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Associations Between Metabolic Syndrome and Mortality From Cardiovascular Disease in Japanese General Population, Findings on Overweight and Non-Overweight Individuals

—— Ibaraki Prefectural Health Study ——

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Background: The impact of being overweight, as a component of the metabolic syndrome (MetS), for cardiovascular disease (CVD) mortality was investigated and compared with the predictive value of MetS by 2 different definitions.

Methods and Results: A 12-year prospective study of 30,774 Japanese men and 60,383 women aged 40–79 years was conducted. The multivariate hazard ratio (HR; 95% confidence interval) of total CVD mortality for overweight subjects with ≥2 additional risk factors with reference to subjects with 0 of 4 MetS components was 1.83 (1.41–2.38) for men and 1.90 (1.45–2.49) for women, and for non-overweight subjects with ≥2 additional risk factors 1.75 (1.38–2.24) and 1.97 (1.52–2.55), respectively. The proportion of excess CVD deaths in the latter group was 1.5-fold higher than that in the former group. Multivariate HRs of coronary heart disease and total CVD mortality for MetS by the modified criteria of the American Heart Association/National Heart, Lung, and Blood Institute were 1.62 (1.31–2.00) and 1.23 (1.09–1.39), respectively, for men and 1.32 (1.05–1.65) and 1.12 (1.00–1.25), respectively, for women. The respective HRs for MetS by the International Diabetic Federation definition did not reach statistical significance, except for coronary heart disease in men.

Conclusions: Non-overweight individuals with metabolic risk factors, as well as overweight individuals with such factors, should be targeted to reduce the CVD burden in the general population. (*Circ J* 2009; **73:** 1635 – 1642)

Key Words: Cardiovascular disease; Follow-up studies; Metabolic syndrome; Mortality; Risk factors

The metabolic syndrome (MetS) is known as an important risk factor for cardiovascular disease (CVD) and mortality in Western populations.[1–3] Several cohort studies of Asians have also shown that MetS according to the Adult Treatment Panel Ⅲ guideline of the National Cholesterol Education Program (NCEP/ATPⅢ) definition is positively associated with CVD events and mortality.[4–7] Different clinical criteria for MetS have been developed over the past decade. The NCEP expert panel and the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) considers that each metabolic factor has the same importance, whereas the International Diabetes Federation (IDF) and Japanese Society of Internal Medicine requires central obesity as an essential component of the diagnosis for MetS.[8–11] A recent report of a Japanese cohort study showed that clustering of metabolic risk factors is related to CVD mortality, irrespective of being overweight.[6] Thus, it is uncertain whether overweight as a component of MetS has a significant contribution in identifying a high-risk subgroup of CVD among Japanese people, who are characterized by a low prevalence of obese individuals, lower mortality from ischemic heart disease and higher mortality from stroke, compared with Western populations.

We investigated the impact of being overweight as a component of MetS for CVD mortality in the Japanese general population, and compared the prevalence and predictive value of MetS using the AHA/NHLBI and IDF definitions.

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Table 1. Diagnostic Criteria for the 4 Definitions of MetS

	NCEP/ATPIII	AHA/NHLBI	IDF	Japanese Society of Internal Medicine
	≥3 of the following 5 risk factors:	≥3 of the following 5 risk factors:	Central obesity plus any 2 risk factors:	Central obesity plus any 2 risk factors:
Central obesity (waist circumference)	≥102 cm in men, ≥88 cm in women	≥102 cm in men, ≥88 cm in women (for Asian Americans ≥90 cm in men, ≥80 cm in women)	≥94 cm in men, ≥80 cm in women (for Asians ≥90 cm in men, ≥80 cm in women)	≥85 cm in men, ≥90 cm in women
TG	≥150 mg/dl	≥1.7 mmol/L (150 mg/dl) or drug treatment	≥1.7 mmol/L (150 mg/dl) or drug treatment	≥1.7 mmol/L (150 mg/dl) or drug treatment and/or*
HDL-C	<40 mg/dl in men, <50 mg/dl in women	<40 mg/dl in men, <50 mg/dl in women or drug treatment	<1.03 mmol/L (40 mg/dl) in men, <1.29 mmol/L (50 mg/dl) in women or drug treatment	<1.03 mmol/L (40 mg/dl) in men and women or drug treatment
BP	SBP ≥130 mmHg or DBP ≥85 mmHg	SBP ≥130 mmHg or DBP ≥85 mmHg or drug treatment	SBP ≥130 mmHg or DBP ≥85 mmHg or drug treatment	SBP ≥130 mmHg or DBP ≥85 mmHg or drug treatment
Fasting glucose	≥110 mg/dl	≥100 mg/dl or drug treatment	≥5.6 mmol/L (100 mg/dl) or previously diagnosed type 2 diabetes	≥110 mg/dl or drug treatment

*In the definition of the Japanese Society of Internal Medicine, triglycerides and HDL-C are combined into 1 component of dyslipidemia.
MetS, metabolic syndrome; NCEP/ATPIII, National Cholesterol Education Program-Adult Treatment Panel III; AHA/NHLBI, American Heart Association/National Heart, Lung, and Blood Institute; IDF, International Diabetes Federation; TG, triglycerides; HDL, high-density lipoprotein; BP, blood pressure (S, systolic; D, diastolic).

