Table 2. Age-Adjusted HRs for the Development of CVD According to the Cutoff Points of Waist Circumference Among Various Criteria of MetS

MetS Criteria	Waist Cutoff, cm	No. of Subjects	No. of Events	Age-Adjusted HR (95% CI)	*P* Value
Men					
NCEP	≤102	1042	131	1 (referent)	
	>102	8	0	. . .	. . .
IDF (Europids)	<94	972	120	1 (referent)	
	≥94	78	11	1.54 (0.83–2.87)	0.17
IDF (Asians)	<90	873	102	1 (referent)	
	≥90	177	29	1.81 (1.19–2.74)	0.005
Japanese	<85	621	77	1 (referent)	
	≥85	429	54	1.22 (0.86–1.73)	0.28
Women					
NCEP	<88	1069	82	1 (referent)	
	≥88	333	33	1.22 (0.81–1.82)	0.34
IDF (Asians)	<80	601	38	1 (referent)	
	≥80	801	77	1.46 (0.99–2.16)	0.05
Japanese	<90	1113	89	1 (referent)	
	≥90	289	26	1.05 (0.68–1.62)	0.83

adjusted population-attributable risk percents for MetS defined by the IDF, modified NCEP, and modified Japanese criteria were comparably higher than those for MetS defined by the other criteria in both sexes, and all of the population-attributable risk percents were larger in women than in men.

To investigate the necessity of central obesity defined as a waist circumference of ≥90 cm in men and ≥80 cm in women for predicting CVD in the modified Japanese criteria, the previously mentioned risk factor-adjusted HR according to the number of MetS components other than waist circumference were estimated by the presence or absence of central obesity (Table 4). In the subjects who had central obesity, the HR of CVD increased significantly as the number of MetS components increased, whereas this trend was not observed in the subjects without central obesity. In the subjects with central obesity, the risk of CVD significantly increased if subjects had 2 or more MetS components compared with individuals who had no MetS component (one component: adjusted HR=1.13; 95% CI, 0.53 to 2.40; P=0.74; 2 components: adjusted HR=2.47; 95% CI, 1.21 to 5.04; P=0.01; 3 components: adjusted HR=3.09; 95% CI, 1.40 to 6.79; P=0.005). Similar relationships were found when CVD was stratified into ischemic stroke and coronary heart disease.

Because diabetes and hypertension are strong risk factors for CVD, we examined both the combined and separate effects of MetS and diabetes or hypertension on the development of CVD. As shown in Table 5, compared with nondiabetic subjects without MetS, nondiabetic subjects with MetS had significantly higher multivariate-adjusted HR of ischemic stroke (adjusted HR=1.65; 95% CI, 1.04 to 2.62; P=0.03); HR was markedly higher than that in diabetic subjects with MetS (adjusted HR=5.35; 95% CI, 3.28 to 8.73; P<0.001). However, no elevation was found in diabetic subjects without MetS. Similar associations were observed for coronary heart disease. Likewise, the multivariate-adjusted HR of ischemic stroke was significantly higher in normotensive subjects with MetS (adjusted HR=2.13; 95% CI, 1.03 to 4.39; P=0.04) and in hypertensive subjects with MetS (adjusted HR=3.17; 95% CI, 2.01 to 5.02; P<0.001) but was not significant in hypertensive subjects without MetS. Similar patterns were seen for coronary heart disease. Significant interactions between MetS and diabetes were revealed in the risk of ischemic stroke and coronary heart disease (P<0.01), whereas the interactions between MetS and hypertension were not significant.

Discussion

Using data from a 14-year follow-up study of a general Japanese population, we demonstrated that the optimal cutoff point of waist circumference for predicting CVD in Japanese was 90 cm in men and 80 cm in women. In the comparison of various MetS criteria, the modified Japanese criteria set, which uses this cutoff point instead of the original one, was a better predictor for incident CVD in both sexes. According to this criteria set, in subjects with central obesity only, the HR of future CVD increased as the number of MetS components increased, and a significantly elevated risk was identified in subjects who had ≥2 MetS components compared with those who had no MetS component. Furthermore, the significant effects of MetS on the development of ischemic stroke and coronary heart disease were independent of hypertension and diabetes. These findings suggest that the modified Japanese criteria are better for predicting CVD in Japanese.

The existence of different criteria sets for MetS has caused a great deal of confusion in routine practice in Japan. Whereas the IDF criteria are recommended internationally, the Japanese criteria are commonly used in Japan. The established MetS criteria are based mainly on "expert" opinions, and the evidence derived from prospective studies is scarce.[12] Thus, it remains uncertain whether the threshold at which each MetS component is defined as positive or negative is optimal or even useful for predicting the risk of

Table 3. Age- or Multivariate-Adjusted HRs and Population-Attributable Risk Percents of MetS Defined by Various Criteria for the Development of CVD

MetS Criteria	Population at Risk, n	No. of Events	Age-Adjusted HR (95% CI)	*P* Value	Multivariate-Adjusted HR (95% CI)	*P* Value	Population-Attributable Risk Percents
Men							
NCEP							
Mets (−)	874	100	1 (referent)		1 (referent)		
Mets (+)	176	31	1.63 (1.09–2.44)	0.01	1.55 (1.03–2.33)	0.03	8.4
IDF for Asians							
Mets (−)	909	106	1 (referent)		1 (referent)		
Mets (+)	141	25	1.95 (1.26–3.02)	0.003	1.96 (1.25–3.08)	0.003	11.4
Japanese							
Mets (−)	825	97	1 (referent)		1 (referent)		
Mets (+)	225	34	1.40 (0.95–2.07)	0.09	1.28 (0.86–1.91)	0.21	5.7
Modified NCEP							
Mets (−)	823	91	1 (referent)		1 (referent)		
Mets (+)	227	40	1.74 (1.20–2.52)	0.003	1.66 (1.14–2.43)	0.008	12.5
Modified Japanese							
Mets (−)	945	107	1 (referent)		1 (referent)		
Mets (+)	105	24	2.58 (1.65–4.02)	<0.001	2.49 (1.57–3.94)	<0.001	13.0
Women							
NCEP							
Mets (−)	1,090	71	1 (referent)		1 (referent)		
Mets (+)	312	44	1.74 (1.19–2.54)	0.004	1.65 (1.13–2.43)	0.01	12.6
IDF for Asians							
Mets (−)	918	53	1 (referent)		1 (referent)		
Mets (+)	484	62	1.82 (1.26–2.63)	0.001	1.79 (1.23–2.60)	0.002	21.4
Japanese							
Mets (−)	1,289	96	1 (referent)		1 (referent)		
Mets (+)	113	19	1.96 (1.20–3.21)	0.007	1.89 (1.15–3.10)	0.01	6.7
Modified NCEP							
Mets (−)	963	53	1 (referent)		1 (referent)		
Mets (+)	439	62	1.96 (1.36–2.84)	<0.001	1.88 (1.30–2.74)	<0.001	21.6
Modified Japanese							
Mets (−)	1,142	68	1 (referent)		1 (referent)		
Mets (+)	260	47	2.39 (1.65–3.48)	<0.001	2.27 (1.55–3.32)	<0.001	19.1

Note: Multivariate adjustment was made for age, serum total cholesterol, proteinuria, electrocardiogram abnormalities, alcohol intake, smoking habits, and regular exercise.

CVD. The findings of our study indicate that the definition of MetS by the modified Japanese criteria confers greater accuracy in predicting CVD events compared with the other ones. There are some possible explanations for this superiority. First, this criteria set adopted the optimal cutoff value of waist circumference for predicting vascular events in the present cohort. An optimal cutoff point of waist circumference for having cardiovascular risk factors has been discussed extensively in several cross-sectional studies of Asian populations. Hara et al showed in a receiver operating characteristic analysis that 85 cm for men and 78 cm for women were the best values for predicting other MetS features in a Japanese population.[13] Similar analyses reported that 90 cm in men and 84 cm in women was optimal in Japanese American[14] and 85 cm in men and 80 cm in women in Chinese populations.[15,16] However, no studies showed an optimal cutoff value of waist circumference for CVD risk in a prospective cohort design. Our finding is the first evidence that the optimal cutoff point of waist circumference for predicting CVD was 90 cm in men and 80 cm in women in a general Japanese population. This evidence might be extrapolated to other Asian populations having similar physiques and genetics.

Second, when we used our modified Japanese criteria, the HR of cardiovascular events rose obviously as the number of MetS components increased only in subjects with central obesity. Thus, to treat waist circumference as an essential component would likely improve the precision of the prediction of cardiovascular events in the current subjects. There has been controversy over the necessity of central obesity for

Table 4. Multivariate-Adjusted HRs for the Development of CVD According to the No. of MetS Components by the Presence or Absence of Central Obesity

	No. of MetS Components	Population at risk, n	No. of Events	Multivariate-Adjusted HR (95% CI)	*P* for Trend
Cardiovascular disease					
Central obesity (−)	0	509	31	1 (referent)	
	1	563	64	1.32 (0.85–2.04)	
	2	311	32	1.07 (0.64–1.78)	
	3	91	13	1.39 (0.71–2.73)	0.58
Central obesity (+)	0	259	10	1 (referent)	
	1	354	25	1.13 (0.53–2.40)	
	2	261	47	2.47 (1.21–5.04)	
	3	104	24	3.09 (1.40–6.79)	<0.001
Ischemic stroke					
Central obesity (−)	0	509	19	1 (referent)	
	1	563	39	1.37 (0.78–2.40)	
	2	311	16	1.02 (0.51–2.01)	
	3	91	4	0.84 (0.28–2.52)	0.76
Central obesity (+)	0	259	6	1 (referent)	
	1	354	15	1.31 (0.50–3.42)	
	2	261	30	2.95 (1.18–7.34)	
	3	104	16	3.99 (1.47–10.84)	<0.001
Coronary heart disease					
Central obesity (−)	0	509	16	1 (referent)	
	1	563	31	1.13 (0.61–2.09)	
	2	311	16	0.84 (0.41–1.73)	
	3	91	10	1.76 (0.77–4.02)	0.56
Central obesity (+)	0	259	4	1 (referent)	
	1	354	11	1.10 (0.34–3.57)	
	2	261	24	2.85 (0.95–8.56)	
	3	104	13	3.50 (1.07–11.49)	0.001

Note: Central obesity was defined by waist circumference of ≥90 cm in men and ≥80 cm in women. Multivariate adjustment was made for age, serum total cholesterol, proteinuria, electrocardiogram abnormalities, alcohol intake, smoking habits, and regular exercise.

the diagnosis of MetS. In NIPPON DATA90, a Japanese cohort study, the risk of CVD death increased significantly as the number of MetS components rose both in nonobese participants and obese ones.[8] On the other hand, in the present study, a clear trend in the risk of CVD occurrence was observed only in the subjects with central obesity. This inconsistency in findings might be caused by the difference in populations and the definition of obesity. In the NIPPON DATA90 study, BMI was substituted for waist circumference in the MetS definition. However, there is often remarkable heterogeneity of waist circumference among individuals with similar BMI values. It has been also shown that, among obese individuals, waist circumference indicates an increased risk of CVD, and this association is independent of the risk predicted by increased BMI.[17] Thus, the use of BMI instead of waist circumference may lead to a misdiagnosis of MetS.

