cohort study was approved by the Institutional Review Board of the National Cardiovascular Center.

2.2. Baseline examination

Blood samples were collected after the participants had fasted for at least 10 h. The samples were centrifuged immediately and a routine blood examination was performed that included serum total cholesterol (TC), HDL cholesterol, TG and glucose levels.

Blood pressure was measured in triplicate on the right arm after 5 min of rest by well-trained physicians using a standard mercury sphygmomanometer. The average of the second and third measurements was used for analysis. Hypertension was defined as either a systolic blood pressure (SBP) $\geq$ 140 mmHg, a diastolic blood pressure (DBP) $\geq$ 90 mmHg or the use of antihypertensive agents. Diabetes was defined as a fasting serum glucose $\geq$ 7.0 mmol/L (126 mg/dL), the use of anti-diabetic agents, or both. Height with bare feet and weight in light clothing were measured. Waist circumference (WC) was measured at umbilical level in a standing position. Metabolic syndrome (MetS) was defined using modified NCEP-ATP III criteria [13], of which abdominal obesity was defined according to the International Obesity Task Force central obesity criteria for Asia [15].

Public health nurses obtained information on the smoking, drinking and medical histories.

2.3. Endpoint determination

The endpoint determination was previously reported [4,11–14]. The endpoints of the present study were: (1) the first myocardial infarction (MI) or stroke event; (2) death; (3) leaving Suita city; or (4) December 31, 2005.

The first step in the survey for MI and stroke involved checking the health status of all participants by repeated clinical visits every two years and yearly questionnaires by mail or telephone. In the second step, in-hospital medical records of participants who were suspected of having an MI or stroke were reviewed by registered hospital physicians or research physicians, who were blinded to the baseline information. The criteria for stroke were defined according to the US National Survey of Stroke criteria [16]. For each stroke subtype [i.e., cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage], a definite diagnosis was established based on the computed tomography, magnetic resonance imaging, or autopsy. The criteria for definite and probable MI were defined according to the criteria of the MONICA (Monitoring Trends and Determinants of Cardiovascular Disease) project [17]. Sudden deaths of unknown origin that occurred within 24 h of the onset were classified as MI in the present study.

2.4. Statistical analysis

The relationship between serum lipids and the risk of MI and stroke was described by dividing the participants into four groups stratified by the combination of serum levels of TG and non-HDLC. We used 1.7 mmol/L (150 mg/dL) of serum TG as a cut-off point for high serum TG according to the classification of NCEP-ATP III [9] and that of the Japan Atherosclerosis Society [3]. The category of non-HDLC $\geq$4.9 mmol/L (190 mg/dL) was defined as a high serum non-HDLC, which was equivalent to 6.2 mmol/L (240 mg/dL) of TC or 4.1 mmol/L (160 mg/dL) of LDL-C, because non-HDLC was usually 0.8 mmol/L (30 mg/dL) higher than LDL-C [9,18–19].

Continuous variables between groups were compared by analysis of variance and categorical variables were compared by a chi-square test. The hazard ratio (HR) for MI or stroke was calculated using a proportional hazards model adjusted for age, hypertension (dichotomous variable), diabetes, HDL-C, body mass index (BMI), smoking (never-smoked; ex-smoker; current smoker) and drinking (never-drank; ex-drinker; regular drinker) (model 1). Sex-combined analysis with further adjustment for sex was also performed. Another statistical model after replacement of BMI and hypertension with WC and SBP level (continuous variable) was also performed (model 2).

All confidence intervals were estimated at the 95% level and significance was set at a P value of <0.05. The Statistical Package for the Social Sciences (SPSS Japan Inc. version 15.0J, Tokyo, Japan) was used for all the analyses.

3. Results

The median and interquartile range of serum TG in the baseline survey was 1.29 mmol/L (0.90, 1.90) in men and 0.98 mmol/L (0.73, 1.41) in women. The mean baseline serum non-HDLC was 3.93 $\pm$ 0.91 mmol/L in men and 4.03 $\pm$ 1.03 mmol/L in women.

The means or prevalence of major cardiovascular risk factors in each group stratified by the combination of serum levels of TG and non-HDLC are summarized in Table 1. There was no significant difference in mean age and the prevalence of smoking among the TG and non-HDLC groups for men. There were significant differences in all other variables. Mean BMI, waist circumference and the prevalence of hypertension and diabetes were highest in the high-TG/high non-HDLC group, whereas the values of these parameters were lowest in the low-TG/low-non-HDLC group for both sexes. The prevalence of Mets was much higher in the high-TG groups than in the low-TG groups irrespective of non-HDLC level.

The total person-years were 59,774 (27,461 for men and 32,313 for women), with a mean follow-up period of 11.7 years. During the follow-up period, there were 113 first MIs and 180 first strokes. The strokes consisted of 28 intracerebral hemorrhages, 116 cerebral infarctions, 21 subarachnoid hemorrhages and 15 unclassified cases.

Table 2 shows the number of cases, age and multivariable-adjusted HRs for MI stratified by TG and non-HDLC. Compared with the low TG/low non-HDLC group, the HR for MI in the high TG/high non-HDLC group was 2.05 (95% confidence interval, CI, 1.08–3.90) in men, 3.79 (95% CI, 1.58–9.14) in women and 2.55 (95% CI, 1.53–4.24) in both sexes combined in multivariable adjusted model 1. We did not observe a significant increase in the HR for MI in the other groups. Similar results were observed after replacement of BMI and hypertension with WC and SBP level (model 2).

Table 3 shows the multivariable-adjusted HRs for cerebral infarction stratified by levels of TG and non-HDLC. Compared with the low TG/low non-HDLC group, the HR for cerebral infarction in the high TG alone group (high TG/low non-HDLC group) was 1.45 (95% CI, 0.84–2.50) in men, 2.09 (95% CI, 0.92–4.73) in women and 1.63 (95% CI, 1.03–2.56) in both sexes combined in statistical model 1. There was no significant increase of cerebral infarction in the other groups. Similar results were also observed in statistical model 2.

The incidence of total stroke, intracerebral hemorrhage and subarachnoid hemorrhage was not related to TG and non-HDLC levels in either sex. When the participants were divided into two groups by age (<60 and $\geq$60), the results of all the analyses listed above were similar in both age groups (data not shown).

4. Discussion

To our knowledge, this is the first cohort study in Japan to clarify the risk for MI and ischemic stroke of high serum level of TG, non-HDLC and both. The risk for MI of both high serum TG and non-HDLC was considerably higher than the risk without both or with only one. This relationship was similarly observed in both men and

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Table 1
Means and prevalence of major cardiovascular risk factors in each group stratified by the combination of serum levels of triglycerides (TG) and non-high-density lipoprotein cholesterol (non-HDLC).