Methods

Study Population

The surveyed population comprised 96,433 persons (32,915 men, 63,518 women) aged 40–79 years living in Ibaraki Prefecture, Japan, who participated in annual community-based health checkups in 1993 (Ibaraki Prefectural Health Study). The health examinations were conducted by municipalities under the legal requirement for health and medical services for the aged. Because we excluded employees who had their annual health checkups conducted by their employers under the Industrial Safety and Health Law, the number of female participants exceed that of males. Of 85 communities, 38 were included in this study. The participating communities entrusted their health examinations to the Ibaraki Health Service Association and also the management of the basic resident register to the Ibaraki Accounting Center. The communities were distributed evenly across the prefecture because 5–11 communities participated from each of the middle, northern, southern, eastern, and western areas. The participation rate for health checkups was 36.4% in these areas, and was similar to the rate for Ibaraki prefecture in 1993 (35.8%). Persons with a history of stroke (n=935) or heart disease (n=4,433) were excluded, and the data of the remaining 91,157 persons (30,774 men, 60,383 women) were used for the analysis. The study protocol was approved by the Ethics Committee of the Ibaraki Prefectural Office.

Mortality Surveillance

Mortality surveys were conducted by systematic review of the death certificates and resident registrations, with the cooperation of public health centers and municipal government offices. The underlying causes of death were coded according to the International Classification of Diseases, 9th revision (ICD-9, 1993–1994) and 10th revision (ICD-10, 1995–2005). Follow-up was conducted until the end of 2005. Persons who moved out of the communities during the follow-up numbered 3,226 (3.5%), and 9,282 persons (10.2%) died. Such individuals were censored at the date of moving or of death. The median follow-up period for all participants was 12.0 years. Cause-specific mortality was also determined individually in terms of total stroke (ICD-9 codes 430–438; ICD-10 codes I60–I69), hemorrhagic stroke (codes 431–432; I60–I61, I69.0, I69.1), ischemic stroke (codes 433–434, 437.7A, 437.7B; I63, I69.3), coronary heart disease (codes 410–414; I20–I25), and total CVD (codes 393–459; I00–I99).

Measurement of Risk Factors

At baseline survey, body mass index (BMI) was calculated as weight (kg) divided by square of height (m^2). Height in stocking feet and weight in light clothing were measured. The proportion of obesity (BMI ≥30 kg/m^2) was only 1.7% in men and 3.4% in women. Serum triglyceride (TG) and serum total cholesterol (TC) levels were measured with enzyme methods using an RX-30 device (JEOL Ltd, Tokyo, Japan). High-density lipoprotein-cholesterol (HDL-C) was measured with a phosphotungstic acid magnesium method using an MTP-32 device (Corona Electric, Ibaraki, Japan). The measurement of these lipids in the laboratory of the Ibaraki Health Service Association was standardized by the laboratory of the Osaka Medical Center for Health Science and Promotion under the laboratory network program of the US Centers for Disease Control and Prevention (Atlanta, GA, USA).[12] Blood pressure (BP) was measured by trained observers using a standard mercury sphygmomanometer on the right arm of seated participants after a 5-min rest. Plasma glucose levels were measured with a glucose oxidase electrode method using a GA1140 device (ARKRAY, Inc, Kyoto, Japan). Fasting was not required. The time since the last meal was <2 h (25%), 2 h (25%), 3–7 h (33%) and ≥8 h (17%).

An interview was conducted to ascertain smoking status, number of cigarettes smoked per day, usual weekly intake of alcohol in "go" units (a Japanese traditional unit of volume corresponding to 23 g ethanol), which was converted to grams of ethanol per day, and histories of stroke and heart

disease. Histories of CVD were also determined by interview in which the subjects were asked if they had been diagnosed as stroke and/or heart disease. Symptoms typical of stroke and coronary heart disease or findings on brain imaging studies and/or ECG were not taken into account.

Definitions of MetS

The components of MetS were defined as: (1) overweight: BMI ≥25 kg/m^2, (2) elevated TGs: ≥1.69 mmol/L (150 mg/dl), (3) reduced HDL-C: <1.03 mmol/L (40 mg/dl) for men and <1.29 mmol/L (50 mg/dl) for women, (4) elevated BP: ≥130/85 mmHg and/or antihypertensive medication use, and (5) elevated glucose: ≥5.55 mmol/L (100 mg/dl) fasting or ≥7.22 mmol/L (130 mg/dl) non-fasting, and/or on treatment for diabetes mellitus. Because waist circumference was not measured in our study, BMI ≥25 kg/m^2 was used as the criterion for being overweight for the analyses; this BMI level is reported to correspond well to the Asian criterion for high waist circumference ≥90 cm in men and ≥80 cm in women.[13] Non-fasting plasma glucose was also used as a criterion for glucose intolerance, because the fasting plasma glucose level was not measured in four-fifths of the participants. We defined elevated glucose as glucose ≥5.55 mmol/L (100 mg/dl) in fasting blood samples and ≥7.22 mmol/L (130 mg/dl) in non-fasting ones.

