Original Article

Metabolic Syndrome and the Risk of Ischemic Heart Disease and Stroke among Middle-Aged Japanese

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Limited information is available regarding risk of cardiovascular disease and trends for the metabolic syndrome in Asia. We examined the impact of the metabolic syndrome and its components on risk of cardiovascular disease among middle-aged Japanese according to four criteria. We followed 2,613 subjects from a rural Japanese community who participated in cardiovascular health examinations between 1990 and 1993. After 27,477 person-years of follow-up through 2003, there were 42 incidents of ischemic heart disease, 73 total strokes (54 ischemic and 18 hemorrhagic), and 115 total cases of cardiovascular disease. The metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII), American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI), International Diabetes Federation (IDF), and Japanese criteria. The multivariable hazard ratios (95%CI) associated with the metabolic syndrome based on NCEP-ATPIII criteria were 2.1 (1.1–4.0) for ischemic heart disease, 1.7 (1.0–2.7) for total stroke, 2.0 (1.2–3.5) for ischemic stroke, 1.1 (0.4–2.8) for hemorrhagic stroke, 2.0 (1.3–3.1) for ischemic cardiovascular disease, and 1.7 (1.2–2.5) for total cardiovascular disease. The population-attributable fractions of the metabolic syndrome based on NCEP-ATPIII criteria were 26–27% for ischemic heart disease and ischemic stroke and 20% for total cardiovascular disease. The metabolic syndrome based on AHA/NHLBI, IDF and Japanese criteria had weaker associations with risk of cardiovascular disease, and the association with risk of ischemic heart disease was not statistically significant. The metabolic syndrome based on NCEP-ATP III criteria predicted risks of ischemic heart disease, ischemic stroke and total cardiovascular disease, whereas that based on three other criteria predicted them less effectively. (*Hypertens Res* 2008; 31: 1887–1894)

***Key Words*: metabolic syndrome, ischemic heart disease, stroke, follow-up study, Japanese**

Introduction

The metabolic syndrome is associated with increased risks of both type 2 diabetes and cardiovascular disease (*1–8*). The criteria of metabolic syndrome defined by the Third Report of the National Cholesterol Educational Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cho-

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lesterol in Adults (Adult Treatment Panel III; NCEP-ATP III) (*9*) have been widely accepted. Recently, the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) provided new guidelines for the diagnosis of the metabolic syndrome (*10*). The definition adopted by both NCEP-ATP III and AHA/NHLBI was based on five commonly measured clinical criteria whereas the criteria proposed by the International Diabetes Federation (IDF) (*11*) and the new Japanese definition (*12*) were based on a precondition for the presence of abdominal obesity.

A recent prospective study in Japan has shown that the metabolic syndrome and its components, defined by modified NCEP-ATP III criteria, were associated with an increased risk of ischemic cardiovascular disease (*13*). Another Japanese study of diabetic patients showed an increased risk of cardiovascular disease associated with the metabolic syndrome based on NCEP-ATPIII but not IDF criteria (*14*, *15*). To our knowledge, there are no studies that have examined whether the criteria of the metabolic syndrome can accurately predict the risk of incident cardiovascular disease among the general Japanese population. Limited prospective studies have been undertaken in Asian populations (*13*, *16–18*).

In the present study, we examined the association between the metabolic syndrome and risks of ischemic heart disease and stroke in Japanese men and women according to four different criteria of the metabolic syndrome.

Methods

Study Populations

The subjects were residents of Kyowa, a rural farming community in the Ibaraki Prefecture, mid-eastern Japan (census population in 1990 of ages 40–69: $n=6{,}520$), where annual cardiovascular health examinations have been conducted since 1981 (*19*). Residents aged ≥40 years old were invited annually by the municipal government to be assessed for several cardiovascular risk factors as a part of community stroke prevention program. Overall participation rates were approximately 60–70% from 1990 to 2003.