Variables	Low TG/low Non-HDLC		Low TG/high Non-HDLC		High TG/low Non-HDLC		High TG/high Non-HDLC		*P* value
Men									
No. of subjects	1532		117		550		205		
Non-HDLC (stratum mean), mmol/L	3.6	(0.7)	5.4	0.4	4.0	0.6	5.5	0.5	
Triglycerides (stratum median), mmol/L	1.0	(0.8, 1.3)*	1.3	(1.0, 1.5)*	2.2	(1.9, 2.9)*	2.4	(2.0, 3.7)*	
Age, years	55.8	(13.5)	57.4	(12.9)	54.8	(12.7)	54.8	(11.8)	0.16
HDLC, mmol/L	1.4	(0.3)	1.3	(0.3)	1.1	(0.3)	1.1	(0.2)	<0.01
BMI, kg/m^2	22.2	(2.8)	23.1	(3.1)	23.8	(2.6)	24.2	(2.6)	<0.01
Waist circumference, cm	80.8	(7.9)	82.7	(8.6)	85.7	(7.0)	86.3	(6.9)	<0.01
Systolic blood pressure, mmHg	127	(21)	129	(20)	130	(20)	132	(21)	<0.01
Diastolic blood pressure, mmHg	78	(12)	79	(12)	81	(11)	82	(11)	<0.01
Hypertension, %	30.0		35.0		36.4		38.0		0.01
Diabetes, %	4.8		4.3		7.5		9.3		0.02
Metabolic syndrome, %**	4.5		4.3		45.1		47.8		<0.01
Smoking, %									
Current smoker	49.9		43.6		53.5		47.3		0.51
Ex-smoker	30.3		35.0		28.4		32.7		
Never-smoker	19.8		21.4		18.2		20.0		
Drinking, %									
Current drinker	76.0		63.2		76.4		69.3		0.02
Ex-drinker	3.6		6.0		2.9		5.4		
Never-drinker	20.4		30.8		20.7		25.4		
Women									
No. of subjects	1956		290		256		192		
Non-HDLC (stratum mean), mmol/L	3.6	(0.7)	5.5	(0.5)	4.2	(0.5)	5.8	(0.8)	
Triglycerides (stratum median), mmol/L	0.9	(0.7, 1.1)*	1.2	(0.9, 1.4)*	2.0	(1.8, 2.4)*	2.4	(2.0, 3.0)*	
Age, years	51.5	(12.9)	59.3	(9.6)	57.9	(11.2)	60.7	(8.8)	<0.01
HDLC, mmol/L	1.5	(0.3)	1.4	(0.3)	1.2	(0.3)	1.1	(0.3)	<0.01
BMI, kg./m2	21.7	(3.1)	22.9	(3.1)	23.6	(3.3)	24.2	(3.1)	<0.01
Waist circumference, cm	75.5	(9.8)	79.8	(9.7)	82.7	(10.0)	83.5	(9.7)	<0.01
Systolic blood pressure, mmHg	121	(21)	131	(21)	132	(21)	137	(21)	<0.01
Diastolic blood pressure, mmHg	73	(12)	79	(12)	79	(12)	80	(13)	<0.01
Hypertension, %	20.4		37.9		37.1		48.4		<0.01
Diabetes, %	2.4		4.5		6.6		7.8		<0.01
Metabolic syndrome, %**	7.5		19.3		66.8		74.5		<0.01
Smoking, %									
Current smoker	11.8		8.6		14.5		16.1		0.04
EX-smoker	3.5		2.8		2.7		6.3		
Never-smoker	84.7		88.6		82.8		77.6		
Drinking, %									
Current drinker	34.9		29.3		28.5		24.5		<0.01
Ex-drinker	1.8		0.3		0.8		4.2		
Never-drinker	63.3		70.3		70.7		71.4		

TG, triglycerides; non-HDLC, non-high-density lipoprotein cholesterol; BMI, body mass index. Brackets indicate standard deviation.
Analysis of variance was used for comparisons of multiple group means and the chi-square test was used to compare proportions.

* Inter-quartile range.

** MetS was defined using modified NCEP-ATP III. Abdominal obesity was defined as a waist circumference ≥0.90 m in men and ≥ 0.80 m in women. High blood pressure was defined as average systolic/diastolic blood pressures of ≥ 130/85 mm Hg and/or current medication for hypertension. High triglyceride was defined as serum triglycerides of ≥1.7 mmol/L. Low HDL cholesterol was defined as serum HDL cholesterol levels of <1.03 mmol/L in men and of <1.29 mmol/L in women. High blood glucose was defined as fasting blood glucose of ≥6.1 mmol/L and/or current use of anti-diabetic medication. MetS was defined as the presence of three or more of these components.

women. In contrast, the risk for ischemic stroke was highest in the participants with high TG alone.

TG-rich lipoproteins have been shown to be atherogenic, and thus, they are associated with coronary atherosclerosis [9,19–20]. As NCEP-ATP III pointed out [9], elevated non-HDLC is a good therapeutic target in patients with high TG, because the serum concentration of non-HDLC reflects not only LDL-C but also the cholesterol content of all other TG-rich and apolipoprotein B containing lipoproteins, such as very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), small dense LDL particles and their remnant lipoproteins [19–20]. In the Helsinki Heart study [21], most of the risk for coronary heart disease (CHD) was confined to participants with high levels of both TG and LDL-C. In the West of Scotland Coronary Prevention Study [22], a higher incidence of CHD was observed in men in both the pravastatin and placebo groups when TG was at or above the median level. Pischon et al. suggested that TG added significant information to non-HDLC for CAD risk prediction in a nested case-control study [23]. Our findings are consistent with previous studies.

Similar to previous studies in Japan [4,10], we found no association between non-HDLC and cerebral infarction even in the presence of high serum TG, which may be due to a lower prevalence of atherothrombotic infarction than in Western populations. The ARIC study indicated that TC was associated with increased risk of non-lacunar, non-embolic stroke (atherothrombotic infarction), but not with lacunar or embolic stroke [24]. A recent report from a Japanese rural population showed that LDL-C is a risk factor for only atherothrombotic infraction [25]. Unfortunately, due to the relatively small stroke cases in our study, we were not able to demonstrate an association between any subtype of cerebral infarction and non-HDLC.

It is not clear why participants with high TG alone showed the increased risk for cerebral infarction in the present study. In a meta-analysis of 26 cohort studies in Asia-Pacific area, partici-

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Table 2
Age and multivariable-adjusted hazard ratios (95% confidence intervals) for myocardial infarction stratified by TG and non-HDLC groups in an 11.7-year prospective study of 5098 Japanese men and women.

	Low TG/low Non-HDLC	Low TG/high Non-HDLC	High TG/low Non-HDLC	High TG/high Non-HDLC
Men				
Person-years	17410	1288	6358	2404
Case, *n*	45	6	11	14
Age adjusted	1.00	1.63 (0.70-3.83)	0.76 (0.39-1.48)	2.74(1.50-5.02)
Model 1[a]	1.00	1.48 (0.62-3.49)	0.63 (0.32-1.26)	2.05(1.08-3.90)
Model 2[b]	1.00	1.55 (0.66-3.66)	0.64 (0.32-1.29)	2.10 (1.10-3.98)
Women				
Person-years	23652	3455	2936	2270
Case, *n*	14	5	6	12
Age adjusted	1.00	1.59 (0.57-4.40)	2.28 (0.88-5.94)	4.88 (2.25-10.6)
Model 1[a]	1.00	1.63 (0.58-4.26)	1.99 (0.71-5.57)	3.79 (1.58-9.14)
Model 2[b]	1.00	1.55 (0.55-4.38)	1.92 (0.69-5.34)	3.18 (1.34-7.52)
Men and women				
Person-years	41062	4743	9294	4674
Case, *n*	59	11	17	26
Age adjusted	1.00	1.51 (0.79-2.89)	1.04 (0.60-1.78)	3.42 (2.15-5.44)
Model 1[a]	1.00	1.42 (0.74-2.74)	0.86 (0.49-1.53)	2.55 (1.53-4.24)
Model 2[b]	1.00	1.45 (0.75-2.79)	0.87 (0.49-1.54)	2.48 (1.49-4.10)

TG, triglycerides; non-HDLC, non high-density lipoprotein cholesterol.
[a] Multivariable adjusted for age, body mass index, hypertension, diabetes, HDL (high-density lipoprotein) cholesterol, cigarette smoking and alcohol intake by a Cox proportional hazard model. Sex was also adjusted in the men and women combined model.
[b] Replacement of body mass index and hypertension as covariates in model 1 with waist circumference and systolic blood pressure level.

pants grouped in the highest fifth of serum TG had a 50% increased risk of stroke compared with those in the lowest fifth [26]. Recent reviews have also concluded that hypertriglyceridemia seems to be a causal risk factor for ischemic stroke [7–8]. However, above-mentioned findings were not able to explain the low incidence of cerebral infarction in the high TG/high non-HDLC group in the present study. An elevated risk for MI might mask the relationship between TG and cerebral infarction; because there would be no further follow-up after a first MI. Another large study concerning about the relationship between serum TG and stroke should be needed.

Recently, we have reported that high serum LDLC and non-HDLC are both associated with an increased risk of MI; and the predictive value of non-HDLC for MI is almost similar to that of LDL-C [4]. However, we did not use serum TG as a covariate to avoid over-adjustment, because difference between serum level of LDLC and non-HDLC was automatically determined by serum TG level when serum LDLC value was calculated by the Friedewald formula [27]. Considering all the findings together, non-HDLC and TG may be recommended as beneficial screening markers for primary prevention of CAD in the Japanese community, as they are less expensive and more convenient because non-HDLC can be calculated irrespective of serum TG level.

The present study has some limitations. First, the single TG and non-HDLC measurement at the baseline survey may have underestimated the relationship between these lipids and cardiovascular disease due to regression dilution bias. Furthermore, we did not evaluate longitudinal trend for each risk factor and its medication status after baseline survey. Especially, hypertriglyceridemia is associated with not only present existence of metabolic components, such as hypertension and diabetes, but also new onset

Table 3
Age and multivariable-adjusted hazard ratios (95% confidence intervals) for cerebral infarction stratified by TG and non-HDLC groups in an 11.7-year prospective study of 5098 Japanese men and women.