As shown in **Table 1**, MetS was defined as the presence of 3 or more of the components (overweight, elevated TGs, reduced HDL-C, elevated BP and elevated glucose) according to the modified criteria of AHA/NHLBI, and the presence of 2 or more of the same cardiovascular risk factors (elevated TGs, reduced HDL-C, elevated BP and elevated glucose) among overweight persons according to the modified criteria of the IDF. The AHA/NHLBI definition included non-overweight people with 3 or 4 abnormalities of TGs, HDL-C, BP and glucose, who would not be classified as MetS by the IDF criteria.

Statistical Analysis

Sex-specific hazard ratios (HRs) of CVD mortality and the corresponding 95% confidence intervals (95%CI) were calculated with reference to the risk for individuals without each of MetS components or with none of the components, or without MetS, using the Cox proportional hazards model. Elevated TC was defined as ≥5.69 mmol/L (220 mg/dl). We adjusted for age at baseline (years), and for other potential confounding factors including cigarette smoking (never-smokers, ex-smokers, current smokers of 1–19, 20–29 and ≥30 cigarettes/day), usual alcohol intake (never, former, current <23 g/day, 23–45, 46–68 and ≥69 g/day ethanol), time since last meal (<2, 2, 3–7 and ≥8 h) and sex-specific quartiles of serum TC levels.

Participants were stratified into categories according to the number of metabolic risk factors (BMI< or ≥25 kg/m^2 plus 0, 1, 2, 3 or more (≥3), or 2 or more (≥2) of additional risk factors except being overweight). The HRs and corresponding 95%CI of death were calculated with reference to persons with 0 of 4 MetS components. We conducted tests for trend across the categories of the number of metabolic risk factors by assigning median values for each category (0, 1, 2 and ≥3) and testing the significance of this variable. The HRs of mortality for MetS according to the IDF and AHA/NHLBI definitions were also calculated with reference to individuals without MetS. P values for statistical tests were 2-tailed and P<0.05 was regarded as statistically significant. The SAS statistical package (version 9.1; SAS Institute Inc, Cary, NC, USA) was used for the analyses. We also calculated population attributable fractions (PAF) to examine the contribution of the MetS and its components to the risk of CVD mortality, using multivariate HRs of statistical significance and the proportion of cases in each category. PAF was estimated as $[p(HR\text{-}1)]/[1+p(HR\text{-}1)]$, where p is the proportion of cases falling into the category and HR is the HR in the category.[14]

Results

During the 12-year follow-up, there were 9,282 deaths (5,124 for men; 4,158 for women), comprising 1,317 deaths from total stroke, 569 from hemorrhagic stroke, 716 from ischemic stroke, 704 from coronary heart disease, and 2,674 from total CVD.

Table 2 presents the sex-specific HRs (95%CI) for mortality from hemorrhagic stroke, ischemic stroke and coronary heart disease according to metabolic risk factors. Age-adjusted HR for mortality from hemorrhagic stroke was 1.9 in both sexes in the presence of elevated BP. Age-adjusted HRs for mortality from ischemic stroke ranged from 1.3 to 1.5 in the presence of elevated BP and reduced HDL-C in men, and were between 1.5 and 1.7 in the presence of elevated BP and glucose levels in women. Age-adjusted HRs of mortality from coronary heart disease ranged from 1.4 to 1.6 in the presence of elevated BP, elevated glucose and reduced HDL-C in men, and were between 1.4 and 1.9 in the presence of elevated BP and glucose levels in women. Age-adjusted HRs for mortality from total CVD ranged from 1.2 to 1.6 in the presence of elevated BP, elevated glucose and reduced HDL-C in men, and were between 1.4 and 1.7 in the presence of elevated BP and glucose levels in women. Elevated TC was associated with increased mortality from coronary heart disease in men, but not in women. Smoking was associated with increased mortality from hemorrhagic stroke in women, and coronary heart disease and total CVD in both sexes. These associations remained statistically significant after adjustment for confounding factors. Associations between being overweight and diseases outcomes were generally weak and only significant for coronary heart disease in men.

The PAFs of these 4 outcomes were approximately 20–40% for elevated BP in both sexes, whereas the PAFs of coronary heart disease and total CVD were approximately 10–20% for elevated glucose in both sexes, and approximately 20–25% for smoking in men.

