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.

References

1. Kannel WB, McGee DL. Diabetes and cardiovascular disease: the Framingham Study. *JAMA*. 1979;241:2035–2038.
2. Tuomilehto J, Rastenyte D, Jousilahti P, Sarti C, Vartiainen E. Diabetes mellitus as a risk factor for death from stroke. Prospective study of the middle-aged Finnish population. *Stroke*. 1996;27:210–215.
3. Park S, Barrett-Connor E, Wingard DL, Shan J, Edelstein S. GHb is a better predictor of cardiovascular disease than fasting or postchallenge plasma glucose in women without diabetes: the Rancho Bernardo Study. *Diabetes Care*. 1996;19:450–456.
4. Fujishima M, Kiyohara Y, Kato I, Ohmura T, Iwamoto H, Nakayama K, Ohmori S, Yoshitake T. Diabetes and cardiovascular disease in a prospective population survey in Japan: the Hisayama Study. *Diabetes*. 1996;45(suppl 3):S14–S16.
5. Lowe LP, Liu K, Greenland P, Metzger BE, Dyer AR, Stamler J. Diabetes, asymptomatic hyperglycemia, and 22-year mortality in black and white men: the Chicago Heart Association Detection Project in Industry Study. *Diabetes Care*. 1997;20:163–169.
6. Tominaga M, Eguchi H, Manaka H, Igarashi K, Kato T, Sekikawa A. Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose: the Funagata Diabetes Study. *Diabetes Care*. 1999;22:920–924.

7. Barzilay JI, Spiekerman CF, Wahl PW, Kuller LH, Cushman M, Furberg CD, Dobs A, Polak JF, Savage PJ. Cardiovascular disease in older adults with glucose disorders: comparison of American Diabetes Association criteria for diabetes mellitus with WHO criteria. *Lancet.* 1999;354: 622–625.
8. The DECODE Study Group on behalf of the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med.* 2001; 161:397–405.
9. Saydah SH, Miret M, Sung J, Varas C, Gause D, Brancati FL. Postchallenge hyperglycemia and mortality in a national sample of US adults. *Diabetes Care.* 2001;24:1397–1402.
10. Smith NL, Barzilay JI, Shaffer D, Savage PJ, Heckbert SR, Kuller LH, Kronmal RA, Resnick HE, Psaty BM. Fasting and 2-hour postchallenge serum glucose measures and risk of incident cardiovascular events in the elderly: the Cardiovascular Health Study. *Arch Intern Med.* 2002;162: 209–216.
11. Wen CP, Cheng TY, Tsai SP, Hsu HL, Wang SL. Increased mortality risks of pre-diabetes (impaired fasting glucose) in Taiwan. *Diabetes Care.* 2005;28:2756–2761.
12. Kanaya AM, Herrington D, Vittinghoff E, Lin F, Bittner V, Cauley JA, Hulley S, Barrett-Connor E. Impaired fasting glucose and cardiovascular outcomes in postmenopausal women with coronary artery disease. *Ann Intern Med.* 2005;142:813–820.
13. Zhang Y, Galloway JM, Welty TK, Wiebers DO, Whisnant JP, Devereux RB, Kizer JR, Howard BV, Cowan LD, Yeh J, Howard WJ, Wang W, Best L, Lee ET. Incidence and risk factors for stroke in American Indians: the Strong Heart Study. *Circulation.* 2008;118:1577–1584.
14. Ohmura T, Ueda K, Kiyohara Y, Kato I, Iwamoto H, Nakayama K, Nomiyama K, Ohmori S, Yoshitake T, Shinkawa A, Hasuo Y, Fujishima M. Prevalence of type 2 (non-insulin-dependent) diabetes mellitus and impaired glucose tolerance in the Japanese general population: the Hisayama Study. *Diabetologia.* 1993;36:1198–1203.
15. Special report from the National Institute of Neurological Disorders and Stroke. Classification of cerebrovascular diseases III. *Stroke.* 1990;21: 637–676.
16. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med.* 1998;15:539–553.
17. Qiao Q, Jousilahti P, Eriksson J, Tuomilehto J. Predictive properties of impaired glucose tolerance for cardiovascular risk are not explained by the development of overt diabetes during follow-up. *Diabetes Care.* 2003;26:2910–2914.
18. Blake DR, Meigs JB, Muller DC, Najjar SS, Andres R, Nathan DM. Impaired glucose tolerance, but not impaired fasting glucose, is associated with increased levels of coronary heart disease risk factors: results from the Baltimore Longitudinal Study on Aging. *Diabetes.* 2004;53: 2095–2100.
19. Tai ES, Goh SY, Lee JJ, Wong MS, Heng D, Hughes K, Chew SK, Cutter J, Chew W, Gu K, Chia KS, Tan CE. Lowering the criterion for impaired fasting glucose: impact on disease prevalence and associated risk of diabetes and ischemic heart disease. *Diabetes Care.* 2004;27: 1728–1734.
20. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care.* 2003;26:3160–3167.
21. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation.* 2005;112:2735–2752.
22. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome—a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med.* 2006;23:469–480.
23. Kim SH, Chunawala L, Linde R, Reaven GM. Comparison of the 1997 and 2003 American Diabetes Association classification of impaired fasting glucose: impact on prevalence of impaired fasting glucose, coronary heart disease risk factors, and coronary heart disease in a community-based medical practice. *J Am Coll Cardiol.* 2006;48:293–297.
24. Levitzky YS, Pencina MJ, D'Agostino RB, Meigs JB, Murabito JM, Vasan RS, Fox CS. Impact of impaired fasting glucose on cardiovascular disease: the Framingham Heart Study. *J Am Coll Cardiol.* 2008;51:264–270.

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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 (≥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 ≥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 ≥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 ≥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, ≥90 cm in men and ≥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 ≥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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References

[1] Sudlow CLM, Warlow CP. Comparable studies of the incidence of stroke and its pathological types: results from an international collaboration. Stroke 1997;28:491–9.
[2] Special report from the National Institute of Neurological Disorders and Stroke. Classification of cerebrovascular diseases III. Stroke 1990;21:637–76.
[3] Kubo M, Hata J, Doi Y, et al. Secular trends in the incidence of and risk factors for ischemic stroke and its subtypes in Japanese population. Circulation 2008;118:2672–8.
[4] Tanizaki Y, Kiyohara Y, Kato I, et al. Incidence and risk factors for subtypes of cerebral infarction in a general population: the Hisayama Study. Stroke 2000;31:2616–22.