	Low TG/low Non-HDLC	Low TG/high Non-HDLC	High TG/low Non-HDLC	High TG/high Non-HDLC
Men				
Person-years	17410	1288	6358	2404
Case, *n*	46	2	22	5
Age adjusted	1.00	0.53 (0.13-2.19)	1.51 (0.91-2.52)	0.99 (0.39-2.51)
Model 1[a]	1.00	0.54 (0.13-2.25)	1.45 (0.84-2.50)	0.92 (0.35-2.38)
Model 2[b]	1.00	0.56 (0.14-2.31)	1.48 (0.86-2.56)	0.75 (0.26-2.14)
Women				
Person-years	23652	3455	2936	2270
Case, *n*	20	8	10	3
Age adjusted	1.00	1.77 (0.78-4.02)	2.62 (1.23-5.60)	0.81 (0.24-2.72)
Model 1[a]	1.00	1.52 (0.66-3.50)	2.09 (0.92-4.73)	0.69 (0.20-2.44)
Model 2[b]	1.00	1.54 (0.67-3.54)	2.10 (0.93-4.73)	0.77 (0.22-2.71)
Men and women				
Person-years	41062	4743	9294	4674
Case, *n*	66	10	32	8
Age adjusted	1.00	1.14 (0.58-2.23)	1.82 (1.19-2.79)	0.94 (0.45-1.95)
Model 1[a]	1.00	1.12 (0.57-2.20)	1.63 (1.03-2.56)	0.79 (0.37-1.69)
Model 2[b]	1.00	1.12 (0.57-2.21)	1.62 (1.03-2.55)	0.69 (0.62-1.88)

TG, triglycerides; non-HDLC, non high-density lipoprotein cholesterol.
[a] Multivariable adjusted for age, body mass index, hypertension, diabetes, HDL (high-density lipoprotein) cholesterol, cigarette smoking and alcohol intake by a Cox proportional hazard model. Sex was also adjusted in the men and women combined model.
[b] Replacement of body mass index and hypertension (prevalence) as covariates in model 1 with waist circumference and systolic blood pressure levels.

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of them in the future [28,29]. Second, we did not measure serum apolipoprotein B (apoB) [22], apolipoprotein A1 (ApoA1) and LP(a) [30], which some previous studies have shown to be strong risk factors for CAD [22]. Third, a recent study indicated that non-fasting TG is a better predictor of CAD than fasting TG [31]. However, in a large individual based meta-analysis in the Asia-Pacific region [26], most blood samples were collected during fasting, and there was a significant positive relationship between serum TG and CAD or stroke.

In conclusion, a combination of higher serum levels of TG and non-HDLC is associated with an increased risk of MI in a Japanese population. Furthermore, the risk for ischemic stroke was highest in the participants with high TG alone; however, further research should be needed. High serum levels of TG and non-HDLC are both important targets for the prevention of cardiovascular disease, which requires evidence-based guidelines for management in the primary care setting.

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The Relationship Between Waist Circumference and the Risk of Stroke and Myocardial Infarction in a Japanese Urban Cohort

The Suita Study

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Background and Purpose—Body mass index is most commonly used as the obesity index. Recently, waist circumference (WC) has been shown to be associated with the risk of cardiovascular disease (CVD). However, no studies have observed an association between WC and CVD in Japan. We examined the relationships of WC and body mass index with CVD in a Japanese urban population.

Methods—We studied 5474 Japanese individuals (aged 30 to 79 years without CVD at baseline) who completed a baseline survey and received follow-up through December 2005. WC was measured at the umbilical level of participants in the standing position to the nearest 1 cm. The Cox proportional hazard ratios for CVD according to the quartiles of WC were calculated after adjustment for age, smoking, and drinking status.

Results—During a mean follow-up of 11.7 years, 207 strokes and 133 myocardial infarctions were documented. In women, compared with the lowest quartile (WC <70 cm), the hazard ratio (95% CIs) after adjusting for age, smoking, and drinking in the highest quartile (WC ≥84 cm) were 1.85 (1.03 to 3.31) for CVD and 2.64 (1.16 to 6.03) for stroke. However, no such relationships of WC with CVD or stroke risk were observed in men. After further adjustment of hypertension, diabetes, and hypercholesterolemia, all of the mentioned relationships were not statistically significant. No associations of body mass index with CVD or strokes were observed.

Conclusions—WC may be a better predictor for CVD or stroke in Japanese women. **(*Stroke*. 2010;41:00-00.)**

Key Words: abdominal obesity ■ cardiovascular disease ■ epidemiology ■ prospective studies ■ stroke ■ waist circumference

The increasing prevalence of obesity worldwide has led to concern about the impact of obesity on the risk of cardiovascular disease (CVD).[1] Body mass index is most commonly used as the measurement of obesity. Recently, abdominal obesity measured by waist circumference (WC) has been shown to be associated with the risk of CVD.[2,3] However, no cohort study on the relationship between WC and the risk of CVD has been performed in Japan. We therefore examined the relationship of WC and body mass index with the incidence of CVD and stroke in a Japanese urban population.

Methods

The Suita Study starting from September 1989, a random sampling of Japanese urban residents, has been described previously (response rate: 53%).[4–6] Participants (n=5474) who attended the baseline examination without a history of CVD were followed up. The details of the methods and confirmation of stroke and myocardial infarction in the Suita Study have been described elsewhere.[4–6] The follow-up was continued until one of the following end points, whichever came first: date of the first myocardial infarction or stroke event, date of death, date of leaving Suita, or December 31, 2005. This study was approved by the Institutional Review Board of the National Cardiovascular Center.

Analyses of variance and χ^2 tests were used to compare mean values and frequencies. The Cox proportional hazard ratios and 95% CIs for CVD were calculated according to the quartiles of WC after adjusting for age, smoking, and drinking status. All statistical analyses were performed with SPSS (Version 13.0J; SPSS Japan Inc, Tokyo, Japan).

Results

During a mean follow-up of 11.7 years, we documented 207 strokes and 133 myocardial infarctions. As shown in Table 1,

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Table 1. Baseline Characteristics of Subjects According to Quartile of WC by 2560 Men and 2914 Women Aged 30 to 79: The Suita Study, 1989–1994, Japan

	WC				
	Q1 (Low)	Q2	Q3	Q4 (High)	*P*
Women					
No. of subjects	702	679	739	794	
Waist circumference, cm*	54–69	70–75	76–83	84–121	<0.001
Age, years*	49±13	52±13	55±12	60±11	<0.001
Body mass index, kg/m^2*	19.6±1.9	21.1±2.0	22.5±2.2	25.3±3.2	<0.001
Hypertension, %†	14	20	27	46	<0.001
Diabetes, %†	1	2	3	7	<0.001
Hypercholesterolemia, %†	32	36	45	54	<0.001
Smoking status (current/quit/never), %†	14/3/83	12/3/85	12/3/85	11/5/84	0.092
Drinking status (current/quit/never), %†	34/1/64	34/2/63	32/1/67	31/1/67	0.512
Men					
No. of subjects	564	711	627	658	
Waist circumference, cm*	57–76	77–82	83–87	88–124	<0.001
Age, years*	56±14	54±13	56±13	57±12	0.003
Body mass index, kg/m^2*	19.7±1.8	21.9±1.6	23.5±1.6	25.9±2.3	<0.001
Hypertension, %†	24	29	35	46	<0.001
Diabetes, %†	4	6	5	9	0.013
Hypercholesterolemia, %†	19	27	33	34	<0.001
Smoking status (current/quit/never), %†	56/27/17	55/24/20	45/37/18	44/35/21	<0.001
Drinking status (current/quit/never), %†	71/4/25	76/4/28	77/4/19	76/4/20	0.287

Data indicate frequencies or means±SDs.
*Analysis of variance was performed.
†χ^2 test was performed.
Q indicates quartile; Hypertension, systolic blood pressure/diastolic blood pressure ≥140/90 mm Hg or current use of antihypertensive medications; diabetes, fasting plasma glucose levels ≥7.0 mmol/L or nonfasting plasma glucose levels ≥11.1 mmol/L or current use of antidiabetic medications; hypercholesterolemia, total serum cholesterol levels ≥5.7 mmol/L or current use of antihyperlipidemic medications.

both men and women with higher WC were older; had a higher prevalence of hypertension, diabetes, and hypercholesterolemia; and had a lower prevalence of current smokers. The correlations between body mass index and WC were 0.84 in men and 0.75 in women.

