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ORIGINAL ARTICLE

The impact of the metabolic syndrome and its components on the incidence of ischemic heart disease and stroke: the Japan public health center-based study

Hiroyuki Noda[1,2], Hiroyasu Iso[1], Isao Saito[3], Masamitsu Konishi[3], Manami Inoue[4] and Shoichiro Tsugane[4], for the JPHC Study Group

In this study, we aimed to examine the impact of the metabolic syndrome and its components on the risk of cardiovascular disease among a relatively less-obese population. A total of 8249 men and 15 064 women, aged 40–69 years, with no history of ischemic heart disease, stroke and/or cancer completed a risk-factor survey between 1993 and 1995. The metabolic syndrome was defined based on modified criteria of the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) and the International Diabetes Federation (IDF). Systematic cardiovascular surveillance was carried out throughout 2003, and 693 events of ischemic heart disease and stroke were identified. We observed significant associations of the metabolic syndrome with the risk of ischemic heart disease and ischemic stroke, but not with hemorrhagic stroke. The multivariable hazard ratio (95% confidence interval) of ischemic heart disease among men for the metabolic syndrome based on the AHA/NHLBI criteria was 2.25 (1.44–3.51) and that of ischemic stroke was 1.88 (1.40–2.52). The respective hazard ratios for the metabolic syndrome based on the IDF criteria were 1.61 (0.99–2.64) for ischemic heart disease and 1.94 (1.41–2.68) for ischemic stroke. The population-attributable fraction (PAF) of the metabolic syndrome based on the AHA/NHLBI criteria was higher than that based on the IDF criteria: 19 *vs.* 12% (*P* for difference=0.003) for ischemic cardiovascular disease among men, because non-overweight men with ⩾2 risk factors were also at high risk (20% of the PAF). Our data suggest that the metabolic syndrome based on the AHA/NHLBI criteria predicts ischemic cardiovascular disease better than the syndrome based on the IDF criteria, because of the exclusion of non-overweight high-risk individuals from the reference group.
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INTRODUCTION

The metabolic syndrome has been addressed as one of the major public health targets worldwide.[1–2] Some committees have engineered definitions of the metabolic syndrome;[3–7] the Japanese government started a nation-wide intervention strategy for the metabolic syndrome in April 2008.[8]

Traditionally, the metabolic syndrome involves obesity,[9] leads to a cluster of other cardiovascular risk factors and increases the risk of cardiovascular disease.[10–17] The American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) defined the metabolic syndrome as a constellation of cardiovascular risk factors including obesity,[5] whereas the criteria of the International Diabetes Federation (IDF)[6] were based on the presence of obesity. The metabolic syndrome, by the IDF criteria, is defined as a condition of obese persons with certain cardiovascular risk factors; thus, non-obese persons are not diagnosed with the metabolic syndrome, even if they have any of these cardiovascular risk factors. Earlier Japanese studies showed that underweight individuals also had a high risk of hemorrhagic stroke,[18] due to various pathological mechanisms.[19] It is of value to examine the criteria of the metabolic syndrome that effectively predict the risk of cardiovascular disease among less-obese populations, such as the Japanese.[20]

We examined the contribution of the metabolic syndrome and its components to the incidence of ischemic heart disease and stroke

[1]Public Health, Department of Social and Environmental Medicine, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka, Suita, Osaka, Japan; [2]Harvard Center for Population and Development Studies, Harvard School of Public Health, Cambridge, Massachusetts, USA; [3]Department of Public Health, Social Medicine and Medical Informatics, Ehime University Graduate School of Medicine, Shitsukawa, Toon, Ehime, Japan and [4]Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo, Japan
Correspondence: Professor H Iso, Public Health, Department of Social and Environmental Medicine, Osaka University, Graduate school of Medicine, 2-2 Yamadaoka, Shuita, Osaka 565-0871 Japan.
E-mail: iso@pbhel.med.osaka-u.ac.jp
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among Japanese men and women, among whom there is a low prevalence of obesity.

METHODS

Study cohort

We used two cohorts in this study. The Japan Public Health Center-based Prospective Study (JPHC Study) initiated the first (Cohort I) and the second cohort (Cohort II), registered in 27 administrative districts supervised by nine public health centers.[21] The subjects were identified using population registries maintained by the local municipalities. Data regarding lifestyle, serum total and high-density lipoprotein (HDL) cholesterol, serum triglycerides, glucose, blood pressure, height in stocking feet and weight in light clothing were available for 8582 men and 15 521 women aged 40–69 years; these subjects responded to the self-administered questionnaire and undertook health examinations conducted by municipal governments in 1995 (Cohort I) and 1993–1994 (Cohort II). Together, these questionnaires and health examinations represented the baseline survey. We excluded the subjects who reported having cancer, myocardial infarction, angina pectoris or stroke at the baseline survey, leaving 23 313 people (8249 men and 15 064 women) for analysis. We informed all study subjects of the study details. The protocol of the study was approved by the institutional review board of the National Cancer Center, Tokyo, Japan.

The subjects were followed-up from the date of the baseline survey to 31 December 2003. Residence and survival were confirmed annually using the residential registers maintained by each municipality. For subjects who moved out of the study area, we used the data reported by the municipal office within the area to which they had moved. In Japan, residency and death registration are required by law, and the registries are believed to be complete. Information on the cause of death was obtained through the death certificate provided by the Ministry of Health, Labor, and Welfare after the Ministry of Internal Affairs and Communications granted permission. The study protocol was approved by the Human Ethics Review Committees of the National Cancer Center and the University of Tsukuba.

Baseline survey

Serum total and HDL cholesterol and triglycerides were measured in 23 laboratories. The precision and accuracy of lipid measurement in all laboratories were satisfactory, according to the Osaka Medical Center for Health Science and Promotion, a member of the Cholesterol Reference Method Laboratory Network.[22] Arterial blood pressure was measured using a standard mercury sphygmomanometer applied to the right arm of the seated participant after a 5-min rest. Height in stocking feet and weight in light clothing were measured. Body mass index (BMI) was calculated as weight (kg) divided by the square of the height in meters (m^2). A self-administrated questionnaire was carried out to ascertain the smoking status, the number of cigarettes smoked per day and the usual weekly intake of alcohol in *go* units (a Japanese traditional unit of volume corresponding to 23 g ethanol).

