	1 (referent)		1 (referent)	
	6.7 to 7.7	4079	6	1.4	1.16 (0.43 to 3.15)	0.77	0.91 (0.33 to 2.52)	0.86
	7.8 to 11.0	3430	6	1.5	1.10 (0.40 to 2.97)	0.86	0.82 (0.29 to 2.29)	0.70
	≥11.1	1323	14	8.5	6.49 (2.93 to 14.36)	<0.001	4.44 (1.85 to 10.62)	<0.001

Multivariable adjustment was made for age, systolic blood pressure, electrocardiogram abnormalities, body mass index, total and high-density lipoprotein cholesterol, smoking habits, alcohol intake, and regular exercise.

in either sex. Diabetes was a significant risk factor for ischemic stroke in both sexes and for CHD in women. These significant associations also remained robust even after adjustment for the previously mentioned confounding factors (ischemic stroke: multivariable-adjusted HR=2.54, 95% CI, 1.40 to 4.63, P=0.002 in men; multivariable-adjusted HR=2.02, 95% CI, 1.07 to 3.81, P=0.03 in women; CHD: multivariable-adjusted HR=3.46, 95% CI, 1.59 to 7.54, P=0.002 in women). When ischemic stroke was classified as either lacunar or nonlacunar infarction, diabetes was an independent risk factor for lacunar infarction in women (multivariable-adjusted HR=2.65, 95% CI, 1.19 to 5.93, P=0.02) and nonlacunar infarction in men (HR=3.78, 95% CI, 1.74 to 8.19, P=0.001) after adjustment for other confounding factors (Table 5).

Discussion

Using data from a 14-year follow-up study of a defined general Japanese population, we demonstrated that diabetes defined by the OGTT is an independent risk factor for the development of ischemic stroke in both sexes and CHD in women after adjustment for other confounding factors. Furthermore, we found that diabetes significantly increased the risk of lacunar infarction in women and nonlacunar infarction in men. By contrast, an FPG level of 5.6 to 6.0 mmol/L, a newly extended range from the American Diabetes Association, was not associated with ischemic stroke or CHD in either sex. In women with the FPG levels of 6.1 to 6.9 mmol/L, the age-adjusted incidence of ischemic stroke increased significantly; however, this association was attenuated after multivariable adjustment.

Very few prospective studies have provided evidence of the associations between glucose tolerance levels defined by the OGTT and the incidence of stroke and CHD. Only investigators of the Strong Heart Study of American Indians have evaluated the association of glucose tolerance status defined by the 1998 World Health Organization criteria with the risk of developing stroke. The results showed that, compared with the subjects with NGT, subjects with diabetes had a 2-fold higher risk of stroke, but subjects with IFG or IGT did not have a higher risk.[13] In a follow-up examination of a Finnish population who was free of diabetes at baseline, diabetes that developed during the follow-up was a significant risk factor for CHD, but baseline IGT was not.[17] These findings are in accordance with those of the present study. In our study, diabetes was significantly associated with the development of ischemic stroke in both sexes as well as CHD in women, but such an association was not observed for CHD in men. Although the precise reasons for this sex difference in the CHD risk conferred by diabetes are unknown, the higher prevalence of smoking in men may be responsible for this phenomenon; a smoking habit, which is a major risk factor for CHD, is considered to increase the risk of CHD in subjects with normal glucose levels, which would weaken the association of diabetes with CHD in men. Several cohort studies indicated that elevated 2-hour PG levels of 7.8 to 11.0 mmol/L, a category of IGT, was associated with an increased mortality from cardiovascular disease.[6–8,18,19] However, there have been some epidemiological studies in which IGT was not a risk factor for cardiovascular death.[3,5,9] In the present study, IGT was not associated with the development of ischemic stroke or CHD. However, our previous study of

Table 4. Age-Adjusted Incidence and Age- and Multivariable-Adjusted HRs and Their 95% CIs for the Development of Cardiovascular Diseases According to Glucose Tolerance Levels Defined by the WHO Criteria