Table 3 presents the multivariate HRs for mortality from ischemic stroke, coronary heart disease and total CVD according to the number of metabolic risk factors stratified by BMI. In both men and women, a dose–response relationship was found between the number of metabolic risk factors and the HR of mortality from each endpoint for both non-overweight and overweight subgroups. The multivariate HR (95%CI) of total CVD was 1.75 (1.38–2.24) in non-overweight persons with ≥2 risk factors (components of MetS except for overweight) and 1.83 (1.41–2.38) in overweight persons with ≥2 risk factors in men. The respective HRs were 1.97 (1.52–2.55) and 1.90 (1.45–2.49) in women. The HRs of mortality from total CVD for overweight individuals with ≥2 risk factors were similar to those for non-overweight persons with ≥2 other MetS components in both men and women. The PAF in the former category was 10%, and 15% in the latter among both men and women. Furthermore, we also calculated age-specific

Table 2. Sex-Specific HRs (95%CI) of Cardiovascular Disease Mortality According to Metabolic Risk Factors

	No. of persons	Person-years	Hemorrhagic stroke				Ischemic stroke				Coronary heart disease				Total cardiovascular disease			
			No.of deaths	Age-adjusted HR (95%CI)	Multivariate HR (95%CI)	PAF, %	No.of deaths	Age-adjusted HR (95%CI)	Multivariate HR (95%CI)	PAF, %	No.of deaths	Age-adjusted HR (95%CI)	Multivariate HR (95%CI)	PAF, %	No.of deaths	Age-adjusted HR (95%CI)	Multivariate HR (95%CI)	PAF, %
Men																		
Non-overweight	22,362	250,754	171	1.00	1.00		336	1.00	1.00		268	1.00	1.00		1,033	1.00	1.00	
Overweight	8,412	96,790	42	0.75 (0.54–1.06)	0.81 (0.58–1.15)		68	0.72 (0.56–0.94)*	0.77 (0.59–1.01)		112	1.34 (1.07–1.67)*	1.39 (1.11–1.75)†	10	299	0.96 (0.85–1.10)	1.02 (0.90–1.17)	
Normal TGs	19,366	216,800	159	1.00	1.00		284	1.00	1.00		238	1.00	1.00		911	1.00	1.00	
Elevated TGs	11,408	130,745	54	0.68 (0.50–0.93)*	0.74 (0.54–1.02)		120	0.99 (0.80–1.23)	1.01 (0.81–1.26)		142	1.25 (1.01–1.54)*	1.20 (0.96–1.49)		421	1.01 (0.90–1.13)	1.03 (0.91–1.16)	
Normal HDL-C	25,033	283,144	170	1.00	1.00		317	1.00	1.00		282	1.00	1.00		1,046	1.00	1.00	
Reduced HDL-C	5,741	64,401	43	1.17 (0.84–1.63)	1.11 (0.78–1.57)		87	1.34 (1.06–1.70)*	1.32 (1.03–1.68)*	6	98	1.62 (1.29–2.04)‡	1.49 (1.17–1.89)†	8	286	1.29 (1.14–1.48)‡	1.24 (1.09–1.42)†	4
Normal BP	8,438	97,546	28	1.00	1.00		53	1.00	1.00		55	1.00	1.00		182	1.00	1.00	
Elevated BP	22,336	249,998	185	1.87 (1.25–2.79)†	1.91 (1.27–2.86)†	40	351	1.52 (1.14–2.03)†	1.52 (1.13–2.03)†	27	325	1.58 (1.19–2.11)†	1.67 (1.25–2.23)‡	33	1,150	1.59 (1.36–1.86)‡	1.61 (1.38–1.89)‡	31
Normal glucose	21,299	241,841	138	1.00	1.00		267	1.00	1.00		233	1.00	1.00		853	1.00	1.00	
Elevated glucose	9,475	105,704	75	1.19 (0.89–1.57)	1.23 (0.92–1.66)		137	1.13 (0.92–1.39)	1.14 (0.92–1.41)		147	1.37 (1.12–1.69)†	1.43 (1.15–1.78)†	12	479	1.23 (1.10–1.37)‡	1.24 (1.11–1.40)‡	7