The highest quartile of WC was associated with a significant increase in the risk of CVD and stroke compared with the lowest quartile in women but not in men (Table 2). Moreover, in women, the association between WC and CVD disappeared after further adjustment for hypertension, diabetes, and hypercholesterolemia. These associations were not also statistically significant even after removing subjects with any of mentioned 3 risk factors (data not shown). When we sequentially changed the cutoff values of WC, an increased risk of CVD was observed in women with WC ≥80 cm (Figure). No associations of body mass index with CVD or strokes were observed (data not shown).

Discussion

In this cohort study, abdominal obesity (WC ≥80 cm) was positively associated with CVD in women, which is the first study of the relationships in Japan. In the 2 large cohort studies in the Western population,[2,3] WC was positively associated with the risk of CVD. However, the current study only observed the positive relationships of WC with CVD and stroke in women. The reasons for the sex difference are unclear but may involve differences in race, lifestyle background, severity of obesity, or prevalence of risk factors in nonobese subjects.

Abdominal obesity, strongly correlated with WC, has been associated with insulin resistance,[7] diabetes,[8] lipid abnormalities,[9] and blood pressure elevation.[10] The association between WC and CVD disappeared after further adjustment for cardiovascular risk factors or removing subjects with diabetes, hypertension, or hypercholesterolemia. Therefore, WC might be likely on the causal pathway leading to the more proximal risk factors for CVD and contributes to risk through those factors. Abdominal obesity without other cardiovascular risk factors does not predict the risk of CVD. However, it should be careful that increasing abdominal obesity might lead to those factors.

Our study has the following limitations: regression dilution bias, small sample size for subgroup analysis, lifestyle background, and measurement of WC at the umbilical level rather than at the midpoint between the

Table 2. Age- and Multivariable-Adjusted Hazard Ratios (95% CIs) for CVD According to WC Quartile by Sex

	Q1 (Low)	Q2	Q3	Q4 (High)	*P* for Trend
Women					
Waist circumference, cm	54–69	70–75	76–83	84–121	
Person-years	8686	8334	8880	9008	
Cardiovascular disease					
No. of cases	15	23	35	63	
Age-adjusted	1	1.27 (0.66–2.44)	1.50 (0.81–2.76)	1.84 (1.04–3.27)	0.02
Multivariable-adjusted	1	1.30 (0.67–2.54)	1.57 (0.84–2.91)	1.85 (1.03–3.31)	0.02
Stroke					
No. of cases	7	15	27	42	
Age-adjusted	1	1.82 (0.74–4.49)	2.55 (1.10–5.92)	2.80 (1.24–6.33)	0.01
Multivariable-adjusted	1	1.78 (0.71–4.46)	2.57 (1.10–6.00)	2.64 (1.16–6.03)	0.01
Myocardial infarction					
No. of cases	8	8	8	21	
Age-adjusted	1	0.83 (0.31–2.24)	0.64 (0.24–1.73)	1.12 (0.49–2.55)	0.67
Multivariable-adjusted	1	0.91 (0.33–2.49)	0.72 (0.26–1.96)	1.26 (0.54–2.97)	0.50
Men					
Waist circumference, cm	57–76	77–82	83–87	88–124	
Person-years	6443	8185	7304	7183	
Cardiovascular disease					
No. of cases	43	53	45	63	
Age-adjusted	1	1.13 (0.75–1.69)	0.91 (0.60–1.39)	1.25 (0.85–1.85)	0.41
Multivariable-adjusted	1	1.13 (0.75–1.69)	0.92 (0.60–1.40)	1.33 (0.89–1.97)	0.28
Stroke					
No. of cases	22	28	32	34	
Age-adjusted	1	1.15 (0.65–2.01)	1.22 (0.71–2.11)	1.31 (0.77–2.25)	0.31
Multivariable-adjusted	1	1.14 (0.65–2.00)	1.25 (0.72–2.16)	1.40 (0.82–2.41)	0.20
Myocardial infarction					
No. of cases	21	25	13	29	
Age-adjusted	1	1.09 (0.61–1.95)	0.55 (0.27–1.10)	1.20 (0.68–2.10)	0.92
Multivariable-adjusted	1	1.10 (0.61–1.97)	0.55 (0.27–1.10)	1.29 (0.72–2.29)	0.79

Multivariable adjustments were performed for age, smoking, and drinking status.
Q indicates quartile.

lower rib and the iliac crest. However, the correlation coefficients between values measured by using the both methods for measurement of WC were reported to be high.[11]

In conclusion, our findings suggested that WC was associated with an increased risk of CVD and stroke in Japanese women. From a public health perspective, measurement of WC could be a useful tool for use in preliminary screening for high risk of CVD.

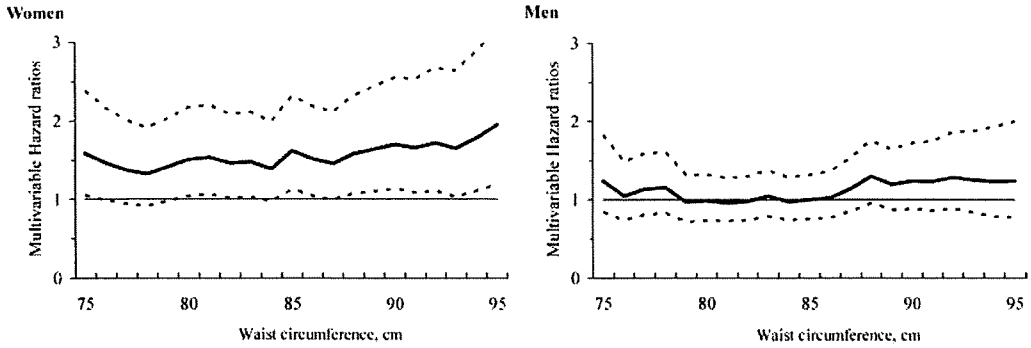

Figure. The risk for CVD through sequential changes in WC in men and women. Solid line indicates hazard ratios for CVD according to different cutoff values of WC. Dotted lines indicate 95% CIs for each WC.

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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

A free communication on a portion of this study was presented at the 18th Scientific Meeting of the European Society of Hypertension/the 22nd Scientific Meeting of the International Society of Hypertension held in Berlin in June 2008.

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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

neurological deficits persisting for more than 24 h, and the stroke was then classified as cerebral infarction, cerebral haemorrhage, subarachnoid haemorrhage or undetermined type of stroke. Cerebral infarction was further divided into four clinical categories: lacunar infarction, atherothrombotic infarction, cardioembolic infarction or undetermined type of cerebral infarction, based on the Classification of Cerebrovascular Disease III proposed by the National Institute of Neurological Disorders and Stroke [17], the criteria for the type of stroke of the TOAST study [18] and the Cerebral Embolism Task Force [19].

During the follow-up period, a total of 410 patients (200 men and 210 women) developed a first-ever stroke, and 381 of these (93%) underwent morphological examinations, including an examination of the cerebrospinal fluid, cerebral angiography, recent brain imaging including computed tomography and magnetic resonance imaging, echocardiography, carotid duplex imaging, and autopsy. Autopsies were performed on 303 stroke cases (74%). Of the 410 stroke cases that developed, 374 (181 men and 193 women) who participated in a follow-up examination within the 7 years previous to the stroke occurrence were eligible for the present study. These stroke cases were divided into 270 cases of cerebral infarction (128 men and 142 women), 68 of cerebral haemorrhage (45 and 23), 32 of subarachnoid haemorrhage (6 and 26) and four of an undetermined type of stroke (2 and 2). The cerebral infarction cases were further subdivided into 153 cases of lacunar infarction (72 and 81), 58 of atherothrombotic infarction (26 and 32), 51 of cardioembolic infarction (28 and 23) and eight of an undetermined type of cerebral infarction (2 and 6).

Statistical analysis

The incidence of stroke and its subtypes was calculated by the pooling of repeated-observations method [12,20,21]. This technique is a generalized person-years approach that incorporates all repeated examinations. It treats each examination interval as a mini follow-up study, in which the nearest risk factor measurements are employed to predict an event in the interval. Observations over multiple intervals are pooled into a single sample to predict the short-term risk of an event. The incidence was compared and the hazard ratios were estimated by the time-dependent Cox's proportional hazards model, in which risk factors other than age and sex were allowed to change in accordance with data from the five follow-up examinations. $P < 0.05$ was considered to indicate statistical significance.