	WHO Criteria	Person-Years	No. of Events	Age-Adjusted Incidence per 1000 Person-Years	Age-Adjusted HR (95% CI)	*P*	Multivariable-Adjusted HR (95% CI)	*P*
Ischemic stroke								
Men	NGT	7397	29	4.6	1 (referent)		1 (referent)	
	Hyperglycemia	4863	32	6.6	1.47 (0.89 to 2.43)	0.14	1.32 (0.79 to 2.23)	0.29
	IFG	987	2	1.9	0.45 (0.11 to 1.89)	0.28	0.41 (0.10 to 1.74)	0.23
	IGT	2183	11	5.0	1.10 (0.55 to 2.21)	0.78	0.91 (0.44 to 1.89)	0.79
	Diabetes	1694	19	11.3	2.55 (1.43 to 4.55)	0.001	2.54 (1.40 to 4.63)	0.002
Women	NGT	11 769	35	3.6	1 (referent)		1 (referent)	
	Hyperglycemia	5600	36	5.7	1.60 (1.00 to 2.56)	0.049	1.34 (0.82 to 2.20)	0.25
	IFG	807	7	7.9	2.20 (0.98 to 4.97)	0.06	1.89 (0.82 to 4.34)	0.13
	IGT	3224	13	3.4	1.01 (0.53 to 1.92)	0.97	0.88 (0.46 to 1.70)	0.71
	Diabetes	1569	16	9.3	2.46 (1.36 to 4.46)	0.003	2.02 (1.07 to 3.81)	0.03
CHD								
Men	NGT	7415	37	5.9	1 (referent)		1 (referent)	
	Hyperglycemia	4979	38	7.8	1.31 (0.83 to 2.07)	0.24	1.10 (0.69 to 1.76)	0.69
	IFG	982	5	4.9	0.89 (0.35 to 2.27)	0.81	0.80 (0.31 to 2.05)	0.64
	IGT	2244	18	8.0	1.33 (0.76 to 2.35)	0.32	1.11 (0.62 to 2.00)	0.72
	Diabetes	1754	15	9.4	1.53 (0.84 to 2.78)	0.17	1.26 (0.67 to 2.35)	0.47
Women	NGT	11 932	16	1.5	1 (referent)		1 (referent)	
	Hyperglycemia	5759	21	3.1	2.07 (1.07 to 3.99)	0.03	1.52 (0.76 to 3.04)	0.23
	IFG	871	1	0.9	0.65 (0.09 to 4.88)	0.67	0.48 (0.06 to 3.76)	0.48
	IGT	3278	6	1.6	1.05 (0.41 to 2.70)	0.92	0.82 (0.31 to 2.15)	0.68
	Diabetes	1610	14	6.9	4.82 (2.34 to 9.94)	<0.001	3.46 (1.59 to 7.54)	0.002

Multivariable adjustment was made for age, systolic blood pressure, electrocardiogram abnormalities, body mass index, total and high-density lipoprotein cholesterol, smoking habits, alcohol intake, and regular exercise.

WHO indicates World Health Organization.

a 5-year follow-up of the same cohort showed that IGT was an independent risk factor for the occurrence of cardiovascular disease.[4] During a long follow-up period, a potential change in the glucose tolerance of participants may occur, which would induce some misclassification and weaken the relationship between 2-hour PG levels and cardiovascular disease. Thus, the association between the prediabetic range of 2-hour PG and cardiovascular events would attenuate over time.

The American Diabetes Association lowered the FPG cutoff point from 6.1 to 5.6 mmol/L in 2003.[20] This decision was prompted partly by population-based studies showing that the cutoff point of 5.6 mmol/L would increase the sensitivity of predicting future diabetes. In addition, this change was also intended to improve the selection of individuals at risk for cardiovascular diseases.[20] Two major organizations recently adopted the cutoff point of 5.6 mmol/L in the diagnostic criteria of metabolic syndrome.[21,22] Thus, it is very important to appropriately determine the FPG cutoff value for the prediction of cardiovascular disease. However, there is less evidence concerning the positive association between FPG levels of 5.6 to 6.0 mmol/L and the risk of cardiovascular disease. A recent study of a community-based medical center in the United States found that individuals with glucose of 5.6 to 6.0 mmol/L had lower prevalence of most CHD risk factors compared with individuals with glucose of 6.1 to 6.9 mg/dL.[23] Furthermore, some epidemiological studies have shown that the mortality and incidence of cardiovascular disease did not increase in those with FPG levels of 5.6 to 6.0 mmol/L.[11,12,19,24] These findings, together with those of the present study, suggest that FPG levels of 5.6 to 6.0 mmol/L are not associated with the risk of cardiovascular disease.

Conflicting data for FPG levels of 6.1 to 6.9 mmol/L as a risk factor for cardiovascular disease also exist. At least 4 studies have shown no significantly increased risk of cardiovascular disease in those with FPG levels of 6.1 to 6.9 mmol/L,[6,8,18,19] although others have found that this glucose range is a significant risk factor for cardiovascular disease.[7,11,12,24] In our study, the age-adjusted incidence of ischemic stroke was significantly higher in women with FPG levels of 6.1 to 6.9 mmol/L than in those with normal FPG levels, but after controlling for confounding risk factors, the risk was no longer statistically significant. Other known cardiovascular risk factors such as hypertension, obesity, and dyslipidemia tend to accumulate at this glucose level.[23] Thus, FPG levels of 6.1 to 6.9 mmol/L seem to have increased the risk of ischemic stroke through other coexisting risk factors in our population.