In the present study, we included a total of 2,660 subjects (998 men and 1,662 women) aged 40–69 who participated in cardiovascular health examinations between 1990 and 1993 that included waist circumference measurements. After exclusion of persons with a history of ischemic heart disease ($n=15$) or stroke ($n=32$) at baseline, a total of 2,613 subjects were followed-up through 2003 to examine the association between the metabolic syndrome and risks of ischemic heart disease and stroke. There were 17 individuals (0.7%) who moved out of the community during the follow-up period, according to municipal emigration office records. Forty-three (1.6%) people died during the follow-up. These cases were censored at the date of emigration or death, respectively. The median follow-up period was 10.5 years.

The study was approved by the Medical Ethics Committee of the University of Tsukuba.

Endpoint Determination

The follow-up was conducted by annual cardiovascular risk surveys in order to obtain information about ischemic heart disease and stroke incidents from the participants. For non-participants, these endpoints were ascertained by mailed questionnaire and by the use of death certificates. From death certificates, cases with stroke as an underlying cause of death ("International Classification of Diseases," 9th ed., pp. 410–414, 428, 429 and 430–438) were selected. We also used national insurance claims, ambulance records, reports by local physicians and public health nurses for case ascertainment. To confirm the diagnosis, all living patients were telephoned or visited to obtain their medical history and records. For deaths, we obtained information from families and reviewed medical records.

The criteria for ischemic heart disease were modified from those of the WHO Expert Committee (*20*). Definite myocardial infarctions were indicated by typical chest pain, lasting for ≥30 min with the appearance of abnormal and persistent Q or QS waves on the electrocardiogram, changes in cardiac enzyme activity, or both. Probable myocardial infarctions were indicated by typical chest pain for which the findings of electrocardiogram or enzyme activity were not available. Angina pectoris was defined as repeated episodes of chest pain during effort, especially when walking, usually disappearing rapidly after the cessation of effort or use of sublingual nitroglycerin. Sudden cardiac death was defined as death within 1 h of symptom onset, a witnessed cardiac arrest, or abrupt collapse not preceded by more than 1 h of symptoms. Ischemic heart disease included definite or probable myocardial infarction, angina pectoris, and sudden cardiac death.

Stroke was defined as a focal neurological disorder with rapid onset that persisted at least 24 h or until death. The determination of incident stroke was based on clinical criteria (*21*). Stroke events were further subclassified as subarachnoid hemorrhage, intraparenchymal hemorrhage, ischemic stroke (non-embolic or embolic), primarily based on CT and/or MRI (*22*). Stroke cases without the imaging studies were subclassified according the clinical criteria (*21*) as subarachnoid hemorrhage, intraparenchymal hemorrhage, ischemic stroke, or stroke of undetermined type. The proportion of stroke cases confirmed by CT or MRI was 92% for total stroke, 100% for subarachnoid hemorrhage, 86% for intraparenchymal hemorrhage, and 94% for ischemic stroke.

A panel of three or four physician-epidemiologists made the final diagnosis of ischemic heart disease and stroke, blinded to the data of risk factor surveys.

Measurements

Height in stocking feet and weight in light clothing were measured. Body mass index was calculated as weight (kg) divided

by square of height (m^2). Well-trained observers measured the waist circumference of the subjects at the level of the umbilicus to the nearest 1 cm while subjects were standing and breathing normally. Blood pressure was measured by well-trained technicians using mercury sphygmomanometers on the right arm of seated participants after at least 5 min of rest. Blood was drawn from seated participants into a plain, siliconized glass tube, and serum was separated. Serum glucose was measured by the hexokinase method. Fasting was not required. The distribution of time since the last meal was <2 h (40%), 2 h (35%), 3–7 h (19%) and ≥8 h (6%).

An interview was conducted to ascertain daily alcohol intake, number of cigarettes smoked per day, use of medication for diabetes mellitus and hypertension, and past history of stroke and ischemic heart disease. Persons who smoked at least 1 cigarette/d were defined as current smokers, and those who had not smoked for ≥3 months were defined as former smokers.