Results

Baseline characteristics

Table 1 shows the mean values or frequencies of risk factors for stroke at each examination by sex. The mean age was 56 years for men and 57 years for women at

Table 1 Means (±SD) or frequencies of risk factors at each examination among men and women

	Men						Women					
Risk factors	1961 ($n=707$)	1967 ($n=559$)	1974 ($n=396$)	1978 ($n=341$)	1983 ($n=278$)	1988 ($n=259$)	1961 ($n=914$)	1967 ($n=768$)	1974 ($n=599$)	1978 ($n=546$)	1983 ($n=436$)	1988 ($n=442$)
Age (years)	56 ± 11	60 ± 10	66 ± 9	68 ± 7.3	72 ± 7	75 ± 6	57 ± 12	61 ± 10	67 ± 9	69 ± 8	72 ± 7	75 ± 6
Systolic blood pressure (mmHg)	135 ± 26	141 ± 28	145 ± 26	139 ± 23	142 ± 24	140 ± 23	135 ± 26	137 ± 27	146 ± 26	145 ± 23	148 ± 24	143 ± 25
Diastolic blood pressure (mmHg)	79 ± 14	82 ± 14	80 ± 12	79 ± 11	80 ± 12	77 ± 12	77 ± 13	79 ± 13	79 ± 12	79 ± 11	79 ± 11	75 ± 11
Blood pressure category (%)												
Optimal (<120/80 mmHg)	30.0	24.5	17.7	20.2	15.5	18.9	32.4	29.0	15.0	13.9	11.2	15.6
Normal (120–129/80–84 mmHg)	18.3	13.8	13.9	14.7	16.2	16.2	16.1	13.9	13.4	13.2	10.8	15.4
High-normal (130–139/85–89 mmHg)	13.3	14.0	13.6	18.8	14.4	15.4	14.3	12.1	14.0	15.0	15.4	14.3
Grade 1 (140–159/90–99 mmHg)	19.4	22.2	27.5	27.0	31.3	30.9	19.4	25.4	30.2	32.1	31.2	30.8
Grade 2 (160–179/100–109 mmHg)	10.6	14.7	15.4	13.2	15.5	11.6	10.9	11.5	16.2	18.9	22.5	16.5
Grade 3 (≥180/110 mmHg)	8.5	10.9	11.9	6.2	7.2	7.0	6.9	8.1	11.2	7.0	8.9	7.5
Antihypertensive agent (%)	2.1	15.4	13.6	19.8	24.1	23.9	2.2	18.1	12.0	17.6	23.6	25.1
Left ventricular hypertrophy (%)[a]	22.0	17.5	19.4	19.1	23.3	18.2	10.3	10.2	10.2	15.0	21.9	14.8
ST depression (%)[b]	2.1	1.1	5.3	2.6	3.0	3.9	3.8	2.6	7.5	5.3	6.0	6.4
Atrial fibrillation (%)[c]	0.7	1.1	3.3	3.2	3.7	4.3	0.7	0.8	1.3	1.3	1.0	2.1
Glucose intolerance (%)	12.2	15.2	20.7	21.4	22.3	25.9	4.8	5.1	9.8	11.7	13.8	25.2
Body mass index (kg/m^2)	21.5 ± 2.4	21.5 ± 2.4	21.2 ± 2.7	21.4 ± 3.0	21.3 ± 3.2	21.5 ± 3.0	21.7 ± 2.9	22.1 ± 3.3	22.2 ± 3.5	22.2 ± 3.4	22.0 ± 3.4	22.1 ± 3.5
Total cholesterol (mmol/l)	3.9 ± 0.9	4.1 ± 0.8	4.6 ± 0.9	4.6 ± 1.0	4.8 ± 1.0	4.6 ± 1.0	4.2 ± 1.0	4.6 ± 1.0	5.1 ± 0.9	5.3 ± 1.0	5.4 ± 1.0	5.4 ± 1.1
Proteinuria (%)	7.1	3.8	16.4	6.3	13.6	8.5	9.4	3.6	13.4	4.8	9.4	7.8
Smoking habits (%)	76.2	70.2	67.0	60.7	52.5	45.2	17.1	14.9	12.2	11.3	8.3	10.9
Alcohol intake (%)	69.3	61.7	61.5	55.1	54.0	52.1	8.3	4.7	5.2	6.4	6.4	6.1

[a]Minnesota code 3-1. [b]Minnesota codes 4-1, 2, 3 except for 3-1. [c]Minnesota code 8-3.

baseline. The mean systolic blood pressure levels and frequency of hypertension (grades 1–3) slightly increased from 1961 to 1988 for both men and women. The frequency of patients taking antihypertensive agents increased from 2.1% in 1961 to 23.9% in 1988 among men and from 2.2 to 25.1% among women. The frequency of glucose intolerance and mean total cholesterol levels also increased from 1961 to 1988 in both sexes.

Incidence and adjusted hazard ratio for stroke and its subtypes

Tables 2 and 3 show the age-adjusted incidence of total stroke and its subtypes according to the blood pressure categories of the JSH 2009 guidelines [3] by sex. The incidence of total stroke and its subtypes, except for that of subarachnoid haemorrhage, was higher in men than in women. In both sexes, the stroke incidence increased steeply with elevation in blood pressure levels (both P for trend <0.0001); the differences between optimal blood pressure and grades 1–3 hypertension were statistically significant (all $P < 0.01$). These associations remained significant even after controlling for age, LVH, ST depression and atrial fibrillation on ECG, glucose intolerance, BMI, total cholesterol, smoking habits and alcohol intake in either sex (both P for trend <0.0001). Similar patterns were observed for cerebral infarction in both sexes and for cerebral haemorrhage in men (all P for trend <0.0001). For women, the incidence of cerebral haemorrhage significantly increased in grade 2 hypertension ($P = 0.02$), as did the incidence of subarachnoid haemorrhage in grade 3 hypertension ($P = 0.01$). For men, subarachnoid haemorrhage did not show a clear relationship with the blood pressure categories, probably due to the small number of events. With regard to subtypes of cerebral infarction, the incidence of lacunar infarction increased with elevation of blood pressure levels in both sexes (both P for trend <0.0001). In contrast, the incidence of atherothrombotic infarction sharply increased in grade 3 hypertension for both sexes (both $P < 0.05$), and the incidence of cardioembolic infarction significantly increased in grade 3 hypertension for women ($P = 0.04$). Comparable associations were observed between blood pressure categories and stroke even after excluding patients taking antihypertensive agents at each examination.

Risk stratification

Figure 1 shows the age-adjusted incidence of stroke by risk groups defined by the risk stratification system proposed by the JSH 2009 guidelines [3] among men and women. The stroke incidence increased steeply with the elevation of risk levels for men and women (both P for trend <0.0001): compared to the no-additive risk group, the stroke incidence was significantly higher in the moderate and high-risk groups for both sexes (all $P < 0.05$) and also in the low-risk group for women ($P = 0.008$).

Table 2 Incidence and adjusted hazard ratio for total stroke and its types by blood pressure categories among men

