are needed in an era of growing obesity to offer clues for their prevention.

The Japan Arteriosclerosis Longitudinal Study-Existing Cohorts Combine (JALS-ECC) is a pooling project based on individual participant data from existing high-quality prospective cohort studies in Japan. This meta-analysis of 16 cohort studies allowed detailed investigations with more than 1000 stroke events and about 200 myocardial infarction (MI) events from more than 400 000 person-years of follow-up in middle-aged and older Japanese men and women.

WHAT IS KNOWN

- Obesity (body mass index ≥30 kg/m^2) is an established risk factor for cardiovascular disease; however, elevation of body mass index within normal to overweight range has not been evaluated sufficiently across different cardiovascular diseases.

WHAT THE STUDY ADDS

- Elevation of body mass index even within normal to overweight range was positively associated with an increased risk of cardiovascular disease in both men and women.
- Effects of increased body mass index on stroke incidence were mediated largely by elevated blood pressure. Obesity control including prevention of weight gain will play an important role as a way to prevent and control hypertension and thus stroke.
- Obesity independently increased the risk of myocardial infarction, implying additional importance of obesity control.
- A rise in weight in the population should be prevented vigorously, and weight control should be emphasized in those with elevated weight regardless of age and sex even in relatively lean populations.

Methods

Study Population

The rationale, study design, and methods of the JALS-ECC have been described elsewhere.[11] In brief, cohort studies were potentially eligible for inclusion in this project if they satisfied the following criteria: (1) Japanese population; (2) prospective cohort study; (3) at least 3000 persons-years of follow-up; (4) date of birth (or age), sex, height, weight, blood pressure, and total cholesterol recorded at baseline; and (5) date of death or the age at death (for death from stroke or coronary heart disease, at least) recorded during follow-up. Quality control of collected cohort data was performed at the JALS Coordinating Center. Consequently, individual records for each of 66 691 participants ages 18 to 99 years in 21 cohort studies were included in this project, with 82.7% of the participants from community-based cohorts and 17.3% from work site–based cohorts. Baseline years of the cohorts ranged from 1985 to 1999. Mean ages at baseline and at the end of follow-up in the community-based cohorts were 57.2 and 66.7 years and 48.8 and 55.0 years in work site–based cohorts, respectively. Permission to submit cohort data to the JALS central office was obtained from each institute's review board for ethical issues.

Baseline Data

The JALS study group requested for each participant: date of baseline survey, date of birth or age at baseline, sex, height, weight, systolic and diastolic blood pressure (SBP and DBP), serum total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, glucose, smoking status (current, past, and never) and alcohol drinking habits, and history of CVD, hypertension, hypercholesterolemia, and diabetes mellitus (DM). In each cohort, weight and height were measured with the subjects in typical indoor clothing but without shoes; weight to the nearest 0.5 kg, and height to the nearest 1 cm. BMI (kg/m^2) was calculated as weight (in kg) divided by the square of height (in meters). In the present analyses, we considered age, sex, BMI, SBP, TC, and smoking status and alcohol drinking habits as essential variables because all the cohorts did not necessarily obtain all data. As additional analyses, history of DM or HDL cholesterol was further adjusted in a subsample in which these variables were available.

End Points

In each cohort, vital status and the incidence of stroke and/or MI were ascertained during the follow-up period using population-based stroke and/or MI registration systems, death certificates, hospital medical records, and/or questionnaires. The diagnosis of stroke was based on 24 hours or more of typical clinical features and characteristic changes on computed tomographic and/or MRI brain scans and was typically based on criteria from the MONICA study[12] or from the WHO.[13] The diagnosis of MI was based on chest pain, cardiac enzyme levels, and ECGs and was typically based on criteria from the MONICA study.[12] Disease classifications were made using the 9th revision of the International Classification of Diseases (ICD) as follows: stroke (ICD9: 430, 431, 433, 434, 436), cerebral infarction (ICD9: 433 to 434), cerebral hemorrhage (ICD9: 431), subarachnoid hemorrhage (ICD9: 430), and MI (ICD9: 410).

Exclusions

From 21 cohorts of the JALS-ECC, 3 cohorts were excluded because they lacked stroke and MI incidence end points, and 2 cohorts were excluded because did not assess baseline BMI. From the remaining 60 616 participants in 16 cohorts, participants age <40 years or ≥90 years (n=7484), those lacking baseline data on blood pressure, serum TC, smoking, and/or alcohol drinking habits (n=6828), and those with a history of CVD (n=570) were excluded. Among the remaining 45 734 participants, 499 participants (1.1%) dropped out during the follow-up period. Thus, this report was based on a total of 45 235 participants (19 760 men and 25 475 women). Among the 16 cohorts, analyses for stroke were performed in 15 cohorts (38 515 participants) in which stroke events were surveyed; analyses for MI were performed in 13 cohorts (33 128 participants) in which MI events were surveyed; and analyses for CVD or ischemic CVD (cerebral infarction and MI) were performed in 12 cohorts (26 408 participants) in which both stroke and MI events were surveyed.