[5] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.
[6] Alberti KGMM, Zimmet P, Shaw J. Metabolic syndrome: a new world-wide definition: a consensus statement from the International Diabetes Federation. Diabet Med 2006;23:469–80.
[7] Committee to Evaluate Diagnostic Standards for Metabolic Syndrome. Definition and the diagnostic standard for metabolic syndrome. Nippon Naika Gakkai Zasshi 2005;94:794–809 [in Japanese].
[8] Ninomiya T, Kubo M, Doi Y, et al. Impact of metabolic syndrome on the development of cardiovascular disease in a general Japanese population: the Hisayama Study. Stroke 2007;38:2063–9.
[9] Doi Y, Ninomiya T, Hata J, et al. Proposed criteria for metabolic syndrome in Japanese based on prospective evidence: the Hisayama Study. Stroke 2009;40:1187–94.
[10] McNeill AM, Rosamond WD, Girman CJ, et al. The metabolic syndrome and 11-year risk of incident cardiovascular disease in the Atherosclerosis Risk in Communities Study. Diabetes Care 2005;28:385–90.
[11] Koren-Morag N, Goldbourt U, Tanne D. Relation between the metabolic syndrome and ischemic stroke or transient ischemic attack: a prospective cohort study in patients with atherosclerotic cardiovascular disease. Stroke 2005;36:1366–71.
[12] Najarian RM, Sullivan LM, Kannel WB, et al. Metabolic syndrome compared with type 2 diabetes mellitus as a risk factor for stroke: the Framingham Offspring Study. Arch Intern Med 2006;166:106–11.
[13] Chen HJ, Bai CH, Yeh WT, et al. Influence of metabolic syndrome and general obesity on the risk of ischemic stroke. Stroke 2006;37:1060–4.
[14] Kurl S, Laukkanen JA, Niskanen L, et al. Metabolic syndrome and the risk of stroke in middle-aged men. Stroke 2006;37:806–11.
[15] Boden-Albala B, Sacco RL, Lee HS, et al. Metabolic syndrome and ischemic stroke risk: Northern Manhattan Study. Stroke 2008;39:30–5.
[16] Katsuki S. Epidemiological and clinicopathological study on cerebrovascular disease in Japan. Prog Brain Res 1966;21:64–89.
[17] Cerebral Embolism Task Force. Cardiogenic brain embolism: the second report of the Cerebral Embolism Task Force. Arch Neurol 1989;46:727–43.
[18] Milionis HJ, Kostapanos MS, Liberopoulos EN, et al. Different definitions of the metabolic syndrome and risk of first-ever acute ischaemic non-embolic stroke in elderly subjects. Int J Clin Pract 2007;61:545–51.
[19] Kawamoto R, Tomita H, Oka Y, et al. Metabolic syndrome as a predictor of ischemic stroke in elderly persons. Intern Med 2005;44:922–7.
[20] Yokokawa H, Goto A, Terui K, et al. Prevalence of metabolic syndrome and serum marker levels in patients with four subtypes of cerebral infarction in Japan. J Clin Neurosci 2008;15:769–73.
[21] Park K, Yasuda N, Toyonaga S, et al. Significant associations of metabolic syndrome and its components with silent lacunar infarction in middle aged subjects. J Neurol Neurosurg Psychiatry 2008;79:719–21.
[22] Fisher CM. Lacunar strokes and infarcts: a review. Neurology 1982;32:871–6.
[23] Ryo M, Nakamura T, Kihara S, et al. Adiponectin as a biomarker of the metabolic syndrome. Circ J 2004;68:975–81.
[24] Matsuzawa Y. Adiponectin: identification, physiology and clinical relevance in metabolic and vascular disease. Atherosclerosis Suppl 2005;6:7–14.
[25] Shimomura I, Funahashi T, Takahashi M, et al. Enhanced expression of PAI-1 in visceral fat: possible contributor to vascular disease in obesity. Nat Med 1996;2:800–3.
[26] Eren M, Painter CA, Atkinson JB, et al. Age-dependent spontaneous coronary arterial thrombosis in transgenic mice that express a stable form of human plasminogen activator inhibitor-1. Circulation 2002;106:491–6.
[27] Bonora E, Kiechi S, Willeit J, et al. Carotid atherosclerosis and coronary heart disease in the metabolic syndrome: prospective data from the Bruneck Study. Diabetes Care 2003;26:1251–7.
[28] Bang OY, Kim JW, Lee JH, et al. Association of the metabolic syndrome with intracranial atherosclerotic stroke. Neurology 2005;65:296–8.
[29] Watanabe H, Tanabe N, Watanabe T, et al. Metabolic syndrome and risk of development of atrial fibrillation: the Niigata Preventive Medicine Study. Circulation 2008;117:1255–60.

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Trends in prevalence of Alzheimer's disease and vascular dementia in a Japanese community: the Hisayama Study

Sekita A, Ninomiya T, Tanizaki Y, Doi Y, Hata J, Yonemoto K, Arima H, Sasaki K, Iida M, Iwaki T, Kanba S, Kiyohara Y. Trends in prevalence of Alzheimer's disease and vascular dementia in a Japanese community: the Hisayama Study.

Objective: To examine secular trends in the prevalence of Alzheimer's disease (AD) and vascular dementia (VD) in a general Japanese population.
Method: Four cross-sectional examinations were conducted among residents of a Japanese community aged ≥65 in 1985, 1992, 1998 and 2005.
Results: The age- and sex-adjusted prevalence of all-cause dementia significantly increased with time (6.0% in 1985, 4.4% in 1992, 5.3% in 1998 and 8.3% in 2005; *P* for trend = 0.002). A similar trend was observed for AD (1.1%, 1.3%, 2.3% and 3.8% respectively; *P* for trend < 0.001), while the age- and sex-adjusted prevalence of VD and other/unclassified dementia showed J-shaped patterns (for VD: 2.3%, 1.5%, 1.5% and 2.5%, respectively, *P* for trend = 0.82; for other/unclassified dementia: 2.6%, 1.7%, 1.5% and 2.0%, *P* for trend = 0.26). The prevalence of AD was likely to increase with time from 1985 to 2005 among subjects aged 75 or older. The ratio of the prevalence of VD to that of AD decreased with time (2.1 in 1985, 1.2 in 1992, 0.7 in 1998 and 0.7 in 2005).
Conclusion: Our findings suggest that the prevalence of all-cause dementia and AD significantly increased over the past two decades in the general Japanese population.