Serum total cholesterol and high-density lipoprotein (HDL)-cholesterol after heparin-manganese precipitation were measured by the Liebermann-Burchard direct method using the Autoanalyzer II (Technicon, Tarrytown, USA) at the Osaka Medical Center for Health Science and Promotion. The laboratory has been standardized under the CDC-NHLBI Lipid Standardization Program, Centers for Disease Control and Prevention, Atlanta, and successfully met the criteria for precision and accuracy of triglyceride and total and HDL-cholesterol measurements as an international member of the US National Cholesterol Reference Method Laboratory Network (CRMLN) (*23*).

Definition of the Metabolic Syndrome

According to the modified NCEP-ATPIII definition (*9*), subjects who had three or more of the following criteria were identified as having the metabolic syndrome: 1) triglycerides ≥1.69 mmol/L (≥150 mg/dL), 2) HDL cholesterol <1.03 mmol/L (<40 mg/dL) for men and <1.29 mmol/L (<50 mg/dL) for women, 3) blood pressure ≥130/85 mmHg, or use of antihypertensives, 4) fasting glucose ≥6.11 mmol/L (≥110 mg/dL) or non-fasting glucose ≥7.77 mmol/L (≥140 mg/dL), or on treatment, or 5) abdominal obesity—modified waist circumference cutoffs (≥90 cm for men and ≥80 cm for women) were used (*24*) instead of the waist circumference cutoffs (>102 cm for men and >88 cm for women) proposed in the existing NCEP-ATPIII criteria.

According to the AHA/NHLBI definition (*10*), the metabolic syndrome was defined as the presence of three or more of the following: 1) elevated triglyceride level ≥1.69 mmol/L (≥150 mg/dL) or on treatment, 2) reduced HDL-cholesterol <1.03 mmol/L (<40 mg/dL) for men and <1.29 mmol/L (<50 mg/dL) for women, or on treatment, 3) elevated blood pressure ≥130/85 mmHg, or use of antihypertensive medication, 4) elevated fasting glucose ≥5.56 mmol/L (≥100 mg/dL) or non-fasting glucose ≥7.22 mmol/L (≥130 mg/dL), or on treatment, or 5) abdominal obesity, waist circumference ≥90 cm for men and ≥80 cm for women.

According to the new IDF definition (*11*) (the IDF consensus worldwide definition of the metabolic syndrome [article online]: available from http://www.idf.org/webdata/docs/IDF_Meta_def_final.pdf/), Japanese people were defined as having the metabolic syndrome if the subjects had abdominal obesity (waist circumference cutoffs ≥90 cm for men and ≥80 cm for women) plus two or more of the following risk factors: 1) elevated triglyceride level ≥1.69 mmol/L (≥150 mg/dL) or on treatment, 2) low HDL cholesterol <1.03 mmol/L (<40 mg/dL) for men and <1.29 mmol/L (<50 mg/dL) for women or on treatment, 3) high blood pressure ≥130/85 mmHg or use of antihypertensives, or 4) high fasting glucose ≥5.56 mmol/L (≥100 mg/dL) or non-fasting glucose ≥7.22 mmol/L (≥130 mg/dL) or on treatment.

According to the Japanese definition (*12*), the metabolic syndrome was identified if subjects had abdominal obesity (waist circumference ≥85 cm for men and ≥90 cm for women), in addition to two or more of the following criteria: 1) triglyceride level ≥1.69 mmol/L (≥150 mg/dL) or on treatment, 2) HDL cholesterol <1.03 mmol/L (<40 mg/dL) or on treatment, 3) blood pressure ≥130/85 mmHg or use of antihypertensive medication, or 4) fasting glucose ≥6.11 mmol/L (≥110 mg/dL) or non-fasting glucose ≥7.77 mmol/L (≥140 mg/dL) or on treatment.

Statistical Analysis

Age-adjusted mean values or the prevalence of metabolic syndrome, its components and other cardiovascular risk factors were compared between incident cases of ischemic heart disease and stroke and non-cases using the analysis of covariance or χ^2 tests.