Statistical Analyses

We grouped subjects according to the World Health Organization classification[14]; however, because of the small number of samples in underweight (<18.5, 4.7%) and obese (≥30.0, 2.3%) categories, we collapsed them with the adjacent categories. We then divided the category with BMI 23 or lower by additional cutoff point (21) to describe incidence within normal range. Consequently, the following 5 categories were used: BMI <21.0, 21.0 to 22.9, 23.0 to 24.9, 25.0 to 27.4, and ≥27.5. A fixed-effect Poisson regression model with a fixed effect representing a combination of cohort enrollment year (1980s or 1990s) and cohort characteristics (community-based or work site–based) provided multivariate-adjusted hazard ratios (HRs) for each BMI category taking <21 as the reference. The multivariate model initially adjusted for age, current smoking, and current drinking habits. Probability values and HRs described in the text were derived from this model if not specified otherwise. SBP and TC were then separately and simultaneously adjusted for as mediation analyses. If the final model still showed a significant association of

Table 1. Proportions or Mean Values (Standard Deviations) of Baseline Risk Factors According to BMI Categories

		BMI Categories, kg/m^2					
	All	<21.0	21.0–22.9	23.0–24.9	25.0–27.4	27.5+	P*
Men							
n	19 760	4997	5426	4855	3263	1219	
Age, y	55.4 (10.3)	57.8 (11.1)	55.3 (10.2)	54.3 (9.8)	54.1 (9.5)	53 (9.1)	<0.0001
Height, cm	163.0 (7.0)	162.4 (7.1)	162.8 (7.0)	163.1 (6.8)	163.7 (6.9)	163.9 (7.0)	<0.0001
Weight, kg	61.1 (9.5)	51.6 (5.5)	58.4 (5.2)	63.8 (5.6)	69.9 (6.2)	78.3 (8.3)	<0.0001
TC, mg/dL	193.9 (36.1)	182.4 (33.1)	191.4 (35.4)	199.1 (35.8)	203.3 (36.4)	206 (37.0)	<0.0001
SBP, mm Hg	131.3 (18.9)	128.1 (19.6)	129.3 (18.4)	132.3 (18.3)	135.3 (18.2)	138.3 (18.2)	<0.0001
DBP, mm Hg	79.6 (11.7)	76.3 (11.3)	78.1 (11.3)	80.6 (11.3)	83.2 (11.5)	86.3 (11.7)	<0.0001
Antihypertensive medication, %†	11.7	8.7	9.6	12.6	15.7	19.6	<0.0001
Current smoker, %	54.5	63.1	55.0	51.6	46.3	50.5	<0.0001
Current drinker, %	71.1	69.0	71.5	72.6	71.7	70.8	0.0019
Women							
n	25 475	6051	6481	5907	4598	2438	
Age, y	56.5 (10.2)	56.4 (11.4)	55.6 (10.3)	56.5 (9.8)	57.2 (9.5)	57.4 (9.3)	<0.0001
Height, cm	149.8 (6.3)	150.2 (6.6)	150.1 (6.3)	149.8 (6.0)	149.2 (6.0)	148.9 (5.9)	<0.0001
Weight, kg	52.4 (8.1)	44 (4.8)	49.7 (4.4)	53.8 (4.5)	58.1 (4.9)	65.8 (7.1)	<0.0001
TC, mg/dL	203.1 (36.0)	196.3 (34.5)	201.5 (35.6)	204.6 (36.1)	207.7 (35.9)	211.8 (37.0)	<0.0001
SBP, mm Hg	129.2 (19.2)	123.6 (18.9)	127 (18.6)	130.2 (18.2)	133.7 (18.6)	138.4 (18.9)	<0.0001
DBP, mm Hg	76.2 (11.1)	72.3 (10.5)	74.8 (10.7)	76.8 (10.5)	79.3 (10.8)	82.5 (11.2)	<0.0001
Antihypertensive medication, %†	14.8	8.1	11.5	15.5	20.7	29.0	<0.0001
Current smoker, %	4.3	5.1	4.0	3.8	4.1	4.8	0.0058
Current drinker, %	12.7	13.0	13.8	12.8	12.1	10.2	0.0001

*Continuous variables were tested by ANOVA and categorical variables were tested by χ^2 tests for the differences across BMI categories.
†Proportions among 11 741 men and 13 174 women for whom the data were available.

BMI with incidence, further adjustment was attempted for history of DM and HDL cholesterol to evaluate their mediation effects in the available sample (n=26 694, 58.8% of total sample). These variables were entered into the model as fixed effects. For each end point—total stroke, cerebral infarction, cerebral hemorrhage, MI, ischemic CVD, and total CVD—analyses were done for men and women, separately.

Supplementarily, stratified analyses were performed by age (≤60 or >60), current smoking, hypercholesterolemia, and hypertension to evaluate possible effect modification. Hypercholesterolemia was defined total cholesterol ≥5.69 mmol/L (220 mg/dL) or use of cholesterol-lowering medication. Hypertension was defined SBP/DBP ≥140/90 mm Hg or use of hypertensive medication. These stratified analyses were carried out in the sex-combined sample after confirming that there was no significant sex-BMI category interaction by likelihood ratio test caused by the small number of events among women. Finally, we conducted analyses excluding events within 1 year of baseline in an attempt to eliminate the potential effect of occult disease on baseline BMI. Age-adjusted incidence rate was obtained by standardizing it to the age distribution of the total sample (n=45 235) and expressed as the number per 10 000 person-years. HR estimates and 95% confidence intervals (CIs) were determined by PROC GLIMMIX in the SAS program for Windows, Release 9.13 (SAS Institute Inc, Cary, NC). The linear trend of HRs across the BMI categories was tested, when appropriate, by a continuous variable assigning the median value of each quintile to corresponding individuals. Forest plots were used to qualitatively assess heterogeneity of associations between BMI and outcomes among included cohorts. These figures are also shown in sex-combined fashion due to small number of events in some cohorts. A probability value less than 0.05 was considered statistically significant.