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Key words: dementia; Alzheimer's disease; vascular dementia; prevalence; secular trend

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Significant outcomes

- The prevalence of all-cause dementia significantly increased over the past 20 years in a general population of Japanese elderly.
- The prevalence of Alzheimer's disease in 2005 was approximately threefold higher than that in 1985.
- The ratio of the prevalence of vascular dementia to that of Alzheimer's disease decreased with time.

Limitations

- The diagnosis of dementia and its types was made based only on clinical findings.
- There was a variation in participation rate among the four cross-sectional examinations.
- We have no information regarding factors that contributed to trends in the prevalence of dementia.

Introduction

Approximately 24.3 million people suffer from dementia globally, and this number is expected to double every 20 years to 81.1 million by 2040 because of the rapid increase in the number of the elderly worldwide (1). In Japan, where the elderly population has been increasing faster than in other

countries and the ratio of the elderly to the total population has become the highest in the world, dementia has become a serious social, medical and economic problem. Effective prevention requires a strategy based on information about the morbidity of dementia and its subtypes and its secular trends in general populations. A number of studies have investigated the prevalence of dementia and its subtypes in various populations worldwide (2–8). However, only a few population-based studies have investigated secular trends in the prevalence of dementia in defined populations (9–14), and there were very few studies examining these trends in the 2000s.

Aims of the study

The aim of this analysis was to investigate secular trends in the prevalence of all-cause dementia and dementia subtypes over the past two decades in a general population of Japanese elderly.

Material and methods

Study population

The Hisayama Study is a prospective cohort study of cerebro-cardiovascular diseases in a subrural community, the town of Hisayama, which is adjacent to the metropolitan area of Fukuoka, Japan. The population of the town has distributions of age, occupational status and nutrient intake that are almost identical with those for the whole of Japan (15). The population of the town has been stable for 50 years. As a part of the study, four cross-sectional examinations of dementia have been conducted on Hisayama residents aged 65 or older (10, 16, 17). In 1985, a total of 938 residents in that age group were invited to participate in a cross-sectional examination of dementia. After exclusion of 26 subjects who died, 10 who moved out of the town before the examination and 15 who refused the examination, 887 subjects (353 men and 534 women) underwent the examination (participation rate 94.6%) (Table 1). In a similar manner, we examined 1189 subjects (475 men and 714 women) among 1231 residents (participation rate 96.6%) in 1992, 1437 subjects (571 men and 866 women) among 1442 residents (participation rate 99.7%) in 1998 and 1566 subjects (612 men and 954 women) among 1711 residents (participation rate 91.5%) in 2005. The number of elderly subjects increased during the study period because of aging of the population, which was consistent with the national trend.

Table 1. Demographic characteristics of subjects and diagnostic procedures of dementia in each examination

	Year of examination			
	1985 (n = 887)	1992 (n = 1189)	1998 (n = 1437)	2005 (n = 1566)
Age, years	73.7 ± 6.4	74.2 ± 6.9	74.8 ± 7.2	75.9 ± 7.4
Women, %	60.2	60.1	60.3	60.9
Participation rate, %	94.6	96.6	99.7	91.5
Neuropsychological test	HDS	HDS HDS-R MMSE	HDS-R	HDS-R MMSE
Diagnosis of dementia	DSM-III	DSM-III-R	DSM-III-R	DSM-III-R

HDS, Hasegawa's Dementia Rating Scale; HDS-R, HDS, revised version; MMSE, Mini-Mental State Examination; DSM-III, Diagnostic and Statistical Manual of Mental Disorders, third edition; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, revised third edition.

Survey of dementia

We carried out a two-phase survey of dementia at each examination. The first screening survey included neuropsychological tests [Hasegawa's Dementia Scale (HDS) (18) in 1985; HDS, HDS revised version (HDS-R) (19) and Mini-Mental State Examination (MMSE) (20) in 1992; HDS-R in 1998; and HDS-R and MMSE in 2005] and questionnaires regarding psychological and medical symptoms, medical conditions and activities of daily living (Table 1). HDS and HDS-R are neuropsychological tests that are widely utilized in Japan and comprised of questions regarding orientation, memory function, common knowledge and calculation capacities. We confirmed the excellent agreement among these tests in 1992 (agreement rate = 95% and kappa coefficient = 0.77 between MMSE and HDS; agreement rate = 96% and kappa coefficient = 0.81 between MMSE and HDS-R). The assessment of neuropsychological tests was performed by investigators who were trained in advance in the use of the tests. For subjects whose test scores were below the cutoff points (22/32.5 for HDS, 21/30 for HDS-R and MMSE), comprehensive investigations, including interviews of the families or attending physicians, physical and neurological examinations and a review of the clinical records, were conducted.

Diagnosis of dementia

The diagnosis of dementia was made clinically based on the guidelines of the Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III) (21) in 1985 and those of the DSM-III revised version (DSM-III-R) (22) in 1992, 1998 and 2005 by trained neurologists/psychia-

trists who were supervised by a single neurologist (Y.K.) over the study period (Table 1). We used Karasawa's criteria (23) for the clinical evaluation of dementia as supplementation. The latter has been widely used for epidemiological research on dementia in Japan and divides cases with dementia into four grades of severity according to loss of intellectual abilities, severity of interference with social and occupational functioning and inability to care for oneself. The ischemic score of Hachinski et al. (24) was also used to differentiate vascular dementia (VD) from Alzheimer's disease (AD).

Among a total of 887 subjects screened in 1985, 114 (12.9%) underwent the secondary comprehensive investigation, and of those, 59 (6.7%) were diagnosed as having dementia. Similarly, 194 subjects (16.3%) in 1992, 258 (18.0%) in 1998 and 395 (25.2%) in 2005 underwent comprehensive investigations, and of those, 68 (5.7%), 102 (7.1%) and 195 (12.5%), respectively, were diagnosed as having dementia.

Statistical analysis

Adjusted prevalence of dementia was estimated with 95% confidence interval (CI) by the direct method with 5-year age groupings, where the total population in Japan at the time of the initial examination was used as a standard population. Differences in the adjusted prevalence of dementia were tested, and the adjusted odds ratio (OR) and 95% CI were estimated using the logistic regression model including age taken as a continuous variable and sex.

Ethical considerations

The study protocol was approved by the Human Ethics Review Committee of the Graduate School of Medical Sciences, Kyushu University.

Results

Demographic characteristics of the subjects in the examinations conducted in 1985, 1992, 1998 and 2005 are shown in Table 1. The mean age was slightly increased from 73.7 years in 1985 to 75.9 years in 2005. Women accounted for approximately 60% of total subjects over the four examinations.