In the present study, the risk of CVD occurrence was higher for the modified Japanese MetS criteria than for the IDF criteria despite the identical condition regarding central obesity. One possibility for this is that the definitions of hyperglycemia and dyslipidemia are different between the 2 sets of MetS criteria. In our subjects, the definitions of hyperglycemia and dyslipidemia in Japanese criteria were superior to those in the other criteria for the prediction of the development of CVD (data not shown). These facts may explain why the modified Japanese criteria had a higher HR. Further studies are needed to optimize the cutoff points of fasting plasma glucose and lipid levels for predicting cardiovascular events.

In our study, there was no large difference in waist circumference between our men and women (82.0 cm versus 81.1 cm). On the other hand, the optimal cutoff point of waist circumference for predicting CVD was lower in women (80 cm) than in men (90 cm). It is known that men are prone to intra-abdominal fat accumulation, whereas women are prone to subcutaneous fat accumulation.[18] Because men would have more intra-abdominal fat than women at a given waist circumference, it may be valid to select a lower cutpoint of waist circumference for men than for women. However, recent epidemiological studies using CT revealed that women

Table 5. Multivariate-Adjusted HRs for the Development of Ischemic Stroke and Coronary Heart Disease According to the Presence or Absence of MetS and Diabetes as well as Hypertension

		Ischemic Stroke		Coronary Heart Disease	
	Population at Risk, n	No. of Events	Multivariate-Adjusted HR (95% CI)	No. of Events	Multivariate-Adjusted HR (95% CI)
Diabetes					
DM (−)+MetS (−)	1956	93	1 (referent)	79	1 (referent)
DM (−)+MetS (+)	274	25	1.65 (1.04–2.62)*	22	2.01 (1.22–3.32)†
DM (+)+MetS (−)	131	6	0.77 (0.33–1.77)	9	1.18 (0.59–2.38)
DM (+)+MetS (+)	91	21	5.35 (3.28–8.73)†‡	15	5.13 (2.89–9.11)†‡
Hypertension					
HT (−)+MetS (−)	1355	48	1 (referent)	39	1 (referent)
HT (−)+MetS (+)	114	9	2.13 (1.03–4.39)*	8	2.43 (1.11–5.30)*
HT (+)+MetS (−)	732	51	1.36 (0.90–2.06)	49	1.39 (0.89–2.17)
HT (+)+MetS (+)	251	37	3.17 (2.01–5.02)†‡	29	3.45 (2.06–5.80)†‡

Note: Multivariate adjustment was made for age, serum total cholesterol, proteinuria, electrocardiogram abnormalities, alcohol intake, smoking habits, and regular exercise.

*$P<0.05$, †$P<0.01$ versus reference.

‡$P<0.01$ versus DM (+)+MetS (−) or HT (+)+MetS (−).

DM indicates diabetes; HT, hypertension.

who had more visceral fat tended to have more metabolic risk factors for CVD compared with men.[19,20] The cause of this sex difference is uncertain but may be related to a higher amount of hepatic free fatty acid delivery derived from visceral fat in women than in men.[21] These findings imply that it is reasonable to choose the lower cutoff point of waist circumference for women than for men. Furthermore, the population-attributable risk percents for any MetS criteria sets were larger in women than in men. These findings also suggest that MetS has a stronger influence on women than on men.

The American Diabetes Association/European Association for the Study of Diabetes says that MetS has been imprecisely defined, that its pathogenesis is uncertain, and that its value as a CVD risk marker is doubtful. Furthermore, it recommends that clinicians should evaluate and manage all CVD risk factors without regard to whether a patient meets the criteria for a diagnosis of MetS. Certainly, Sone et al documented that the diagnosis of MetS using the modified NCEP criteria was not useful for predicting CVD in patients with diabetes.[22] However, our stratified analysis indicated that MetS is a significant risk factor for CVD in both nondiabetic and normotensive individuals. Moreover, the present study revealed that the risk of CVD was higher in subjects with MetS than in those with diabetes or hypertension. These results imply that MetS plays a main role in the development of CVD in the general population, including patients with mild diabetes and hypertension. In the general Japanese population, blood pressure levels decreased significantly with time due to the increment in the use of antihypertensive medication, whereas metabolic disorders greatly increased in recent periods.[2,23] Even with advances in therapeutic agents, it is difficult to treat MetS and diabetes because lifestyle modifications are also needed. These disorders remain large problems for the prevention of CVD, especially in developed countries.

Additionally, our subjects showed a synergistic effect between MetS and diabetes for the development of CVD. The conditions of MetS are accompanied by adipokine disorders, inducing inflammatory cytokines and immune response, and endothelial dysfunction, which promotes the development of atherosclerosis.[24] On the other hand, hyperglycemia in diabetes itself directly affects the progression of atherosclerosis through the increase in nonenzymatic glycation of proteins and lipids,[25] the production of reactive oxygen species,[26] and the activation of protein kinase C[27] isoform and the hexosamine biosynthetic pathway.[28] It is therefore speculated that MetS and diabetes mutually enhance the risk of CVD by distinct mechanisms.

In our men, the cutoff value of waist circumference derived from the receiver operating characteristic analysis (80.2 cm) was much lower than that derived from the cohort study (90 cm), and the former was not a significant predictor of incident CVD in the follow-up study. This suggests that a value defined by maximizing the sensitivity and specificity would be not always best.

The strengths of our study include its longitudinal population-based design, the long duration of follow-up, the sufficient number of CVD events, and the almost perfect follow-up of subjects. However, 2 limitations of the present study should be discussed. One is that the diagnosis of MetS was based on a single measurement of its components at baseline as was the case in other epidemiological studies. During the follow-up, risk factor levels were changed due to modifications in lifestyle or medication, and misclassification of MetS was 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. The other limitation is that the present study lacked information on drugs, fibrates, and nicotinic acid, affecting the metabolism of HDL cholesterol and triglycerides. However, these medications were rarely

used in our country at this study's 1988 baseline. This suggests that such a bias did not invalidate the present findings.

In conclusion, the present analysis has clearly demonstrated that the optimal cutoff point of waist circumference is 90 cm in men and 80 cm in women and that the modified Japanese criteria of MetS with this cutoff point as an essential component better predicted CVD in the general Japanese population than did the other criteria sets. Furthermore, the increasing effects of MetS on the development of ischemic stroke and coronary heart disease were independent of hypertension and diabetes. High-risk strategies using this criteria set offer additional protection against CVD.

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Disclosures

None.

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Impact of Metabolic Syndrome Compared With Impaired Fasting Glucose on the Development of Type 2 Diabetes in a General Japanese Population

The Hisayama study

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OBJECTIVE — We examined whether metabolic syndrome predicts incident type 2 diabetes more effectively than impaired fasting glucose (IFG) in a general Japanese population.

RESEARCH DESIGN AND METHODS — A total of 1,935 nondiabetic subjects aged 40–79 years were followed-up prospectively for a mean of 11.8 years.

RESULTS — During the follow-up, 286 subjects developed type 2 diabetes. Compared with those without metabolic syndrome, the multivariate-adjusted hazard ratio (HR) for incident type 2 diabetes was significantly higher in subjects of both sexes with metabolic syndrome, even after adjustment for confounding factors, age, family history of diabetes, total cholesterol, alcohol intake, smoking habits, and regular exercise (men: HR 2.58 [95% CI 1.85–3.59]; women: 3.69 [2.58–5.27]). The multivariate-adjusted HR of metabolic syndrome for type 2 diabetes was slightly lower in men and similar in women compared with that of IFG. The multivariate-adjusted HR for type 2 diabetes rose progressively as the number of metabolic syndrome components increased in both subjects with and without IFG. In stratified analysis, the multivariate-adjusted risk of type 2 diabetes was significantly higher in subjects with metabolic syndrome alone (2.37 [1.45–3.88]) or IFG alone (3.49 [2.57–4.74]) and markedly increased in subjects with both metabolic syndrome and IFG (6.76 [4.75–9.61]) than in subjects with neither metabolic syndrome nor IFG. Furthermore, the multivariate-adjusted risk for type 2 diabetes was also significantly higher in subjects with both metabolic syndrome and IFG than in those with either one alone (both $P < 0.001$).

CONCLUSIONS — Our findings suggest that metabolic syndrome significantly increases the risk of incident type 2 diabetes, independent of IFG, and is therefore a valuable tool to identify individuals at high risk of type 2 diabetes.

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Metabolic syndrome consists of a clustering of cardiovascular risk factors, such as central obesity, elevated blood pressure, glucose intolerance, and dyslipidemia, and individuals with this condition have an elevated risk of developing cardiovascular diseases (1–5) and type 2 diabetes in different ethnic populations (1–4,6–11). Thus, the concept of metabolic syndrome could be used to reduce the incidence of these diseases worldwide. However, a number of experts in the field of diabetes have questioned whether the idea of metabolic syndrome is useful and valuable (12–14). Because all of the criteria sets for metabolic syndrome have included the component of impaired fasting glucose (IFG), which is a powerful predictor of type 2 diabetes, detractors have questioned whether the more complex definition of metabolic syndrome is better than a simple measurement of fasting plasma glucose (FPG). However, reported findings concerning this issue are controversial: a cohort study has shown that the ability of metabolic syndrome to predict type 2 diabetes was superior to that of IFG alone (3), whereas in other studies, the value of metabolic syndrome was comparable or inferior to that of IFG alone (2,6,7). Furthermore, most of these epidemiological studies were performed in Western populations, and this subject has not been assessed sufficiently in Asian populations.