A modified definition by the AHA/NHLBI[5] and the IDF[6] was used to categorize the subjects according to the number of components of the metabolic syndrome shown. As waist circumference was not measured in this study, BMI $\geqslant 25.0\,kg\,m^{-2}$ was used as the criterion for obesity; this BMI level was reported to correspond well with the Asian criterion for high waist circumference of $\geqslant 85$ cm in men and $\geqslant 90$ cm in women and $100\,cm^2$ of visceral fat area.[23] The components of the metabolic syndrome were defined as follows: (1) high blood pressure: blood pressure $\geqslant 130/85$ mm Hg and/or medication use; (2) high glucose: glucose $\geqslant 5.55\,mmol\,l^{-1}$ (100 mg per 100 ml) fasting or $\geqslant 7.77\,mmol\,l^{-1}$ (140 mg per 100 ml) non-fasting and/or on treatment; (3) low HDL cholesterol: HDL cholesterol $< 1.03\,mmol\,l^{-1}$ (40 mg per 100 ml) for men and $< 1.29\,mmol\,l^{-1}$ (50 mg per 100 ml) for women; (4) high triglycerides: high serum triglycerides $\geqslant 1.69\,mmol\,l^{-1}$ (150 mg per 100 ml); and (5) overweight: BMI $\geqslant 25.0\,kg\,m^{-2}$. The metabolic syndrome was defined as the presence of three or more of the components (high blood pressure, high glucose, low HDL cholesterol, high triglycerides and overweight) according to the modified criteria of the AHA/NHLBI and the presence of two or more of the cardiovascular risk factors (high blood pressure, high glucose, low HDL cholesterol and high triglycerides) among individuals who were overweight according to the modified criteria of the IDF.

Confirmation of ischemic heart disease and stroke subtypes

For confirmation of cardiovascular events, a total of 78 hospitals were registered in the sampling area of the study cohort.[24] All were major hospitals capable of treating patients with acute ischemic heart disease and stroke. To reduce uncaptured events, we also sent follow-up questionnaires to participants and reviewed death certificates for identifying suspected cardiovascular events. Therefore, all suspected events of cardiovascular disease were collected using ascertainment resources, including active patient notification, follow-up questionnaires and death certificate diagnoses. For the final diagnosis of cardiovascular events, physicians blinded to the patients' lifestyle data reviewed the medical records at each hospital.

The details of the surveillance for ischemic heart disease were described earlier.[25] Myocardial infarction was confirmed in the medical records according to the criteria of the Multinational MONItoring of trends and determinants in CArdiovascular disease (MONICA) project,[26] which requires evidence from electrocardiograms, cardiac enzymes and/or autopsy. When such workup was not performed and typical chest pain was present, a probable diagnosis was made. In the absence of diagnosis for myocardial infarction, deaths that occurred within 1 h from the onset of symptoms were regarded as sudden cardiac deaths.

Strokes were confirmed according to the criteria of the National Survey of Stroke,[27,28] which requires a constellation of neurological deficits of sudden or rapid onset lasting at least 24 h or until death. For each subtype of stroke (namely, hemorrhagic stroke (intraparenchymal hemorrhage and subarachnoid hemorrhage) or ischemic stroke (thrombotic or embolic stroke)), a definite diagnosis was established based on the examination of computer tomographic scan, magnetic resonance images or autopsy.

Statistical analysis

Outcome was defined as the new development of a primary ischemic heart disease or stroke during the study period. For each subject, person-months of follow-up were calculated from the baseline questionnaire collected to the first endpoint, death, emigration or 1 January 2004, whichever came first. Overall, 3% of the subjects had moved out of the communities (740 people) or were lost to follow-up (45 people) and were treated as censored.

Sex-specific hazard ratios of ischemic heart disease, stroke subtypes and the respective 95% confidence intervals (95% CI) were calculated with reference to the risk of individuals without the metabolic syndrome, without each individual component or with none of these components, using the Cox proportional hazards model. The multivariable hazard ratios were adjusted for potential confounding factors, including age at baseline (years), study area (nine public health center areas), time since last meal (< 8 h *vs.* $\geqslant 8$ h), total cholesterol levels (mg per 100 ml), smoking status (never smoked, ex-smokers, < 20 cigarettes per day, 20–29 cigarettes per day, $\geqslant 30$ cigarettes per day) and ethanol intake (non-drinkers, occasional drinkers (< 75 or 75–149 g per week), 150–299, 300–449, or $\geqslant 450$ g per week). The sex-specific association between the metabolic syndrome and the risk of cardiovascular disease was examined, stratified by the presence or absence of overweight. We also calculated the population-attributable fraction (PAF) to examine the contribution of the metabolic syndrome and its components to the risk of cardiovascular disease, using multivariable hazard ratios and the proportion of cases in each category.[29] The PAF was estimated as $pd \times (HR-1)/HR$, where pd is the proportion of cases falling into the category and HR the hazard ratio in the category. The 95% confidence limits (95% CL) for the PAF were calculated using the bootstrap method.[30]

All statistical tests were two-sided and a *P*-value < 0.05 was regarded as statistically significant. All statistical analyses were conducted using the SAS, version 9.13 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

A total of 23 313 people (8249 men and 15 064 women) were followed for a median of 11. 0 years; 395 men and 298 women presented with cardiovascular disease as either ischemic heart disease (82 men and 40 women) or stroke (314 men and 258 women). Ischemic heart disease included 95 definite myocardial infarctions, 9 probable myocardial infarctions and 18 sudden cardiac deaths. We also identified the stroke

subtypes: ischemic stroke (206 men and 142 women) or hemorrhagic stroke (108 men and 116 women). Hemorrhagic stroke was classified into either intraparenchymal hemorrhage (90 men and 70 women) or subarachnoid hemorrhage (18 men and 46 women). Of the total cardiovascular disease events, the percentage of ischemic cardiovascular disease (ischemic heart disease and ischemic stroke combined) was 72.9% in men and 61.1% in women. The incidence of stroke (398 incidents per 100 000 person-years in men and 172 incidents per 100 000 person-years in women) was 3.8-fold higher in men and 6.5-fold higher in women than that of ischemic heart disease (104 incidents per 100 000 person-years in men and 27 incidents per 100 000 person-years in women). With regard to stroke incidence, the percentage of intraparenchymal hemorrhage was 29% in men and 27% in women.

Men were older and had higher mean systolic and diastolic blood pressure, serum glucose and triglycerides compared with women. Moreover, men had lower mean total and HDL cholesterol and BMI compared with women (Table 1). Men were more likely to use medication for diabetes, drink heavily, smoke and have metabolic syndrome; however, they were less likely to use medication for hypertension. The percentage of obesity ($BMI \geqslant 30\,kg\,m^{-2}$) was 2.3% in men and 4.0% in women.

We showed a significant increased risk of ischemic cardiovascular disease with regard to each component of the metabolic syndrome in men (Table 2). The multivariable hazard ratio of ischemic cardiovascular disease among men was 2.37 (1.72–3.25) for high blood pressure, 1.46 (1.13–1.89) for high glucose, 1.82 (1.36–2.42) for low HDL cholesterol, 1.50 (1.16–1.94) for high triglycerides and 1.44 (1.12–1.85) for being overweight among men. These associations were weaker among women (Table 3); the respective hazard ratios were 2.28 (1.57–3.31), 1.44 (0.99–2.08), 1.40 (1.04–1.90), 1.17 (0.83–1.65) and 1.13 (0.83–1.53) for high blood pressure, high glucose, low HDL cholesterol, high triglycerides and for being overweight.

There was no significant excess risk of hemorrhagic stroke for any component of the metabolic syndrome, except for high blood pressure. Among men, the multivariable hazard ratio for high blood pressure was 2.75 (1.62–4.67) for hemorrhagic stroke, 2.77 (1.55–4.95) for intraparenchymal hemorrhage and 2.52 (0.70–8.98) for subarachnoid hemorrhage. The respective hazard ratios were 3.98 (2.38–6.64), 4.75 (2.33–9.67) and 3.13 (1.48–6.58) among women.