Person-years were calculated as the sum of individual follow-up time until the occurrence of incident ischemic heart disease, stroke, death, emigration, or until the end of 2003. The hazard ratios of ischemic heart disease and stroke and the respective 95% confidence intervals (CI) were calculated with reference to the risk of individuals without the metabolic syndrome using the Cox proportional hazards model. The results were adjusted for age (years), and other potential confounding variables such as smoking status (never, former, and current smokers), alcohol intake category (never, former, and current <46, 46–68 and ≥69 g/d ethanol), time since last meal (<2, 2, 3–7, and ≥8 h), and total serum cholesterol levels (mmol/L). The proportional hazards assumption was tested using an interaction terms of time by metabolic syndrome and was not violated for each analysis. We also calculated the population attributable fraction (PAF) to examine the contribution of the metabolic syndrome to risk of cardiovascular disease using multivariable hazard ratios of statistical significance and the proportions of cases in each categories (*25*). PAF was estimated as $Pd \times (HR - 1)/HR$, where Pd is the proportion of cases falling into the metabolic syndrome category

Table 1. Sex-Specific Baseline Characteristics of Cardiovascular Disease Cases and Non-Cases among Japanese Aged 40–69 Years

	Ischemic heart disease	Total stroke	Ischemic stroke	Hemorrhagic stroke	Ischemic cardiovascular disease	Total cardiovascular disease	Non-cases
Men							
n	28	31	26	5	52	60	908
Age, years	59.5±2*	60.2±2†	60.0±2*	61.6±4	59.6±1*	59.9±1‡	55.6±0.3
Systolic blood pressure, mmHg	138±3	146±3‡	147±3‡	139±7	141±2‡	141±2‡	134±0.5
Diastolic blood pressure, mmHg	82±2	84±2*	84±2	85±5	83±2*	83±1	80±0.3
Use of antihypertensive medication, %	32*	18	19	14	25	23	17
High blood pressure, %	47†	34	34	34	39*	36*	24
Body mass index, kg/m^2	23.5±0.5	23.6±0.5	23.8±0.5	22.6±1.3	23.7±0.4	23.5±0.4	23.7±0.1
Waist circumference, cm	82.9±1.5	84.0±1.4	85.1±1.6	78.3±3.5	84.4±1.1	83.5±1.0	84.0±0.3
Waist circumference (≥85 cm), %	42	50	53	38	49	46	49