The purpose of the present study was to investigate the association between metabolic syndrome and the development of type 2 diabetes in a prospective study of a defined Japanese population, taking into account comprehensive risk factors. In addition, we compared which of the two measures, metabolic syndrome or IFG, better predicted incident type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study population and follow-up survey

A population-based prospective study of cardiovascular disease and its risk factors has been underway since 1961 in the town of Hisayama, a suburb of the Fukuoka metropolitan area on Japan's Kyushu Island. In 1988, a screening survey for the present study was performed in the town. A detailed description of this survey was published previously (15). In brief, of the total of 3,227 residents aged 40–79 years based on the town registry, 2,587 residents (participation rate,

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80.2%) consented to take part in a comprehensive assessment. After exclusion of 82 subjects who had already had breakfast, 10 subjects who were receiving insulin therapy, and 15 subjects who complained of nausea or general fatigue during the ingestion of glucose, a total of 2,480 subjects completed a 75-g oral glucose tolerance test. Among these, 297 subjects with diabetes, 52 subjects for whom there was no measurement of waist circumference, and 2 subjects who died before the start of follow-up were excluded, and the remaining 2,129 subjects (894 men and 1,235 women) were enrolled in the baseline examination.

The baseline subjects were followed-up prospectively from December 1988 to November 2002 by repeated health examinations. Of the baseline subjects, 1,935 subjects (793 men and 1,142 women) who underwent reexaminations were finally selected for the present study (follow-up rate, 90.9%; mean follow-up period, 11.8 years; mean frequency of follow-up examinations, 6.9 times). One subject who developed overt type 1 diabetes clinically during the follow-up period was censored at the time.

Clinical evaluation and laboratory measurements

In the baseline and follow-up examinations, the study subjects underwent an oral glucose tolerance test between 8:00 and 10:30 A.M. after an overnight fast of at least 12 h. Blood for the glucose assay was obtained by venipuncture into tubes containing sodium fluoride at fasting and at 2-h postload. Plasma glucose concentrations were determined by the glucose oxidase method. According to the American Diabetes Association criteria in 2003 (16), diabetes was defined as FPG concentrations of ≥7.0 mmol/l and/or 2-h postload glucose concentrations of ≥11.1 mmol/l and/or the use of antidiabetes medication. Total and HDL cholesterol and triglycerides were determined enzymatically.

At the baseline examination, waist circumference was measured by a trained staff member at the umbilical level with the subject standing. Blood pressure was obtained three times using a mercury sphygmomanometer with the subject in a sitting position; the average values were used in the analyses. Each participant completed a self-administered questionnaire covering medical history, antidiabetes and antihypertension treatments, alcohol intake, smoking habits, and physical activity at the screening. Diabetes in first- or second-degree relatives was taken to indicate a family history of diabetes. Alcohol intake and smoking habits were classified as either current use or not. Subjects engaging in sports at least three times per week during their leisure time were defined as the regular-exercise group.

Table 1—*Baseline characteristics of subjects by the presence or absence of incident type 2 diabetes, 1988*

	No developed diabetes	Developed diabetes
n	1,649	286
Age (years)	57 ± 10	56 ± 9
Men (%)	39.3	50.7
FPG (mmol/l)	5.4 ± 0.5	5.9 ± 0.6
Two-hour postload glucose (mmol/l)	6.4 ± 1.5	7.5 ± 1.8
Family history of diabetes (%)	6.3	14.0
Waist circumference (cm)	80.8 ± 9.0	85.0 ± 8.7
Total cholesterol (mmol/l)	5.35 ± 1.06	5.39 ± 1.07
HDL cholesterol (mmol/l)	1.32 ± 0.30	1.26 ± 0.30
Triglycerides (mmol/l)	1.09 (0.40–2.98)	1.43 (0.45–4.49)
Systolic blood pressure (mmHg)	130 ± 19	137 ± 19
Diastolic blood pressure (mmHg)	77 ± 11	82 ± 12
Elevated blood pressure (%)	48.8	67.8
Current drinking (%)	28.6	39.2
Current smoking (%)	21.6	31.8
Regular exercise (%)	11.3	6.6

Data are means ± SD, %, or geometric means (95% CI) for triglycerides (because of the skewed distribution). Elevated blood pressure was defined as blood pressure ≥130/85 mmHg and/or current use of antihypertension agents.

Definition of metabolic syndrome

The criteria set for metabolic syndrome used in this study was defined by the updated 2005 National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) (17). By this definition, metabolic syndrome includes the presence of at least three of five factors: elevated FPG (≥5.6 mmol/l), central obesity for Asians (waist circumference ≥90 cm in men and ≥80 cm in women), elevated triglycerides (≥1.68 mmol/l), reduced HDL cholesterol (<1.03 mmol/l for men and <1.29 mmol/l for women), and elevated blood pressure (blood pressure ≥130/85 mmHg and/or current use of antihypertension agents).

Statistical analysis

The SAS software package (version 8.2; SAS Institute, Cary, NC) was used to perform all statistical analyses. Serum triglycerides were transformed into logarithms to improve the skewed distribution. Multivariate-adjusted hazard ratios (HRs) and their 95% CIs were estimated with the use of the Cox proportional hazards model. $P < 0.05$ was considered statistically significant in all analyses.

Ethical considerations

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 all participants.

RESULTS — During the follow-up, 286 subjects (145 men and 141 women) developed type 2 diabetes. The baseline clinical characteristics of subjects by the presence or absence of incident type 2 diabetes are shown in Table 1. The mean values of fasting and 2-h postload glucose, waist circumference, triglycerides, and systolic and diastolic blood pressures and the frequencies of men, family history of diabetes, elevated blood pressure, alcohol intake, and smoking habits were higher in subjects who developed type 2 diabetes than in those who did not develop it, and subjects with incident type 2 diabetes had lower HDL cholesterol and lower frequency of regular exercise. The mean values for age and total cholesterol did not differ between the groups.

The multivariate-adjusted HRs for the development of type 2 diabetes associated with metabolic syndrome and its individual components were estimated by sex (Table 2). The multivariate analysis showed that metabolic syndrome was a

Table 2—*Multivariate-adjusted HRs for the development of type 2 diabetes associated with metabolic syndrome and its individual components*

	Population at risk (*n*)	No. events	Multivariate-adjusted HR (95% CI)	*P*
Men				
Updated 2005 NCEP ATP III				
(−)	597	82	1 (referent)	
(+)	196	63	2.58 (1.85–3.59)	<0.001
IFG				
(−)	401	35	1 (referent)	
(+)	392	110	3.76 (2.57–5.52)	<0.001
Central obesity				
(−)	667	103	1 (referent)	
(+)	126	42	2.28 (1.58–3.29)	<0.001
Reduced HDL cholesterol				
(−)	614	108	1 (referent)	
(+)	179	37	1.32 (0.90–1.95)	0.16
Elevated triglycerides				
(−)	579	84	1 (referent)	
(+)	214	61	2.05 (1.46–2.88)	<0.001
Elevated blood pressure				
(−)	338	41	1 (referent)	
(+)	455	104	2.17 (1.49–3.17)	<0.001
Women				
Updated 2005 NCEP APT III				
(−)	723	52	1 (referent)	
(+)	419	89	3.69 (2.58–5.27)	<0.001
IFG				
(−)	685	47	1 (referent)	
(+)	457	94	3.50 (2.45–5.00)	<0.001
Central obesity				
(−)	496	39	1 (referent)	
(+)	646	102	1.96 (1.35–2.85)	<0.001
Reduced HDL cholesterol				
(−)	631	64	1 (referent)	
(+)	511	77	1.55 (1.10–2.18)	0.01
Elevated triglycerides				
(−)	973	105	1 (referent)	
(+)	169	36	2.28 (1.54–3.37)	<0.001
Elevated blood pressure				
(−)	598	51	1 (referent)	
(+)	544	90	2.49 (1.74–3.58)	<0.001

Data are *n* or HR (95% CI). IFG, FPG levels of 5.6–6.9 mmol/l; central obesity, waist circumference of ≥90 cm in men and ≥80cm in women; reduced HDL cholesterol, HDL cholesterol levels of <1.03 mmol/l in men and <1.29 mmol/l in women; elevated triglycerides, triglyceride levels of ≥1.68 mmol/l; elevated blood pressure, blood pressure ≥130/85 mmHg and/or current use of antihypertension agents. Multivariate adjustment was made for age, family history of diabetes, total cholesterol, alcohol intake, smoking habits, and regular exercise.

significant risk factor for type 2 diabetes in men and women, even after adjustment for the following confounding factors: age, family history of diabetes, total cholesterol, alcohol intake, smoking habits, and regular exercise (men: multivariate-adjusted HR, 2.58 [95% CI 1.85–3.59], $P < 0.001$; women: 3.69 [2.58–5.27], $P < 0.001$). All components of metabolic syndrome in both sexes, except for reduced HDL cholesterol in men, were significantly associated with future type 2 diabetes. Among the individual components of metabolic syndrome, IFG was the strongest predictor of incident type 2 diabetes in both sexes (men: 3.76 [2.57–5.52], $P < 0.001$; women: 3.50 [2.45–5.00], $P < 0.001$). Compared with that of IFG, the multivariate-adjusted HR of metabolic syndrome for developing type 2 diabetes was slightly lower in men and similar in women. Furthermore, even when the cutoff point of waist circumference for U.S. individuals was used (>102 cm in men and >88 cm in women) in the metabolic syndrome criteria instead of the cutoff point for Asians, the HR of metabolic syndrome for incident type 2 diabetes was substantially unchanged (men: 2.48 [1.76–3.51], $P < 0.001$; women: 3.22 [2.27–4.55], $P < 0.001$).