Men with metabolic syndrome based on the AHA/NHLBI criteria (25.1% of the population) had a 2.3-fold higher risk of ischemic heart disease and a 1.9-fold higher risk of ischemic stroke, although men with metabolic syndrome based on the IDF criteria (18.5% of the population) had a non-significant excess risk of ischemic heart disease and a 1.9-fold higher risk of ischemic stroke compared with men without metabolic syndrome, after adjusting for age, study area and other cardiovascular risk factors. The multivariable hazard ratios for ischemic cardiovascular disease were 1.97 (1.54–2.51) for metabolic syndrome based on the AHA/NHLBI criteria and 1.82 (1.39–2.38) for metabolic syndrome based on the IDF criteria among men. The respective hazard ratios among women were 1.51 (1.10–2.06) and 1.49 (1.06–2.08).

The PAFs of ischemic heart disease, total stroke and stroke subtypes were between 43 and 69% for high blood pressure among men and women; these values were much higher than those of the other components. The PAF (95% CL) of ischemic cardiovascular disease was 19% (11,26) for the metabolic syndrome based on the AHA/NHLBI criteria and 12% (6,18) for the metabolic syndrome based on the IDF criteria among men (P for difference=0.003), whereas the respective PAF among women was 12% (2,21) and 8% (1,16) (P for difference=0.12).

We found no significant excess risk of hemorrhagic stroke for the metabolic syndrome based on either the AHA/NHLBI or the IDF criteria among both men and women.

Increasing the number of metabolic syndrome components increased the risk of ischemic heart disease among men and that of ischemic stroke among men and women (P for trend <0.0001) (Tables 4 and 5). Although women with 1–3 components had a higher risk of hemorrhagic stroke than did women with 0 or 4 components, there was no dose-response association between the number of components of the metabolic syndrome and the risk for either sex (P for trend >0.05). Further, there was no dose-response association of the metabolic syndrome components with either intraparenchymal or subarachnoid hemorrhage (P for trend >0.05).

We also analyzed the association between the metabolic syndrome and the risk of ischemic cardiovascular disease after study participants were stratified into non-overweight and overweight individuals (Table 6). Among men, the multivariable hazard ratio of ischemic cardiovascular disease was 1.90 (1.14–3.14) in non-overweight persons with 1 risk factor (any component of the metabolic syndrome, except overweight), 2.72 (1.65–4.48) in non-overweight persons with $\geqslant 2$ risk factors, 2.23 (1.21–4.11) in overweight persons with 1 risk factor and 3.61 (2.17–6.00) in overweight persons with $\geqslant 2$ risk factors. The respective hazard ratios were 1.73 (0.99–3.02), 2.08 (1.19–3.64), 1.73(0.91–3.27) and 2.38 (1.36–4.18) among women. The prevalence was 29% in non-overweight persons with 1 risk factor, 24% in non-

Table 1 Sex-specific baseline characteristics of cardiovascular risk factors, the metabolic syndrome based on modified criteria of the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) and the International Diabetes Federation (IDF) and its components

	Means/percentages		
	Men	*Women*	P-*value*
Age, years	55.3	54.6	<0.0001
Systolic blood pressure, mm Hg	133.1	130.0	<0.0001
Diastolic blood pressure, mm Hg	80.5	77.3	<0.0001
Hypertension medication use (%)	16.0	17.9	0.0001
Glucose, mg per 100 ml	109.6	101.8	<0.0001
Diabetes medication use (%)	1.9	1.5	0.02
HDL cholesterol, mg per 100 ml	54.5	58.2	<0.0001
Triglycerides, mg per 100 ml	139.8	118.2	<0.0001
Body mass index, $kg\,m^{-2}$	23.7	23.8	<0.0001
Obesity ($BMI \geqslant 30\,kg\,m^{-2}$) (%)	2.3	4.0	<0.0001
Total cholesterol, mg per 100 ml	196.0	209.8	<0.0001
Current smokers (%)	40.2	2.6	<0.0001
Heavy drinkers (%)	16.7	0.2	<0.0001
Metabolic syndrome (%)			
Criteria based on AHA/NHLBI	25.0	22.1	<0.0001
Criteria based on IDF	18.5	16.5	0.0001
High blood pressure (%)	63.7	56.3	<0.0001
High glucose (%)	29.3	15.5	<0.0001
Low HDL cholesterol (%)	15.0	28.8	<0.0001
High triglycerides (%)	30.7	22.7	<0.0001
Overweight (%)	31.2	33.4	0.0005

Analysis of covariance and Mantel–Haenszel chi-squared tests were used to compare the mean value of age and age-adjusted mean values and percentages for cardiovascular risk factors, metabolic syndrome and its components.

Table 2 Sex-specific hazard ratios (95% confidence interval) and population-attributable fraction (95% confidence limits) of cardiovascular disease according to the metabolic syndrome based on modified criteria of the American Heart Association/National Heart, Lung, and the Blood Institute (AHA/NHLBI) and international diabetes federation (IDF) and its components among men