The strengths of our study include its longitudinal population-based design, long duration of follow-up, perfect follow-up of subjects, sufficient number of cardiovascular events, and accuracy of diagnosis of cardiovascular disease. One limitation of our study is that the diagnosis of glucose

Table 5. Age-Adjusted Incidence and Age- and Multivariable-Adjusted HRs and Their 95% CIs for the Development of Lacunar and Nonlacunar Infarctions According to Glucose Tolerance Levels Defined by the WHO Criteria

	WHO Criteria	Person-Years	No. of Events	Age-Adjusted Incidence per 1000 Person-Years	Age-Adjusted HR (95% CI)	*P*	Multivariable-Adjusted HR (95% CI)	*P*
Lacunar infarction								
Men	NGT	7397	14	2.3	1 (referent)		1 (referent)	
	Hyperglycemia	4863	13	2.7	1.19 (0.56 to 2.54)	0.65	0.99 (0.45 to 2.18)	0.99
	IFG	987	1	1.0	0.44 (0.06 to 3.38)	0.43	0.43 (0.06 to 3.28)	0.41
	IGT	2183	6	2.7	1.19 (0.46 to 3.11)	0.72	0.91 (0.32 to 2.57)	0.86
	Diabetes	1694	6	3.6	1.64 (0.63 to 4.28)	0.31	1.44 (0.54 to 3.86)	0.47
Women	NGT	11 769	19	2.0	1 (referent)		1 (referent)	
	Hyperglycemia	5600	23	3.8	1.97 (1.07 to 3.65)	0.03	1.62 (0.85 to 3.11)	0.14
	IFG	807	4	4.8	2.42 (0.82 to 7.13)	0.11	2.02 (0.67 to 6.09)	0.21
	IGT	3224	8	2.1	1.21 (0.53 to 2.78)	0.66	1.04 (0.44 to 2.43)	0.94
	Diabetes	1569	11	6.7	3.26 (1.54 to 6.89)	0.002	2.65 (1.19 to 5.93)	0.02
Nonlacunar infarction								
Men	NGT	7397	15	2.3	1 (referent)		1 (referent)	
	Hyperglycemia	4863	19	3.9	1.74 (0.88 to 3.42)	0.11	1.67 (0.83 to 3.37)	0.15
	IFG	987	1	0.9	0.45 (0.06 to 3.44)	0.44	0.41 (0.05 to 3.12)	0.39
	IGT	2183	5	2.3	1.00 (0.36 to 2.76)	1.00	0.91 (0.33 to 2.57)	0.87
	Diabetes	1694	13	7.7	3.44 (1.63 to 7.23)	0.001	3.78 (1.74 to 8.19)	0.001
Women	NGT	11 769	16	1.7	1 (referent)		1 (referent)	
	Hyperglycemia	5600	13	1.9	1.18 (0.57 to 2.47)	0.66	1.01 (0.46 to 2.20)	0.99
	IFG	807	3	3.1	1.94 (0.56 to 6.67)	0.29	1.78 (0.50 to 6.38)	0.38
	IGT	3224	5	1.3	0.80 (0.29 to 2.18)	0.66	0.70 (0.25 to 1.98)	0.51
	Diabetes	1569	5	2.6	1.58 (0.58 to 4.32)	0.37	1.26 (0.43 to 3.69)	0.67

Multivariable adjustment was made for age, systolic blood pressure, electrocardiogram abnormalities, body mass index, total and high-density lipoprotein cholesterol, smoking habits, alcohol intake, and regular exercise.

WHO indicates World Health Organization.

tolerance status was based on a single measurement of glucose levels at baseline as was the case in most other epidemiological studies. During the follow-up, risk factor levels were changed due to modifications in lifestyle or medication, and misclassification of glucose tolerance categories was possible. This could have weakened 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, diabetes defined by an OGTT was an independent risk factor for cardiovascular disease, except for CHD in men. Notably, the new range in the 2003 American Diabetes Association criteria for IFG (FPG of 5.6 to 6.0 mmol/L) was not associated with ischemic stroke or CHD in either sex. The IFG category of the 1997 criteria (FPG of 6.1 to 6.9 mmol/L) increased the risk of ischemic stroke in women, although this association was not independent of other known risk factors. Because the risks of stroke and CHD and the prevalence of diabetes differ among races, further investigations are required to clarify the relationship between hyperglycemia and type of cardiovascular disease in other ethnic populations.

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Disclosures

None.