Because IFG is a strong predictor of future type 2 diabetes, the associations between the number of the other metabolic syndrome components and the development of type 2 diabetes were examined among individuals with or without IFG in men and women together (Table 3). In subjects with normal FPG levels, the multivariate-adjusted HRs for type 2 diabetes rose significantly as the number of metabolic syndrome components increased (one component: multivariate-adjusted HR 1.76 [95% CI 0.88–3.50]; two components: 2.49 [1.22–5.06]; three components: 3.71 [1.72–8.02]; and four components: 5.90 [2.24–15.53]; $P_{trend} < 0.001$). Similar relationships were also observed in subjects with IFG (one component: 2.38 [1.30–4.35]; two components: 2.98 [1.62–5.47]; three components: 4.61 [2.48–8.56]; and four components: 4.22 [2.01–8.83]; $P_{trend} < 0.001$).

Finally, we examined the combined as well as separate effects of metabolic syndrome and IFG on the development of type 2 diabetes. In this analysis, metabolic syndrome was defined as the presence of at least three metabolic syndrome components, not including the component of elevated FPG. As shown in the Figure 1, the multivariate-adjusted HR for future type 2 diabetes was significantly higher in subjects with metabolic syndrome alone and in those with IFG alone than in those with neither metabolic syndrome nor IFG; the former was slightly lower than the latter, but there was no significant difference between the two (metabolic syndrome alone: multivariate-adjusted HR 2.37 [95% CI 1.45–3.88], $P < 0.001$; IFG alone: 3.49 [2.57–4.74], $P < 0.001$). Furthermore, the subjects who had both metabolic syndrome and IFG had a markedly higher HR for the development of type 2 diabetes (6.76 [4.75–9.61], $P < 0.001$). The risk of future type 2 diabetes was also significantly higher in subjects with both metabolic syndrome and IFG than in subjects with metabolic syndrome alone (2.82 [1.74–4.57], $P < 0.001$) as well as in those with IFG alone (1.94 [1.44–2.62], $P < 0.001$).

Table 3—*Multivariate-adjusted HRs for the development of type 2 diabetes associated with the number of metabolic syndrome components excluding IFG by the presence or absence of IFG*

FPG levels	No. of metabolic syndrome components excluding IFG	Population at risk (*n*)	No. events	Multivariate-adjusted HR (95%CI)	P_{trend}
Normal	0	285	12	1 (referent)	
	1	399	26	1.76 (0.88–3.50)	
	2	236	22	2.49 (1.22–5.06)	
	3	126	15	3.71 (1.72–8.02)	
	4	40	7	5.90 (2.24–15.53)	<0.001
IFG	0	122	13	1 (referent)	
	1	278	61	2.38 (1.30–4.35)	
	2	243	62	2.98 (1.62–5.47)	
	3	153	51	4.61 (2.48–8.56)	
	4	53	17	4.22 (2.01–8.83)	<0.001

Data are *n* or HR (95% CI). Multivariate adjustment was made for age, sex, family history of diabetes, total cholesterol, alcohol intake, smoking habits, and regular exercise. Normal, FPG levels of <5.6 mmol/l; IFG, FPG levels of 5.6–6.9 mmol/l.

CONCLUSIONS — Using data from a 14-year follow-up study of a defined general Japanese population, we demonstrated that metabolic syndrome determined by the updated 2005 NCEP ATP III criteria was an independent risk factor for the development of type 2 diabetes in both sexes even after adjustment for comprehensive risk factors. The HR of metabolic syndrome for developing type 2 diabetes was slightly lower in men and similar in women compared with that of IFG. When subjects were stratified by the presence or absence of IFG, the risk of future type 2 diabetes rose significantly as the number of metabolic syndrome components increased in both FPG level groups. Furthermore, metabolic syndrome that did not include the IFG component was also a significant risk factor for developing type 2 diabetes, and the coexistence of metabolic syndrome and IFG greatly increased the risk of future type 2 diabetes. These findings suggest that the diagnosis of metabolic syndrome as well as that of IFG is a valuable tool to identify individuals at increased risk of type 2 diabetes.

In Japan, there has been only one prospective study to date that found a significant association between metabolic syndrome determined by the World Health Organization definition and incident type 2 diabetes among Japanese male workers (18). To our knowledge, the present study is the first report to indicate that metabolic syndrome was associated significantly with future type 2 diabetes for individuals of both sexes in a general Japanese population. Several epidemiological studies examined the relationship between metabolic syndrome determined by the updated 2005 NCEP ATP III criteria and incident diabetes (3,4,9–11), and the risks of incident diabetes associated with metabolic syndrome have differed among these investigations. In the Framingham Offspring Study, subjects with metabolic syndrome had an 8.6-fold higher risk of future type 2 diabetes than those without metabolic syndrome (4). The San Antonio Heart Study, which consisted predominantly of Hispanics, also showed that the diabetes risk was 6.9-fold higher in subjects with metabolic syndrome than that in subjects without metabolic syndrome (3). A similar increased risk of diabetes was observed among subjects with metabolic syndrome in an Ital-

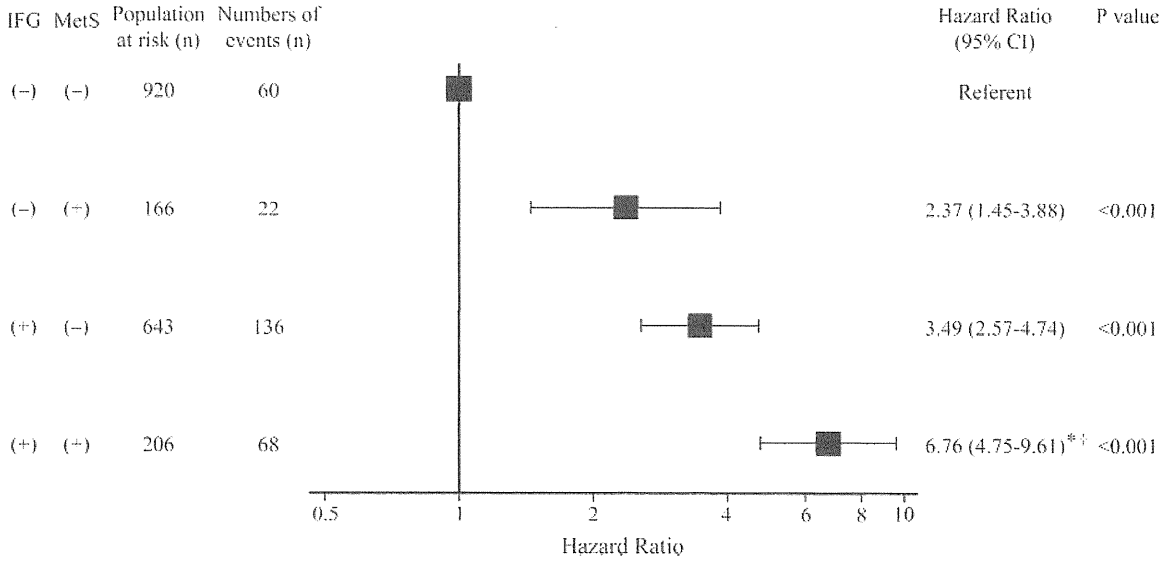

Figure 1—*Multivariate-adjusted HRs for the development of type 2 diabetes according to the presence or absence of metabolic syndrome and IFG. Metabolic syndrome (MetS) was defined as the presence of at least three metabolic syndrome components other than that related to FPG. Multivariate adjustment was made for age, sex, family history of diabetes, total cholesterol, alcohol intake, smoking habits, and regular exercise. The centers of the boxes are placed at the estimates of HRs. Error bars indicate 95% CIs. IFG indicates FPG levels of 5.6–6.9 mmol/l. *P < 0.001 vs. IFG (−) and MetS (+). †P < 0.001 vs. IFG (+) and MetS (−).*

ian population study (6.2-fold) (11). On the other hand, metabolic syndrome increased the risk of diabetes two- to fourfold in studies of Chinese populations (9,10). In the present analysis, the risk of developing type 2 diabetes was nearly threefold higher in men and fourfold higher in women with metabolic syndrome than in those without it, and these figures were much lower than the figures in Western populations but comparable to those of other Asian populations. Furthermore, even when the definition of waist circumference for U.S. individuals was used (>102 cm in men and >88 cm in women) in the metabolic syndrome criteria set, the risk of future type 2 diabetes among subjects with metabolic syndrome was hardly altered. Taken together, these findings suggest that metabolic syndrome is less strongly associated with increased risk of type 2 diabetes in Asian populations than in Western populations. Although the reason for this difference is unclear, the diversity of etiology for type 2 diabetes among races could explain it. That is, an epidemiological study has shown that the levels of insulin secretion and resistance differed among various ethnic groups in the U.S. (19); Asians had lower levels of insulin secretion than other ethnic groups, whereas whites, especially Hispanics, were more insulin resistant than Asians. In addition, Japanese diabetic individuals were found to have lower BMI levels than western diabetic individuals (20). Thus, we speculate that insulin resistance may play a lesser role than impaired insulin secretion in the development of type 2 diabetes among Asian populations. These findings may indicate one reason that the impact of metabolic syndrome, which has features of insulin resistance, on the development of type 2 diabetes is lower in Asian populations, including ours, than in Western populations.

There has been controversy over whether metabolic syndrome is better than IFG for detecting subjects at high risk of type 2 diabetes. The San Antonio Heart Study revealed that metabolic syndrome was a better predictor of diabetes than IFG (3), whereas other epidemiological studies including ours (2,6,7) showed that metabolic syndrome was comparable or inferior to IFG as a predictor of diabetes. This discrepancy also may result from the difference in the degree of insulin resistance among the populations, because the study subjects in the San Antonio Heart Study were more obese than those in other studies. Thus, metabolic syndrome might be less effective in predicting incident type 2 diabetes in relatively lean ethnic groups. In our study, however, the risk of type 2 diabetes rose progressively as the number of the other metabolic syndrome components increased, not only in subjects with IFG but also in those with normal FPG levels. Moreover, our stratified analysis indicated that metabolic syndrome defined without the FPG component was also a significant risk factor for future type 2 diabetes in individuals both with and without IFG. These results imply that metabolic syndrome excluding the FPG component is also an independent risk factor for incident type 2 diabetes. On the other hand, in our study, the coexistence of metabolic syndrome and IFG appeared to increase the risk of future type 2 diabetes compared with either one alone. Other epidemiological studies have also shown that type 2 diabetes prediction was greatly enhanced by adding information on metabolic variables to that of IFG (21–23). Thus, metabolic syndrome would provide additional information beyond that provided by IFG alone in regard to the development of type 2 diabetes.