Results

Mean baseline age and BMI were 55.4 years and 23.0 kg/m^2 in men and 56.5 years and 23.4 kg/m^2 in women (Table 1). Higher BMI was associated with higher TC, SBP, and DBP in both men and women. In men, age was inversely associated with BMI. Women in the lowest BMI category were oldest on average, but mean age tended to increase in the subsequent BMI categories. Current smoking was most prevalent in the lowest BMI category in both sexes.

There were 1113 total strokes and 190 MI events during 337 287 person-years for the stroke analyses, 261 702 person-years for the MI analyses, and 206 011 person-years for the total CVD analyses. Among stroke events with reported stroke subtype information, 725 were classified as cerebral infarction and 229 as cerebral hemorrhage. There was no heterogeneity among the cohorts in the association of BMI with any cardiovascular diseases events (P for heterogeneity >0.4, MI shown in Figure 1, cerebral infarction shown in Figure 2, and cerebral hemorrhage shown in Figure 3).

In men, the incidence of cerebral infarction was increased 86% in subjects with BMI ≥27.5 compared with those with BMI <21.0 after adjusting for age, current smoking, and current drinking habits (Table 2). Risks of cerebral infarction tended to increase for each successive BMI category (trend P=0.007). Further adjustment for possible mediating factors (SBP and TC) attenuated the association (HR, 1.51; 95% CI, 0.99 to 2.30). Similarly, in men, BMI was positively associ-

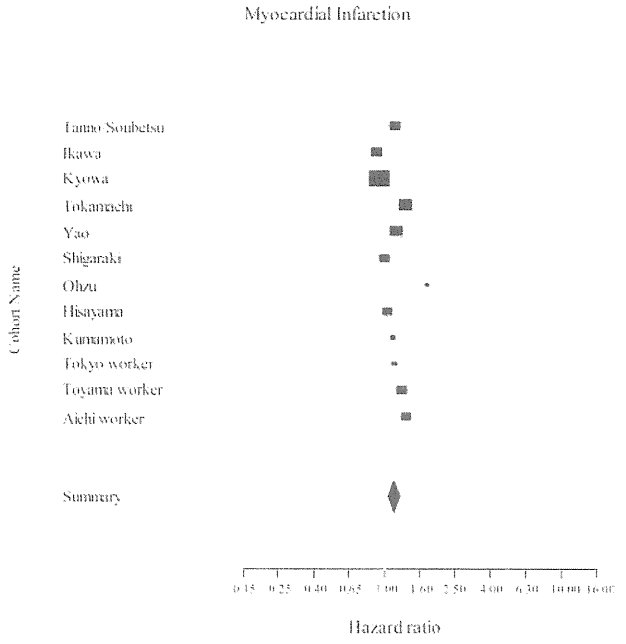

Figure 1. Fixed-effect Poisson regression model was used to determine age, current smoking, and current drinking habits by adjusted HRs of MI per each 2 kg/m^2 increment in BMI. The HR from each cohort was plotted in the Forest plot for a qualitative assessment of heterogeneity in the associations among included cohorts. *P* for heterogeneity=0.61.

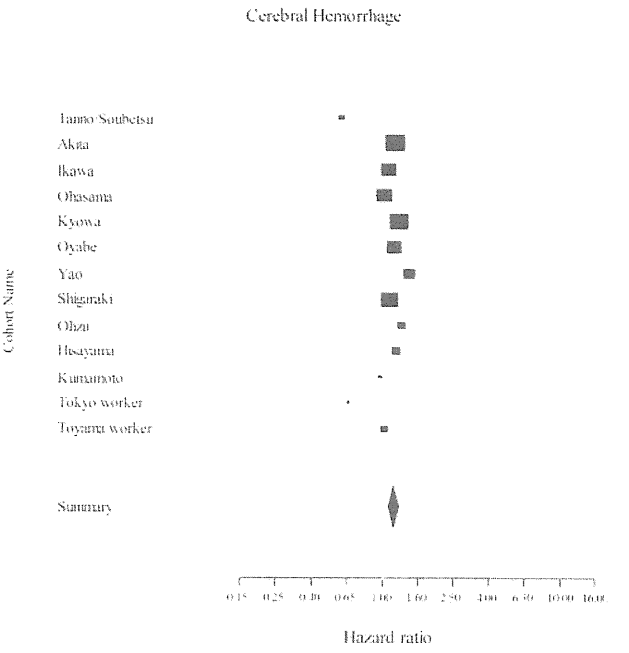

Figure 3. Fixed-effect Poisson regression model was used to determine age, current smoking, and current drinking habits by adjusted HRs of cerebral hemorrhage per each 2 kg/m^2 increment in BMI. The HR from each cohort was plotted in the Forest plot for a qualitative assessment of heterogeneity in the associations among included cohorts. *P* for heterogeneity=0.60.

ated with risk of cerebral hemorrhage (HR, 2.51; 95% CI, 1.21 to 5.20); this, however, appeared to be highly mediated by SBP (HR, 1.85; 95% CI, 0.89 to 3.86 after adjustment for SBP). For MI, the HR was 3.16 (95% CI, 1.66 to 6.01) for