Waist circumference (≥90 cm), %	24	41*	41	38	34	32	24
Serum total cholesterol, mmol/L	5.13±0.16	4.87±0.16	4.97±0.17	4.35±0.39	5.06±0.12	5.00±0.11	4.96±0.03
Hypercholesterolemia, %	15	14	17	2	16	16	20
Serum triglycerides, mmol/L	2.13±0.21	1.82±0.20	1.96±0.21	1.13±0.49	2.07±0.15	1.95±0.14	1.79±0.04
Hypertriglyceridemia, %	49	40	47	1	50	43	42
Serum HDL-cholesterol, mmol/L	1.25±0.07	1.36±0.06	1.33±0.07	1.49±0.16	1.29±0.05	1.33±0.05	1.33±0.01
Low HDL-cholesterol, %	10	16	19	1	15	13	19
Serum glucose, mmol/L	8.16±0.45*	8.90±0.41‡	9.09±0.44‡	7.79±0.99	8.61±0.33‡	8.46±0.31‡	7.02±0.08
Glucose abnormality, % (≥6.11mmol/L)	6	28‡	30‡	19	18‡	17†	7
Current smokers, %	59	66	67	62	61	61	53
Ethanol intake, g/d	28.0±4.6	25.4±4.3	26.9±4.7	17.1±10.8	27.8±3.4	27.1±3.1	22.9±0.8
Women							
n	14	42	28	13	40	55	1,590
Age, years	65.6±2‡	62.9±1‡	63.0±2‡	62.2±2†	63.9±1‡	63.6±1‡	54.8±0.2
Systolic blood pressure, mmHg	130±4	136±3*	135±3	139±4*	133±3	134±2	130±0.4
Diastolic blood pressure, mmHg	75±3	79±2	77±2	83±3*	77±2	78±1	77±0.3
Use of antihypertensive medication, %	21	30	35	21	31*	28	19
High blood pressure, %	35	34	39	28	38*	35	24
Body mass index, kg/m^2	24.4±0.8	25.5±0.5‡	25.7±0.6†	25.4±0.9	25.3±0.5†	25.3±0.4‡	23.8±0.1
Waist circumference, cm	84.4±2.5	84.1±1.4*	84.7±1.7*	82.9±2.6	84.6±1.5*	84.0±1.3*	81.0±0.2
Waist circumference (≥90 cm), %	41*	27	29	25	33*	29*	18
Waist circumference (≥80 cm), %	64	56	34	36	65	59	55
Serum total cholesterol, mmol/L	5.41±0.25	5.07±0.15	5.02±0.18	5.15±0.26	5.18±0.15	5.19±0.13	5.26±0.02
Hypercholesterolemia, %	34	22	22	24	27	27	31
Serum triglycerides, mmol/L	1.52±0.23	1.47±0.13	1.49±0.16	1.46±0.24	1.49±0.14	1.48±0.12	1.47±0.02
Hypertriglyceridemia, %	40	43*	46*	40	42	41*	29
Serum HDL-cholesterol, mmol/L	1.32±0.09	1.40±0.05	1.40±0.06	1.40±0.09	1.38±0.05	1.39±0.05	1.46±0.01
Low HDL-cholesterol, %	61*	41	44	36	50*	45*	32
Serum glucose, mmol/L	7.11±0.50	6.96±0.29	7.12±0.36	6.42±0.52	6.90±0.30	6.83±0.26	6.42±0.05
Glucose abnormality, % (≥6.11 mmol/L)	12	15‡	16†	7	13†	13‡	4
Current smokers, %	8	8	8	9	9	8	5
Ethanol intake, g/d	0.4±1.4	2.2±0.8	2.5±1.0	1.8±1.5	1.9±0.9	1.8±0.7	1.1±0.1