	High Blood pressure	*High Glucose*	*Low HDL cholesterol*	*High Triglycerides*	*Overweight*	*Metabolic syndrome*	
						AHA/NHLBI	*IDF*
No. of persons	5305	2425	1244	2533	2572	2073	1530
Person-years	50 711	23 064	11 680	23 923	24 738	19 657	14 583
Ischemic heart disease							
No.	65	31	28	41	34	37	23
Age and area-adjusted HR	1.97 (1.14–3.38)	1.54 (0.98–2.42)	3.08 (1.94–4.90)	2.55 (1.63–3.98)	1.72 (1.10–2.69)	2.62 (1.69–4.06)	1.87 (1.15–3.05)
Multivariable HR	2.32 (1.34–4.03)	1.81 (1.12–2.91)	2.48 (1.53–4.03)	1.76 (1.10–2.81)	1.65 (1.05–2.59)	2.25 (1.44–3.51)	1.61 (0.99–2.64)
PAF (%)	45 (21,69)	17 (3,31)	20 (7,33)	22 (4,39)	16 (1,31)	25 (10,40)	11 (−1,23)
Stroke							
No.	265	98	51	101	102	102	78
Age and area-adjusted HR	2.54 (1.87–3.46)	1.08 (0.85–1.37)	1.20 (0.89–1.63)	1.32 (1.04–1.69)	1.21 (0.95–1.54)	1.58 (1.25–2.01)	1.65 (1.27–2.14)
Multivariable HR	2.49 (1.82–3.40)	1.13 (0.88–1.46)	1.23 (0.90–1.69)	1.28 (1.00–1.65)	1.26 (0.99–1.61)	1.61 (1.26–2.05)	1.71 (1.31–2.22)
PAF (%)	51 (37,64)	4 (−4,11)	3 (−2,8)	7 (0,15)	7 (−1,14)	12 (6,19)	10 (5,16)
Ischemic stroke							
No.	174	71	39	69	66	72	53
Age and area-adjusted HR	2.40 (1.64–3.51)	1.27 (0.95–1.70)	1.44 (1.01–2.04)	1.47 (1.09–1.97)	1.31 (0.97–1.76)	1.85 (1.39–2.47)	1.88 (1.37–2.58)
Multivariable HR	2.36 (1.60–3.47)	1.34 (0.99–1.82)	1.48 (1.03–2.14)	1.42 (1.04–1.93)	1.37 (1.01–1.85)	1.88 (1.40–2.52)	1.94 (1.41–2.68)
PAF (%)	49 (31,66)	9 (−1,18)	6 (0,13)	10 (1,19)	9 (0,17)	16 (8,25)	13 (6,19)
Hemorrhagic stroke							
No.	91	27	12	32	36	30	25
Age and area-adjusted HR	2.82 (1.67–4.75)	0.77 (0.50–1.20)	0.78 (0.43–1.43)	1.09 (0.71–1.66)	1.04 (0.69–1.56)	1.16 (0.76–1.78)	1.30 (0.82–2.04)
Multivariable HR	2.75 (1.62–4.67)	0.81 (0.51–1.28)	0.79 (0.43–1.47)	1.07 (0.69–1.65)	1.08 (0.71–1.63)	1.19 (0.77–1.83)	1.34 (0.84–2.12)
PAF (%)	54 (31,76)	−6 (−18,6)	−3 (−10,4)	2 (−11,14)	2 (−11,16)	4 (−7,16)	6 (−4,16)
Intraparenchymal hemorrhage							
No.	76	21	12	28	31	26	22
Age and area-adjusted HR	2.88 (1.62–5.12)	0.73 (0.44–1.19)	0.95 (0.52–1.76)	1.18 (0.75–1.86)	1.07 (0.68–1.67)	1.23 (0.78–1.94)	1.38 (0.85–2.24)
Multivariable HR	2.77 (1.55–4.95)	0.74 (0.44–1.24)	1.00 (0.53–1.88)	1.15 (0.71–1.84)	1.06 (0.68–1.67)	1.21 (0.76–1.93)	1.36 (0.83–2.23)
PAF (%)	54 (30,78)	−8 (−21,5)	0 (−8,8)	4 (−9,17)	2 (−13,17)	5 (−7,18)	6 (−5,18)
Subarachnoid hemorrhage							
No.	15	6	0	4	5	4	3
Age and area-adjusted HR	2.52 (0.72–8.79)	1.00 (0.37–2.70)	—	0.72 (0.23–2.23)	0.89 (0.31–2.55)	0.87 (0.29–2.66)	0.92 (0.26–3.21)
Multivariable HR	2.52 (0.70–8.98)	1.09 (0.38–3.09)	—	0.74 (0.23–2.38)	1.23 (0.42–3.64)	1.04 (0.33–3.22)	1.18 (0.33–4.25)
PAF (%)	50 (−12,113)	3 (−29,34)	—	−8 (−38,22)	5 (−23,33)	1 (−24,25)	3 (−17,22)
Ischemic cardiovascular disease							
No.	239	102	67	110	100	109	76
Age and area-adjusted HR	2.30 (1.68–3.14)	1.34 (1.05–1.72)	1.86 (1.41–2.45)	1.74 (1.36–2.22)	1.42 (1.11–1.82)	2.06 (1.62–2.62)	1.88 (1.44–2.45)
Multivariable HR	2.37 (1.72–3.25)	1.46 (1.13–1.89)	1.82 (1.36–2.42)	1.50 (1.16–1.94)	1.44 (1.12–1.85)	1.97 (1.54–2.51)	1.82 (1.39–2.38)
PAF (%)	48 (35,62)	11 (4,19)	10 (5,16)	13 (4,21)	11 (3,18)	19 (11,26)	12 (6,18)
Total cardiovascular disease							
No.	330	129	79	142	136	139	101
Age and area-adjusted HR	2.43 (1.86–3.18)	1.17 (0.94–1.44)	1.54 (1.20–1.97)	1.54 (1.24–1.90)	1.30 (1.05–1.61)	1.77 (1.44–2.18)	1.70 (1.35–2.13)
Multivariable HR	2.46 (1.87–3.23)	1.25 (1.00–1.56)	1.52 (1.18–1.97)	1.38 (1.10–1.72)	1.33 (1.07–1.65)	1.73 (1.40–2.13)	1.67 (1.33–2.11)
PAF (%)	50 (38,61)	7 (0,13)	7 (2,12)	10 (3,17)	9 (2,15)	15 (9,21)	10 (5,15)

Abbreviations: HR, Hazard ratio; PAF, population-attributable fraction.
Multivariable hazard ratio was adjusted for age, study area, time since last meal, total cholesterol levels, smoking status and ethanol intake.
High blood pressure: blood pressure $\geqslant$130/85 mm Hg and/or medication use.
High glucose: glucose $\geqslant 5.55\,mmol\,l^{-1}$ (100 mg per 100 ml) for fasting or $\geqslant$7,77 $mmol\,l^{-1}$ (140 mg per 100 ml) for non-fasting, and/or on treatment.
Low HDL cholesterol: HDL cholesterol $< 1.03\,mmol\,l^{-1}$ (40 mg per 100 ml) for men and $< 1.29\,mmol\,l^{-1}$ (50 mg per 100 ml) for women.
High triglycerides: high serum triglycerides $\geqslant 1.69\,mmol\,l^{-1}$ (150 mg per 100 ml)
Overweight: BMI $\geqslant 25.0\,kg\,m^{-2}$.

Table 3 Sex-specific hazard ratios (95% confidence interval) and population-attributable fraction (95% confidence limits) of cardiovascular disease according to the metabolic syndrome based on modified criteria of the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) and the International Diabetes Federation (IDF), and its components among women