Type of stroke			Hypertension			P trend
	Optimal	Normal	High-normal	Grade 1	Grade 2	Grade 3	
Total stroke							
Age-adjusted incidence (per 1000 person-years)	3.1	5.3	5.4	10.0**	20.9**	54.2**	<0.0001
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	1.64 (0.76–3.56)	1.52 (0.70–3.31)	3.31 (1.73–6.32)**	4.22 (2.16–8.25)**	5.75 (2.93–11.30)**	<0.0001
Cerebral infarction							
Age-adjusted incidence (per 1000 person-years)	2.4	2.8	3.8	6.9**	8.9**	19.5**	<0.0001
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	1.38 (0.54–3.48)	1.37 (0.55–3.41)	3.10 (1.47–6.55)**	3.29 (1.50–7.21)**	4.88 (2.24–10.65)**	<0.0001
Lacunar							
Age-adjusted incidence (per 1000 person-years)	1.4	1.1	1.8	4.8**	6.4**	11.2**	<0.0001
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	1.11 (0.29–4.15)	1.49 (0.45–4.96)	3.09 (1.13–8.47)*	3.26 (1.14–9.30)*	4.66 (1.63–13.32)**	0.0003
Atherothrombotic							
Age-adjusted incidence (per 1000 person-years)	0.0	1.0	0.4	1.0	1.1	6.1*	0.0001
Multivariate-adjusted hazard ratio (95% CI)	–	1 (reference)	0.45 (0.04–4.94)	2.27 (0.48–10.87)	2.48 (0.47–12.97)	5.08 (1.04–24.89)*	0.0004
Cardioembolic							
Age-adjusted incidence (per 1000 person-years)	1.0	0.7	1.6	1.1	1.2	1.5	0.18
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	0.89 (0.19–4.12)	0.81 (0.18–3.79)	1.52 (0.44–5.21)	0.99 (0.24–4.14)	1.39 (0.32–6.06)	0.57
Cerebral haemorrhage							
Age-adjusted incidence (per 1000 person-years)	0.4	0.9	1.2	3.0*	7.4**	34.3**	<0.0001
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	2.22 (0.37–13.34)	2.95 (0.53–16.38)	5.59 (1.21–25.75)*	9.30 (1.98–43.61)**	12.04 (2.47–58.66)**	<0.0001
Subarachnoid haemorrhage							
Age-adjusted incidence (per 1000 person-years)	0.3	1.6	0.0	0.1	0.5	0.3	0.66
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	3.28 (0.28–38.13)	–	1.16 (0.07–19.67)	1.90 (0.09–41.01)	3.41 (0.15–76.27)	0.83

Hazard ratios are adjusted for age, sex, left ventricular hypertrophy, ST depression, atrial fibrillation, glucose intolerance, body mass index, total cholesterol, smoking habits and alcohol intake. * $P < 0.05$. ** $P < 0.01$ vs. normal blood pressure for atherothrombotic infarction and vs. optimal blood pressure for other types of stroke.

Table 3 Incidence and adjusted hazard ratio for total stroke and its types by blood pressure categories among women

Type of stroke	Optimal	Normal	High-normal	Hypertension			P trend
				Grade 1	Grade 2	Grade 3	
Total stroke							
Age-adjusted incidence (per 1000 person-years)	2.0	2.5	3.9	6.3**	11.8**	22.4**	<0.0001
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	1.53 (0.60–3.89)	2.19 (0.93–5.16)	3.92 (1.84–8.35)**	4.89 (2.24–10.67)**	7.51 (3.39–16.64)**	<0.0001
Cerebral infarction							
Age-adjusted incidence (per 1000 person-years)	1.4	2.1	2.0	4.6**	6.1**	14.3**	<0.0001
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	1.78 (0.58–5.47)	1.91 (0.65–5.65)	3.91 (1.52–10.06)**	4.38 (1.66–11.57)**	7.14 (2.68–19.05)**	<0.0001
Lacunar							
Age-adjusted incidence (per 1000 person-years)	0.6	1.8	2.0	2.5*	3.3**	6.8**	<0.0001
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	3.71 (0.76–18.00)	4.68 (1.01–21.62)	4.82 (1.11–20.90)*	6.25 (1.41–27.76)*	8.28 (1.82–37.70)**	0.002
Atherothrombotic							
Age-adjusted incidence (per 1000 person-years)	0.6	0.3	0.0	0.9	1.4	5.3*	0.002
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	0.50 (0.05–5.59)	–	2.26 (0.48–10.64)	1.92 (0.37–9.87)	3.68 (0.71–19.07)	0.02
Cardioembolic							
Age-adjusted incidence (per 1000 person-years)	0.2	0.0	0.0	1.1	1.1	1.4*	0.001
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	–	–	4.26 (0.50–36.59)	4.73 (0.49–45.67)	11.09 (1.18–104.43)*	0.0008
Cerebral haemorrhage							
Age-adjusted incidence (per 1000 person-years)	0.2	0.5	0.6	0.5	4.6*	2.4	0.01
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	3.27 (0.29–36.62)	4.76 (0.48–47.33)	4.33 (0.47–39.71)	13.11 (1.45–18.55)*	7.40 (0.59–92.52)	0.02
Subarachnoid haemorrhage							
Age-adjusted incidence (per 1000 person-years)	0.4	0.0	1.3	1.0	1.0	5.4*	0.001
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	–	2.22 (0.36–13.67)	3.62 (0.73–17.93)	4.03 (0.71–22.97)	10.50 (1.86–59.20)**	0.0009

Hazard ratios are adjusted for age, sex, left ventricular hypertrophy, ST depression, atrial fibrillation, glucose intolerance, body mass index, total cholesterol, smoking habits and alcohol intake. * $P < 0.05$, ** $P < 0.01$ vs. optimal blood pressure.

Fig. 1

Age-adjusted incidence of total stroke by risk groups among men and women. *$P < 0.05$, †$P < 0.01$ vs no additive risk.

Discussion

The present analysis demonstrated strong associations between the blood pressure categories defined by the JSH 2009 guidelines [3] and the incidence of stroke among general Japanese patients. The incidence of total stroke increased with elevation of blood pressure categories and became significantly higher in patients with grades 1–3 hypertension than in those with optimal blood pressure levels. There were also strong associations between the JSH 2009 blood pressure categories and most of the stroke subtypes. These associations did not change even after adjustment for other cardiovascular risk factors. The incidence of stroke also increased with elevation of the risk levels defined by the risk stratification system recommended by the guidelines. A cohort study conducted in Japan has also demonstrated the validity of the risk stratification system of the JSH 2009 guidelines [22]. These findings support the hypothesis that the blood pressure classification and risk stratifications recommended by the JSH 2009 guidelines [3] are useful in predicting the risk of stroke among Japanese.

The incidence of stroke in each blood pressure category in the present analysis was similar to that obtained from other observational studies conducted in Japan [23,24], but was higher than that observed in Western populations [25,26]. These findings are consistent with those of previous epidemiological and clinical studies that demonstrated heterogeneous risks of stroke between Asian and Western populations [5,7,27].

Large-scale cohort studies have clearly demonstrated that blood pressure levels predicted future stroke events in Japan [10,12,23,24,28–32] as well as other countries around the world [7,8]. A number of cohort studies have demonstrated separately significant effects of blood

pressure on the risks of cerebral infarction and cerebral haemorrhage [7,8]. However, few observational studies have examined the association between blood pressure and the risks of cerebral infarction subtypes [6,33]. Our study confirmed the results from previous observational studies and provided more detailed information about the strong association of blood pressure levels with the risks of stroke subtypes in a general population of Japanese. This finding is directly in line with beneficial effects of blood pressure-lowering treatment for most of the stroke subtypes observed in randomized controlled trials [34–37].

In our study, despite the significant associations between blood pressure categories and the incidence of most stroke subtypes, the magnitude and patterns of the impact of blood pressure categories were different among stroke subtypes. The incidence of lacunar infarction in men and women and that of cerebral haemorrhage in men continuously increased with rising blood pressure categories, and the differences were significant between optimal blood pressure and grades 1–3 hypertension, whereas the incidence of atherothrombotic infarction in both sexes and that of cardioembolic infarction and subarachnoid haemorrhage in women significantly increased in grade 3 hypertension. Cerebral haemorrhage and lacunar infarction occur primarily in conjunction with arteriolosclerosis of the cerebral penetrating arteries. These arteries are tiny and mostly arise from larger arteries as unbranching end arteries, and are considered to be directly influenced by blood pressure [38]. In contrast, atherosclerotic diseases of cervical or intracranial large arteries, including atherothrombotic infarction and possibly subarachnoid haemorrhage, generally progress as part of a slow pathoanatomic process that may take a long time to reach a clinical end stage [39], and therefore only severe hypertension may have been able to accelerate the atherosclerotic process in our patients. The weak association between blood pressure and cardioembolic infarction may be due to the fact that hypertension indirectly influences the onset of cardioembolic infarction through the development of embolic sources such as atrial fibrillation and myocardial infarction.

There are several potential limitations to the findings in our study. First, it is possible that our results are biased, because some patients did not return for the follow-up examinations. However, more than 80% of the total number of surviving stroke-free patients participated in each examination, suggesting that such a bias did not invalidate the present findings. Second, we were unable to ascertain all risk factors, TOD and cardiovascular disease for the risk stratification of patients; for example, a family history of premature cardiovascular disease, subclinical atherosclerosis and low estimated glomerular filtration rate were difficult to identify. This limitation was likely to contribute to an underestimation of the stroke risk associated with risk groups, and our estimates for the impact of risk groups on the risk of stroke are probably quite conservative. Finally, cardiovascular risk factors and the risks of stroke and its subtypes have changed in Japan during the long-term follow-up period. However, we used the pooling of repeated-observations method, in which risk factors were allowed to change in accordance with data from the follow-up examinations, and therefore this bias is not likely to invalidate the present findings.