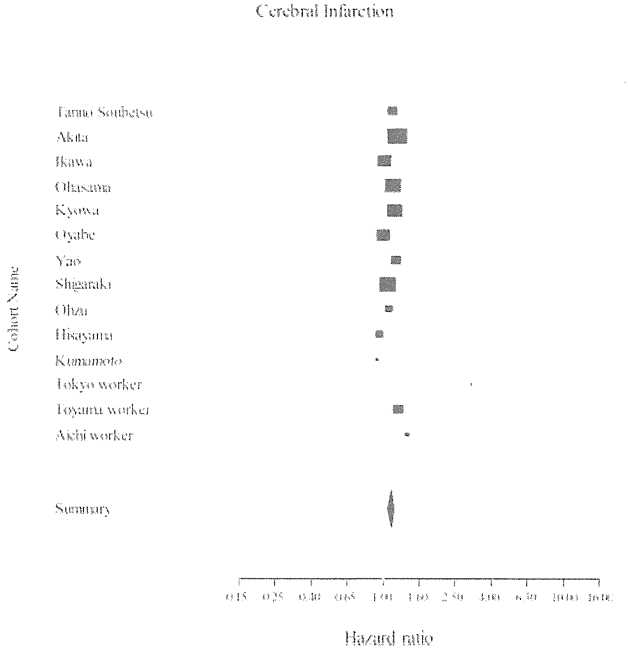

Figure 2. Fixed-effect Poisson regression model was used to determine age, current smoking, and current drinking habits by adjusted HRs of cerebral infarction per each 2 kg/m^2 increment in BMI. The HR from each cohort was plotted in the Forest plot for a qualitative assessment of heterogeneity in the associations among included cohorts. *P* for heterogeneity=0.58.

BMI ≥27.5 versus BMI <21.0 only in men, which appeared only partly mediated by TC and SBP (trend P=0.012 after adjustment for TC and SBP). Further adjustment for history of DM and HDL cholesterol in a subsample in which these variables were available did not eliminate the MI-BMI association (trend P=0.004 data not shown in the table).

In women, both cerebral infarction and hemorrhage were significantly and positively associated with BMI (Table 3). Although the association with cerebral hemorrhage was largely mediated by SBP (trend P=0.17 after adjustment for SBP), BMI showed a somewhat independent association with cerebral infarction (trend P=0.044 after adjustment for SBP). No association was observed between BMI and MI in women.

Analyses excluding events within 1 year after baseline produced similar results in both men and women. Associations were similar in the stratified analyses by age or current smoking habit for all end points (all trend P<0.05). Cerebral infarction and MI were similarly associated with BMI within cholesterol strata (all trend P<0.05). Although incidence rates of these end points in subjects with hypertension were much higher than the rates in those without it, associations with BMI were more prominent for nonhypertensive subjects (Table 4).

Discussion

In the present meta-analysis of prospective studies of a relatively lean population, incidence of cerebral infarction and hemorrhage in both sexes and that of myocardial infarction in men were associated positively and linearly with the degree of obesity as measured by BMI. The associations

Table 2. Hazard Ratios and 95% Confidence Intervals for CVD According to BMI Categories in Men

End Points Model	<21.0 HR (95% CI)	21.0–22.9 HR (95% CI)	23.0–24.9 HR (95% CI)	25.0–27.4 HR (95% CI)	27.5+ HR (95% CI)	Trend *P*
Total stroke						
n of cases/N	147/4383	167/4869	138/4364	82/2992	42/1132	
Age-adjusted incidence rate	36.1	44.8	44.4	43.7	57.6	
Model 1	1	1.29 (1.03–1.61)	1.30 (1.03–1.64)	1.24 (0.94–1.63)	1.81 (1.28–2.56)	0.003
+SBP	1	1.24 (0.99–1.55)	1.15 (0.91–1.46)	1.04 (0.79–1.38)	1.48 (1.04–2.10)	0.17
+SBP+TC	1	1.25 (1.00–1.56)	1.17 (0.92–1.48)	1.06 (0.80–1.40)	1.50 (1.06–2.14)	0.13
Cerebral infarction						
n of cases/N	111/4383	117/4869	108/4364	58/2992	29/1132	
Age-adjusted incidence rate	26.2	31.5	35.2	32.5	41.1	
Model 1	1	1.23 (0.95–1.60)	1.41 (1.08–1.84)	1.23 (0.89–1.69)	1.77 (1.17–2.68)	0.007
+SBP	1	1.19 (0.92–1.55)	1.28 (0.97–1.67)	1.06 (0.77–1.47)	1.50 (0.99–2.28)	0.12
+SBP+TC	1	1.19 (0.92–1.55)	1.28 (0.98–1.68)	1.06 (0.76–1.47)	1.51 (0.99–2.30)	0.12
Cerebral hemorrhage						
n of cases/N	23/4383	33/4869	21/4364	19/2992	11/1132	
Age-adjusted incidence rate	6.0	8.6	6.4	8.7	14.0	
Model 1	1	1.47 (0.86–2.51)	1.10 (0.61–2.01)	1.54 (0.83–2.86)	2.51 (1.21–5.20)	0.045
+SBP	1	1.40 (0.82–2.39)	0.95 (0.52–1.73)	1.22 (0.66–2.28)	1.85 (0.89–3.86)	0.32
+SBP+TC	1	1.41 (0.83–2.42)	0.97 (0.53–1.77)	1.26 (0.67–2.36)	1.92 (0.91–4.03)	0.26
MI						
n of cases/N	26/3918	5/4231	33/3864	27/2632	15/1011	
Age-adjusted incidence rate	8.5	8.4	12.5	18.9	25.2	
Model 1	1	1.07 (0.61–1.85)	1.68 (1.00–2.83)	2.21 (1.28–3.83)	3.16 (1.66–6.01)	<0.001
+SBP	1	1.03 (0.60–1.80)	1.54 (0.91–2.59)	1.90 (1.09–3.30)	2.65 (1.38–5.08)	<0.001
+SBP+TC	1	0.93 (0.54–1.63)	1.30 (0.77–2.21)	1.53 (0.87–2.69)	2.12 (1.10–4.10)	0.012
Ischemic CVD						
n of cases/N	77/3304	82/3674	96/3373	51/2361	30/924	
Age-adjusted incidence rate	32.4	37.1	49.6	44.3	64.8	
Model 1	1	1.25 (0.91–1.71)	1.74 (1.28–2.35)	1.39 (0.97–1.99)	2.16 (1.41–3.30)	<0.001
+SBP	1	1.20 (0.88–1.64)	1.58 (1.16–2.14)	1.19 (0.83–1.72)	1.84 (1.20–2.83)	0.008
+SBP+TC	1	1.17 (0.85–1.60)	1.51 (1.11–2.05)	1.13 (0.78–1.63)	1.75 (1.13–2.70)	0.022
Total CVD						
n of cases/N	97/3304	111/3674	113/3373	64/2361	37/924	
Age-adjusted incidence rate	40.9	48.4	57.4	53.5	76.4	
Model 1	1	1.30 (0.99–1.72)	1.57 (1.19–2.07)	1.34 (0.98–1.85)	2.03 (1.39–2.98)	<0.001
+SBP	1	1.24 (0.94–1.64)	1.39 (1.06–1.83)	1.11 (0.80–1.54)	1.65 (1.12–2.43)	0.036
+SBP+TC	1	1.22 (0.93–1.61)	1.35 (1.02–1.78)	1.07 (0.77–1.49)	1.59 (1.08–2.35)	0.070