The prevalence of all-cause dementia in the four examinations is shown in Table 2. The age- and sex-adjusted prevalence of all-cause dementia significantly increased from 6.0% in 1985 to 8.3% in 2005 (P for trend = 0.002) and was 1.34-fold (P = 0.08) higher in 2005 than in 1985. This trend was observed in the age- and sex-adjusted prevalence of all-cause dementia for both sexes but was only significant for women (P for trend = 0.007).

Table 3 shows the secular trends in the prevalence of dementia by subtypes. The age- and sex-adjusted prevalence of AD significantly increased from 1.1% in 1985 to 3.8% in 2005 (P for trend <0.001) and was 2.00-fold higher in 1998 (P = 0.04) and 3.28-fold higher in 2005 ($P < 0.001$) than in 1985. The age- and sex-adjusted prevalence of VD showed a decreasing trend between 1985 and 1998 (from 2.3% to 1.5%) and then an increasing trend to 2.5% in 2005. A similar trend

Table 2. Secular trends in prevalence of all-cause dementia from 1985 to 2005

	Year of examination				
	1985	1992	1998	2005	P for trend
Total					
Population at risk	887	1189	1437	1566	0.002
No. of cases of dementia	59	68	102	195	
Crude prevalence (%) (95% CI)	6.7 (5.0–8.3)	5.7 (4.4–7.1)	7.1 (5.7–8.5)	12.5 (10.7–14.2)	
Age- and sex-adjusted prevalence (%) (95% CI)	6.0 (4.4–7.6)	4.4 (3.3–5.6)	5.3 (4.2–6.4)	8.3 (7.0–9.5)	
Age- and sex-adjusted odds ratio (95% CI)	1 (reference)	0.70 (0.48–1.03)	0.78 (0.55–1.12)	1.34 (0.97–1.87)	
Women					
Population at risk	534	714	866	954	0.007
No. of cases of dementia	40	51	77	141	
Crude prevalence (%)(95% CI)	7.5 (5.2–9.8)	7.1 (5.2–9.1)	8.9 (6.9–10.9)	14.8 (12.3–17.2)	
Age-adjusted prevalence (%) (95% CI)	6.6 (4.5–8.6)	5.3 (3.8–6.8)	6.4 (4.9–7.9)	9.3 (7.7–10.9)	
Age-adjusted odds ratio (95% CI)	1 (reference)	0.73 (0.46–1.17)	0.83 (0.54–1.29)	1.39 (0.93–2.10)	
Men					
Population at risk	353	475	571	612	0.13
No. of cases of dementia	19	17	25	54	
Crude prevalence (%) (95% CI)	5.4 (3.0–7.8)	3.6 (1.9–5.3)	4.4 (2.7–6.1)	8.8 (6.5–11.2)	
Age- adjusted prevalence (%) (95% CI)	5.4 (3.0–7.8)	3.6 (1.9–5.3)	4.2 (2.6–5.9)	7.2 (5.3–9.2)	
Age-adjusted odds ratio (95% CI)	1 (reference)	0.63 (0.32–1.25)	0.67 (0.36–1.27)	1.25 (0.71–2.20)	

95% CI: 95% confidence interval.

Table 3. Secular trends in prevalence of dementia subtypes from 1985 to 2005

	Year of examination				
	1985 (n = 887)	1992 (n = 1189)	1998 (n = 1437)	2005 (n = 1566)	P for trend
Alzheimer's disease					
No. of cases of dementia	12	21	49	96	<0.001
Crude prevalence (%) (95% CI)	1.4 (0.6–2.1)	1.8 (1.0–2.5)	3.4 (2.5–4.4)	6.1 (4.9–7.4)	
Age- and sex-adjusted prevalence (%) (95% CI)	1.1 (0.4–1.7)	1.3 (0.7–1.9)	2.3 (1.6–3.0)	3.8 (3.0–4.6)	
Age- and sex-adjusted odds ratio (95% CI)	1 (reference)	1.11 (0.53–2.32)	2.00* (1.04–3.87)	3.28** (1.75–6.14)	
Vascular dementia					
No. of cases of dementia	21	22	25	51	0.82
Crude prevalence (%) (95% CI)	2.4 (1.4–3.4)	1.9 (1.1–2.6)	1.7 (1.1–2.4)	3.3 (2.4–4.2)	
Age- and sex-adjusted prevalence (%) (95% CI)	2.3 (1.3–3.3)	1.5 (0.8–2.2)	1.5 (0.9–2.1)	2.5 (1.7–3.2)	
Age- and sex-adjusted odds ratio (95% CI)	1 (reference)	0.70 (0.38–1.29)	0.58 (0.32–1.06)	0.95 (0.56–1.62)	
Other/unclassified dementia					
No. of cases of dementia	26	25	28	48	0.26
Crude prevalence (%) (95% CI)	2.9 (1.8–4.1)	2.1 (1.3–2.9)	1.9 (1.2–2.7)	3.1 (2.2–3.9)	
Age- and sex-adjusted prevalence (%) (95% CI)	2.6 (1.6–3.7)	1.7 (1.0–2.4)	1.5 (0.9–2.2)	2.0 (1.4–2.7)	
Age- and sex-adjusted odds ratio (95% CI)	1 (reference)	0.61 (0.35–1.08)	0.50 (0.29–0.87)	0.69 (0.41–1.14)	

95% CI: 95% confidence interval; *P < 0.05, **P < 0.01 vs. 1985.