In our study, reduced HDL cholesterol was not a significant risk factor for developing type 2 diabetes in men, although lower HDL cholesterol has often been shown to be a strong predictor of diabetes in other epidemiological studies (2,6,7,9,21–23). The reasons for this discrepancy are not precisely known, but a higher prevalence of drinking habits in our men (61%) relative to our women (9%) may contribute to this phenomenon. It is known that heavy alcohol intake augments the risk of diabetes (24), whereas it increases serum HDL cholesterol levels (25). These effects of alcohol intake could weaken the association between HDL cholesterol levels and the risk of diabetes.

The strengths of our study include a longitudinal population-based design, a long duration of follow-up, a sufficient number of type 2 diabetes events, a high follow-up rate, and the use of an oral glucose tolerance test for the diagnosis of diabetes. However, two limitations of the present study should be discussed. One is that the diagnosis of metabolic syndrome was based on a single measurement of its components at baseline, as was the case in other epidemiological studies. The risk factor levels might have changed during the follow-up because of modifications in lifestyle or medication. The other limitation is that the present study lacked information on antilipidemic drugs, such as fibrates and nicotinic acid, which could have affected the metabolism of HDL cholesterol and triglycerides, although these medications were rarely used in our country by 1988, the time of the baseline. These limitations may have led to misclassification of metabolic syndrome. These biases have the potential to underestimate the association between metabolic syndrome and incident type 2 diabetes, and thus the true impact of metabolic syndrome on the occurrence of type 2 diabetes may be stronger than that shown in our findings. For this reason, we believe that these limitations would not have substantially altered our conclusions.

In summary, the present analysis clearly demonstrated that metabolic syndrome was a significant risk factor for developing type 2 diabetes in both sexes in a general Japanese population. Although the ability of metabolic syndrome to predict type 2 diabetes was comparable or inferior to that of IFG, the effects of metabolic syndrome on the development of type 2 diabetes were independent of IFG. These findings suggest that the diagnosis of metabolic syndrome is useful and valuable for predicting type 2 diabetes even in relatively lean Asians. Further studies are needed to verify these findings in other populations.

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LDL Cholesterol and the Development of Stroke Subtypes and Coronary Heart Disease in a General Japanese Population

The Hisayama Study

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Background and Purpose—Although the relation between serum LDL cholesterol level and coronary heart disease (CHD) is well established, its relation with stroke subtypes is less clear.

Methods—A total of 2351 inhabitants age ≥40 years in a Japanese community were followed up for 19 years.

Results—During follow-up, 271 subjects developed stroke and 144 developed CHD. Whereas the age- and sex-adjusted incidences of CHD significantly increased with increasing LDL cholesterol levels (P for trend <0.001), the associations between LDL cholesterol level and the incidences of ischemic or hemorrhagic stroke were not significant. The age- and sex-adjusted incidences of atherothrombotic infarctions (ATIs) and lacunar infarctions (LIs) significantly increased with increasing LDL cholesterol level (P for trend=0.03 for ATIs and=0.02 for LIs), but no such association was observed for cardioembolic infarction. After multivariate adjustment, the positive associations of LDL cholesterol level with the risks of ATI and CHD remained significant (P for trend=0.02 for ATIs and=0.03 for CHD), whereas the association with LIs was not significant. The risk of ATI significantly increased in the fourth quartile of LDL cholesterol compared with the first quartile (multivariate-adjusted hazard ratio=2.84; 95% CI, 1.17 to 6.93). The multivariate-adjusted risks for developing nonembolic infarction (ATIs and LIs) and CHD were significantly elevated in the groups with elevated LDL cholesterol values with and without the metabolic syndrome.

Conclusions—Our findings suggest that an elevated LDL cholesterol level is a significant risk factor for developing ATI as well as CHD, and these associations are independent of the metabolic syndrome. (***Stroke.* 2009;40:382-388.)**

Key Words: epidemiology ■ cholesterol ■ lipoproteins ■ risk factors

Increased blood cholesterol levels are causally related to an increased risk of coronary heart disease (CHD).[1] In contrast, the relation between total cholesterol levels and the risk of stroke remains unclear because of conflicting results reported in the literature.[2,3] The inconsistent results may be due to several reasons. First, because stroke is a heterogeneous syndrome of different etiologic origins, lipid abnormalities may be important for some subtypes of stroke but not for others. An inverse association has been observed between total cholesterol and hemorrhagic stroke,[2,4] and there is a positive association between total cholesterol and ischemic stroke.[2,5] Furthermore, the association may be different for ischemic stroke subtypes.[6] Second, lipoprotein subfractions are considered to exert varying influence on stroke risk.[7] It is possible that the protective effect of HDL cholesterol against stroke weakens the positive association between total cholesterol and stroke in instances where lipoprotein subfractions are counted together. The association between cholesterol and stroke, therefore, needs to be discussed on the basis of stroke subtypes and lipoprotein subfractions.

Together with the results from prospective studies, the positive association between LDL cholesterol level and the risk of CHD has been confirmed by lipid-lowering randomized trials.[8] On the other hand, whereas statins significantly reduced the risk of stroke,[8] the risk reduction for stroke in trials in which subjects were treated with nonstatins was not significant,[9] suggesting that statins involve mechanisms other than cholesterol lowering for the prevention of stroke. Therefore, the true association between LDL cholesterol and the risk of stroke remains unknown. The purpose of this study was to evaluate the association between LDL cholesterol

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level and the development of stroke by its subtypes as well as of CHD in a prospective study of a general Japanese population.

Subjects and Methods

Study Population

Since 1961, we have been conducting a long-term, prospective cohort study of cardiovascular disease (CVD) in the town of Hisayama, a suburb of Fukuoka city in southern Japan. In 1983, a screening survey for the present study was performed in the town. A total of 2548 residents age ≥40 years (80.7% of the total population of this age group) consented to participate in the examination. Of these, 197 subjects were excluded for the following reasons: past history of stroke or myocardial infarction (MI; n=89), blood samples not being collected or collected after a meal (n=86), and excessively high value of triglycerides (≥4.48 mmol/L) for which the Friedewald formula loses its validity[10] (n=22). The remaining 2351 subjects (991 men, 1360 women) were included in this study.

Follow-Up Survey

This population was followed up prospectively for 19 years, from November 1983 through October 2002, by annual health examinations. For subjects who did not undergo regular examinations or who moved out of Hisayama, health status was checked yearly by mail or telephone. We also established a daily monitoring system, which connected us with local physicians and the members of the Health and Welfare Office for the town, and through the system we gathered information on new events of CVD, including suspected cases. When stroke or CHD occurred or was suspected, physicians in the study team examined the subject and evaluated his/her detailed clinical information. The clinical diagnosis of stroke or CHD was based on the patient's history, physical and neurologic examinations, and ancillary laboratory examinations. When a subject died, an autopsy was performed at the Department of Pathology of Kyushu University. During the follow-up period, 1 subject was lost to follow-up, 707 subjects died, and 555 subjects (78.5%) underwent autopsy examination.

Definition of Cardiovascular Events

The diagnosis and classification of stroke were determined on the basis of clinical information, including brain computed tomography and magnetic resonance imaging, cerebral angiography, echocardiography, carotid duplex imaging, or autopsy findings. In principle, stroke was defined as a sudden onset of nonconvulsive and focal neurologic deficits persisting for >24 hours, and the stroke was then classified as either hemorrhagic or ischemic. Hemorrhagic stroke included cerebral hemorrhage and subarachnoid hemorrhage. Ischemic stroke was further divided into 4 clinical categories: atherothrombotic infarction (ATI), lacunar infarction (LI), cardioembolic infarction (CEI), and undetermined subtype of ischemic stroke (UND), based on the Classification of Cerebrovascular Disease III proposed by the National Institute of Neurological Disorders and Stroke,[11] as well as on the basis of the diagnostic criteria of the Trial of Org10172 in Acute Stroke Treatment (TOAST) Study[12] and the Cerebral Embolism Task Force.[13]

Details of the diagnostic criteria for ischemic stroke subtypes have been described previously.[14] In brief, 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. LI was diagnosed as the presence of a relevant brainstem, basal ganglia, or subcortical hemispheric lesion with a diameter <1.5 cm demonstrated on brain imaging or autopsy and no evidence of cerebral cortical or cerebellar impairment. 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.[13] The category of UND included all ischemic stroke cases for which the subtype could not be determined because of insufficient clinical or morphologic information. We considered morphologic findings to be significant and used clinical features as reference information. Cases with cerebrovascular diseases with distinct pathology, such as collagen disease, hematologic disorder, trauma, chronic subdural hematoma, or moyamoya disease, were excluded from the evaluation.

During the follow-up period, we identified 271 first-ever stroke events. All of the stroke cases underwent morphologic evaluation that included brain imaging and autopsy; 269 subjects (99.3%) underwent brain imaging studies, and autopsies were performed on 128 subjects of 157 deceased stroke cases (81.5%), including 2 subjects who were not examined by brain imaging. When sufficient clinical and morphologic information was obtained, a diagnosis of cerebral infarction subtype was defined as "definite." When the amount of either type of information was insufficient, the diagnosis level was defined as "probable." On the basis of the aforementioned criteria, stroke cases were divided into 80 hemorrhagic strokes and 191 ischemic strokes (51 ATIs, 93 LIs, 46 CEIs, and 1 UND). Among 191 ischemic strokes, 182 were defined as definite and 9 as probable. In this study, we present the data regarding definite and probable stroke cases together, because these combined data were almost identical to those for definite cases only.

The criteria for the diagnosis of CHD included first-ever acute MI, silent MI, sudden cardiac death within 1 hour after the onset of acute illness, coronary artery angioplasty, and bypass grafting. The diagnosis of MI was based on detailed clinical information and at least 2 of the following findings: typical clinical symptoms, ECG evidence of MI, elevated cardiac enzymes, or morphologic findings including echocardiographic, scintigraphic, or angiographic abnormalities compatible with myocardial injury. Silent MI was defined as myocardial scarring without any historical indication of clinical symptoms and/or abnormal cardiac enzyme changes.[15] During the follow-up period, we identified 144 first-ever events of CHD.