	High Blood pressure	*High Glucose*	*Low HDL cholesterol*	*High Triglycerides*	*Overweight*	*Metabolic syndrome*	
						AHA/NHLBI	*IDF*
No. of persons	8421	2327	4324	3420	5037	3315	2485
Person-years	84 048	23 020	42 983	33 823	50 310	32 948	24 744
Ischemic heart disease							
No.	33	8	15	8	10	10	6
Age and area-adjusted HR	2.68 (1.17–6.15)	1.16 (0.53–2.52)	1.42 (0.74–2.72)	0.74 (0.33–1.63)	0.64 (0.31–1.31)	0.99 (0.48–2.04)	0.79 (0.33–1.89)
Multivariable HR	2.80 (1.22–6.44)	1.33 (0.58–3.04)	1.37 (0.71–2.64)	0.70 (0.31–1.58)	0.63 (0.31–1.31)	1.00 (0.48–2.06)	0.80 (0.33–1.92)
PAF (%)	53 (22,84)	5 (−12,22)	10 (−12,33)	−9 (−28,11)	−14 (−37,8)	0 (−19,19)	−4 (−18,11)
Stroke							
No.	211	52	88	68	101	86	64
Age and area-adjusted HR	2.76 (2.00–3.80)	1.22 (0.90–1.66)	1.15 (0.89–1.49)	1.10 (0.83–1.46)	1.16 (0.91–1.50)	1.47 (1.13–1.91)	1.42 (1.07–1.89)
Multivariable HR	2.83 (2.05–3.90)	1.28 (0.93–1.77)	1.12 (0.86–1.46)	1.14 (0.85–1.52)	1.19 (0.92–1.53)	1.49 (1.14–1.94)	1.44 (1.08–1.92)
PAF (%)	53 (40,66)	4 (−2,11)	4 (−5,12)	3 (−4,10)	6 (−3,15)	11 (3,19)	8 (1,14)
Ischemic stroke							
No.	113	33	55	44	59	53	41
Age and area-adjusted HR	2.15 (1.42–3.26)	1.42 (0.96–2.10)	1.42 (1.01–1.99)	1.30 (0.90–1.87)	1.31 (0.93–1.83)	1.67 (1.19–2.36)	1.72 (1.19–2.48)
Multivariable HR	2.15 (1.42–3.26)	1.47 (0.97–2.22)	1.41 (1.00–1.98)	1.33 (0.91–1.95)	1.31 (0.93–1.84)	1.67 (1.18–2.36)	1.71 (1.18–2.47)
PAF (%)	43 (23,62)	7 (−2,17)	11 (−1,23)	8 (−3,18)	10 (−2,22)	15 (4,26)	12 (3,21)
Hemorrhagic stroke							
No.	98	19	33	24	42	33	23
Age and area-adjusted HR	3.80 (2.28–6.33)	0.99 (0.60–1.63)	0.88 (0.58–1.31)	0.87 (0.55–1.37)	1.00 (0.69–1.47)	1.23 (0.82–1.85)	1.09 (0.69–1.72)
Multivariable HR	3.98 (2.38–6.64)	1.05 (0.63–1.77)	0.84 (0.55–1.26)	0.91 (0.57–1.45)	1.04 (0.71–1.52)	1.27 (0.85–1.92)	1.12 (0.71–1.77)
PAF (%)	63 (47,79)	1 (−8,9)	−6 (−18,7)	−2 (−12,8)	1 (−12,15)	6 (−5,17)	2 (−7,11)
Intraparenchymal hemorrhage							
No.	61	14	16	15	27	19	14
Age and area-adjusted HR	4.61 (2.27–9.37)	1.24 (0.68–2.26)	0.65 (0.37–1.14)	0.94 (0.53–1.68)	1.11 (0.68–1.80)	1.15 (0.68–1.96)	1.10 (0.61–1.97)
Multivariable HR	4.75 (2.33–9.67)	1.23 (0.66–2.30)	0.65 (0.37–1.14)	0.97 (0.53–1.76)	1.13 (0.69–1.83)	1.16 (0.68–1.98)	1.11 (0.61–2.00)
PAF (%)	69 (50,88)	4 (−8,16)	−12 (−27,2)	−1 (−13,12)	4 (−13,22)	4 (−9,17)	2 (−9,13)
Subarachnoid hemorrhage							
No.	37	5	17	9	15	14	9
Age and area-adjusted HR	2.98 (1.42–6.27)	0.63 (0.25–1.62)	1.29 (0.71–2.36)	0.77 (0.37–1.61)	0.87 (0.46–1.61)	1.36 (0.72–2.57)	1.07 (0.52–2.23)
Multivariable HR	3.13 (1.48–6.58)	0.75 (0.28–1.96)	1.15 (0.62–2.12)	0.82 (0.39–1.76)	0.91 (0.49–1.71)	1.44 (0.76–2.74)	1.14 (0.54–2.38)
PAF (%)	55 (28,82)	−4 (−16,8)	5 (−17,27)	−4 (−20,12)	−3 (−25,19)	9 (−9,28)	2 (−12,17)
Ischemic cardiovascular disease							
No.	146	41	70	52	69	63	47
Age and area-adjusted HR	2.25 (1.55–3.26)	1.36 (0.96–1.93)	1.42 (1.05–1.92)	1.16 (0.84–1.62)	1.13 (0.84–1.53)	1.50 (1.10–2.05)	1.49 (1.07–2.09)
Multivariable HR	2.28 (1.57–3.31)	1.44 (0.99–2.08)	1.40 (1.04–1.90)	1.17 (0.83–1.65)	1.13 (0.83–1.53)	1.51 (1.10–2.06)	1.49 (1.06–2.08)
PAF (%)	45 (28,62)	7 (−2,15)	11 (0,22)	4 (−5,13)	4 (−6,15)	12 (2,21)	8 (1,16)
Total cardiovascular disease							
No.	244	60	103	76	111	96	70
Age and area-adjusted HR	2.75 (2.03–3.71)	1.21 (0.91–1.62)	1.18 (0.93–1.51)	1.05 (0.80–1.37)	1.08 (0.85–1.37)	1.40 (1.09–1.79)	1.33 (1.02–1.74)
Multivariable HR	2.83 (2.09–3.82)	1.28 (0.95–1.73)	1.15 (0.90–1.47)	1.07 (0.81–1.40)	1.10 (0.87–1.40)	1.42 (1.11–1.81)	1.35 (1.03–1.77)
PAF (%)	53 (41,65)	4 (−2,11)	5 (−4,13)	2 (−5,8)	3 (−5,12)	9 (2,17)	6 (0,12)

Adjustment variables, abbreviations and definition of metabolic syndrome components are the same as shown in the footnotes of Table 2.

Table 4 Sex-specific hazard ratios (95% confidence interval) and population-attributable fraction (95% confidence limits) of cardiovascular disease according to the number of components of the metabolic syndrome among men