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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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ORIGINAL ARTICLE

Body mass index and stroke incidence in a Japanese community: the Hisayama study

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Although obesity is one of the major risk factors for coronary heart disease, its role in the development of stroke remains controversial. A total of 2421 residents, aged 40–79 years of a Japanese community were followed up prospectively for 12 years. The subjects were divided into four groups according to body mass index (BMI) levels (<21.0, 21.0–22.9, 23.0–24.9 and ⩾25.0 kg m^{-2}). During the follow-up, 107 ischemic and 51 hemorrhagic strokes occurred. The age-adjusted incidence of ischemic stroke for men significantly increased with increasing BMI levels (*P* for trend=0.005). This association remained substantially unchanged even after adjustment for other risk factors: namely, systolic blood pressure, electrocardiogram abnormalities, diabetes, total cholesterol, high-density lipoprotein-cholesterol, triglycerides, smoking habits, alcohol intake and regular exercise (*P* for trend<0.001). Compared with that of the BMI levels of <21.0 kg m^{-2}, the multivariate-adjusted risk of ischemic stroke was significant even in the BMI levels of 23.0–24.9 kg m^{-2} (multivariate-adjusted hazard ratio (HR)=3.12; 95% confidence interval (CI), 1.24–7.87; *P*=0.02) as well as in the BMI levels of ⩾25 kg m^{-2} (multivariate-adjusted HR=5.59; 95% CI, 2.09–14.91; *P*<0.001). In stratified analyses, the risk of ischemic stroke for men synergistically increased in subjects having both obesity and diabetes or a smoking habit. We found no significant associations between BMI levels and ischemic stroke in women and between BMI levels and hemorrhagic stroke in either sex. In conclusion, our findings suggest that overweight and obesity are independent risk factors for ischemic stroke in Japanese men.
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Keywords: body mass index; incidence; obesity; prospective study; stroke

INTRODUCTION

Stroke is a leading cause of death[1] and permanent disability in middle-aged and elderly people in Japan[2–4] as well as in other developed countries.[5] In Japan, the prevalence of obesity has increased rapidly along with the westernization of lifestyle,[6] although it remains considerably lower than that in Western populations.[7] Increased body mass index (BMI) is tightly related to an increased risk of coronary heart disease,[8] but its association with stroke is less well recognized because of conflicting results reported in the literature. Some cohort studies have found a positive association between BMI and the risk of stroke,[8–14] whereas others have shown no apparent association[15–18] or have even reported an inverse or a U-shaped association.[19–22] In Japan, no prospective study has provided incidence data on this issue nor observed a positive association between BMI and the risk of stroke until now.[21,22] Based on its pathogenesis, stroke is divided into several clinical subtypes, and the effects of BMI on stroke are considered to be different among these subtypes.[8,19] In addition, obesity is an important risk factor for hypertension, diabetes mellitus and dyslipidemia, which are known as major risk factors for stroke,[23,24] and therefore, whether obesity itself independently increases the risk of stroke remains controversial.

In the present article, we investigated the association between BMI and the occurrence of stroke by its subtype based on records of a prospective study of a general Japanese population, taking other known risk factors into account.

METHODS

Study population

In 1988, a screening survey for the present study was performed in the town of Hisayama, a suburb of the Fukuoka metropolitan area in southern Japan. Of a total of 3227 residents aged 40–79 years on the town registry, 2587 consented to participate in the examination (participation rate, 80.2%) and underwent a comprehensive assessment. After excluding 82 subjects who had already had breakfast, 10 who were on insulin therapy and 15 due to complaints of nausea or general fatigue during the ingestion of glucose, a total of 2480 subjects completed a 75-g oral glucose tolerance test. From a total of 2490 subjects including 10 on insulin therapy, 68 who had a history of stroke or coronary heart disease based on questionnaires and medical records, and one who died

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before follow-up was started were excluded. The remaining 2421 (1037 men and 1384 women) were enrolled in this study.

Baseline data collection

At baseline, body height and weight were measured in light clothing without shoes, and BMI ($kg\,m^{-2}$) was calculated as an indicator of obesity. Information on antihypertensive treatment, smoking habits, alcohol intake and regular exercise were obtained with the use of a standard questionnaire. Subjects who reported smoking at least one cigarette per day were defined as current smokers, and subjects who reported consuming alcohol at least once a month were regarded as current drinkers. Subjects engaging in sports at least three times a week during their leisure time made up a regular exercise group. Sitting systolic and diastolic blood pressures were measured three times after a rest of at least 5 min by a standard mercury sphygmomanometer with a standard cuff. The average of three measurements was used for data analysis. Hypertension was defined as a systolic blood pressure $\geqslant 140$ mm Hg, a diastolic blood pressure $\geqslant 90$ mm Hg or current use of antihypertensive agents. ECG abnormalities were defined as left ventricular hypertrophy (Minnesota code 3–1), ST depression (4–1, 2 and 3) and/or atrial fibrillation (8–3). Blood samples were drawn after an overnight fast of at least 12 h. Fasting and 2-h post-load plasma glucose levels were determined by the glucose-oxidase method. Diabetes mellitus was defined as fasting plasma glucose $\geqslant 7.0\,mmol\,l^{-1}$, 2-hour post-load plasma glucose $\geqslant 11.1\,mmol\,l^{-1}$, or current use of insulin or oral medication for diabetes. Total cholesterol, high-density lipoprotein-cholesterol and triglyceride levels were all determined enzymatically.