n indicates number; N, number of subjects.

Incidence rate was adjusted to the age distribution of total sample (n=45 235) and expressed as the number per 10 000 person-years.

Model 1: Adjusted for age and current smoking and current drinking habits.

Stroke analyses were carried out using data from 15 cohorts (17 740 men); MI analysis, 13 cohorts (15 656 men); and ischemic (cerebral infarction and MI) and total CVD analyses, 12 cohorts (13 636 men).

between stroke, especially cerebral hemorrhage, and BMI in both sexes were largely mediated by blood pressure, but BMI tended to explain incidence of cerebral infarction independent of TC and SBP. Although further mediation analyses using DM history information in the available sample were possible, the results would not be readily interpretable because SBP adjustment alone significantly attenuated the association. Thus, the association of cerebral infarction with BMI largely appears to be mediated by SBP. In contrast, the association of MI incidence with BMI in men was strong and was independent of TC and SBP. Even further adjustment for history of DM and HDL cholesterol did not eliminate the association. Although residual confounding caused by measurement error of these covariates is possible, other factors that accompany obesity may increase MI risk, such as prothrombotic factors[15] or low-grade systematic inflammation.[16] In any case, the present results imply that avoidance of obesity offers the potential of reducing CVD in Japan.

Table 3. Hazard Ratios and 95% Confidence Intervals for CVD According to BMI Categories in Women