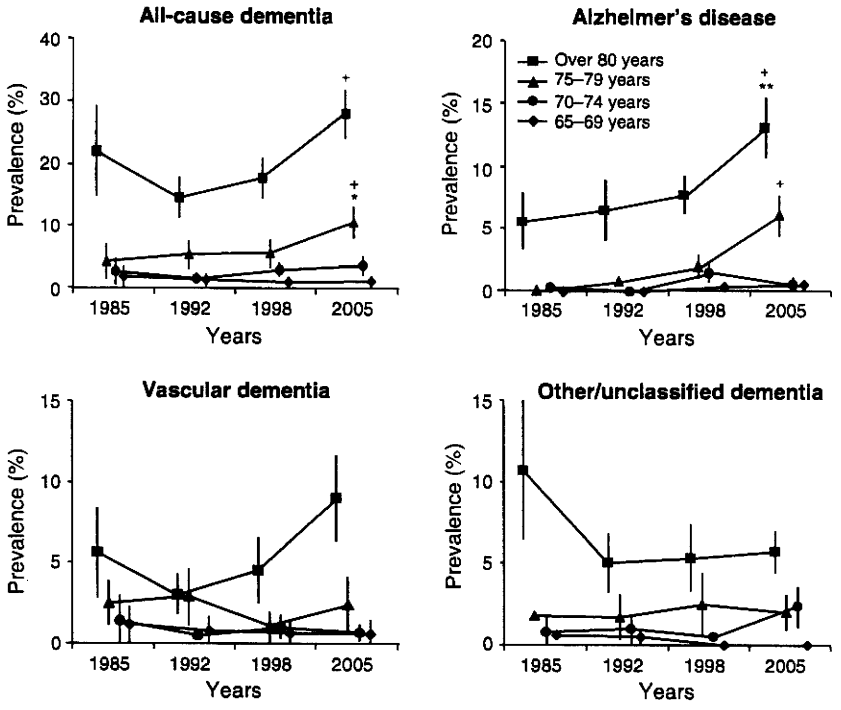

Fig. 1. Secular trends in sex-adjusted prevalence of dementia and its subtypes according to age groups. *P < 0.05, **P < 0.01 vs. 1985, +P for trend < 0.01. The vertical bars of 95% confidence intervals of adjusted prevalence were truncated at zero or more.

was observed for other/unclassified dementia. As a result, the ratio of the prevalence of VD to that of AD decreased with time (2.1 in 1985, 1.2 in 1992, 0.7 in 1998 and 0.7 in 2005).

Figure 1 shows the secular trends in the sex-adjusted prevalence of all-cause dementia and its subtypes according to age groups. The prevalence of all-cause dementia significantly increased from 1985 to 2005 among subjects aged 75 or older (P for trend < 0.01). Such a trend was also observed for the prevalence of AD in the same age group (P for trend < 0.01). The prevalence of VD tended to increase among subjects aged 80 or older in recent years (P for trend = 0.06). There were no clear changes in the prevalence of others/unclassified dementia.

Discussion

The present analysis of repeated cross-sectional examinations in a general population of Japanese elderly demonstrated that the prevalence of all-cause dementia significantly increased from 1985 to 2005. A similar trend was observed for AD but not

for VD. The prevalence of all-cause dementia and AD increased with time among subjects aged 75 or older, while increasing prevalence of VD was observed among subjects aged 80 or older.

Several population-based observational studies have reported secular trends in the prevalence of dementia (9–14). The Lundby Study conducted repeated cross-sectional examinations of dementia in a Swedish community and found no significant changes in the prevalence of senile dementia and multi-infarct dementia from 1945–1957 to 1957–1972 (9). The ZARADEMP project has also found no clear difference in the prevalence of dementia in a Southern European population in 1988–1989 and the prevalence in 1994–1996 (13). In contrast, an observational study from Rochester, Minnesota, in the USA demonstrated that the prevalence of dementia and AD significantly increased from 1975 to 1985 (11). An observational study from Beijing, China, also reported that the prevalence of dementia was slightly higher in 1997 than in 1986 and that AD increased its ranking from the second most common type of dementia (1986) to the most common type (1997) (12). An epidemiological study in the town of Daisen, Japan, has also demonstrated that the prevalence of all-cause dementia, AD and VD increased from 1980 to 2000 (14). In the present study, the prevalence of all-cause dementia and AD increased from 1985 to 2005 in a Japanese community. Although results obtained from Western countries were inconclusive, there may be an increasing burden of dementia in Asian countries.

The ratio of the prevalence of VD to that of AD has been shown to be an effective index for comparing the prevalence of VD and AD in various regions (3). In their recent review, Suh and Shah (3) used this ratio to compare the prevalence of VD and AD in numerous countries and found that AD was more prevalent than VD in USA and Europe. On the other hand, in Asian countries (China, Korea and Japan), there has been a temporal change in the VD/AD ratio. Although VD was more prevalent than AD in Asian countries before 1989, AD has become nearly twice as prevalent as VD since early 1990s (3). The present study confirms the findings of previous observational studies and suggests that AD has become more prevalent than VD in the Asian region in recent years.

The causes of the increase in the prevalence of all-cause dementia and AD observed in our study were not completely resolved. Aging of the study population may be a probable cause of these findings, because age is one of the strongest risk factors for cognitive decline (16, 25). However, the increasing trends in the prevalence of dementia remained significant even after controlling for the confounding effects of age using two different statistical methods, i.e. the direct method using 5-year age groupings and the logistic regression model including age taken as a continuous covariate. Therefore, aging of the study population is not likely to be a leading cause for increasing prevalence of dementia. Another possible cause would be the recent increase in the prevalence of metabolic disorders, such as obesity, hypercholesterolemia and glucose intolerance (15), which have been associated with the risk of AD (26–33).

Another interesting finding of the present study is that the age- and sex-adjusted prevalence of VD decreased from 1985 to 1998 and then increased in 2005, although the trend was not significant. A J-shaped trend in VD was observed among subjects aged 80 or older. VD has not only been shown to be associated with metabolic disorders but also with hypertension. Therefore, the decline in the prevalence of VD in the 1990s may have been ascribable to an improvement in the management of hypertension. In fact, during this period, the incidence and mortality of stroke significantly decreased in Japan, especially among the elderly (34). Without doubt, the popularization of antihypertensive therapy greatly contributed to this welcome trend. However, the steep increase in metabolic disorders and partly insufficient control of hypertension, especially among the elderly, may be responsible for the increasing prevalence of VD in recent years.

In Japan, the number of elderly subjects who lived in old-age homes or were institutionalized in other medical care facilities increased during the study period along with the improvement in the national medical care system for the elderly. Thus, the increase in subjects with dementia in our study may have been attributable to more effective management of these patients in recent years. However, this influence was suggested to be limited because the increase in the prevalence was observed only for AD but not for VD and other/unclassified dementia, and the 10-year survival rates were not significantly different among dementia subtypes in Hisayama residents (17).

The strengths of our study include its long observational period, high participation rates and relatively consistent way to diagnose dementia. The study has three limitations. First, the diagnosis of dementia and its types was made based only on clinical findings. However, we used typical dementia – i.e., AD and VD – as target disease, and the prevalences of all-cause dementia, AD and VD were similar to those obtained from other

observational studies in Asian regions (5, 35–41). Therefore, we believe that this bias is not likely to invalidate the present findings. Second, there was a variation in participation rate among the four cross-sectional examinations. It is generally agreed that an acceptable participation rate in a population-based study, i.e., a rate that practically eliminates the threat of selection bias attributable to non-participants, is above 70% of the target population (42, 43). We enrolled more than 90% of residents in every examination, and, therefore, we believe that the findings of the present study reflect the actual secular trends in prevalence in the Japanese population. Third, we have no information regarding factors that contributed to trends in the prevalence of dementia.