Values are mean±SEM, or proportions, adjusted for age. Serum triglycerides and glucose values were also adjusted for time since last meal. Test for significance from non-cases: *$p<0.05$, †$p<0.01$, ‡$p<0.001$. HDL, high-density lipoprotein.

Table 2. Hazard Ratios (HR), Population Attributable Fraction (PAF), and 95% Confidence Interval (CI) of Cardiovascular Disease Associated with the Metabolic Syndrome in Japanese Aged 40–69 Years

Metabolic syndrome	NCEP-ATP III criteria		AHA/NHLBI criteria		IDF criteria		Japanese criteria	
	No	Yes	No	Yes	No	Yes	No	Yes
No. at risk	1,808	805	1,750	863	1,919	694	2,174	439
Person-years	18,999	8,478	18,373	9,104	20,142	7,336	22,838	4,639
Ischemic heart disease								
No. of cases	20	22	20	22	25	17	30	12
Age-adjusted HR (95% CI)	1.0	1.9 (1.1–3.6)*	1.0	1.7 (0.9–3.2)	1.0	1.4 (0.8–2.7)	1.0	1.6 (0.8–3.1)
Multivariable HR (95% CI)	1.0	2.1 (1.1–4.0)*	1.0	1.9 (1.0–3.5)	1.0	1.8 (0.9–3.4)	1.0	1.1 (0.5–2.2)
PAF (95% CI), %		27 (−0.5–48)		—		—		—
Total stroke								
No. of cases	38	35	37	36	43	30	50	23
Age-adjusted HR (95% CI)	1.0	1.6 (1.0–2.6)*	1.0	1.5 (1.0–2.4)	1.0	1.5 (0.9–2.4)	1.0	1.9 (1.1–3.1)*
Multivariable HR (95% CI)	1.0	1.7 (1.0–2.7)*	1.0	1.6 (1.0–2.5)	1.0	1.6 (1.0–2.7)	1.0	1.8 (1.1–3.1)*
PAF (95% CI), %		19 (−1–35)		—		—		14.0
Ischemic stroke								
No. of cases	26	28	26	28	29	25	35	19
Age-adjusted HR (95% CI)	1.0	1.9 (1.1–3.3)*	1.0	1.7 (1.0–2.9)	1.0	1.9 (1.1–3.2)*	1.0	2.2 (1.3–3.9)†
Multivariable HR (95% CI)	1.0	2.0 (1.2–3.5)*	1.0	1.8 (1.0–3.1)*	1.0	2.2 (1.2–3.9)†	1.0	2.0 (1.1–3.6)*
PAF (95% CI), %		26 (2–44)		23 (−3–42)		25 (4–42)		18 (−0.6–33)
Hemorrhagic stroke								
No. of cases	11	7	10	8	13	5	14	4
Age-adjusted HR (95% CI)	1.0	1.1 (0.4–2.9)	1.0	1.2 (0.5–3.2)	1.0	0.8 (0.3–2.3)	1.0	1.2 (0.4–3.5)
Multivariable HR (95% CI)	1.0	1.1 (0.4–2.8)	1.0	1.2 (0.5–3.2)	1.0	0.7 (0.3–2.2)	1.0	1.4 (0.5–4.6)
PAF (95% CI), %		—		—		—		—
Ischemic cardiovascular disease								
No. of cases	44	48	44	48	51	41	62	30
Age-adjusted HR (95% CI)	1.0	1.9 (1.3–2.9)†	1.0	1.7 (1.1–2.6)*	1.0	1.7 (1.1–2.6)*	1.0	2.0 (1.3–3.0)†
Multivariable HR (95% CI)	1.0	2.0 (1.3–3.1)†	1.0	1.8 (1.2–2.7)†	1.0	2.0 (1.3–3.2)†	1.0	1.5 (1.0–2.4)
PAF (95% CI), %		26 (8–41)		23 (4–38)		23 (7–36)		—
Total cardiovascular disease								
No. of cases	59	56	58	57	68	47	81	34
Age-adjusted HR (95% CI)	1.0	1.7 (1.2–2.4)†	1.0	1.5 (1.1–2.2)*	1.0	1.5 (1.0–2.1)*	1.0	1.7 (1.1–2.5)*
Multivariable HR (95% CI)	1.0	1.7 (1.2–2.5)†	1.0	1.6 (1.1–2.3)*	1.0	1.6 (1.1–2.4)*	1.0	1.4 (0.9–2.1)
PAF (95% CI), %		20 (4–33)		18 (1–31)		16 (2–28)		—

*$p<0.05$, †$p<0.01$. Multivariable HR adjusted for age, time since last meal, cigarette smoking, alcohol intake and serum total cholesterol.

and HR is hazard ratio in that category. The Greenland formula was used to calculate 95% CI (*26*).

SAS statistical software (version 9.13; SAS Institute Inc., Cary, USA) was used for the analyses, and $p<0.05$ was regarded as statistically significant

Results

After 27,477 person-years of follow-up, we documented 42 incident cases of ischemic heart disease (1.5 per 1,000 person-years), 73 incident cases of total stroke (2.7 per 1,000 person-years), 54 incident cases of ischemic stroke (2.0 per 1,000 person-years), 18 incident cases of hemorrhagic stroke (0.7 per 1,000 person-years), 92 incident cases of ischemic cardiovascular disease (3.4 per 1,000 person-years), and 115 incident cases of total cardiovascular disease (4.2 per 1,000 person-years).