Risk Factors

Blood samples were drawn after an overnight fast of at least 12 hours. All measurements were done within 24 hours after venipuncture in the central study laboratory (Japan Medical Laboratory Inc, Fukuoka, Japan), which participated in the Centers for Disease Control and Prevention Lipid Standardization Program. Total cholesterol and triglyceride levels were measured enzymatically. Measurement of HDL cholesterol was performed after precipitation of VLDL and LDL with dextran sulfate and magnesium. LDL cholesterol concentration was calculated with the Friedewald formula.[10] Plasma glucose levels were determined by the glucose oxidase method. Sitting blood pressure (BP) was measured with a sphygmomanometer 3 times at the right upper arm after at least 5 minutes of rest, and the mean of the 3 measurements was used in the analysis. Hypertension was defined as a BP ≥140/90 mm Hg and/or current treatment with antihypertensive agents. ECG abnormalities were defined as left ventricular hypertrophy (Minnesota code 3-1), ST-segment depression (Minnesota codes 4-1,2,3), or atrial fibrillation (Minnesota code 8-3). Body height and weight were measured in light clothing without shoes, and body mass index (BMI; kg/m^2) was calculated. Information on alcohol consumption, smoking habits, and physical activity during leisure time was obtained by the use of a questionnaire. Alcohol consumption and smoking habits were classified as either current use or not. Those subjects who engaged in sports or other forms of exertion ≥3 times per week during their leisure time were designated the regular-exercise group. We defined the presence of the metabolic syndrome according to the National Cholesterol Education Program Expert Panel criteria[16] with a minor modification. The presence of the metabolic syndrome was based on the existence of 3 or more of the following components: (1) BMI ≥25 kg/m^2 as a substitute for waist circumference[17]; (2) fasting triglyceride concentration ≥1.68 mmol/L; (3) HDL cholesterol concentration <1.03 mmol/L in men and <1.29 mmol/L in women; (4) BP ≥130/85 mm Hg or use of antihypertensive drugs; and (5) fasting plasma glucose value ≥6.1 mmol/L or current use of antidiabetic drugs.

Statistical Analysis

To analyze LDL cholesterol level as a categorical variable, we classified the subjects into 4 groups according to quartiles of LDL

Table 1. Age- and Sex-Adjusted Mean Values or Frequencies of Risk Factors for CVD According to LDL Cholesterol Quartiles at Baseline

	Quartile of LDL Cholesterol Levels, mmol/L				
Risk Factor	≤2.65 (n=586)	2.66 to 3.24 (n=591)	3.25 to 3.88 (n=585)	≥3.89 (n=589)	*P* Value for Trend
Men, %	57.4	44.1	39.2	31.5	<0.001
Age, y	56±11	57±11	57±11	59±11	<0.001
Total cholesterol, mmol/L	4.03±0.57	4.81±0.41	5.40±0.43	6.45±0.68	<0.001
HDL cholesterol, mmol/L	1.36±0.42	1.35±0.36	1.34±0.37	1.31±0.33	<0.001
Triglycerides, mmol/L	1.15±0.75	1.07±0.51	1.12±0.53	1.32±0.58	<0.001
Fasting blood glucose, mmol/L	4.66±0.92	4.75±0.96	4.76±0.93	4.96±1.14	<0.001
Systolic BP, mm Hg	132±22	132±21	135±22	138±21	<0.001
Diastolic BP, mm Hg	81±12	81±12	82±11	83±10	<0.001
Hypertension, %	39.7	41.4	43.8	48.5	0.01
ECG abnormalities,* %	20.6	19.4	21.0	18.4	0.12
BMI, kg/m^2	21.9±3.0	22.2±3.1	23.0±3.1	23.5±3.1	<0.001
Current drinking, %	42.2	33.3	31.8	27.9	<0.001
Current smoking, %	30.7	28.5	28.3	26.5	<0.001
Regular exercise,† %	9.0	7.9	9.5	5.7	0.03

Data are mean±SD or percent. Percentage of men was age adjusted. Mean age was sex adjusted.

*Minnesota codes 3–1; 4–1, –2, –3; or 8–3.

†Engaging in sports or other forms of exertion regularly ≥3 times per week during leisure time.

cholesterol level: ≤2.65, 2.66 to 3.24, 3.25 to 3.88, and ≥3.89 mmol/L. Serum triglyceride levels were logarithmically transformed to improve the skewed distribution. Age- and sex-adjusted mean values of the possible risk factors were calculated by the ANCOVA method, and their trends across LDL cholesterol levels were tested by multiple-regression analysis. Frequencies of risk factors were adjusted for age and sex by the direct method and were examined for trends by the Cochran-Mantel-Haenszel test. The incidences of CVD were calculated by the person-year method and were adjusted for age and sex by the direct method according to 10-year age groups. Differences in age- and sex-adjusted incidences between LDL cholesterol quartiles were tested by Cox proportional-hazards regression analysis. The age- and sex-adjusted or multivariate-adjusted hazard ratios (HRs) and 95% CIs were also calculated by the Cox proportional-hazards model. All statistical analyses were performed with the SAS program package. $P<0.05$ was considered statistically significant in all analyses.

Results

The age- and sex-adjusted mean values or frequencies of risk factors for CVD are listed by quartiles of LDL cholesterol levels at baseline in Table 1. The frequencies of male sex, current drinking, current smoking, and regular exercise and the mean values of HDL cholesterol declined with increasing LDL cholesterol level, whereas mean values of age, total cholesterol, triglycerides, fasting blood glucose, systolic and diastolic BPs, BMI, and frequency of hypertension significantly increased with rising LDL cholesterol level. The frequency of ECG abnormalities was not different among serum LDL cholesterol levels.

Table 2 shows the age- and sex-adjusted incidences of CVD according to quartiles of LDL cholesterol levels. No significant associations were observed between LDL cholesterol levels and the incidences of stroke, whether ischemic or hemorrhagic. In regard to subtypes of ischemic stroke, the incidences of ATI and LI significantly increased with increasing LDL cholesterol level (P for trend=0.03 for ATI and=0.02 for LI), and there were significant differences between the first and fourth quartiles of LDL cholesterol for both subtypes (age- and sex-adjusted HR=2.31; 95% CI, 1.03 to 5.16; P=0.04 for ATI; age- and sex-adjusted HR=2.00; 95% CI, 1.05 to 3.80; P=0.03 for LI; Table 3). No such association was observed for CEI. The incidence of CHD also significantly increased with increasing LDL cholesterol level (P for trend <0.001), and compared with the first quartile, the incidence was significantly higher in the third (age- and sex-adjusted HR=1.77; 95% CI, 1.07 to 2.91; P=0.03; Table 3) and fourth (age- and sex-adjusted HR=2.00; 95% CI, 1.22 to 3.28; P=0.006) quartiles.

As shown in Table 3, the positive associations between LDL cholesterol level and risk of ATI and CHD remained significant even after adjustment for age, sex, HDL cholesterol, triglycerides, systolic BP, ECG abnormalities, fasting blood glucose, BMI, current drinking, current smoking, and regular exercise (P for trend=0.02 for ATI and=0.03 for CHD). Compared with the first quartile, the risk of ATI was significantly high in the fourth quartile after adjustment for the aforementioned confounding factors (multivariate-adjusted HR=2.84; 95% CI, 1.17 to 6.93; P=0.02). On the other hand, the negative association between LDL cholesterol and the risk of CEI appeared to be significant after multivariate adjustment (P for trend=0.03), and the risk of CEI was significantly lower in the fourth quartile than in the first quartile (multivariate-adjusted HR=0.34; 95% CI, 0.12 to 0.96; P=0.04). A similar association was observed when LDL cholesterol was examined on a continuous scale.

Because not only LDL cholesterol but also other metabolic factors may be strong risk factors for CVD, we examined the combined as well as the separate effects of elevated LDL cholesterol level and the metabolic syndrome on the development of selected CVDs. As shown in the Figure, we

Table 2. Age- and Sex-Adjusted Incidences (per 1000 Person-Years) of CVD According to LDL Cholesterol Quartiles

	Quartile of LDL Cholesterol Levels, mmol/L				
	≤2.65 (n=586)	2.66 to 3.24 (n=591)	3.25 to 3.88 (n=585)	≥3.89 (n=589)	*P* Value for Trend
Stroke					
No. of events	56	62	74	79	
Age- and sex-adjusted incidence	7.4	8.1	10.1	10.2	0.13
Ischemic stroke					
No. of events	37	47	47	60	
Age- and sex-adjusted incidence	4.9	6.3	6.8	7.9	0.07
Atherothrombotic					
No. of events	9	12	9	21	
Age- and sex-adjusted incidence	1.2	1.6	1.2	3.3*	0.03
Lacunar					
No. of events	14	21	25	33	
Age- and sex-adjusted incidence	2.0	2.6	2.9	3.8*	0.02
Cardioembolic					
No. of events	14	14	12	6	
Age- and sex-adjusted incidence	1.7	2.1	2.4	0.8	0.07
Hemorrhagic stroke					
No. of events	19	15	27	19	
Age- and sex-adjusted incidence	2.6	1.8	3.3	2.3	0.95
CHD					
No. of events	25	28	43	48	
Age- and sex-adjusted incidence	3.4	3.4	5.5*	6.6†	<0.001

*$P<0.05$, †$P<0.01$ vs lowest quartile.

estimated the HRs for the occurrence of nonembolic infarction, including ATI and LI, as well as of CHD, by dividing the subjects into 4 groups according to the presence or absence of high LDL cholesterol levels (the fourth quartile, ≥3.89 mmol/L for nonembolic infarction; the third and fourth quartiles, ≥3.25 mmol/L for CHD) and the metabolic syndrome after adjustments for age, sex, ECG abnormalities, current drinking, current smoking, and regular exercise. Compared with a reference group with neither high LDL cholesterol levels nor the metabolic syndrome, the risk of developing nonembolic infarction was significantly high in the group with high LDL cholesterol levels alone and in the group with both high LDL cholesterol levels and the metabolic syndrome, whereas it was marginally significant for the group with the metabolic syndrome alone. Similarly, the risk for the development of CHD was elevated in both the group with high LDL cholesterol without the metabolic syndrome and the group with high LDL cholesterol and the metabolic syndrome. The risk of CHD was also significant for the group with the metabolic syndrome alone.