Follow-up survey

The subjects were followed up prospectively for 12 years from December 1988 to November 2000 by repeated health examinations and by a daily monitoring system established by the study team and local physicians or members of the Health and Welfare Office of the town. Health status was checked once yearly by mail or telephone for any subjects who did not undergo a regular examination or who moved out of town. Study-team physicians performed physical and neurological examinations on all subjects who developed stroke and collected the relevant clinical information, including that on the disease course. During the follow-up period, only one subject was lost to follow-up, and 339 subjects died; among those who died, autopsy was performed on 253 (74.6%).

Stroke, defined as sudden onset of a non-convulsive and focal neurological deficit persisting for >24 h, was classified as ischemic stroke, cerebral hemorrhage, subarachnoid hemorrhage or undetermined type.[25] The clinical diagnosis of stroke and its subtypes was determined on the basis of a detailed history, neurological examination and ancillary laboratory examinations. In this paper, we focused on ischemic and hemorrhagic stroke (cerebral hemorrhage and subarachnoid hemorrhage). During the follow-up period, we identified 107 cases of first-ever ischemic stroke (47 men and 60 women) and 51 cases of first-ever hemorrhagic stroke (21 men and 30 women), consisting of 34 cases of cerebral hemorrhage and 17 cases of subarachnoid hemorrhage. All of the stroke cases were examined by computed tomography and/or magnetic resonance imaging.

Statistical analysis

All statistical analyses were performed with the SAS program package Ver 9.2 (SAS Institute Inc, Cary, NC, USA). All tests were two-sided, and values of $P<0.05$ were considered statistically significant in all analyses. The subjects were divided into four groups according to BMI levels (<21.0, 21.0–22.9, 23.0–24.9 and $\geqslant 25.0\,kg\,m^{-2}$). Because of the skewed distribution of serum triglycerides, this value was log-transformed for statistical analysis. The age-adjusted mean values of risk factors were calculated by the analysis of covariance method, and their trends across BMI levels were tested by multiple regression analysis. Frequencies of risk factors were adjusted for age by the direct method and were examined for trends by the Cochran–Mantel–Haenszel test. The incidence of stroke was calculated by the person-year method and was adjusted for the age distribution of the study population by the direct method. Differences in the incidence of stroke among BMI levels were tested by the Cox proportional hazards model. The age- and multivariate-adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) were also calculated using the Cox proportional hazards model. The multivariate adjustment was made for age, systolic blood pressure, ECG abnormalities, diabetes, total cholesterol, high-density lipoprotein-cholesterol, triglycerides, smoking habits, drinking status and regular exercise. To assess whether synergistic effect was observed between obesity and each of other risk factors, we added a multiplicative interaction term to the relevant Cox model.

Ethical considerations

The study protocol was approved by the Human Ethics Review Committee of Kyushu University Graduate School of Medical Sciences, and a written informed consent was obtained from the study participants.

RESULTS

Characteristics of the subjects

The age-adjusted mean values or frequencies of risk factors by BMI levels at baseline are shown by sex (Table 1). Mean age significantly decreased with rising BMI levels for men, but such an association was not observed for women. In both sexes, the mean values of systolic and diastolic blood pressures, total cholesterol and triglycerides, and the frequencies of hypertension, antihypertensive drug use and diabetes increased significantly, whereas the mean high-density lipoprotein-cholesterol levels decreased significantly with increasing BMI levels. The frequency of smoking habits for men and that of ECG abnormalities for women decreased significantly with increasing BMI levels. No dose-response relationships were observed between BMI levels and the frequencies of alcohol intake or regular exercise for both sexes.

Impact of BMI on stroke

As shown in Figure 1, the age-adjusted incidence of ischemic stroke for men increased with increasing BMI levels: the difference was significant between the BMI level of $<21.0\,kg\,m^{-2}$ and that of $\geqslant 25.0\,kg\,m^{-2}$ (age-adjusted HR=3.32; 95% CI, 1.43–7.72; $P=0.005$; Table 2). This association remained substantially unchanged even after adjustment for other risk factors (Table 2). The multivariate-adjusted risk of ischemic stroke was significant even in the subjects with BMI levels of 23.0–24.9 $kg\,m^{-2}$ (multivariate-adjusted HR=3.12; 95% CI, 1.24–7.87; $P=0.02$) as well as in those with BMI levels of $\geqslant 25\,kg\,m^{-2}$ (multivariate-adjusted HR=5.59; 95% CI, 2.09–14.91; $P<0.001$). We found no significant associations between BMI levels and the incidence of ischemic stroke in women and between BMI levels and the incidence of hemorrhagic stroke in either sex (Figure1 and Table 2).