End Points Model	<21.0 HR (95% CI)	21.0–22.9 HR (95% CI)	23.0–24.9 HR (95% CI)	25.0–27.4 HR (95% CI)	27.5+ HR (95% CI)	Trend *P*
Total stroke						
n of cases/N	108/4911	110/5255	121/4753	120/3766	78/2090	
Age-adjusted incidence rate	21.9	23.3	26.8	313	34.8	
Model 1	1	1.05 (0.81–1.38)	1.22 (0.94–1.58)	1.45 (1.12–1.89)	1.65 (1.23–2.21)	<0.001
+SBP	1	0.99 (0.76–1.29)	1.09 (0.84–1.42)	1.23 (0.94–1.60)	1.31 (0.97–1.76)	0.028
+SBP+TC	1	1.00 (0.77–1.31)	1.10 (0.85–1.44)	1.25 (0.96–1.62)	1.33 (0.98–1.79)	0.021
Cerebral infarction						
n of cases/N	61/4911	58/5255	67/4753	75/3766	41/2090	
Age-adjusted incidence rate	12.3	12.3	14.8	19.3	18.4	
Model 1	1	1.01 (0.71–1.45)	1.22 (0.86–1.73)	1.64 (1.17–2.30)	1.56 (1.05–2.32)	0.001
+SBP	1	0.96 (0.67–1.37)	1.10 (0.78–1.56)	1.40 (0.99–1.97)	1.25 (0.84–1.87)	0.050
+SBP+TC	1	0.96 (0.67–1.39)	1.11 (0.78–1.57)	1.41 (1.00–1.99)	1.27 (0.85–1.90)	0.044
Cerebral hemorrhage						
n of cases/N	26/4911	22/5255	24/4753	28/3766	22/2090	
Age-adjusted incidence rate	4.8	4.6	5.3	7.3	9.4	
Model 1	1	0.88 (0.50–1.55)	1.02 (0.58–1.78)	1.43 (0.83–2.45)	1.98 (1.12–3.52)	0.010
+SBP	1	0.80 (0.45–1.41)	0.87 (0.49–1.52)	1.12 (0.65–1.93)	1.41 (0.79–2.52)	0.17
+SBP+TC	1	0.81 (0.46–1.43)	0.89 (0.50–1.55)	1.15 (0.67–1.99)	1.44 (0.80–2.59)	0.15
MI						
n of cases/N	13/4389	17/4494	11/4047	17/2975	6/1567	
Age-adjusted incidence rate	3.3	4.5	3.0	6.0	3.6	
Model 1	1	1.37 (0.66–2.83)	0.92 (0.41–2.06)	1.73 (0.83–3.57)	1.15 (0.44–3.04)	0.42
+SBP	1	1.26 (0.61–2.60)	0.79 (0.35–1.78)	1.43 (0.69–2.97)	0.89 (0.33–2.36)	0.89
+SBP+TC	1	1.14 (0.55–2.36)	0.73 (0.32–1.64)	1.26 (0.60–2.62)	0.78 (0.29–2.09)	0.86
Ischemic CVD						
n of cases/N	51/3249	44/3268	45/2893	51/2143	24/1219	
Age-adjusted incidence rate	19.1	18.3	18.6	26.5	20.4	
Model 1	1	0.98 (0.65–1.46)	1.02 (0.68–1.52)	1.41 (0.96–2.09)	1.12 (0.69–1.82)	0.19
+SBP	1	0.92 (0.62–1.38)	0.94 (0.63–1.40)	1.25 (0.84–1.86)	0.95 (0.58–1.55)	0.60
+SBP+TC	1	0.91 (0.61–1.37)	0.92 (0.62–1.38)	1.23 (0.83–1.83)	0.93 (0.57–1.53)	0.65
Total CVD						
n of cases/N	76/3249	64/3268	73/2893	78/2143	47/1219	
Age-adjusted incidence rate	27.7	26.8	30.5	40.9	40.8	
Model 1	1	0.94 (0.67–1.31)	1.10 (0.80–1.52)	1.46 (1.07–2.01)	1.49 (1.04–2.15)	0.003
+SBP	1	0.88 (0.63–1.23)	1.00 (0.72–1.38)	1.26 (0.92–1.74)	1.22 (0.84–1.77)	0.077
+SBP+TC	1	0.87 (0.62–1.22)	0.99 (0.72–1.37)	1.25 (0.91–1.73)	1.21 (0.84–1.76)	0.087

n indicates number; N, number of subjects.

Incidence rate was adjusted to the age distribution of total sample (n=45 235) and expressed as the number per 10 000 person-years.

Model 1: Adjusted for age and current smoking and current drinking habits.

Stroke analyses were carried out using data from 15 cohorts (20 775 women); MI analysis, 13 cohorts (17 472 women); and ischemic (cerebral infarction and MI) and total CVD analyses, 12 cohorts (12 772 women).

This pattern of BMI independently associated with MI is consistent with most previous reports.[4,17–20] Most studies conclude that the effect of obesity on stroke was explained by etiologically mediating factors that accompany obesity. For example, a significant association of BMI with stroke was explained by hypertension, hypercholesterolemia, and DM in the Framingham study.[17] The relative risk for ischemic stroke was successively significantly attenuated by adjustments for hypertension, hypercholesterolemia, and DM in the Women's Health Study.[5] The association of BMI with intracerebral hemorrhage was no longer significant after adjustment for blood glucose, cholesterol, and SBP in Korean women.[19] Other studies suggest some residual association of BMI with stroke[4,18,20] after controlling for the established risk factors associated with adiposity.

Although we found that the incidence of cerebral hemorrhage was associated positively with BMI, previous studies are less consistent. No[21,22] inverse or J-shaped[6] associations

Table 4. Hazard Ratios and 95% Confidence Intervals of Stroke and MI According to BMI Categories in Subjects With or Without Hypertension

	BMI Categories, kg/m^2						
End Points	n of Cases/N	<21.0 HR (95% CI)	21.0–22.9 HR (95% CI)	23.0–24.9 HR (95% CI)	25.0–27.4 HR (95% CI)	27.5+ HR (95% CI)	Trend *P*
Cerebral infarction							
Without hypertension	257/24 404	1	1.23 (0.88–1.72)	1.31 (0.91–1.87)	1.72 (1.17–2.53)	1.82 (1.07–3.08)	0.002
With hypertension	468/14 311	1	1.03 (0.78–1.35)	1.17 (0.89–1.53)	1.07 (0.80–1.43)	1.19 (0.85–1.68)	0.29
Cerebral hemorrhage							
Without hypertension	63/24 404	1	1.16 (0.59–2.32)	0.94 (0.44–2.05)	1.46 (0.67–3.18)	2.79 (1.18–6.59)	0.067
With hypertension	166/14 311	1	1.05 (0.65–1.67)	0.91 (0.56–1.47)	1.13 (0.70–1.83)	1.36 (0.79–2.32)	0.32
MI							
Without hypertension	64/20 291	1	1.06 (0.52–2.17)	1.57 (0.79–3.14)	2.36 (1.13–4.93)	2.08 (0.69–6.25)	0.016
With hypertension	126/12 837	1	1.22 (0.70–2.14)	1.19 (0.67–2.08)	1.58 (0.91–2.76)	1.69 (0.88–3.23)	0.061

n indicates number; N, number of subjects.
All HRs were adjusted for age, sex, and current smoking and current drinking habits.
Hypertension was defined as those who reported the use of antihypertensive medications or SBP and/or DBP was ≥140/90 mm Hg.
Interactions for BMI category by hypertension tested in Model 1 using likelihood ratio test with 5 degrees of freedom were significant ($P<0.05$) for all end points.