Discussion

In a long-term, prospective study of a general Japanese population, we demonstrated positive and significant associations between serum LDL cholesterol level and risk for the development of ATI and CHD. These associations remained unchanged even after adjustment for other lipid fractions as well as other confounding factors, namely, age, sex, systolic BP, ECG abnormalities, fasting blood glucose, BMI, current drinking, current smoking, and regular exercise. In addition, the impact of high LDL cholesterol on CVD appeared to be similar to that of the metabolic syndrome. On the other hand, the association between LDL cholesterol level and the risk of CEI was negative and significant after adjusting for the aforementioned risk factors. To our knowledge, this is the first prospective cohort study to investigate the association between LDL cholesterol and the development of subtypes of ischemic stroke.

Several prospective studies have investigated the association between LDL cholesterol and ischemic stroke, but the results were not unanimous. The Cardiovascular Health Study[18] reported a positive association between LDL cholesterol and the risk of ischemic stroke, whereas the Atherosclerosis Risk in Communities Study[19] and the Framingham Study[20] found no clear associations. In the present analysis, LDL cholesterol level was not clearly associated with the risks of stroke and ischemic stroke, but these associations were heterogeneous across ischemic stroke subtypes. Because LI and CEI seem to have a less potent relation with elevated LDL cholesterol,[21,22] inclusion of those subtypes may mask the positive association between LDL cholesterol and ATI. This heterogeneity in the associations of LDL cholesterol level and ischemic stroke subtypes may be a reason for the controversial results obtained from previous studies that investigated the outcome of "total" ischemic stroke.

Table 3. Age-, Sex-, and Multivariate-Adjusted HRs and 95% CIs for the Development of CVD According to LDL Cholesterol Quartiles

	Quartile of LDL Cholesterol Levels, mmol/L					
	≤2.65 (n=586)	2.66 to 3.24 (n=591)	3.25 to 3.88 (n=585)	≥3.89 (n=589)	*P* Value for Trend	Continuous Scale
Stroke						
No. of events	56	62	74	79		
Age- and sex-adjusted HR (95% CI)	1.0	0.96 (0.66–1.37)	1.12 (0.84–1.69)	1.23 (0.86–1.75)	0.13	1.08 (0.95–1.23)
Multivariate-adjusted HR (95% CI)	1.0	0.94 (0.64–1.38)	1.15 (0.79–1.67)	1.23 (0.84–1.81)	0.16	1.07 (0.93–1.24)
Ischemic stroke						
No. of events	37	47	47	60		
Age- and sex-adjusted HR (95% CI)	1.0	1.08 (0.70–1.67)	1.17 (0.75–1.80)	1.45 (0.95–2.21)	0.07	1.15 (0.99–1.35)
Multivariate-adjusted HR (95% CI)	1.0	1.05 (0.66–1.66)	1.05 (0.66–1.68)	1.35 (0.85–2.14)	1.19	1.11 (0.94–1.31)
Atherothrombotic						
No. of events	9	12	9	21		
Age- and sex-adjusted HR (95% CI)	1.0	1.14 (0.48–2.71)	0.98 (0.39–2.50)	2.31 (1.03–5.16)*	0.03	1.51 (1.14–1.99)§
Multivariate-adjusted HR (95% CI)	1.0	1.35 (0.54–3.35)	1.19 (0.45–3.17)	2.84 (1.17–6.93)*	0.02	1.60 (1.19–2.16)§
Lacunar						
No. of events	14	21	25	33		
Age- and sex-adjusted HR (95% CI)	1.0	1.29 (0.65–2.54)	1.58 (0.81–3.05)	2.00 (1.05–3.80)*	0.02	1.23 (1.00–1.53)
Multivariate-adjusted HR (95% CI)	1.0	1.19 (0.57–2.50)	1.41 (0.69–2.89)	1.69 (0.83–3.43)	0.11	1.13 (0.90–1.43)
Cardioembolic						
No. of events	14	14	12	6		
Age- and sex-adjusted HR (95% CI)	1.0	0.83 (0.39–1.75)	0.80 (0.37–1.75)	0.39 (0.15–1.04)	0.07	0.71 (0.51–1.00)
Multivariate-adjusted HR (95% CI)	1.0	0.75 (0.34–1.63)	0.59 (0.25–1.38)	0.44 (0.12–0.96)*	0.03	0.64 (0.44–0.94)‡
Hemorrhagic stroke						
No. of events	19	15	27	19		
Age- and sex-adjusted HR (95% CI)	1.0	0.69 (0.35–1.36)	1.24 (0.68–2.24)	0.83 (0.43–1.59)	0.95	0.94 (0.74–1.20)
Multivariate-adjusted HR (95% CI)	1.0	0.71 (0.35–1.47)	1.41 (0.75–2.65)	1.01 (0.50–2.05)	0.53	1.02 (0.79–1.33)
CHD						
No. of events	25	28	43	48		
Age- and sex-adjusted HR (95% CI)	1.0	1.02 (0.60–1.76)	1.77 (1.07–2.91)*	2.00 (1.22–3.28)†	<0.001	1.29 (1.08–1.53)§
Multivariate-adjusted HR (95% CI)	1.0	1.01 (0.56–1.80)	1.68 (0.99–2.84)	1.57 (0.91–2.73)	0.03	1.15 (0.95–1.39)

Multivariate adjustment was made for age, sex, HDL cholesterol, triglycerides, systolic BP, ECG abnormalities, fasting blood glucose, BMI, current drinking, current smoking, and regular exercise. For the continuous scale, HR is given for each 1-mmol/L increase in LDL cholesterol.

*$P<0.05$, †$P<0.01$ vs lowest quartile; ‡$P<0.05$, §$P<0.01$.

The atherogenesis of LDL cholesterol to large vessels, including coronary arteries and other peripheral arteries, is well known, and clinical studies have shown that an elevated LDL cholesterol level is also significantly related to the development of atherosclerotic lesions in extracranial or intracranial large vessels.[23,24] Because ATI is caused by atherosclerotic lesions of those large vessels, the significant association between elevated LDL cholesterol level and the risk of ATI observed in the present analysis is compatible with the evidence of the atherogenic role of LDL cholesterol.

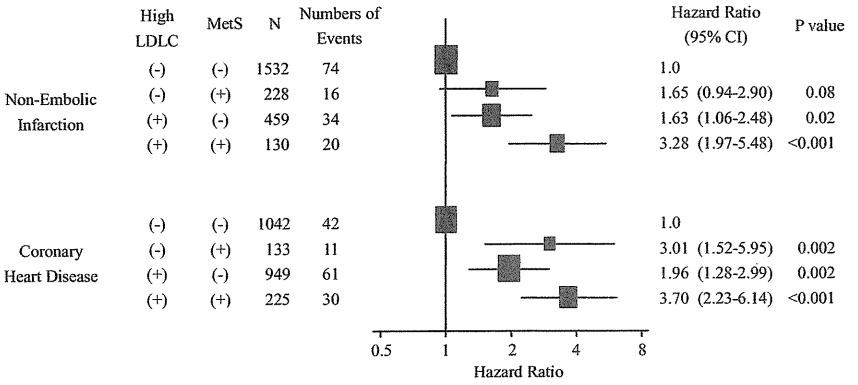

Figure. Multivariate-adjusted HRs for the development of nonembolic infarction and CHD according to the presence or absence of high LDL cholesterol and the metabolic syndrome. Multivariate adjustment was made for age, sex, ECG abnormalities, current drinking, current smoking, and regular exercise. Centers of the boxes are placed at the estimates of HRs. Horizontal lines indicate 95% CIs, and sizes of boxes are proportional to the numbers of events. LDLC indicates LDL cholesterol; MetS, metabolic syndrome.

In our cohort, the association between LDL cholesterol and the risk of LI was no longer significant after multivariate adjustment, suggesting that elevated LDL cholesterol was not an independent risk factor for the development of LI. Our previous report showed that multiple risk factors were related to the occurrence of LI,[14] and case-control studies on the relation between LDL cholesterol level and LI have reported varied associations.[21,22,25] One study reported a significant association between elevated LDL cholesterol and the risk of LI,[25] another study observed lower LDL cholesterol levels in LI cases,[22] and another study found no significant association.[21] Lacunar infarcts occur as a result of multiple mechanisms, such as (1) lipohyalinosis and/or fibrinoid necrosis, (2) microatheroma, (3) atherosclerosis of the basilar and middle cerebral artery stem or proximal division of large vessels, or (4) cardioembolic occlusion.[26] Lipohyalinosis is a vasculopathy caused by hypertension,[26] whereas large-vessel atherosclerosis is affected by risk factors including LDL cholesterol,[23,24] but cardioembolism seems less related to elevated LDL cholesterol.[22,25] These heterogeneous roles for LDL cholesterol in the multiple pathogenesis of LI occurrence might account for the weak association between LDL cholesterol and the risk of LI.

An inverse relation between LDL cholesterol level and the risk of CEI was observed in our earlier population in the 1960s,[14] and the same association was found in the present investigation after adjustment for confounding factors. Although the reason for this association is unknown, a plausible explanation is that a lowered cholesterol level might increase the risk of CEI through the increased occurrence of atrial fibrillation,[27] a predominant risk factor for CEI. Additional clinical and experimental evidence is needed to elucidate the mechanism underlying this association.