Table 1 compares age-adjusted values and proportions of components of the metabolic syndrome and other cardiovascular risk factors between incident cases and non-cases of cardiovascular disease. Compared with non-cases, cases with ischemic heart disease were older, more hypertensive, smoked more, and had higher mean serum total cholesterol, serum triglycerides, and serum glucose levels, and lower mean HDL-cholesterol levels among both men and women. Compared with non-cases, individuals who suffered from ischemic stroke were older, more hypertensive, smoked more, and had higher mean serum triglycerides and serum glucose

Table 3. Multivariable Hazard Ratios of Ischemic Cardiovascular Disease According to the Number of Components of the Metabolic Syndrome, Stratified by the Presence of Abdominal Obesity

Metabolic syndrome	Abdominal obesity (–)			Abdominal obesity (+)		
	No. of components except abdominal obesity			No. of components except abdominal obesity		
	0	1	2+	0	1	2+
NCEP-ATP III criteria						
No. at risk	415	560	495	126	355	662
Person-years	4,392	5,801	5,145	1,354	3,785	7,001
Ischemic cardiovascular disease						
No. of cases	3	16	24	2	6	41
Multivariable HR (95% CI)	1.0	2.4 (0.7–8.4)	3.3 (1.0–11.2)	2.0 (0.3–11.9)	1.6 (0.4–6.6)	5.1 (1.6–16.9)†
AHA/NHLBI and IDF criteria						
No. at risk	378	552	540	113	336	694
Person-years	3,996	5,719	5,623	1,221	3,583	7,336
Ischemic cardiovascular disease						
No. of cases	2	16	25	1	7	41
Multivariable HR (95% CI)	1.0	3.4 (0.8–14.8)	4.3 (1.0–18.3)*	1.5 (0.1–16.3)	2.8 (0.6–13.7)	6.5 (1.6–27.5)*
Japanese criteria						
No. at risk	567	767	499	67	274	439
Person-years	5,948	8,079	5,255	725	2,830	4,639
Ischemic cardiovascular disease						
No. of cases	5	17	28	2	10	30
Multivariable HR (95% CI)	1.0	1.6 (0.6–4.5)	3.4 (1.3–8.9)*	2.4 (0.5–12.2)	2.2 (0.7–6.6)	3.4 (1.3–9.0)*

*$p<0.05$, †$p<0.01$. Multivariable HR adjusted for age, time since last meal, cigarette smoking, alcohol intake and serum total cholesterol. HR, hazard ratio; CI, confidence interval.

levels among both men and women.

The hazard ratios of the metabolic syndrome and cardiovascular disease are shown in Table 2. The metabolic syndrome based on NCEP-ATP III criteria was significantly associated with risks of ischemic heart disease, total stroke, ischemic stroke, ischemic cardiovascular disease, and total cardiovascular disease but was not associated with hemorrhagic stroke. The respective multivariable hazard ratio (95% CI) associated with the metabolic syndrome was 2.1 (1.1–4.0), 1.7 (1.0–2.7), 2.0 (1.2–3.5), 2.0 (1.3–3.1), 1.7 (1.2–2.5) and 1.1 (0.4–2.8). Based on AHA/NHLBI and IDF criteria, we found similar or weaker associations with risks of ischemic stroke, ischemic cardiovascular disease, and total cardiovascular disease, and no significant association with total stroke, hemorrhagic stroke or ischemic heart disease. Using the Japanese criteria, the metabolic syndrome was only significantly associated with risks of total and ischemic strokes; the multivariable hazard ratio (95% CI) was 1.8 (1.1–3.1) and 2.0 (1.1–3.6), respectively.

The PAFs of ischemic heart disease, total stroke, ischemic stroke, ischemic cardiovascular disease, and total cardiovascular disease were between 19% and 27% for the metabolic syndrome based on NCEP-ATP III criteria. The respective PAFs were between 18% and 23% based on AHA/NHLBI criteria and between 16% and 25% based on IDF criteria. The PAFs of total and ischemic strokes for the metabolic syndrome were between 14% and 18% based on Japanese criteria.