In conclusion, the prevalence of all-cause dementia and AD has increased significantly over the past 20 years in a general population of Japanese elderly. The increasing trend seemed to be observed among subjects aged 75 or older. It is important to establish effective prevention strategies for dementia, particularly for AD, in countries such as Japan, where the elderly population is increasing rapidly.

Declaration of interest

None.

References

1. Ferri CP, Prince M, Brayne C et al. Global prevalence of dementia: a Delphi consensus study. Lancet 2005;**366**: 2112–2117.
2. Lobo A, Launer LJ, Fratiglioni L et al. Prevalence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. Neurology 2000;**54**: S4–S9.
3. Suh GH, Shah A. A review of the epidemiological transition in dementia – cross-national comparisons of the indices related to Alzheimer's disease and vascular dementia. Acta Psychiatr Scand 2001;**104**:4–11.
4. Liu L, Guo XE, Zhou YQ, Xia JL. Prevalence of dementia in China. Dement Geriatr Cogn Disord 2003;**15**:226–230.
5. Zhang ZX, Zahner GE, Roman GC et al. Dementia subtypes in China: prevalence in Beijing, Xian, Shanghai, and Chengdu. Arch Neurol 2005;**62**:447–453.
6. Galasko D, Salmon D, Gamst A et al. Prevalence of dementia in Chamorros on Guam: relationship to age, gender, education, and APOE. Neurology 2007;**68**:1772–1781.
7. Saz P, Lopez-Anton R, Dewey ME et al. Prevalence and implications of psychopathological non-cognitive symptoms in dementia. Acta Psychiatr Scand 2009;**119**:107–116.
8. Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia—meta-analysis of 41 robust inception cohort studies. Acta Psychiatr Scand 2009;**119**:252–265.
9. Rorsman B, Hagnell O, Lanke J. Prevalence and incidence of senile and multi-infarct dementia in the Lundby Study: a comparison between the time periods 1947–1957 and 1957–1972. Neuropsychobiology 1986;**15**:122–129.
10. Kiyohara Y, Yoshitake T, Kato I et al. Changing patterns in the prevalence of dementia in a Japanese community: the Hisayama Study. Gerontology 1994;**40**(Suppl 2):29–35.
11. Beard CM, Kokmen E, O'Brien PC, Kurland LT. The prevalence of dementia is changing over time in Rochester, Minnesota. Neurology 1995;**45**:75–79.
12. Li S, Yan F, Li G et al. Is the dementia rate increasing in Beijing? Prevalence and incidence of dementia 10 years later in an urban elderly population. Acta Psychiatr Scand 2007;**115**:73–79.
13. Lobo A, Saz P, Marcos G et al. Prevalence of dementia in a southern European population in two different time periods: the ZARADEMP Project. Acta Psychiatr Scand 2007;**116**:299–307.
14. Wakutani Y, Kusumi M, Wada K et al. Longitudinal changes in the prevalence of dementia in a Japanese rural area. Psychogeriatrics 2007;**7**:150–154.
15. Kubo M, Hata J, Doi Y, Tanizaki Y, Iida M, Kiyohara Y. Secular trends in the incidence of and risk factors for ischemic stroke and its subtypes in Japanese population. Circulation 2008;**118**:2672–2678.
16. Yoshitake T, Kiyohara Y, Kato I et al. Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: the Hisayama Study. Neurology 1995;**45**:1161–1168.
17. Matsui Y, Tanizaki Y, Arima H et al. Incidence and survival of dementia in a general population of Japanese elderly: the Hisayama Study. J Neurol Neurosurg Psychiatry 2009;**80**:366–370.
18. Hasegawa K, Inoue K, Moriya K. An investigation of dementia rating scale for the elderly (in Japanese). Seishin Igaku 1974;**16**:965–969.
19. Katoh S, Simogaki H, Onodera A et al. Development of the revised version of Hasegawa's dementia scale (HDS-R) (in Japanese). Jpn J Geriatr Psychiatry 1991;**2**:1339–1347.
20. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;**12**:189–198.
21. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 3rd edn. Washington, DC: American Psychiatric Association, 1980.
22. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 3rd edn, revised. Washington, DC: American Psychiatric Association, 1987.
23. Tokyo Metropolitan Geriatric Research Institute, Laboratory of Psychiatry. Social and psychiatric realities of the elderly with senile dementia staying at home in the Tokyo metropolitan area (in Japanese). Tokyo: Government Publication of Tokyo Metropolis, 1981.
24. Hachinski VC, Iliff LD, Zilhka E et al. Cerebral blood flow in dementia. Arch Neurol 1975;**32**:632–637.
25. Luck T, Riedel-Heller SG, Luppa M et al. Risk factors for incident mild cognitive impairment-results from the German Study on Aging, Cognition and Dementia in primary care patients (AgeCoDe). Acta Psychiatr Scand 2010;**121**: 260–272.
26. Arvanitakis Z, Wilson RS, Bienias JL, Evans DA, Bennett DA. Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. Arch Neurol 2004;**61**:661–666.
27. Peila R, Rodriguez BL, Launer LJ. Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: the Honolulu-Asia Aging Study. Diabetes 2002;**51**:1256–1262.

28. Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: the Rotterdam Study. Neurology 1999;**53**: 1937–1942.
29. Kivipelto M, Helkala EL, Laakso MP et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. BMJ 2001;**322**:1447–1451.
30. Notkola IL, Sulkava R, Pekkanen J et al. Serum total cholesterol, apolipoprotein E epsilon 4 allele, and Alzheimer's disease. Neuroepidemiology 1998;**17**:14–20.
31. Whitmer RA, Gunderson EP, Quesenberry CP Jr, Zhou J, Yaffe K. Body mass index in midlife and risk of Alzheimer disease and vascular dementia. Curr Alzheimer Res 2007;**4**: 103–109.
32. Hayden KM, Zandi PP, Lyketsos CG et al. Vascular risk factors for incident Alzheimer disease and vascular dementia: the Cache County Study. Alzheimer Dis Assoc Disord 2006;**20**:93–100.
33. Gustafson D, Rothenberg E, Blennow K, Steen B, Skoog I. An 18-year follow-up of overweight and risk of Alzheimer disease. Arch Intern Med 2003;**163**:1524–1528.
34. Kubo M, Kiyohara Y, Kato I et al. Trends in the incidence, mortality, and survival rate of cardiovascular disease in a Japanese community: the Hisayama Study. Stroke 2003;**34**: 2349–2354.
35. Meguro K, Ishii H, Yamaguchi S et al. Prevalence of dementia and dementing diseases in Japan: the Tajiri Project. Arch Neurol 2002;**59**:1109–1114.
36. Yamada T, Hattori H, Miura A, Tanabe M, Yamori Y. Prevalence of Alzheimer's disease, vascular dementia and dementia with Lewy bodies in a Japanese population. Psychiatry Clin Neurosci 2001;**55**:21–25.
37. Ikeda M, Hokoishi K, Maki N et al. Increased prevalence of vascular dementia in Japan: a community-based epidemiological study. Neurology 2001;**57**:839–844.
38. Shibayama H, Kasahara Y, Kobayashi H. Prevalence of dementia in a Japanese elderly population. Acta Psychiatr Scand 1986;**74**:144–151.
39. Jhoo JH, Kim KW, Huh Y et al. Prevalence of dementia and its subtypes in an elderly urban korean population: results from the Korean Longitudinal Study on Health And Aging (KLoSHA). Dement Geriatr Cogn Disord 2008;**26**: 270–276.
40. Ogura C, Nakamoto H, Uema T, Yamamoto K, Yonemori T, Yoshimura T. Prevalence of senile dementia in Okinawa, Japan. Int J Epidemiol 1995;**24**:373–380.
41. Yamada M, Sasaki H, Mimori Y et al. Prevalence and risks of dementia in the Japanese population: RERF's adult health study Hiroshima subjects. Radiation Effects Research Foundation. J Am Geriatr Soc 1999;**47**:189–195.
42. Groves R. Survey errors and survey costs. New York: John Wiley & Sons, 1989.
43. Kasper JD, Shapiro S, Guralnik JM, Bandeen-Roche KJ, Fried LP. Designing a community study of moderately to severely disabled older women: the Women's Health and Aging Study. Ann Epidemiol 1999;**9**:498–507.

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Associations of metabolic factors, especially serum retinol-binding protein 4 (RBP4), with blood pressure in Japanese-the Tanno and Sobetsu study

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Abstract. Excess secretion of various adipocyte-derived molecules has been linked with insulin resistance, obesity, diabetes, inflammation, atherosclerosis, and cardiovascular disease. Retinol-binding protein 4 (RBP4), one of the new adipocytokine, is recently reported to provide a link between insulin resistance and features of metabolic factors. Hypertension is one of the most influential risk factors among cardiovascular disease. We examined the relationship between systolic blood pressure (BP) levels and metabolic factors including homeostasis model assessment of insulin resistance (HOMA-R), high sensitivity c-reactive protein (hs-CRP), adiponectin, and RBP4. The subjects were 153 men aged 59±14 years and 224 women aged 57±14 years who had undergone medical check-ups in rural communities in 2007. Systolic BP was positively correlated with HOMA-R, hs-CRP and RBP4 but not with adiponectin in women. There was a positive significant relationship between serum RBP4 levels and blood pressure in women, but such a relationship was not found in men. Serum RBP4 levels were not correlated with HOMA-R in either men or women. Serum RBP4 levels negatively were correlated with estimated glomerular filtration rate (eGFR) in women but not in men. Multiple regression analysis revealed that serum RBP4 levels significantly were related to systolic BP independently of age, sex, body mass index (BMI), total cholesterol levels and eGFR. Our study showed that increased levels of RBP4 as well as HOMA-R and hs-CRP in women were significantly associated with increased levels of systolic BP.

Key words: RBP4, Blood pressure, Arteriosclerosis, Hypertension, Epidemiology

RETINOL-BINDING PROTEIN 4 (RBP4) is an adipocytokine that was discovered recently while trying to identify the substance responsible for regulating insulin sensitivity in mice either lacking or overexpressing adipocyte-specific glucose transporter 4 (GLUT4) [1]. RBP4 is the only specific transport protein for retinol (vitamin A) in the circulatory system, and its only known function is to deliver retinol to tissues [2]. Initial reports in humans revealed strong correlations between insulin resistance and features of metabolic syndrome [3]. However, several subsequent studies in subjects with obesity or diabetes failed to identify a relationship between RBP4 and insulin sensitivity [4]. Solini *et al.* showed in a small clinical group study in Europe that levels of RBP4 were increased in newly diagnosed hypertensive women and were correlated with the degree of carotid intima-media thickness (IMT), suggesting its possible use as a proxy of early vascular impairment [5].

But there have been few reports based on relatively healthy people in Japanese. We hypothesized that if the relationship between RBP4 and blood pressure is ascertained, RBP4 may have a possible link with increased blood pressure mediated by a pathway different from insulin resistance, environment and heredity pathway.

In this study, we investigated the relationships between systolic blood pressure levels and a number of different parameters, including homeostasis model assessment of insulin resistance (HOMA-R) as an indicator of insulin resistance, high sensitivity c-reactive

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There are no conflicts of interest.

protein (hs-CRP) as an inflammation marker, adiponectin as one of the adipocytokine, and RBP4 as a new remarkable adipocytokine.