Normal TC	24,551	276,423	185	1.00	1.00		340	1.00	1.00		286	1.00	1.00		1,091	1.00	1.00	
Elevated TC	6,223	71,121	28	0.66 (0.44–0.98)*	0.69 (0.46–1.02)		64	0.87 (0.66–1.13)	0.95 (0.72–1.24)		94	1.45 (1.15–1.84)†	1.53 (1.21–1.94)‡	10	241	0.99 (0.86–1.14)	1.05 (0.92–1.21)	
Never smoked	6,824	78,402	50	1.00	1.00		79	1.00	1.00		73	1.00	1.00		269	1.00	1.00	
Ex-smokers	8,120	91,694	56	0.87 (0.60–1.28)	0.88 (0.60–1.29)		103	1.02 (0.76–1.37)	1.01 (0.75–1.36)		84	0.89 (0.65–1.22)	0.89 (0.65–1.22)		334	0.96 (0.82–1.13)	0.94 (0.80–1.11)	
Current smoker	15,830	177,449	107	1.06 (0.76–1.48)	0.99 (0.70–1.40)		222	1.65 (1.28–2.14)‡	1.60 (1.23–2.08)‡	24	223	1.56 (1.20–2.04)†	1.63 (1.25–2.14)‡	25	729	1.45 (1.26–1.66)‡	1.41 (1.22–1.63)‡	18
Women																		
Non-overweight	42,014	488,250	242	1.00	1.00		214	1.00	1.00		217	1.00	1.00		901	1.00	1.00	
Overweight	18,369	215,468	114	0.97 (0.78–1.22)	1.00 (0.80–1.25)		98	0.98 (0.78–1.25)	0.99 (0.78–1.26)		107	1.03 (0.81–1.29)	1.03 (0.82–1.30)		441	1.02 (0.91–1.14)	1.03 (0.92–1.16)	
Normal TGs	41,654	485,071	234	1.00	1.00		190	1.00	1.00		192	1.00	1.00		845	1.00	1.00	
Elevated TGs	18,729	218,646	122	0.92 (0.74–1.15)	0.92 (0.74–1.16)		122	1.11 (0.89–1.40)	1.13 (0.89–1.43)		132	1.19 (0.95–1.48)	1.18 (0.93–1.48)		497	1.01 (0.91–1.13)	1.01 (0.90–1.14)	
Normal HDL-C	40,891	475,864	221	1.00	1.00		201	1.00	1.00		196	1.00	1.00		831	1.00	1.00	
Reduced HDL-C	19,492	227,854	135	1.09 (0.88–1.36)	1.02 (0.83–1.27)		111	0.96 (0.76–1.21)	0.95 (0.75–1.21)		128	1.15 (0.92–1.43)	1.12 (0.89–1.40)		511	1.08 (0.96–1.20)	1.04 (0.93–1.17)	
Normal BP	22,973	268,516	54	1.00	1.00		37	1.00	1.00		54	1.00	1.00		190	1.00	1.00	
Elevated BP	37,410	435,202	302	1.85 (1.37–2.49)‡	1.93 (1.43–2.60)‡	37	275	1.66 (1.17–2.34)†	1.68 (1.19–2.37)†	30	270	1.36 (1.01–1.84)*	1.41 (1.04–1.89)*	20	1,152	1.63 (1.39–1.90)‡	1.67 (1.43–1.96)‡	29
Normal glucose	48,477	565,684	266	1.00	1.00		213	1.00	1.00		203	1.00	1.00		939	1.00	1.00	
Elevated glucose	11,906	138,034	90	1.13 (0.89–1.44)	1.15 (0.89–1.48)		99	1.45 (1.14–1.84)†	1.48 (1.16–1.91)†	9	121	1.92 (1.53–2.40)‡	2.01 (1.59–2.56)‡	17	403	1.38 (1.23–1.55)‡	1.42 (1.25–1.60)‡	8
Normal TC	39,507	461,260	240	1.00	1.00		189	1.00	1.00		199	1.00	1.00		837	1.00	1.00	
Elevated TC	20,876	242,459	116	0.75 (0.60–0.94)*	0.76 (0.61–0.95)*		123	1.01 (0.80–1.26)	1.01 (0.80–1.27)		125	0.96 (0.77–1.21)	0.96 (0.77–1.21)		505	0.93 (0.83–1.03)	0.93 (0.83–1.04)	
Never smoked	56,980	665,764	321	1.00	1.00		295	1.00	1.00		288	1.00	1.00		1,227	1.00	1.00	
Ex-smoker	441	4,880	2	–	–		3	1.52 (0.49–4.75)	1.60 (0.51–5.00)		1	–	–		10	1.27 (0.68–2.37)	1.30 (0.70–2.43)	
Current smoker	2,962	33,074	33	2.62 (1.83–3.74)‡	2.70 (1.87–3.90)‡	8	14	1.20 (0.70–2.05)	1.19 (0.70–2.05)		35	3.14 (2.21–4.46)‡	3.19 (2.23–4.57)‡	10	105	2.22 (1.82–2.70)‡	2.22 (1.81–2.72)‡	6