	Number of components						
	0	*1*	*2*	*3*	*4+*	*2+*	*3+*
No. of persons	1314	2627	2235	1404	669	4308	2073
Person-years	12 699	25 192	21 444	13 433	6 224	41 101	19 657
Ischemic heart disease							
No.	5	12	28	23	14	65	37
Age and area-adjusted HR	1.0	1.12 (0.40–3.19)	3.22 (1.24–8.34)	4.39 (1.67–11.56)	5.91 (2.12–16.44)	3.98 (1.60–9.90)	4.86 (1.91–12.39)
Multivariable HR	1.0	1.16 (0.41–3.30)	3.13 (1.20–8.19)	3.86 (1.45–10.28)	5.06 (1.80–14.19)	3.68 (1.47–9.23)	4.25 (1.65–10.93)
PAF (%)		2 (−13,17)	23 (8,39)	21 (9,33)	14 (5,23)	58 (33,82)	35 (19,50)
Stroke							
No.	26	102	84	66	36	186	102
Age and area-adjusted HR	1.0	1.76 (1.15–2.72)	1.79 (1.15–2.78)	2.41 (1.53–3.80)	2.91 (1.75–4.82)	2.15 (1.42–3.24)	2.57 (1.67–3.95)
Multivariable HR	1.0	1.72 (1.12–2.65)	1.76 (1.13–2.74)	2.40 (1.51–3.80)	2.97 (1.78–4.94)	2.12 (1.40–3.21)	2.57 (1.66–3.98)
PAF (%)		14 (4,23)	12 (4,19)	12 (6,18)	8 (4,12)	31 (18,45)	20 (12,28)
Ischemic stroke							
No.	15	65	54	45	27	126	72
Age and area-adjusted HR	1.0	1.86 (1.06–3.26)	1.96 (1.11–3.48)	2.91 (1.62–5.22)	3.86 (2.05–7.27)	2.52 (1.47–4.30)	3.20 (1.83–5.60)
Multivariable HR	1.0	1.80 (1.02–3.17)	1.91 (1.07–3.40)	2.86 (1.58–5.17)	3.91 (2.06–7.40)	2.47 (1.44–4.24)	3.18 (1.81–5.59)
PAF (%)		14 (2,26)	12 (3,22)	14 (7,22)	10 (5,15)	36 (21,52)	24 (15,33)
Hemorrhagic stroke							
No.	11	37	30	21	9	60	30
Age and area-adjusted HR	1.0	1.64 (0.83–3.21)	1.56 (0.78–3.11)	1.75 (0.84–3.64)	1.64 (0.68–3.95)	1.63 (0.86–3.11)	1.72 (0.86–3.43)
Multivariable HR	1.0	1.62 (0.82–3.18)	1.55 (0.77–3.11)	1.76 (0.84–3.68)	1.71 (0.70–4.16)	1.64 (0.85–3.14)	1.74 (0.86–3.51)
PAF (%)		13 (−4,30)	10 (−5,25)	8 (−2,19)	3 (−3,10)	22 (−4,47)	12 (−2,26)
Intraparenchymal hemorrhage							
No.	10	29	25	17	9	51	26
Age and area-adjusted HR	1.0	1.41 (0.69–2.91)	1.45 (0.70–3.02)	1.57 (0.72–3.44)	1.81 (0.74–4.47)	1.54 (0.78–3.05)	1.65 (0.79–3.42)
Multivariable HR	1.0	1.40 (0.68–2.87)	1.43 (0.68–3.01)	1.53 (0.69–3.39)	1.80 (0.72–4.47)	1.52 (0.76–3.02)	1.62 (0.77–3.39)
PAF (%)		9 (−10,28)	8 (−8,25)	7 (−6,19)	4 (−3,12)	19 (−10,48)	11 (−5,27)
Subarachnoid hemorrhage							
No.	1	8	5	4	0	9	4
Age and area-adjusted HR	1.0	3.85 (0.48–30.89)	2.62 (0.31–22.47)	3.56 (0.40–31.98)	—	2.53 (0.32–20.03)	2.44 (0.27–21.86)
Multivariable HR	1.0	3.76 (0.46–30.47)	2.65 (0.30–23.22)	4.14 (0.45–37.89)	—	2.75 (0.34–22.11)	2.88 (0.32–26.35)
PAF (%)		33 (−4,70)	17 (−15,50)	17 (−6,39)	—	32 (−16,79)	15 (−11,40)
Ischemic cardiovascular disease							
No.	19	77	82	68	41	191	109
Age and area-adjusted HR	1.0	1.78 (1.08–2.95)	2.38 (1.45–3.93)	3.44 (2.06–5.72)	4.59 (2.66–7.92)	3.02 (1.88–4.85)	3.79 (2.33–6.18)
Multivariable HR	1.0	1.76 (1.07–2.92)	2.34 (1.41–3.86)	3.26 (1.95–5.45)	4.41 (2.54–7.64)	2.92 (1.81–4.70)	3.61 (2.21–5.92)
PAF (%)		12 (2,21)	16 (9,24)	16 (10,23)	11 (7,15)	44 (31,57)	27 (19,35)
Total cardiovascular disease							
No.	30	114	112	89	50	251	139
Age and area-adjusted HR	1.0	1.72 (1.15–2.58)	2.08 (1.39–3.12)	2.82 (1.86–4.26)	3.50 (2.22–5.51)	2.52 (1.72–3.68)	3.03 (2.04–4.50)
Multivariable HR	1.0	1.71 (1.14–2.56)	2.05 (1.37–3.08)	2.72 (1.79–4.13)	3.43 (2.17–5.42)	2.46 (1.68–3.60)	2.94 (1.97–4.38)
PAF (%)		12 (4,20)	15 (8,21)	14 (9,20)	9 (5,13)	38 (26,49)	23 (16,30)

Adjustment variables, abbreviations and definition of metabolic syndrome components are the same as shown in the footnotes of Table 2.

overweight persons with ⩾2 risk factors, 9% in overweight persons with ⩾2 risk factors and 19% in overweight persons with ⩾2 risk factors among men. The respective prevalence was 26, 19, 12 and 16% among women.

Men with ⩾2 risk factors had 20% (12,28) of the PAF in ischemic cardiovascular disease among non-overweight individuals and 19% (13,26) of the PAF among overweight people compared with non-overweight people with no risk factors (as reference). The respective

Table 5 Sex-specific hazard ratios (95% confidence interval) and population-attributable fraction (95% confidence limits) of cardiovascular disease according to the number of components of the metabolic syndrome among women