Materials and Methods

The subjects were recruited from residents of two rural towns (Tanno and Sobetsu) in Hokkaido, the northernmost island of Japan. In July 2007, we carried out regional medical check-ups. A total of 718 subjects (298 men and 420 women) came to the medical check-ups. Medical check-ups were performed between 0600 h and 0900 h. All subjects were in a fasting state. Medical histories including medications, smoking and drinking habits were taken from the subjects. Anthropometric parameters were measured followed by blood pressure (BP) measurements. Then medical examinations and blood collections were conducted. Blood pressure was measured twice consecutively on the upper arm using an automated sphygmomanometer (HEM-907, Omron corporation, Kyoto, Japan) with subjects in a seated resting position, and average blood pressure was used for analysis. Levels of plasma glucose (PG), serum total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL) cholesterol, estimated glomerular filtration rate (eGFR), serum creatinine (SCr), immunoreactive insulin (IRI), hs-CRP and adiponectin were measured in each subject. Biochemical data were measured as follows: PG, hexonase method; total cholesterol, the cholesterol oxidase enzymatic assay method; HDL, the direct method; triglyceride, enzymatic method; SCr, enzymatic method; IRI, enzyme immunoassay method; hs-CRP, nepherometry method. EGFR was calculated by followed the Japanese equation [6]: eGFR (mL/min/1.73m^2) $=194\times SCr^{(-1.094)}\times age^{(-0.287)}\times 0.739$ (if female). Serum RBP4 level was measured using an enzyme-linked immunosorbent assay (ELISA) kit (Immundiagnostik AG, Bensheim, Germany). Cross-validation of this kit with other methods for measuring RBP4, such as quantitative Western blotting, was not performed. Serum adiponectin level was measured using an ELISA kit (human adiponectin ELISA kit; Otsuka Pharmaceutical Co. Tokyo, Japan). Body mass index (BMI) was calculated as body weight (in kilograms) divided by the square of body height (in meters). HOMA-R was used as an indicator of insulin resistance. HOMA-R was calculated by the formula 'IRI (μU/L) × PG (mg/dL) / 405'. Subjects taking any medications were excluded to rule out the effect of any drugs. After excluding 341 of the 718 subjects, 377 subjects remained for analysis. The study protocol was approved by the Ethics Committee of Sapporo Medical University, and written informed consent was obtained from all of the subjects. Statistical analysis was performed with SPSS statistical package software version 12.0J for Windows (SPSS Inc., Chicago, Illinois, USA). The correlation between two variables was evaluated using Pearson's correlation coefficient. Comparison between two groups was done with an unpaired *t* test. Since serum RBP4 level showed an F distribution, natural logarithmic-transformed values were used. Each value is presented as mean±SD. A *p* value of less than 0.05 was considered statistically significant.

Table 1 Baseline characteristics of study subjects

	Men(n=153)	Women(n=224)
Age (years)	59.0±13.9	57.0±13.8
Body mass index (kg/m^2)	23.9±3.3	22.9±3.8*
Systolic BP (mmHg)	131±21	126±24*
Diastolic BP (mmHg)	78±11	74±13*
Total cholesterol (mg/dL)	201±34	205±33
Triglyceride (mg/dL)	120±85	85±42*
HDL cholesterol (mg/dL)	56±14	66±16*
Fasting plasma glucose (mg/dL)	96±11	92±12*
HOMA-R	1.3±1.0	1.1±0.8
High sensitivity CRP (mg/dL)	0.07±0.08	0.05±0.07
Estimated GFR (mL/min/1.73m^2)	86.1±14.9	87.9±19.9
Adiponectin (μg/mL)	9.3±4.6	14.3±6.7*
Retinol-binding protein 4 (mg/L)	33.4±14.6	29.8±14.8*

Data are presented as mean±SD. BP, blood pressure; HDL, high-density lipoprotein; HOMA-R, homeostasis model assessment of insulin resistance; CRP, C-reactive protein; GFR, glomerular filtration rate. *$p < 0.05$ *vs.* men

Results

The subjects included 153 men and 224 women. Men were significantly older than women (59.0±13.9 years *vs.* 57.0±13.8 years). Serum RBP4 level in men was significantly higher than that in women (33.4±14.6mg/L *vs.* 29.8±14.8mg/L). Baseline characteristics are shown in Table 1. No significant correlation between systolic BP and HOMA-R, hs-CRP, adiponectin or RBP4 was found in men (Table 2). Systolic BP was positively correlated with HOMA-R

Table 2 Correlations between SBP and other variables

	Men		Women	
	r	*p*	r	*p*
HOMA-R	0.03	0.71	0.21	0.002
High sensitivity CRP(mg/dL)	-0.03	0.70	0.15	0.038
Adiponectin(μg/mL)	-0.007	0.93	0.10	0.12
Retinol-binding protein 4(mg/L)	0.008	0.92	0.25	<0.0001

SBP, systolic blood pressure; HOMA-R, homeostasis model assessment of insulin resistance; CRP, C-reactive protein

Table 3 Correlations between RBP4 and other variables

	Men		Women	
	r	*p*	r	*p*
Age(years)	-0.14	0.082	0.17	0.01
Body mass index (kg/m^2)	-0.11	0.19	0.049	0.46
Systolic BP(mmHg)	0.008	0.92	0.27	<0.0001
Diastolic BP(mmHg)	0.094	0.25	0.21	0.002
Total cholesterol (mg/dL)	0.20	0.011	0.33	<0.0001
Triglyceride (mg/dL)	0.19	0.017	0.085	0.21
HDL-cholesterol (mg/dL)	0.22	0.006	0.20	0.003
Fasting plasma glucose (mg/dL)	-0.016	0.85	0.035	0.60
HOMA-R	-0.16	0.054	0.025	0.71
High sensitivity-CRP(mg/dL)	-0.17	0.046	0.021	0.77
Estimated GFR(mL/min/1.73m^2)	-0.07	0.39	-0.25	<0.0001
Adiponectin (μg/mL)	0.006	0.94	0.15	0.027

RBP4, Retinol-binding protein 4; BP, blood pressure; HDL, high-density lipoprotein; HOMA-R, homeostasis model assessment of insulin resistance; CRP, C-reactive protein; GFR, glomerular filtration rate

(r=0.21, p=0.002), hs-CRP (r=0.15, p=0.038) and RBP4 (r=0.25, p<0.0001) but not with adiponectin (r=0.10, p=0.12) in women (Table 2). Serum RBP4 level was positively correlated with TC (r=0.20, p=0.011), TG (r=0.19, p=0.017) and HDL cholesterol (r=0.22, p=0.006) in men. Serum RBP4 level was positively correlated with age (r=0.17, p=0.01), systolic BP (r=0.27, p<0.0001), diastolic BP (r=0.21, p=0.002), TC (r=0.33, p<0.0001), HDL cholesterol (r=0.20, p=0.003) and adiponectin (r=0.15, p=0.027) and was negatively correlated with eGFR (r=-0.25, p<0.0001) in women. However, no significant correlations between serum RBP4 level and BMI or HOMA-R were found in either men or women (Table 3). There was a significant positive correlation between RBP4 and systolic BP in women (r=0.27, p<0.0001), but not in men (r=0.008, p=0.92) (Fig. 1). There was a significant positive correlation between serum RBP4 levels and blood pressure categories in women. This correlation was not observed in men (Fig. 2). The categories were in accordance with the Japanese guidelines for the management of hypertension (JSH 2009). In multiple regression analysis using RBP4 as a dependent variable, systolic BP was selected as an independent variable in women but not in men (Table not shown). We then examined the relationship between systolic BP and serum RBP4 level. After adjusting for age, sex, BMI, TC and eGFR, serum RBP4 level was independently correlated with systolic BP (Table 4).