Test for significance: *P<0.05, †P<0.01, ‡P<0.001.
Multivariate HR adjusted for age, serum TC level, cigarette smoking, alcohol intake category, time since last meal.
HR, hazard ratio; CI, confidence interval; PAF, population attributable fraction; TC, total cholesterol. Other abbreviations see in Table 1.

Table 3. Multivariate HRs (95%CIs) of Cause-Specific Mortality According to Metabolic Risk Factors, Stratified by BMI in Men and Women Aged 40–79 Years

	No. at risk	Person-years	Ischemic stroke			Coronary heart disease			Total cardiovascular disease		
			No. of deaths	Multivariate HR§ (95%CI)	PAF, %	No. of deaths	Multivariate HR§ (95%CI)	PAF, %	No. of deaths	Multivariate HR§ (95%CI)	PAF, %
Men No. of metabolic factors											
BMI <25											
0	3,468	40,033	23	1.00		20	1.00		76	1.00	
1	9,010	100,661	152	1.67 (1.08–2.60)*	13	111	1.64 (1.02–2.64)*	10	448	1.63 (1.28–2.08)‡	12
2	6,986	77,785	106	1.58 (1.01–2.49)*	9	82	1.60 (0.98–2.61)	–	344	1.67 (1.30–2.15)‡	9
≥3	2,898	32,275	55	2.07 (1.27–3.38)†	7	55	2.49 (1.48–4.16)‡	8	165	1.97 (1.49–2.58)‡	6
P for trend				0.026			0.002			<0.001	
≥2	9,884	250,754	161	1.72 (1.11–2.66)*	16	137	1.86 (1.16–2.99)*	15	509	1.75 (1.38–2.24)‡	15
BMI ≥25											
0	434	5,154	0	1.00		1	–	–	4	0.59 (0.21–1.60)	–
1	2,232	25,717	17	1.10 (0.58–2.05)	–	26	2.02 (1.12–3.62)*	4	69	1.36 (0.98–1.88)	–
2	3,155	36,338	19	0.95 (0.52–1.75)	–	37	2.09 (1.21–3.61)†	6	103	1.55 (1.15–2.08)†	4
≥3	2,591	29,582	32	1.92 (1.12–3.30)*	5	48	3.08 (1.82–5.21)‡	10	123	2.17 (1.62–2.89)‡	6
P for trend				0.011			0.009			<0.001	
≥2	5,746	96,790	51	1.38 (0.84–2.27)	–	85	2.54 (1.55–4.15)‡	16	226	1.83 (1.41–2.38)‡	10
Women No. of metabolic factors											
BMI <25											
0	10,850	125,746	11	1.00		14	1.00		65	1.00	
1	15,698	183,286	81	2.03 (1.08–3.82)*	14	77	1.87 (1.06–3.31)*	12	335	1.70 (1.30–2.22)‡	11
2	9,983	115,736	77	2.41 (1.28–4.55)†	12	68	2.12 (1.19–3.79)*	10	311	2.02 (1.54–2.65)‡	10
≥3	5,483	63,483	45	2.19 (1.13–4.26)*	6	58	2.73 (1.51–4.92)‡	8	190	1.89 (1.42–2.51)‡	5
P for trend				0.025			0.001			<0.001	
≥2	15,466	488,250	122	2.33 (1.25–4.33)†	18	126	2.35 (1.35–4.10)†	19	501	1.97 (1.52–2.55)‡	15
BMI ≥25											
0	1,668	19,694	2	–	–	1	–	–	9	1.00 (0.50–2.00)	–
1	5,465	64,163	17	1.30 (0.61–2.78)	–	27	1.93 (1.01–3.69)*	5	110	1.66 (1.22–2.26)†	4
2	5,685	66,842	37	2.43 (1.24–4.76)*	7	30	1.81 (0.96–3.42)	–	130	1.66 (1.23–2.24)‡	4
≥3	5,551	64,769	42	2.32 (1.19–4.51)*	6	49	2.55 (1.40–4.64)†	8	192	2.11 (1.59–2.81)‡	6
P for trend				0.104			0.047			0.008	
≥2	11,236	215,468	79	2.37 (1.26–4.46)†	13	79	2.20 (1.24–3.89)†	12	322	1.90 (1.45–2.49)‡	10

Test for significance: *P<0.05, †P<0.01, ‡P<0.001.
§Adjusted for age, serum TC level, cigarette smoking, alcohol intake category, time since last meal.
BMI, body mass index. Other abbreviations see in Tables 1, 2.

HRs of mortality from total CVD according to the number of metabolic risk factors stratified by BMI (<25, ≥25 kg/m^2), and found similar associations in both age subgroups. For example, the PAF of total CVD among men was 17% for overweight individuals with ≥2 risk factors and 17% for non-overweight ones with ≥2 other MetS components in the age subgroups of 40–64 years, and 6% and 16%, respectively, for the older subgroups of 65–79 years. The respective PAFs among women were 10%, 23%, 12% and 16% (not shown in **Table 3**).

Non-overweight individuals with ≥3 risk factors also had a considerable contribution to CVD mortality, even though they were not classified as MetS by the IDF definition. PAF in this category was 6% in men and 5% in women for total CVD mortality. Similar associations were observed for ischemic stroke and coronary heart disease.

Figure shows sex-specific multivariate HRs of mortality from total CVD according to the number of metabolic risk factors stratified by BMI. Although the HR for non-overweight individuals with ≥2 MetS components other than being overweight was similar to that for overweight persons with ≥2 risk factors; the proportion of subjects in the former category was approximately 1.5–2-fold higher than that in the latter. Thus, the number of total CVD deaths for non-overweight individuals with ≥2 MetS components exceeded substantially that for overweight persons with ≥2 risk factors.