	Number of components						
	0	*1*	*2*	*3*	*4+*	*2+*	*3+*
No. of persons	3239	4711	3799	2197	1118	7114	3315
Person-years	32 160	46 920	37 868	21 815	11 133	70 816	32 948
Ischemic heart disease							
No.	4	12	14	8	2	24	10
Age and area-adjusted HR	1.0	1.61 (0.52–5.03)	2.10 (0.69–6.44)	1.99 (0.59–6.72)	0.97 (0.18–5.35)	1.89 (0.65–5.51)	1.65 (0.51–5.33)
Multivariable HR	1.0	1.60 (0.51–4.99)	2.16 (0.70–6.61)	2.03 (0.60–6.86)	0.98 (0.18–5.41)	1.93 (0.66–5.64)	1.67 (0.52–5.43)
PAF (%)		11 (−14,37)	19 (−5,43)	10 (−7,27)	−0 (−8,8)	29 (−10,68)	10 (−12,32)
Stroke							
No.	24	72	76	55	31	162	86
Age and area-adjusted HR	1.0	1.70 (1.07–2.71)	2.01 (1.26–3.19)	2.38 (1.46–3.86)	2.55 (1.49–4.37)	2.21 (1.43–3.41)	2.44 (1.54–3.85)
Multivariable HR	1.0	1.71 (1.07–2.72)	2.05 (1.29–3.26)	2.43 (1.49–3.95)	2.64 (1.54–4.53)	2.26 (1.47–3.49)	2.50 (1.58–3.96)
PAF (%)		12 (3,20)	15 (7,24)	13 (6,19)	7 (3,12)	35 (21,49)	20 (11,29)
Ischemic stroke							
No.	13	36	40	30	23	93	53
Age and area-adjusted HR	1.0	1.48 (0.78–2.80)	1.81 (0.96–3.39)	2.17 (1.13–4.20)	3.17 (1.60–6.31)	2.14 (1.19–3.85)	2.52 (1.36–4.65)
Multivariable HR	1.0	1.46 (0.77–2.76)	1.81 (0.96–3.39)	2.15 (1.11–4.17)	3.16 (1.59–6.30)	2.13 (1.19–3.84)	2.50 (1.35–4.62)
PAF (%)		8 (−4,20)	13 (0,25)	11 (2,21)	11 (4,18)	35 (14,56)	22 (10,35)
Hemorrhagic stroke							
No.	11	36	36	25	8	69	33
Age and area-adjusted HR	1.0	1.99 (1.01–3.92)	2.27 (1.15–4.49)	2.64 (1.29–5.40)	1.62 (0.65–4.04)	2.28 (1.20–4.34)	2.29 (1.15–4.56)
Multivariable HR	1.0	2.02 (1.03–3.98)	2.35 (1.19–4.64)	2.76 (1.35–5.65)	1.74 (0.69–4.36)	2.38 (1.25–4.54)	2.42 (1.21–4.83)
PAF (%)		16 (2,29)	18 (5,30)	14 (5,23)	3 (−3,8)	35 (15,54)	17 (5,28)
Intraparenchymal hemorrhage							
No.	5	23	23	13	6	42	19
Age and area-adjusted HR	1.0	2.74 (1.04–7.23)	3.13 (1.18–8.29)	2.97 (1.05–8.40)	2.62 (0.79–8.65)	3.00 (1.18–7.64)	2.85 (1.06–7.70)
Multivariable HR	1.0	2.78 (1.06–7.35)	3.20 (1.21–8.46)	3.02 (1.07–8.55)	2.74 (0.83–9.09)	3.07 (1.21–7.83)	2.93 (1.08–7.92)
PAF (%)		21 (5,37)	23 (8,37)	12 (2,23)	5 (−2,13)	40 (18,63)	18 (4,32)
Subarachnoid hemorrhage							
No.	6	13	13	12	2	27	14
Age and area-adjusted HR	1.0	1.36 (0.51–3.59)	1.55 (0.58–4.13)	2.38 (0.88–6.44)	0.76 (0.15–3.82)	1.68 (0.69–4.13)	1.83 (0.69–4.84)
Multivariable HR	1.0	1.32 (0.50–3.50)	1.60 (0.60–4.24)	2.50 (0.92–6.75)	0.82 (0.16–4.14)	1.76 (0.71–4.31)	1.94 (0.73–5.14)
PAF (%)		7 (−17,31)	11 (−10,32)	16 (−1,33)	−1 (−8,6)	25 (−10,61)	15 (−6,36)
Ischemic cardiovascular disease							
No.	17	48	54	38	25	117	63
Age and area-adjusted HR	1.0	1.51 (0.87–2.63)	1.87 (1.08–3.24)	2.13 (1.20–3.80)	2.68 (1.44–5.00)	2.09 (1.25–3.49)	2.32 (1.35–3.99)
Multivariable HR	1.0	1.49 (0.86–2.60)	1.88 (1.09–3.26)	2.13 (1.19–3.81)	2.68 (1.43–5.01)	2.09 (1.25–3.50)	2.32 (1.35–4.00)
PAF (%)		9 (−2,20)	14 (3,25)	11 (3,19)	9 (3,15)	34 (15,52)	20 (9,31)
Total cardiovascular disease							
No.	28	84	90	63	33	186	96
Age and area-adjusted HR	1.0	1.69 (1.10–2.60)	2.02 (1.32–3.10)	2.32 (1.48–3.64)	2.32 (1.40–3.86)	2.16 (1.45–3.23)	2.32 (1.52–3.56)
Multivariable HR	1.0	1.70 (1.10–2.60)	2.07 (1.35–3.17)	2.37 (1.51–3.72)	2.40 (1.44–4.00)	2.22 (1.48–3.31)	2.38 (1.55–3.65)
PAF (%)		12 (3,20)	16 (8,24)	12 (6,18)	6 (2,11)	34 (21,47)	19 (11,27)

Adjustment variables, abbreviations and definition of metabolic syndrome components are the same as shown in the footnotes of Table 2.

PAFs were 14% (4,23) and 15% (6,24) among women. Non-overweight persons with $\geqslant 1$ risk factors represented 33% (18,47) of the PAF with regard to ischemic cardiovascular disease among men and 25% (8,41) of the PAF among women, whereas overweight persons with $\geqslant 1$ risk factors represented 23% (15,32) of the PAF among men and 20% (8,32) of the PAF among women (data not shown).

Table 6 Sex-specific hazard ratios (95% confidence interval) and population-attributable fraction (95% confidence limits) of ischemic cardiovascular disease according to the number of components of the metabolic syndrome (except overweight) stratified by overweight (BMI $\geqslant$ 25 kg m^{-2})

	BMI $<$ *25 kg m*$^{-2}$			*BMI* $\geqslant$ *25 kg m*$^{-2}$		
	Number of components except overweight			*Number of components except overweight*		
	0	*1*	*2+*	*0*	*1*	*2+*
Men						
No. of persons	1314	2357	2006	270	772	1530
Person-years	12 699	22 538	19 017	2654	7501	14 583
Ischemic cardiovascular disease						
No.	19	76	92	1	23	76
Age and area-adjusted HR	1.0	1.92 (1.16–3.18)	2.87 (1.75–4.71)	0.29 (0.04–2.13)	2.14 (1.16–3.92)	3.75 (2.26–6.20)
Multivariable HR	1.0	1.90 (1.14–3.14)	2.72 (1.65–4.48)	0.30 (0.04–2.26)	2.23 (1.21–4.11)	3.61 (2.17–6.00)
PAF (%)		13 (4,21)	20 (12,28)	−1 (−2,0)	4 (1,8)	19 (13,26)
Women						
No. of persons	3239	3952	2836	759	1793	2485
Person-years	32 160	39 282	28 144	7638	17 928	24 744
Ischemic cardiovascular disease						
No.	17	48	48	0	22	47
Age and area-adjusted HR	1.0	1.75 (1.01–3.06)	2.06 (1.18–3.61)	—	1.73 (0.92–3.26)	2.40 (1.37–4.20)
Multivariable HR	1.0	1.73 (0.99–3.02)	2.08 (1.19–3.64)	—	1.73 (0.91–3.27)	2.38 (1.36–4.18)
PAF (%)		11 (1,21)	14 (4,23)	—	5 (−1,11)	15 (6,24)

Adjustment variables, abbreviations and definition of metabolic syndrome components were the same as shown at footnotes of Table 2.

DISCUSSION

In this large population-based prospective study of Japanese people, we observed significant associations of the metabolic syndrome with the risk of ischemic heart disease and ischemic stroke, but not with hemorrhagic stroke. People with the metabolic syndrome had 1.5- to 2.0-fold higher risks of ischemic cardiovascular disease than people without it, and the contribution of the metabolic syndrome to ischemic cardiovascular disease was between 8 and 19%. However, the excess risks of or contributions to cardiovascular disease did not exceed those of high blood pressure.