In conclusion, the findings of the present study clearly indicate that the blood pressure classification and risk stratifications recommended by the JSH 2009 guidelines [3] are useful in predicting the risk of stroke among Japanese. Though the magnitude and pattern of the impact of blood pressure were different among stroke subtypes, blood pressure levels were associated with the incidence of most stroke subtypes, suggesting that blood pressure lowering is likely to provide protection against a variety of stroke subtypes.

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There are no conflicts of interest.

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Proposed Criteria for Metabolic Syndrome in Japanese Based on Prospective Evidence

The Hisayama Study

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Background and Purpose—The current criteria of metabolic syndrome (MetS) are not based on evidence derived from prospective studies on cardiovascular disease (CVD).

Methods—In a 14-year follow-up study of 2452 community-dwelling Japanese individuals aged ≥40 years, we examined which of the MetS criteria are most predictive for the development of CVD. During the follow-up, 246 first-ever CVD events occurred.

Results—An optimal cutoff point of waist circumference for predicting CVD was 90 cm in men (age-adjusted hazard ratio=1.81; 95% CI, 1.19 to 2.74; P=0.005) and 80 cm in women (age-adjusted hazard ratio=1.46; 95% CI, 0.99 to 2.16; P=0.05). A comparison of MetS criteria showed that the modified Japanese criteria using this cutoff point instead of the original definition were the strongest predictor of CVD events in both sexes (men: age-adjusted hazard ratio=2.58; 95% CI, 1.65 to 4.02; P<0.001; women: age-adjusted hazard ratio=2.39; 95% CI, 1.65 to 3.48; P<0.001). These observations remained robust even after adjustment for other confounding factors. According to this criteria set, only in the presence of central obesity, the hazard ratios for future CVD increased significantly as the number of MetS components increased, and a significant relationship was identified from 2 or more MetS components compared with individuals who had no MetS component.

Conclusions—Our findings suggest 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 predict CVD in the general Japanese population. (***Stroke*. 2009;40:1187-1194.)**

Key Words: brain infarction ■ coronary artery disease ■ epidemiology ■ metabolic syndrome

Metabolic syndrome (MetS) consists of a clustering of cardiovascular risk factors, and individuals with this condition have an elevated risk of developing cardiovascular diseases and type 2 diabetes.[1] Practical and valuable criteria must be established promptly, because the prevalence of metabolic disorders has been increasing rapidly in recent years in Japan and other countries.[2–4] Over the past decade, several institutions have proposed various criteria in attempts to define MetS as a diagnostic category. Among these, the criteria of the National Cholesterol Education Program's Adult Treatment Panel III (NCEP) has most often been used in the literature.[5] In this criteria set, the cutoff points of waist circumference were 102 cm in men and 88 cm in women; this parameter comprised a component of this syndrome but not a prerequisite for its diagnosis. However, this cutoff level may be unsuitable for Asian populations. For Japanese, 2 sets of diagnostic criteria of MetS exist at the present time, resulting in a great deal of confusion in clinical practice. One set is proposed by the Japanese Society of Internal Medicine (Japanese criteria)[6]; in these criteria, waist circumference is defined as an essential component, and its cutoff value is 85 cm for men and 90 cm for women.[6] The other criteria set is offered by the International Diabetes Federation (IDF), in which ethnic-specific waist circumference cutoff points are used as a requirement of diagnosis.[7] The IDF recommended cutoff levels of 90 cm in men and 80 cm in women for central obesity in Japanese individuals. In the current knowledge, it remains unclear which of these criteria or cutoff points of waist circumference are a better predictor of the development of cardiovascular disease (CVD) in the general population of Japanese. There has also been controversy as to whether the component of waist circumference should be considered a prerequisite for a diagnosis of MetS.[8] The aim of the present article is to derive a better definition from the existing MetS

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criteria for predicting CVD in a prospective study of a defined general population of Japanese.

Materials and Methods

Study Population

In 1988, a screening survey for the present study was performed in the town of Hisayama, a suburb of the Fukuoka metropolitan area on Japan's Kyushu Island. The age and occupational distributions and nutritional intake of the population were almost identical to those of Japan as a whole based on data from the national census and nutrition survey.[9] A detailed description of this survey was published previously.[9] Briefly, a total of 2736 residents aged ≥40 years (80.7% of the total population of this age group) consented to participate in the examination and underwent a comprehensive assessment. After the exclusion of 102 subjects who had a history of coronary heart disease or stroke, as determined by a questionnaire and medical records, one subject for whom no blood sample was obtained, 120 subjects who had already eaten breakfast, and 61 subjects for whom waist circumference was not measured, the remaining 2452 subjects (1050 men and 1402 women) were enrolled in this study.

Follow-Up Survey

The subjects were followed 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 town. We also established a daily monitoring system among the study team and local physicians or members of the town's Health and Welfare Office. 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.

Definition of Cardiovascular Events

CVD was defined as the development of ischemic stroke or coronary heart disease. Each CVD case was coded according to the International Classification of Disease, Ninth Revision (ICD-9) from 1988 to 1996 and Tenth Revision (ICD-10) from 1997 to 2002. Stroke was defined as a sudden onset of nonconvulsive and focal neurological deficit persisting for ≥24 hours.[2] Each diagnosis of ischemic stroke (ICD-9: 434, ICD-10: I63) was made by 2 neurologists (Y.K. and Y.T.) separately using collected clinical and pathological information including brain CT/MRI and autopsy findings based on the Classification of Cerebrovascular Disease III proposed by the National Institute of Neurological Disorders and Stroke.[10] Coronary heart disease included acute myocardial infarction (ICD-9: 410, ICD-10: I21), silent myocardial infarction (ICD-9: 412, ICD-10: I25.2), sudden cardiac death within 1 hour after the onset of acute illness (ICD-9: 798.1, ICD-10: I96.0), or coronary artery disease followed by coronary artery bypass surgery (ICD-9: E878.2, ICD-10: Z95.1) or angioplasty (ICD-9: E879.0, ICD-10: Z95.5).[2] Acute myocardial infarction was diagnosed when a subject met at least 2 of the following criteria: (1) typical symptoms, including prolonged severe anterior chest pain; (2) cardiac enzyme levels more than twice the upper limit of the normal range; (3) evolving diagnostic electrocardiographic changes; and (4) morphological changes, including local asynergy of cardiac wall motion on echocardiography, persistent perfusion defect on cardiac scintigraphy, or myocardial necrosis or scars ≥1 cm long accompanied by coronary atherosclerosis at autopsy. Silent myocardial infarction was defined as myocardial scarring without any historical indication of clinical symptoms or abnormal cardiac enzyme changes. During the 14-year follow-up, 246 first-ever cardiovascular events (131 men and 115 women) occurred. Of these, there were 145 ischemic strokes (66 men and 79 women) and 125 cases of coronary heart disease (78 men and 47 women).

Risk Factor Measurements

At the baseline examination, waist circumference was measured by a trained staff member at the umbilical level with the subject standing. Body height and weight were measured in light clothing without shoes, and body mass index (BMI) was calculated.

To measure blood glucose and lipid levels, blood samples were collected from an antecubital vein between 8:00 and 10:30 AM after an overnight fast of at least 12 hours. Blood for glucose assay was obtained by venipuncture into tubes containing sodium fluoride (NaF), and plasma glucose levels were determined by the glucose–oxidase method. Serum total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride concentrations were determined enzymatically. Blood pressure was measured 3 times using a standard mercury sphygmomanometer in the sitting position after the subject rested for at least 5 minutes. Freshly voided urine samples were collected at the screening, and proteinuria was defined as 1+ or more using a reagent strip. Electrocardiographic abnormalities were defined as left ventricular hypertrophy (Minnesota Code 3 to 1) and/or ST depression (Minnesota code 4–1, 2, 3).

Each participant completed a self-administered questionnaire covering medical history, smoking habits, alcohol intake, and exercise. The questionnaire was checked by trained interviewers at the screening. Smoking habits and alcohol intake were classified as either current habitual use or not. Those subjects who engaged in sports or other forms of exertion ≥3 times a week during their leisure time made up a regular exercise group.