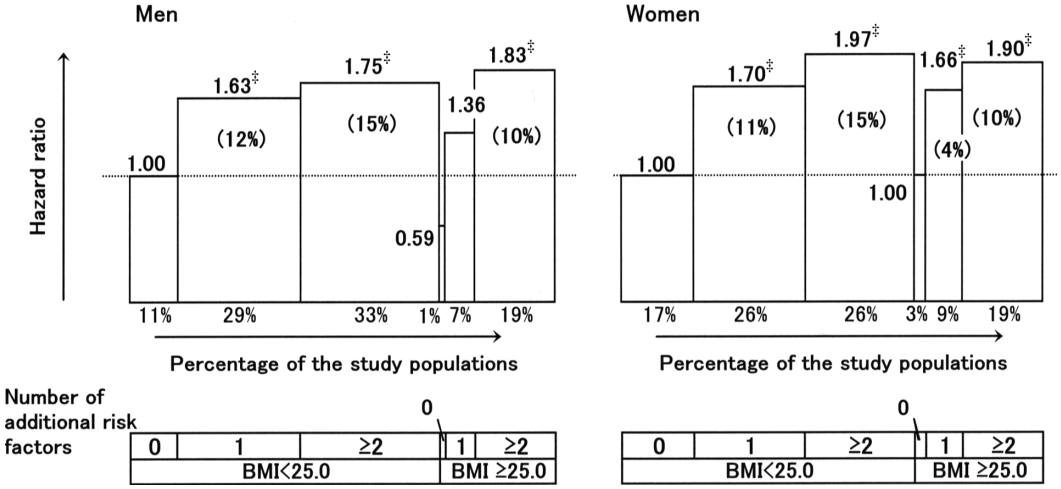

Figure. Sex-specific multivariable hazard ratios for mortality from total cardiovascular disease according to the number of metabolic risk factors, stratified by body mass index (BMI) for men and women aged 40–79 years. The population attributable fractions are shown in parentheses. ‡P<0.001.

Table 4. Prevalence of MetS and Multivariate HRs (95%CIs) of Cause-Specific Mortality According to 2 Definitions

	No. at risk	Person-years	Proportion at risk, %	Ischemic stroke			Coronary heart disease			Total cardiovascular disease		
				No. of deaths	Multivariate HR§ (95%CI)	PAF, %	No. of deaths	Multivariate HR§ (95%CI)	PAF, %	No. of deaths	Multivariate HR§ (95%CI)	PAF, %
Men												
MetS by IDF definition												
No	25,028	81%	281,625	353	1.00	0	295	4.00	0	1,106	1.00	0
Yes	5,746	19%	65,920	51	0.88 (0.66–1.19)	–	85	1.51 (1.18–1.93)†	9	226	1.15 (1.00–1.34)	–
MetS by AHA/NHLBI definition												
No	22,130	72%	249,350	298	1.00	0	240	1.00	0	941	1.00	0
Yes	8,644	28%	98,195	106	1.12 (0.89–1.40)	–	140	1.62 (1.31–2.00)‡	15	391	1.23 (1.09–1.39)‡	6
Women												
MetS by IDF definition												
No	49,147	81%	572,107	233	1.00	0	245	1.00	0	1,020	1.00	0
Yes	11,236	19%	131,611	79	1.20 (0.93–1.55)	–	79	1.12 (0.86–1.44)	–	322	1.10 (0.97–1.25)	–
MetS by AHA/NHLBI definition												
No	43,664	72%	508,624	188	1.00	0	187	1.00	0	830	1.00	0
Yes	16,719	28%	195,094	124	1.19 (0.95–1.49)	–	137	1.32 (1.05–1.65)*	8	512	1.12 (1.00–1.25)	–

Test for significance: *P<0.05, †P<0.01, ‡P<0.001.
§Adjusted for age, serum TCl level, cigarette smoking, alcohol intake category, time since last meal.
Abbreviations see in Tables 1,2.

Similar results were observed for mortality from other endpoints.

Table 4 presents the prevalence of MetS and HRs of CVD mortality for MetS according to the 2 definitions. The prevalence of MetS was 26% according to the AHA/NHLBI criteria and 19% according to the IDF definition in either men or women. Multivariate HRs (95%CI) of mortality from coronary heart disease and total CVD for MetS based on the AHA/NHLBI with reference to individuals without MetS were 1.62 (1.31–2.00) and 1.23 (1.09–1.39), respectively, in men, and 1.32 (1.05–1.65) and 1.12 (1.00–1.25), respectively, in women. The respective HRs for MetS by the IDF definition did not reach statistical significance, except for coronary heart disease in men. The PAF for MetS based on the AHA/NHLBI criteria was 15% for coronary heart disease and 6% for total CVD in men and 8% for coronary heart disease in women. The PAF for MetS based on the IDF criteria was 9% for coronary heart disease in men.