We also analyzed associations of the metabolic syndrome components based on the four criteria and risks of ischemic cardiovascular disease, stratified by the presence of abdominal obesity (Table 3). The multivariate hazard ratio of ischemic cardiovascular disease according to NCEP-ATP III criteria was 3.3 (1.0–11.2) in non-abdominal obese persons with at least two risk factors and 5.1 (1.6–16.9) in abdominal obese persons with at least two risk factors. The respective hazard ratios were 4.3 (1.0–18.3) and 6.5 (1.6–27.5), according to AHA/NHLBI and IDF criteria, and 3.4 (1.3–8.9) and 3.4 (1.3–9.0), according to the Japanese criteria.

Discussion

The metabolic syndrome based on NCEP-ATP III criteria was associated with 2-fold increased risks of ischemic heart disease, ischemic stroke, and total cardiovascular disease, whereas the metabolic syndrome based on AHA/NHLBI, IDF, and Japanese criteria had weaker associations with risk of cardiovascular disease, and the association with risk of ischemic heart disease was not statistically significant. The population attributable fraction of ischemic stroke was lower for the metabolic syndrome based on Japanese criteria than for that based on other criteria. Our results were consistent

with those of other prospective studies that showed that the metabolic syndrome based on NCEP-ATP III criteria was associated with risks of mortality and incidence of cardiovascular disease (*1*, *2*, *4–7*, *13*, *16–18*, *27*, *28*), and that the metabolic syndrome based on IDF criteria was less predictive of cardiovascular disease risk (*29–31*). The metabolic syndrome based on NCEP-ATP III, but not IDF criteria, was associated with cardiovascular disease among male diabetic patients (*14*, *15*).

Based on the Japanese criteria, the excess risk of ischemic cardiovascular disease was similar in non-abdominal obese persons with at least two metabolic risk factors and abdominal obese persons with at least two risk factors. The lack of significant associations of ischemic heart disease and ischemic cardiovascular disease based on the Japanese criteria was due to the inclusion of a high-risk group of persons without abdominal obesity as a reference group. In other words, excess risk of ischemic cardiovascular disease was similar for persons with at least two metabolic risk factors, irrespective of the presence of abdominal obesity. It is controversial whether the abdominal obesity defined by waist circumference should be required for diagnosis of the metabolic syndrome (*27*, *30*). Waist circumference is a valuable component of metabolic syndrome, but the requirement of an increased waist circumference may lead to reduced predictive power for cardiovascular disease (*27*, *29–33*).

The strengths of the present study include the use of standardized measurements of waist circumference, serum lipids, and blood pressure levels. The stroke surveillance was almost complete, and a high percentages of the events were confirmed using imaging studies (92%).

The limitations of the present study were, first, the small number of incident cases, particularly for ischemic heart disease. However, we found a statistically significant association between the metabolic syndrome and risks of ischemic heart disease and ischemic stroke. Second, we collected non-fasting blood samples from 94% of the participants during the 1990–1993 examinations. We used non-fasting data at the baseline examination, in particular, non-fasting serum triglycerides ≥1.69 mmol/L (≥150 mg/dL) as a component of metabolic syndrome. Although the justification of the use for the same cutoff point as fasting status is under debate, the data of non-fasting triglycerides can be used because of their significant predictive power for ischemic heart disease (*34*). We used non-fasting glucose ≥7.77 mmol/L as a component of metabolic syndrome, and we may have misclassified participants with high blood glucose. However, we found no significant difference in the percentage of participants with high blood glucose in non-fasting and fasting blood samples probably because we used the different cutoff points: ≥110 mg/dL for fasting and ≥140 mg/dL for non-fasting. In men, the percentage of high blood glucose was 26% for non-fasting blood samples and 30% for fasting blood samples. In women, the respective percentages were 17% and 14%.

In summary, the metabolic syndrome based on NCEP-ATPIII criteria predicted risks of ischemic heart disease, ischemic stroke and total cardiovascular disease, whereas that based on the other three criteria predicted them to a lesser extent.

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