Definition of Metabolic Syndrome

The Third Report of the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults criteria[5] of MetS include the presence of at least 3 of 5 factors: central obesity (waist circumference >102 cm in men, >88 cm in women), elevated blood pressure (blood pressure ≥130/85 mm Hg and/or current use of antihypertensive agents), elevated fasting plasma glucose (≥6.1 mmol/L and/or current use of antidiabetic medication), reduced HDL cholesterol (<1.03 mmol/L for men, <1.29 mmol/L for women), and elevated triglycerides (≥1.68 mmol/L).

In the IDF criteria,[7] central obesity must be present for a diagnosis of MetS in addition to at least 2 of the other 4 factors. The IDF categories for Asians are: waist circumference ≥90 cm for men and ≥80 cm for women; blood pressure ≥130/85 mm Hg and/or current use of antihypertensive agents; fasting plasma glucose ≥5.6 mmol/L and/or current use of antidiabetic medication; HDL cholesterol <1.03 mmol/L in men and <1.29 mmol/L in women; and triglycerides ≥1.68 mmol/L.

Unlike the other criteria, the Japanese criteria[6] consist of 4 factors, because they deal with HDL cholesterol and triglycerides together and the cutoff value of waist circumference is larger in women than in men. MetS in the Japanese criteria was diagnosed in individuals who had a high waist circumference (≥85 cm in men and ≥90 cm in women) plus any 2 of the following: (1) blood pressures of ≥130/85 mm Hg and/or current use of antihypertensive medicine; (2) fasting plasma glucose ≥6.1 mmol/L and/or current use of antidiabetic medication; and (3) triglycerides ≥1.68 mmol/L and/or HDL cholesterol <1.03 mmol/L in men and women. Additionally, we created 2 new criteria. The modified NCEP and Japanese criteria used a waist circumference of ≥90 cm in men and ≥80 cm in women instead of the original cutoff points.

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. The age- and multivariate-adjusted hazard ratios (HRs) and 95% CIs were estimated with the use of the Cox proportional hazards model. To find the cutoff value of abdominal obesity, we also plotted receiver operating characteristic curves. In this method, the optimal cutoff value of abdominal obesity was defined by maximizing the sensitivity and specificity to the development of CVD.[11] In addition, population-attributable risk percent was estimated for various MetS

Table 1. Characteristics of Subjects by Sex, 1988

	Men (n=1050)	Women (n=1402)	P
Age, years	58 (11)	59 (11)	0.05
Prevalence of MetS			
NCEP	16.8	22.3	<0.001
IDF for Asians	13.4	34.5	<0.001
Japanese	21.4	8.1	<0.001
Modified NCEP	21.6	31.3	<0.001
Modified Japanese	10.0	18.5	<0.001
Waist circumference, cm	82.0 (8.2)	81.1 (10.1)	0.01
BMI, kg/m^2	22.8 (2.9)	23.0 (3.2)	0.37
Systolic blood pressure, mm Hg	134 (20)	132 (21)	0.002
Diastolic blood pressure, mm Hg	81 (11)	76 (11)	<0.001
Elevated blood pressure, %	60.0	51.6	<0.001
Fasting plasma glucose, mmol/L	5.9 (1.3)	5.7 (1.3)	<0.001
Elevated fasting plasma glucose, %	27.2	17.9	<0.001
Total cholesterol, mmol/L	5.11 (1.07)	5.56 (1.07)	<0.001
HDL cholesterol, mmol/L	1.26 (0.31)	1.34 (0.29)	<0.001
Reduced HDL cholesterol, %	22.7	12.9	<0.001
Triglycerides, mmol/L	1.32 (0.41–4.22)	1.06 (0.41–2.72)	<0.001
Elevated triglycerides, %	29.3	16.4	<0.001
Proteinuria, %	7.9	4.1	<0.001
Electrocardiogram abnormalities, %	19.0	13.1	<0.001
Current drinking, %	61.5	8.9	<0.001
Current smoking, %	50.4	6.7	<0.001
Regular exercise, %	11.6	9.2	0.06

Note: All values are given as means (SD) or as percentages except for triglycerides. Triglycerides are shown by geometric means and 95% prediction intervals due to the skewed distribution. Elevated blood pressure: blood pressures of ≥130/85 mm Hg and/or current use of antihypertensive medicine; elevated fasting plasma glucose: fasting plasma glucose ≥6.1 mmol/L and/or current use of antidiabetic medication; reduced HDL cholesterol: HDL cholesterol <1.03 mmol/L; elevated triglycerides: triglycerides ≥1.68 mmol/L; electrocardiogram abnormalities: left ventricular hypertrophy (Minnesota Code 3–1) and/or ST depression (Minnesota Code 4–1, 2, 3).

criteria sets with the following formula: prevalence×(HR−1)/[prevalence×(HR−1)+1].

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 of the participants.

Results

Table 1 shows the subjects' baseline clinical characteristics by sex. The prevalence of MetS defined by the NCEP, IDF for Asians, modified NCEP, and modified Japanese criteria was significantly higher in women than in men, whereas the prevalence of MetS by the Japanese criteria was higher in men. Mean values of waist circumference, systolic and diastolic blood pressures, fasting plasma glucose and triglyceride levels, and frequencies of elevated blood pressure, fasting plasma glucose, and triglycerides, reduced HDL cholesterol, proteinuria, electrocardiographic abnormalities, alcohol intake, and smoking habits were significantly higher in men than in women, whereas women had higher total and HDL cholesterol concentrations. Mean age and BMI and frequency of regular exercise did not differ between the sexes.

To compare the ability to predict CVD at each published cutoff level of waist circumference among the NCEP, IDF, and Japanese MetS criteria, we estimated the age-adjusted HRs and 95% CIs by sex (Table 2). In men, the age-adjusted HR of incident CVD was significantly higher in subjects with a waist of ≥90 cm (IDF criteria for Asians) than in those with a smaller waist (age-adjusted HR=1.81; 95% CI, 1.19 to 2.74; P=0.005), whereas in women, this association was marginally significant at the cutoff level of ≥80 cm (age-adjusted HR=1.46; 95% CI, 0.99 to 2.16; P=0.05). The levels of central obesity determined by the cutoff levels of waist circumference proposed by the NCEP, IDF for Europids, and Japanese criteria were not significant predictors of CVD in either sex.

In the analysis with the receiver operating characteristic curve method, the cutoff point defined as the maximum combination of sensitivity and specificity was 80.2 cm for men and 81.5 cm for women. This cutoff point significantly predicted CVD in women but did not in men (men: age-adjusted HR=1.30; 95% CI, 0.91 to 1.85; P=0.15; women: age-adjusted HR=1.61; 95% CI, 1.11 to 2.35; P=0.01).

Age- and multivariate-adjusted HRs and population-attributable risk percents of various MetS criteria for the development of CVD were estimated by sex (Table 3). The age-adjusted analyses showed that MetS defined by all of the criteria sets, except for the Japanese one in men, was a significant risk factor for CVD. Among these, MetS as determined by the modified Japanese criteria was the strongest predictor for the development of CVD in both sexes (men: age-adjusted HR=2.58; 95% CI, 1.65 to 4.02; P<0.001; women: age-adjusted HR=2.39; 95% CI, 1.65 to 3.48; P<0.001). These findings remained substantially unchanged even after adjustment for the following confounding factors: age, serum total cholesterol, proteinuria, electrocardiographic abnormalities, alcohol intake, smoking habits, and regular exercise. When we divided CVD into ischemic stroke and coronary heart disease, the age-adjusted incidence of ischemic stroke was significantly higher in subjects with MetS defined by the modified Japanese criteria than those without MetS for both sexes (men: 18.0 versus 5.2 per 1000 person-years. P<0.001: women: 9.2 versus 4.0, P<0.001). The same was true incidence of coronary heart disease in both sexes (mean: 10.4 versus 6.4, P=0.003; women: 6.7 versus 2.0, P<0.001). These associations remained significant even after adjustment for the previously mentioned confounding factors (ischemic stroke: HR=3.07; 95% CI, 1.68 to 5.61; P<0.001, in men; HR=2.21; 95% CI, 1.39 to 3.51; P<0.001, in women; coronary heart disease: HR=2.37; 95% CI, 1.28 to 4.39; P=0.006, in men; HR=2.91; 95% CI, 1.62 to 5.22; P<0.001, in women). On the other hand, the multivariate-

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