have been reported. Small numbers of cases, heterogeneity of hemorrhagic strokes,[4] or differences in other factors such as average cholesterol level might contribute to such discrepancies.[23] However, large-scale studies of Korean men and women also reported BMI positively associated with cerebral hemorrhage as well as corroborative evidence that overweight/obesity increases risk of cerebral hemorrhage through the elevation of blood pressure.[19,20]

There are several strengths of the present study, apart from its large-scale and prospective design. We used measured weight and height rather than self-reported measures. We could also examine the potential effect of mild or moderate increases in relative weight in our lean population. The present study included participants from urban and rural areas, or community-based and work site–based cohorts, strengthening the generalizability of the study findings.

There are also several limitations that should be considered. First, other obesity measures incorporating abdominal regional adiposity may better predict individual risk of CVD beyond BMI. It is, however, reported that differences of such measures applied to a population are unlikely to be clinically important.[24,25] Second, it is possible that physical activity may explain or modify some of our findings, although previous studies have shown independent associations of BMI with CVD.[26,27] Another limitation may be the lack of information on ischemic stroke subtypes (lacunar, atherothrombotic. or embolic), which should specifically be addressed in future studies. Furthermore, the number of events was still small, so sex-specific stratified analyses were not feasible.

In conclusion, in the present large, population-based, prospective study of Japanese men and women, greater BMI was associated with an increased risk of total stroke, cerebral infarction, and cerebral hemorrhage in men and women and MI in men. The fact that stroke risks associated with obesity appeared largely explained by concomitant rise in blood pressure emphasizes the role of weight control including prevention of weight gain as a way to prevent and control hypertension and thus stroke. Our finding that obesity independently increased MI risk implies additional importance of obesity control in MI prevention in men. To avoid a possible upturn of stroke and CHD incidence in Japan, we believe that a rise in weight in the population should be prevented vigorously and that weight control should be emphasized in those with elevated weight regardless of age and sex.

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References

1. Ministry of Health, Labor and Welfare. *The National Health and Nutrition Survey in Japan, 2005.* Tokyo, Japan: Daiichi Shuppan; 2007.
2. National Center for Health Statistics Center for Disease Control and Prevention. Prevalence of overweight, obesity and extreme obesity among adults: United States, trends 1976–80 through 2005–2006. Available at: http://www.cdc.gov/nchs/products/pubs/pubd/hestats/overweight/overweight_adult.htm.
3. Ueshima H, Sekikawa A, Miura K, Turin TC, Takashima N, Kita Y, Watanabe M, Kadota A, Okuda N, Kadowaki T, Nakamura Y, Okamura T. Cardiovascular disease and risk factors in Asia: a selected review. *Circulation.* 2008;118:2702–2709.
4. Jood K, Jern C, Wilhelmsen L, Rosengren A. Body mass index in mid-life is associated with a first stroke in men: a prospective population study over 28 years. *Stroke.* 2004;35:2764–2769.
5. Kurth T, Gaziano JM, Rexrode KM, Kase CS, Cook NR, Manson JE, Buring JE. Prospective study of body mass index and risk of stroke in apparently healthy women. *Circulation.* 2005;111:1992–1998.
6. Rexrode KM, Hennekens CH, Willett WC, Colditz GA, Stampfer MJ, Rich-Edwards JW, Speizer FE, Manson JE. A prospective study of body mass index, weight change, and risk of stroke in women. *JAMA.* 1997; 277:1539–1545.
7. Health and Welfare Statistics Association. *Kokumin Eisei no Doko (Trend for national health and hygiene, Japan), 2008.* Tokyo, Japan; 2008.