Combined effects of obesity and other risk factors

Because hypertension, diabetes and smoking habits are major risk factors for ischemic stroke and are concurrently associated with obesity, we examined the combined effects of obesity and these risk factors on the development of ischemic stroke for men after adjustment for the above-mentioned confounding factors, except for the factor which was used for the grouping. As shown in Table 3, multivariate-adjusted HRs of ischemic stroke were significantly higher in the group of obese subjects irrespective of the presence or absence of hypertension. On the other hand, the risk of ischemic stroke synergistically increased in obese subjects with diabetes compared with non-obese subjects without diabetes (multivariate-adjusted HR=7.91; 95% CI, 3.08–20.28; $P<0.001$), whereas such an increased risk was not observed in non-obese subjects with diabetes or in obese subjects without diabetes. A similar synergistic pattern was observed for the coexistence of obesity and smoking habits (multivariate-adjusted HR=3.62; 95% CI, 1.39–9.43; $P=0.008$). A significant interaction between obesity and diabetes was revealed in the risk of ischemic

Table 1 Age-adjusted baseline characteristics according to body mass index level by sex, the Hisayama Study, 1988

	Body mass index, kg m^{-2}				
	<21	*21–22.9*	*23–24.9*	*⩾25*	*P for trend*
Men					
No at risk	283	255	247	252	—
Age (years)	60.5 (0.6)	56.8 (0.6)	56.2 (0.7)	54.4 (0.6)	<0.001
SBP (mm Hg)	127.1 (1.1)	132.2 (1.2)	135.5 (1.2)	141.2 (1.2)	<0.001
DBP (mm Hg)	75.5 (0.6)	79.3 (0.7)	82.0 (0.7)	86.3 (0.7)	<0.001
Hypertension (%)	32.6	37.4	46.9	58.7	<0.001
Antihypertensive drug (%)	9.0	10.8	15.1	23.6	<0.001
ECG abnormalities (%)[a]	20.6	20.9	19.3	18.7	0.28
Diabetes (%)	10.1	16.9	13.6	20.9	0.005
Total cholesterol (mmol l^{-1})	4.95 (0.06)	5.05 (0.07)	5.13 (0.07)	5.31 (0.07)	<0.001
HDL cholesterol (mmol l^{-1})	1.37 (0.02)	1.30 (0.02)	1.22 (0.02)	1.14 (0.02)	<0.001
Triglycerides (mmol l^{-1})	1.01 (0.94–1.07)	1.28 (1.20–1.37)	1.46 (1.36–1.56)	1.77 (1.65–1.90)	<0.001
Smoking (%)	68.7	47.0	44.5	36.6	<0.001
Drinking (%)	59.7	65.9	64.7	58.6	0.63
Regular exercise (%)[b]	12.8	11.1	11.0	10.9	0.34
Women					
No at risk	380	347	318	339	
Age (years)	59.1 (0.5)	57.0 (0.6)	57.0 (0.6)	57.6 (0.6)	0.052
SBP (mm Hg)	125.2 (1.0)	130.2 (1.0)	131.1 (1.1)	136.9 (1.0)	<0.001
DBP (mm Hg)	71.8 (0.5)	74.4 (0.6)	77.0 (0.6)	80.0 (0.6)	<0.001
Hypertension (%)	24.2	30.9	34.5	50.3	<0.001
Antihypertensive drug (%)	7.5	14.1	14.2	21.5	<0.001
ECG abnormalities (%)[a]	15.2	14.3	9.4	11.6	0.03
Diabetes (%)	7.5	6.8	8.8	16.6	<0.001
Total cholesterol (mmol l^{-1})	5.31 (0.05)	5.54 (0.06)	5.74 (0.06)	5.66 (0.06)	<0.001
HDL cholesterol (mmol l^{-1})	1.44 (0.01)	1.35 (0.02)	1.30 (0.02)	1.26 (0.02)	<0.001
Triglycerides (mmol l^{-1})	0.88 (0.84–0.92)	1.04 (0.99–1.09)	1.15 (1.10–1.21)	1.24 (1.18–1.30)	<0.001
Smoking (%)	8.1	3.5	6.6	8.1	0.72
Drinking (%)	9.5	10.3	5.1	10.7	0.79
Regular exercise (%)[b]	9.4	10.5	8.9	6.3	0.11

Abbreviations: DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure.
Data are shown as the means (standard error) or a percentage. Geometric mean values and 95% confidence intervals of serum triglycerides are shown attributable to the skewed distribution. Mean age was not age-adjusted.
[a]Minnesota codes: 3–1, 4–1, 2, 3 or 8–3
[b]Engaging in sports or other forms of exertion regularly ⩾three times a week during leisure time.

stroke (P=0.01), whereas the interactions between obesity and hypertension and between obesity and smoking habits were not significant.