The magnitude of the relative risks of the metabolic syndrome for total cardiovascular incidence and stroke incidence was smaller in our study than in earlier meta-analyses. There was no association between the metabolic syndrome and incidence of ischemic heart disease among women; the relative risk ranged from 1.5 to 2.2 for the incidence of cardiovascular disease, was 1.8 for the incidence of stroke and ranged from 1.5 to 1.6 for the incidence of ischemic heart disease.[15,16]

The contribution of the metabolic syndrome based on the modified criteria of the IDF was lower than that based on the modified criteria of the AHA/NHLBI. The weaker predictive value was because of the inclusion of a high-risk group among non-overweight persons. An earlier study among the Korean population showed that the IDF criteria failed to detect 44.9% of men and 16.6% of women with the metabolic syndrome identified by the revised NCEP/ATP criteria, because of the mis-identification of non-obese high-risk persons.[31] In our Japanese population, non-overweight persons with $\geqslant$2 risk factors constituted a large proportion of the population (24% in men and 19% in women). The PAFs for ischemic cardiovascular disease among non-overweight people with $\geqslant$2 risk factors were 20% in men and 14% in women, similar to or larger than those among overweight people with $\geqslant$2 risk factors.

Moreover, non-overweight men with one risk factor represented a similarly large PAF for cardiovascular disease, whereas overweight men with one risk factor did not. An earlier study also showed that non-overweight persons with one risk factor had a 2.0-fold higher risk of cardiovascular death.[14] In our study, high blood pressure exhibited a higher contribution with regard to the incidence of cardiovascular disease compared with other components of the metabolic syndrome. Earlier studies support the importance of hypertension as a component of the metabolic syndrome and as a risk factor for the development of cardiovascular disease.[32–34] These data suggested that an effect of non-clustered risk factors, such as high blood pressure, should also be taken into account for the prevention of cardiovascular disease among Japanese people, characterized by a low prevalence of obesity.

Metabolic syndrome, as defined by the Japanese committee (Committee to Evaluate Diagnostic Standards for Metabolic Syndrome),[7,17] as well as by the IDF, is a condition in obese persons with certain cardiovascular risk factors. Non-obese persons can therefore be considered not to have the metabolic syndrome, even if they possess any of those cardiovascular risk factors. Our finding showed that these criteria, based on the presence of obesity, dismiss high-risk populations that are not overweight.

There was no dose-response association between the metabolic syndrome and the risk of hemorrhagic stroke. This finding was expected because hemorrhagic stroke has different pathological mechanisms,[19] than those involved in ischemic heart disease or ischemic stroke. Further, being overweight is not associated with the risk of hemorrhagic stroke.[18]

The strengths of this study include the large population-based sample of middle-aged men and women and the use of standardized methods for the measurement of serum lipids and risk characteristics. The stroke surveillance was almost complete and a high

percentage of stroke events was confirmed using imaging studies (97%).

The limitations of the study were, first, that we did not measure waist circumference at the baseline survey. However, earlier studies have shown that a BMI of 25.0 kg m^{-2} is equal to the 100 cm^2 of visceral fat area that defines central obesity,[23] and that an increased risk of cardiovascular disease or that of ischemic heart disease was observed only among people with BMI $\geqslant$25 kg m^{-2}.[18] Second, we used non-fasting data, in particular non-fasting serum triglycerides $\geqslant$1.69 mmol l^{-1} (150 mg per 100 ml), as a component of the metabolic syndrome. Although the justification for the use of the same cutoff point as fasting status is debated, the data represented by non-fasting triglycerides can be used because of its significant predictive ability with regard to ischemic heart disease.[35]

In conclusion, this study provides epidemiological evidence that the metabolic syndrome was associated with the risks of ischemic heart disease and ischemic stroke, but not with the risk of hemorrhagic stroke. The metabolic syndrome based on the AHA/NHLBI criteria predicts the risk of ischemic cardiovascular disease better than that based on the IDF criteria among less-obese populations. This is because non-overweight people with cardiovascular risk factors are also at a high risk for ischemic heart disease and stroke.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

STUDY GROUP MEMBERS

Members of the Japan Public Health Center-based Prospective Study (JPHC Study, principal investigator: S Tsugane) Group are: S Tsugane, M Inoue, T Sobue and T Hanaoka, National Cancer Center, Tokyo; J Ogata, S Baba, T Mannami, A Okayama and Y Kokubo, National Cardiovascular Center, Osaka; K Miyakawa, F Saito, A Koizumi, Y Sano, I Hashimoto and T Ikuta, Iwate Prefectural Ninohe Public Health Center, Iwate; Y Miyajima, N Suzuki, S Nagasawa, Y Furusugi and N Nagai, Akita Prefectural Yokote Public Health Center, Akita; H Sanada, Y Hatayama, F Kobayashi, H Uchino, Y Shirai, T Kondo, R Sasaki, Y Watanabe, Y Miyagawa and Y Kobayashi, Nagano Prefectural Saku Public Health Center, Nagano; Y Kishimoto, E Takara, T Fukuyama, M Kinjo, M Irei and H Sakiyama, Okinawa Prefectural Chubu Public Health Center, Okinawa; K Imoto, H Yazawa, T Seo, A Seiko, F Ito,and F Shoji, Katsushika Public Health Center, Tokyo; A Murata, K Minato, K Motegi and T Fujieda, Ibaraki Prefectural Mito Public Health Center, Ibaraki; K Matsui, T Abe, M Katagiri and M Suzuki, Niigata Prefectural Kashiwazaki and Nagaoka Public Health Center, Niigata; M Doi, A Terao, Y Ishikawa and T Tagami, Kochi Prefectural Chuo-higashi Public Health Center, Kochi; H Sueta, H Doi, M Urata, N Okamoto and F Ide, Nagasaki Prefectural Kamigoto Public Health Center, Nagasaki; H Sakiyama, N Onga, H Takaesu and M Uehara, Okinawa Prefectural Miyako Public Health Center, Okinawa; F Horii, I Asano, H Yamaguchi, K Aoki, S Maruyama, M Ichii and M Takano, Osaka Prefectural Suita Public Health Center, Osaka; Y Tsubono, Tohoku University, Miyagi; K Suzuki, Research Institute for Brain and Blood Vessels Akita, Akita; Y Honda, K Yamagishi and S Sakurai, Tsukuba University, Ibaraki; M Kabuto, National Institute for Environmental Studies, Ibaraki; M Yamaguchi, Y Matsumura, S Sasaki and S Watanabe, National Institute of Health and Nutrition, Tokyo; M Akabane, Tokyo University of Agriculture, Tokyo; T Kadowaki, Tokyo University, Tokyo; M Noda, International Medical Center of Japan, Tokyo; Y Kawaguchi, Tokyo Medical and Dental University, Tokyo; Y Takashima, Kyorin University, Tokyo; K Nakamura, Niigata University, Niigata; S Matsushima and S Natsukawa, Saku General Hospital, Nagano; H Shimizu, Sakihae Institute, Gifu; H Sugimura, Hamamatsu University, Shizuoka; S Tominaga, Aichi Cancer Center Research Institute, Aichi; H Iso, Osaka University, Osaka; M Iida, W Ajiki and A Ioka, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka; S Sato, Osaka Medical Center for Health Science and Promotion, Osaka; E Maruyama, Kobe University, Hyogo; M Konishi, K Okada and I Saito, Ehime University, Ehime; N Yasuda, Kochi University, Kochi; S Kono, Kyushu University, Fukuoka.

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