Discussion

In this large prospective study of the Japanese general population, we showed that contribution of overweight per se to CVD mortality is not obvious compared with elevated glucose and BP. The excess risk of mortality from total CVD and other endpoints was similar for overweight and non-overweight persons with ≥2 metabolic components in both men and women. Because of the 2-fold higher proportion of non-overweight high-risk individuals, the excess proportion of death was obviously larger for non-overweight persons with ≥2 metabolic components than for persons with Mets by the IDF definition.

It is controversial whether central obesity defined by waist circumference or BMI is essential in the diagnosis

of MetS. Previous studies show that central obesity is an important component of MetS, but a large proportion of individuals with normal waist circumference are also characterized by multiple cardiovascular risk factors and increased risk of mortality.[15,16] Nilsson et al reported that the IDF definition was not superior to the NCEP/ATPIII or EGIR (European Group for the Study of Insulin Resistance) definition for the prediction of total CVD events, and that MetS according to the NCEP/ATPIII definition was most predictive.[17] In our study, the prevalence of MetS and the HR of CVD mortality for MetS by the AHA/NHLBI definition was higher than that for MetS by the IDF criteria, because of the considerable contribution of non-overweight individuals with ≥3 risk factors who were not classified as MetS by the IDF definition. Persons with MetS by the AHA/NHLBI definition had a 1.2-fold higher mortality from total CVD than person without MetS, and the contribution of MetS to total CVD was 6%. However, that contribution was one-fifth that of elevated BP for men.

The magnitude of the HRs of MetS for total CVD mortality was somewhat smaller in our study than previously reported.[2,3,17–19] Two large meta-analyses in Western countries indicated that the pooled HRs of total CVD deaths for MetS ranged from 1.7 to 1.9.[2,3] The lower prevalence of obese individuals, lower mortality from ischemic heart disease and higher mortality from hemorrhagic stroke in the Japanese population compared with Western populations may explain the smaller contribution of MetS to CVD, even for middle-aged men, in the present study.

Among the cardiovascular risk factors, elevated BP had the largest impact on mortality from CVD. The PAF of elevated BP ranged from 20% to 40%, which was far larger than that of other metabolic risk factors. Our study also confirmed that the impact of each metabolic risk factor varied among the cardiovascular outcomes. Although elevated BP was strongly associated with mortality from hemorrhagic stroke,[20,21] elevated glucose level was associated with mortality from coronary heart disease[22,23] in both sexes. In men, reduced HDL[24,25] and being overweight[26] were also associated with mortality from coronary heart disease.

In our study, serum TC tended to be inversely associated with mortality from hemorrhagic stroke, whereas elevated TC was associated with mortality from coronary heart disease, which was consistent with results from recent studies in the Asia–Pacific region.[27,28] Being overweight was associated with mortality from coronary heart disease, but not from hemorrhagic or ischemic stroke, which was also consistent with previous Japanese studies.[29–33]

The strengths of our study include the long term follow-up, sufficient number of deaths, complete follow-up of subjects using basic resident registers and systematic review of death certificates, and gender-specific analysis. To our knowledge, this study is the first large-scale prospective study of the Japanese general population to evaluate the gender-specific impact of each metabolic risk factor to mortality from CVD, stratified by BMI.

Study Limitations

First, the subjects of this study were participants in health checkups for residents with a response rate of 36.4%. Further, male participants were resident non-employees, so it is uncertain whether the findings in men can be generalized. However, the potential selection bias may be small because the rate of all-cause mortality was similar for the study subjects and the total Japanese population. The standard mortality ratio of all-cause mortality for the study participants was 95 (95%CI: 86, 103) for men and 100 (95%CI: 89, 110) for women compared with the total Japanese population in 2000.[34,35] Second, we used death certificate diagnoses rather than medical records or autopsy findings. Validation studies have been performed to evaluate the accuracy of death certificate diagnosis between the mid-1980s and the 1990s in Japan.[36–41] The positive predictive value and sensitivity for stroke diagnosis were 95% and 87%, respectively.[36] Moreover, previous studies have shown that the diagnosis on death certificates with regard to total stroke and its subtypes is valid because of the widespread use of CT scanning and MRI in Japanese hospitals.[42,43] As for coronary heart disease, the positive predictive value was lower than that for stroke, ranging from 50% to 78%, but the sensitivity was similar to that for stroke, ranging from 72% to 91%.[36–41] Third, we used BMI to define central obesity because waist circumference was not measured at the baseline examination. BMI has been used to diagnose overweight in many epidemiological studies and is considered to closely correlate with waist circumference.[13] Fourth, non-fasting blood samples were used for four-fifths of the participants at the baseline examination, which may cause misclassification of participants with elevated plasma glucose or elevated TGs.

In conclusion, non-overweight subjects with metabolic risk factors are at high risk of CVD mortality, as well as overweight subjects with such factors, and the excess mortality was 1.5-fold larger in the former than in the latter. The prevention and control of metabolic risk factors other than being overweight may therefore be important to reduce the burden of CVD in the general population.

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Disclosure

None.

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