DISCUSSION

In this prospective study of a community-dwelling Japanese population, we demonstrated that higher BMI was a significant risk factor for the development of ischemic stroke in men. This association remained unchanged even after adjustment for other risk factors. In addition, the combinations of obesity plus diabetes or obesity plus a smoking habit synergistically increased the risk of ischemic stroke. However, there was no significant association between BMI levels and the risk of hemorrhagic stroke in either sex.

Some cohort studies have shown an increased risk of total stroke or ischemic stroke with elevating BMI,[8–14] which is in accord with the findings of the risk of ischemic stroke in our male subjects. On the other hand, other studies have found no association,[15–18] an inverse or a U-shaped association.[19–22] One possible explanation for this difference in findings may be that stroke was not evaluated by its subtype in all these studies, as the effect of obesity is different among stroke subtypes. Another explanation may be that most of these studies used mortality data as an endpoint. Our previous study showed that lower BMI was a significant risk factor for death after total stroke and ischemic stroke.[26] Epidemiological studies of body weight and mortality are affected by methodological problems, such as failure to control the harmful biological effects of smoking and subclinical diseases resulting in weight loss. Thus, the association of BMI with stroke mortality should be interpreted with caution.

In the literature, the associations between BMI levels and the risk of hemorrhagic stroke have been inconsistent, with some studies showing a positive association,[8,11,14] and others showing no, a negative or a U-shaped, association.[9,12,13,16,19,21,22] In the present study, we did not find a clear association between BMI levels and hemorrhagic stroke in men or women. The lack of a clear consensus on this association may be partly due to the low number of cases of hemorrhagic stroke in most of the studies, including our present work, or differences in ethnicities, study populations or study methods. Future studies will be needed to resolve this issue.

A number of studies have reported that the association between BMI and total or ischemic stroke was attenuated or eliminated after adjustment for potential mediators, such as hypertension, diabetes

and dyslipidemia.[9,10,12–14,19,22] In our study, however, the association between BMI and ischemic stroke was not attenuated even after adjusting for these risk factors. This finding indicates an independent effect of overweight and obesity on the development of ischemic stroke. A similar independent association has been observed in other studies of stroke.[10,12,14] These findings, together with our present results, suggest a link between overweight/obesity and ischemic stroke independent of established risk factors. Some investigators have proposed that the increase in prothrombotic factors[27–29] and inflammatory markers,[30–33] and the enhancement of insulin resistance and metabolic syndrome[34] observed among overweight and obese individuals may have a role in their increased risk of ischemic stroke.

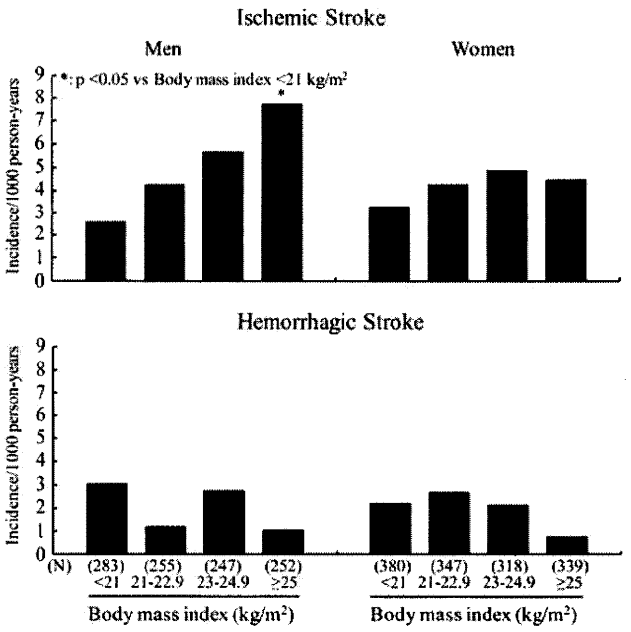

Figure 1 Age-adjusted incidence of stroke by body mass index levels during 12-year follow-up, the Hisayama Study, 1988–2000.

Our stratified analysis showed an extremely increased risk of ischemic stroke in men who have both obesity and diabetes or smoking habits. Although the mechanisms underlying this phenomenon are not clearly understood, a possible explanation can be proposed. Because diabetes and smoking are strong risk factors for the progression of systemic arteriosclerosis, it is reasonable to consider that subjects with these risk factors already have vascular injuries to some extent. Obesity-related disorders, such as inflammation, insulin resistance and metabolic syndrome, may accelerate the progression of preexisting vascular injuries, resulting in an increased risk of ischemic stroke. However, in the present study we did not find that obesity enhanced the effect of hypertension on stroke risk. Although the precise reason for this is not known, the popularization of antihypertensive treatment in our study population might have weakened the synergistic effects of these factors.