8. Kitamura A, Sato S, Kiyama M, Imano H, Iso H, Okada T, Ohira T, Tanigawa T, Yamagishi K, Nakamura M, Konishi M, Shimamoto T, Iida M, Komachi Y. Trends in the incidence of coronary heart disease and stroke and their risk factors in Japan, 1964 to 2003: the Akita-Osaka study. *J Am Coll Cardiol.* 2008;52:71–79.
9. Kubo M, Kiyohara Y, Ninomiya T, Tanizaki Y, Yonemoto K, Doi Y, Hata J, Oishi Y, Shikata K, Iida M. Decreasing incidence of lacunar vs other types of cerebral infarction in a Japanese population. *Neurology.* 2006;66:1539–1544.
10. Ohira T, Shahar E, Chambless LE, Rosamond WD, Mosley TH Jr, Folsom AR. Risk factors for ischemic stroke subtypes: the Atherosclerosis Risk in Communities study. *Stroke.* 2006;37:2493–2498.
11. Japan Arteriosclerosis Longitudinal Study-Existing Cohorts Combine (JALS-ECC): rationale, design, and population characteristics. *Circ J.* 2008;72:1563–1568.
12. WHO MONICA Project. MONICA Manual, revised edition. Geneva: Cardiovascular Diseases Unit, WHO; 1990.
13. World Health Organization. *Cerebrovascular Diseases: Prevention, Treatment, and Rehabilitation.* Geneva, Switzerland; 1971.
14. World Health Organization. BMI classification. Available at: http://apps.who.int/bmi/index.jsp?introPage=intro_3.html. Accessed 4/20, 2010.
15. Aleksic N, Wang YW, Ahn C, Juneja HS, Folsom AR, Wu KK. Assessment of coronary heart disease risk by combined analysis of coagulation factors. *Atherosclerosis.* 2008;198:294–300.
16. Folsom AR, Aleksic N, Catellier D, Juneja HS, Wu KK. C-reactive protein and incident coronary heart disease in the Atherosclerosis Risk In Communities (ARIC) study. *Am Heart J.* 2002;144:233–238.
17. Wilson PW, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. *Arch Intern Med.* 2002;162:1867–1872.
18. Kurth T, Gaziano JM, Berger K, Kase CS, Rexrode KM, Cook NR, Buring JE, Manson JE. Body mass index and the risk of stroke in men. *Arch Intern Med.* 2002;162:2557–2562.
19. Park JW, Lee SY, Kim SY, Choe H, Jee SH. BMI and stroke risk in Korean women. *Obesity (Silver Spring).* 2008;16:396–401.
20. Song YM, Sung J, Davey Smith G, Ebrahim S. Body mass index and ischemic and hemorrhagic stroke: a prospective study in Korean men. *Stroke.* 2004;35:831–836.
21. Hu G, Tuomilehto J, Silventoinen K, Sarti C, Mannisto S, Jousilahti P. Body mass index, waist circumference, and waist-hip ratio on the risk of total and type-specific stroke. *Arch Intern Med.* 2007;167:1420–1427.
22. Oki I, Nakamura Y, Okamura T, Okayama A, Hayakawa T, Kita Y, Ueshima H. Body mass index and risk of stroke mortality among a random sample of Japanese adults: 19-year follow-up of NIPPON DATA80. *Cerebrovasc Dis.* 2006;22:409–415.
23. Sturgeon JD, Folsom AR, Longstreth WT Jr, Shahar E, Rosamond WD, Cushman M. Risk factors for intracerebral hemorrhage in a pooled prospective study. *Stroke.* 2007;38:2718–2725.
24. Gelber RP, Gaziano JM, Orav EJ, Manson JE, Buring JE, Kurth T. Measures of obesity and cardiovascular risk among men and women. *J Am Coll Cardiol.* 2008;52:605–615.
25. Zhang X, Shu XO, Gao YT, Yang G, Li H, Zheng W. General and abdominal adiposity and risk of stroke in Chinese women. *Stroke.* 2009;40:1098–1104.
26. Hu G, Tuomilehto J, Silventoinen K, Barengo N, Jousilahti P. Joint effects of physical activity, body mass index, waist circumference and waist-to-hip ratio with the risk of cardiovascular disease among middle-aged Finnish men and women. *Eur Heart J.* 2004;25:2212–2219.
27. Li TY, Rana JS, Manson JE, Willett WC, Stampfer MJ, Colditz GA, Rexrode KM, Hu FB. Obesity as compared with physical activity in predicting risk of coronary heart disease in women. *Circulation.* 2006;113:499–506.

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

The Hisayama Study

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

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

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

Conclusions—Our findings suggest that diabetes is an independent risk factor for ischemic stroke in both sexes and CHD in women in the Japanese population. (***Stroke.*** **2010;41:203-209.)**

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

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

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

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

Materials and Methods

Study Population

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

Follow-Up Survey

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

Definition of Cardiovascular Events

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

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

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

Risk Factors

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

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

Statistical Analysis

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

Ethical Considerations

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

Results

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

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

Table 1. Characteristics of Subjects by Sex, 1988

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

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

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

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

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

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

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

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

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

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

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

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

Discussion

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

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

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

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

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

WHO indicates World Health Organization.

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

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

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

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

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

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

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

WHO indicates World Health Organization.

tolerance status was based on a single measurement of glucose levels at baseline as was the case in most other epidemiological studies. During the follow-up, risk factor levels were changed due to modifications in lifestyle or medication, and misclassification of glucose tolerance categories was possible. This could have weakened the association found in this study, biasing the results toward the null hypothesis. Therefore, the true association may be stronger than that shown in our study.

In conclusion, diabetes defined by an OGTT was an independent risk factor for cardiovascular disease, except for CHD in men. Notably, the new range in the 2003 American Diabetes Association criteria for IFG (FPG of 5.6 to 6.0 mmol/L) was not associated with ischemic stroke or CHD in either sex. The IFG category of the 1997 criteria (FPG of 6.1 to 6.9 mmol/L) increased the risk of ischemic stroke in women, although this association was not independent of other known risk factors. Because the risks of stroke and CHD and the prevalence of diabetes differ among races, further investigations are required to clarify the relationship between hyperglycemia and type of cardiovascular disease in other ethnic populations.

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Disclosures

None.

References

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

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

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The effect of metabolic syndrome defined by various criteria on the development of ischemic stroke subtypes in a general Japanese population

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ABSTRACT

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

1. Introduction

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

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

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

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2. Methods

2.1. Study population

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

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

2.2. Risk factor measurements

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

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

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

2.3. Definitions of metabolic syndrome

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

2.4. Follow-up survey

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

2.5. Definition of ischemic stroke subtypes

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

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

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

2.6. Statistical analysis

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

3. Results

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

Table 1
Metabolic syndrome criteria used in the present study.

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

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

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

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

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

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

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

Table 2
Clinical characteristics of the study population by sex.

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

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

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

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

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