The results of previous prospective studies of the association between LDL cholesterol and hemorrhagic stroke have been inconsistent; a significant inverse association was reported in women in the Framingham Study,[20] whereas a nonsignificant association was observed in the Cardiovascular Health Study.[18] Lipid-lowering trials recently conducted in Japan[28,29] and a meta-analysis of >90 000 subjects enrolled in statin trials[8] found no apparent increase in the risk of hemorrhagic stroke. A nonsignificant association between LDL cholesterol and the risk of hemorrhagic stroke observed in our data was in accord with the findings of a previous prospective study[18] and intervention trials.[8,28,29]

Several prospective studies conducted in Western countries have reported positive associations between LDL cholesterol and the risk of CHD.[30] Among Japanese, no study has investigated the association between LDL cholesterol level and the risk of CHD, but several prospective studies have shown that total cholesterol is a strong risk factor for CHD.[31,32] The findings obtained from the present analysis support the results from those prospective studies and, for the first time, have demonstrated a positive association between calculated LDL cholesterol and the risk of CHD in a general Japanese population.

The metabolic syndrome has been shown to be a clear risk factor for CVD,[33] but LDL cholesterol level is not involved in the definition of the metabolic syndrome. In the present analysis, comparable and independent effects were observed for elevated LDL cholesterol and the metabolic syndrome on the risks of nonembolic infarction and CHD. The highest risk was observed for the subgroup with both an elevated LDL cholesterol value and the metabolic syndrome. Similar results were found in a prospective study of a Danish cohort.[34] All of these results imply that management of LDL cholesterol as well as the metabolic syndrome is important for the prevention of ischemic stroke and CHD.

The strengths of our study include its longitudinal population-based study design, long duration of follow-up, almost perfect follow-up of subjects, sufficient number of cardiovascular events, and accuracy for diagnosis of CVD, including ischemic stroke subtypes. One limitation of our study is that our findings are based on a 1-time measurement of serum lipids. Subsequent use of cholesterol-lowering agents could have altered lipid levels in some participants; however, this source of variability could not account for the relation observed in the present study, because a random misclassification of such nature would tend to cause an underestimation of study findings and bias the results toward the null hypothesis. Therefore, the true association could be stronger than that observed in our study. Another limitation is that the value of LDL cholesterol was not directly assayed but was calculated by the Friedewald equation. This equation has been adopted in substantial epidemiologic and clinical studies of LDL cholesterol and CVD. It is unlikely that the bias of LDL cholesterol values that occurred through calculation, if any, would have strengthened the association between LDL cholesterol and ATI or CHD observed in the present analysis.

In conclusion, we have shown that elevated LDL cholesterol is a significant risk factor for developing ATI as well as CHD in a general Japanese population. Because LDL cholesterol level is independent of the metabolic syndrome for the development of CVD, lowering a patient's LDL cholesterol level should be considered together with treatment of other metabolic disorders for the prevention of CVD.

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Disclosures

None.

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Impact of blood pressure levels on different types of stroke: the Hisayama study

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Objective **Clinical uncertainty remains whether the blood pressure classification and risk stratifications recommended by the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009) are useful in predicting the risks of stroke and its subtypes in the general Japanese population.**

Methods **A total of 1621 stroke-free residents of a Japanese community aged at least 40 years were followed up for 32 years. Outcomes were total and cause-specific stroke (lacunar infarction, atherothrombotic infarction, cardioembolic infarction, cerebral haemorrhage and subarachnoid haemorrhage). Incidence was calculated by the pooling of repeated observations method.**

Results **The age-adjusted incidence of total stroke rose progressively with higher blood pressure levels in both sexes (both *P* for trend <0.0001). A similar pattern was observed for lacunar infarction in both sexes and for cerebral haemorrhage in men: the differences were significant between optimal blood pressure and grades 1–3 hypertension (all $P<0.05$). The age-adjusted incidence of atherothrombotic infarction in either sex and that of cardioembolic infarction and subarachnoid haemorrhage in women significantly increased in grade 3 hypertension (all $P<0.05$). These associations remained substantially unchanged even after adjustment for other risk factors. In regard to risk stratification, the age-adjusted incidence of stroke significantly increased with the level of risk in both sexes.**

Conclusion **Our findings suggest that the blood pressure classification and risk stratifications recommended by the JSH 2009 guidelines are useful in predicting the risk of stroke in a general Japanese population, but the magnitude and patterns of the impact of blood pressure categories are different among stroke subtypes. *J Hypertens* 27:2437–2443 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Keywords: blood pressure, stroke, stroke subtype, prospective cohort study, risk factor

Abbreviations: JSH, Japanese Society of Hypertension; LVH, left ventricular hypertrophy; TOD, target organ damage

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Introduction

Recent guidelines for the management of hypertension recommend assessment of total cardiovascular risk using risk factors, target organ damage (TOD) and pre-existing cardiovascular disease, as well as blood pressure levels [1–3]. These classifications have primarily been established based on clinical and epidemiological studies that investigated the risks of coronary heart disease, stroke and other forms of cardiovascular diseases in Western populations. However, there has been shown to be significant heterogeneity in the incidences of stroke and the frequencies of stroke subtypes between Asian and Western populations: the stroke incidence is higher, as is the proportion of stroke due to parenchymatous small arterial lesions, in Asian populations than in Western populations [4–7]. Because of the heterogeneity in the pathogenesis of stroke subtypes, the impact of blood pressure levels should be evaluated separately for each stroke subtype. Despite clear evidence of the associations between blood pressure levels and the incidence of total stroke [1–3,7–10], clinical uncertainty remains about the impact of blood pressure on the risks of different types of stroke, particularly on the risks of cerebral infarction subtypes.

The Hisayama study is a prospective cohort study of cardiovascular disease conducted in the town of Hisayama, Japan [6,11,12]. During the study period, 93% of the first-ever stroke patients underwent morphological examinations by autopsy and/or brain imaging, and more than 80% of the total number of surviving patients participated in five repeated follow-up examinations. This characteristic study design provided us an

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opportunity to classify stroke into different types with a high degree of accuracy and to assess the stroke incidence, taking into account the dynamic transition of blood pressure. In the present article, we examined whether the blood pressure classification and risk stratifications recently recommended by the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009) [3] are useful in predicting the occurrence of stroke and its subtypes in Japanese.

Methods

Study population and follow-up survey

In 1961, 1621 stroke-free residents of the town of Hisayama, aged 40 years or over (participation rate 88%), were enrolled in the present study [6,11,12]. Members of this cohort have received follow-up evaluations for 32 years from 1 November 1961 through 30 October 1993. Health examinations were repeated in 1967, 1974, 1978, 1983 and 1988, and the participation rates for these examinations were 96, 87, 85, 81 and 98%, respectively.

For patients who did not undergo regular examinations or who moved out of Hisayama, health status was checked yearly by mail or telephone. We also established a daily monitoring system, which connected us with local physicians and the members of the Health and Welfare Office of the town, and used this system to gather information on new events of stroke, inclusive of suspected cases [6,11,12]. When stroke occurred or was suspected, physicians in the study team examined the patients and evaluated their detailed clinical information. The clinical diagnosis of stroke was based on the patient's history, physical and neurological examinations, and ancillary laboratory examinations. During the follow-up period, 1063 patients died, and 861 of these (81%) underwent autopsy to pathologically verify the cause of death and type of stroke. Only two patients were lost to follow-up.

The ethics committee of Kyushu University approved this study, participants provided written informed consent, and the procedures followed were in accordance with national guidelines.

Risk factor assessment

At each examination, blood pressure was measured three times using a standard sphygmomanometer after resting for at least 5 min in a supine position. Korotkoff phase 5 was taken as the diastolic blood pressure unless the sounds persisted at zero, in which case Korotkoff phase 4 was recorded. The mean of three measurements was used in the present analysis. We collected medical history and lifestyle information and conducted physical and neurological examinations. Information on antihypertensive treatment, smoking habits and alcohol intake was obtained using a standard questionnaire, and these factors were classified as being either habitually used or not used. Left ventricular hypertrophy (LVH; Minnesota code 3-1), ST depression (4-1, 2, 3 except for 3-1) and atrial fibrillation (8-3) on electrocardiography (ECG) were separately evaluated. Body weight and height were measured, and body mass index (BMI, kg/m^2) was calculated. Proteinuria was tested by the sulfosalicylic acid method in 1961 and 1967, and by the test paper method in 1974, 1978, 1983 and 1988. Serum cholesterol levels were determined by the Zak-Henly method, including a modification by Yoshikawa, in 1961 and 1967; by the Zurkowski method in 1974; and by the enzymatic method in 1978, 1983, and 1988 [13,14]. Glucose intolerance was determined by an oral glucose tolerance test in patients with glycosuria in 1961 and 1967, casual blood glucose levels in 1974, 1978 and 1983, and a 75-g oral glucose tolerance test in 1988, as well by reference to any medical history of diabetes at each examination [15,16].

Blood pressure classification and risk stratification

The JSH 2009 guidelines propose the following blood pressure categories: optimal blood pressure (systolic blood pressure < 120 mmHg and diastolic blood pressure < 80 mmHg), normal blood pressure (120–129/80–84 mmHg), high normal blood pressure (130–139/85–89 mmHg), grade 1 hypertension (140–159/90–99 mmHg), grade 2 hypertension (160–179/100–109 mmHg) and grade 3 hypertension ($\geq$180/110 mmHg) [3]. The guidelines also recommend a risk stratification system that determines the whole cardiovascular risk using blood pressure categories and the presence or absence of other risk factors and TOD. In this study, risk factors were defined as age ($\geq$65 years), dyslipidemia (total cholesterol >5.7 mmol/l), glucose intolerance and obesity (BMI $\geq 25\,kg/m^2$), and TOD was defined as electrocardiographic LVH (Minnesota code 3-1) and 1+ or more positive proteinuria. On the basis of the risk stratification system of the JSH 2009 guidelines, we classified patients into four risk groups. Specifically, the no additive risk group included patients with optimal and normal blood pressure and those with high-normal blood pressure who did not have risk factors or TOD. The low-risk group included patients with grade 1 hypertension who did not have risk factors or TOD. The moderate-risk group included patients with high-normal blood pressure and grade 1 hypertension who had one to two risk factors and those with grade 2 hypertension who did not have risk factors or TOD. The high-risk group included patients with high-normal blood pressure and grade 1 hypertension who had three or more risk factors, glucose intolerance or TOD, patients with grade 2 hypertension who had 1 or more risk factors, glucose intolerance or TOD and patients with grade 3 hypertension.

Stroke definition

The diagnosis of stroke was based on clinical information and the autopsy findings [6]. In principle, stroke was defined as a sudden onset of nonconvulsive and focal