In our female subjects, we did not observe a significant association between BMI and the risk of ischemic stroke. Several cohort studies have also examined the effects of BMI on the risk of ischemic stroke in women,[9,13–15,21,22] but the findings were inconsistent, with some studies showing a positive association,[9,13,14] and others showing no association[15,21] like our study. Further studies will be needed to clarify the true association between BMI and stroke in women.

Table 2 Adjusted hazard ratio for stroke incidence according to body mass index level by sex, the Hisayama Study, 1988–2000

Body mass index, kg m^{-2}	*Person year*	*No. of events*	*Age-adjusted HR*	*95% CI*	*Multivariate-adjusted HR*[a]	*95% CI*
Men						
Ischemic stroke						
<21.0	2907	9	1.00	Referent	1.00	Referent
21.0–22.9	2736	10	1.70	0.69–4.20	2.34	0.91–6.00
23.0–24.9	2692	12	2.09	0.88–5.00	3.12	1.24–7.87
25.0≥	2790	16	3.32	1.43–7.73	5.59	2.09–14.91
P for trend			0.005		<0.001	
Hemorrhagic stroke						
<21.0	2907	9	1.00	Referent	1.00	Referent
21.0–22.9	2736	3	0.44	0.12–1.63	0.38	0.10–1.50
23.0–24.9	2692	6	0.89	0.31–2.55	0.90	0.28–2.87
25.0≥	2790	3	0.47	0.12–1.80	0.36	0.08–1.57
P for trend			0.41		0.31	
Women						
Ischemic stroke						
<21.0	4214	15	1.00	Referent	1.00	Referent
21.0–22.9	3935	15	1.41	0.69–2.90	1.37	0.65–2.88
23.0–24.9	3652	15	1.51	0.73–3.10	1.56	0.71–3.43
25.0≥	3794	15	1.41	0.69–2.91	1.27	0.58–2.80
P for trend			0.32		0.55	
Hemorrhagic stroke						
<21.0	4214	10	1.00	Referent	1.00	Referent
21.0–22.9	3935	10	1.26	0.52–3.04	1.32	0.52–3.35
23.0–24.9	3652	7	0.94	0.36–2.49	1.13	0.39–3.25
25.0≥	3794	3	0.38	0.10–1.39	0.35	0.09–1.35
P for trend			0.16		0.16	

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval.
[a]Multivariate adjustment was made for age, systolic blood pressure, ECG abnormalities, diabetes, total and high-density lipoprotein-cholesterols, triglycerides, smoking, drinking and regular exercise.

Table 3 Multivariate-adjusted[a] hazard ratios for the development of ischemic stroke according to the presence or absence of obesity and each established risk factor in men, the Hisayama Study, 1988–2000

		Population at risk	*No. of events*	*HR*	*95% CI*	P *value*
Obesity[b]	*Hypertension*					
No	No	477	14	1.00	Referent	
No	Yes	308	17	1.59	0.76–3.34	0.22
Yes	No	111	7	3.79	1.44–10.00	0.007
Yes	Yes	141	9	2.95	1.19–7.30	0.02
Obesity[b]	*Diabetes*					
No	No	678	25	1.00	Referent	
No	Yes	107	6	1.60	0.65–3.97	0.31
Yes	No	200	8	1.83	0.77–4.38	0.17
Yes	Yes	52	8	7.91	3.08–20.28	<0.001
Obesity[b]	*Smoking*					
No	No	369	17	1.00	Referent	
No	Yes	416	14	1.18	0.56–2.48	0.67
Yes	No	148	8	2.13	0.83–5.46	0.11
Yes	Yes	104	8	3.62	1.39–9.43	0.008

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval.
[a]Multivariate adjustment was made for age, systolic blood pressure, ECG abnormalities, diabetes, total and high-density lipoprotein-cholesterols, triglycerides, smoking, drinking and regular exercise, but the factor which was used for each grouping was excluded from the confounding factors.
[b]Obesity is defined as a body mass index $\geqslant 25\,kg\,m^{-2}$.

The strengths of our study include its longitudinal population-based design, the direct collection of height, weight and biological markers from all participants, long duration of follow-up, perfect follow-up of subjects and accuracy of diagnosis of stroke. One limitation of our study is that our findings are based on a one-time measurement of BMI, as was the case in most other epidemiological studies. During the follow-up, BMI and other risk factor levels were changed due to modifications in lifestyle or medication, and misclassification of BMI categories was possible. This could have weakened the association found in this study, biasing the results toward the null hypothesis. Therefore, the true association may be stronger than that shown here.

In conclusion, our data suggest that overweight and obesity are significant risk factors for the development of ischemic stroke in contemporary Japanese men. In Japan, BMI levels have increased steadily over the last several decades. For prevention of stroke, it is important to correct obesity while controlling other risk factors.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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