What is already known on this subject

Weight change since early adulthood is widely known to be a risk factor for all-cause mortality in Caucasians. However, little is known about the association in the Asian population. Therefore, we examined the association between weight change and specific-cause mortality in a 12.9-year follow-up of a large prospective study in Japan.

What this study adds

This study confirmed that weight loss strongly predicted all-cause, cancer and CVD mortality, primarily for men in an Asian population with low BMI. An unfavourable effect of weight gain was weak at the population level.

women between weight change and all-cause mortality among middle-aged Japanese individuals, regardless of current or early adulthood BMI. In fact, people with a high BMI (≥30 kg/m^2) have shortened longevity in Japan; however, an unfavourable effect of weight gain on mortality was small at the population level.

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APPENDIX A

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Metabolic Syndrome and All-Cause and Cardiovascular Disease Mortality

—— Japan Public Health Center-Based Prospective (JPHC) Study ——

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Background: Although the metabolic syndrome (MetS) is considered to be caused primarily by visceral fat accumulation, epidemiological evidence is lacking as to whether or not obesity is an essential element in the syndrome.

Methods and Results: Between 1990 and 2005, the Japan Public Health Center-based Prospective (JPHC) Study conducted baseline measurements of metabolic risk factors in 12,412 men and 21,639 women, aged 40–69 years, with no history of cardiovascular disease (CVD) or cancer. To clarify the role of obesity, which the definition of MetS in Japan has adopted as an essential criterion, clustering of risk factors in data grouped according to overweight condition was examined. During a 12.3-year follow-up there were 2,040 deaths, including 947 from cancers and 304 from CVD. MetS significantly increased the hazard ratios for all-cause mortality in women and CVD mortality in men. Non-overweight with ≥2 risk factors had a similar impact on all-cause and CVD mortality. Clustering of metabolic factors caused a linear increase in the hazard ratios for mortality.

Conclusions: MetS caused moderate increases in all-cause and CVD mortality. However, the MetS definition requiring obesity may not necessarily identify non-overweight individuals who have a high mortality risk and are more prevalent than subjects with MetS. (*Circ J* 2009; **73:** 878–884)

Key Words: Cardiovascular disease; Cohort study; Epidemiology; Metabolic syndrome; Mortality

The metabolic syndrome (MetS) is considered to have an impact on atherosclerosis development and mortality from all-cause and cardiovascular disease (CVD).[1–3] The syndrome is caused primarily by visceral fat accumulation, which activates several cytokines produced by adipose tissue.[4] The International Diabetes Federation (IDF) definition of MetS requires the presence of central obesity plus 2 of the following factors: raised level of fasting plasma triglycerides or glucose, increased blood pressure (BP) or reduced level of plasma high-density lipoprotein-cholesterol.[5] The Japanese definition also uses different criteria for waist circumference: ≥85 cm for men and ≥90 cm for women.[6]

A Korean study has shown that the IDF definition of MetS is inferior to the definition of the Third Report of the US National Cholesterol Education Program, Adult Treatment Panel III (ATP III) for detecting subjects at high risk of developing CVD.[7] Recently, a European population based study also demonstrated that the IDF definition may not detect non-obese individuals with a high risk of CVD mortality, because of the increased risk in individuals with clustering of risk factors, regardless of the presence or absence of central obesity.[8] These findings raise the question as to whether or not definitions, such as the IDF and the Japanese, that have central obesity as a criterion are adequate for detecting individuals with a high CVD risk.

To better understand the impact of MetS and the clustering of risk factors on mortality we conducted a long-term prospective study of 34,051 Japanese men and women.

Methods

Study Population

The subjects were 12,412 men and 21,639 women, aged 40–69 years, who took part in the Japan Public Health Center-based Prospective (JPHC) Study. For inclusion in the study, subjects could not have a history of ischemic heart disease (IHD), stroke or cancer and had to be available for health checkups of metabolic risk factors. The JPHC Study consisted of Cohorts I and II, which began in 1990 and 1993, respectively, as described elsewhere.[9] Briefly, Cohort I was drawn from residents aged 40–59 years in 5 public health center (PHC) areas (Ninohe PHC of Iwate Prefecture, Yokote PHC of Akita Prefecture, Saku PHC of Nagano Pre-

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Table 1. Baseline Characteristics of Men and Women Grouped According to the Presence or Absence of the Japanese Definition of the MetS

	MetS (Japan)			
	Men		Women	
	Presence	Absence	Presence	Absence
n	1,756	10,656	2,008	19,631
Age, years	53.5	53.8	56.1	52.9
Body mass index, kg/m^2	27.3	22.9	27.9	23.1
Systolic BP, mmHg	142.4	129.5	143.3	126.4
Diastolic BP, mmHg	86.4	78.8	83.9	75.5
Total cholesterol, mmol/L	5.36	5.04	5.74	5.36
HDL-cholesterol, mmol/L	1.17	1.43	1.26	1.54
Triglycerides (median), mmol/L	2.14	1.14	2.02	1.01
Fasting glucose (median), mmol/L	6.1	5.3	5.9	5.1
Smoking status				
Non-smoker, %	62.5	54.1	95.6	94.4
1–19 cigarettes/day, %	15.1	21.1	3.2	4.5
≥20 cigarettes/day, %	22.3	24.8	1.3	1.1
Alcohol consumption, g/week	218.9	194.0	9.8	12.7
Sports and physical exercise, % ≥1 day/week	20.2	20.5	22.0	21.9
Persons taking drugs for, %				
Hypertension	40.6	20.8	54.8	23.6
Hyperlipidemia	7.7	2.3	16.7	4.3
Diabetes	6.3	2.6	7.3	1.6
Gout	5.8	2.8	0.8	0.6
Persons diagnosed by a doctor, %				
Hypertension	52.8	27.2	62.1	31.8
Diabetes	15.1	8.9	12.5	4.0
Liver disease	4.5	4.1	1.1	2.1
Kidney disease	3.5	3.7	4.1	4.4

MetS, metabolic syndrome; BP, blood pressure; HDL, high-density lipoprotein.

fecture, Chubu PHC of Okinawa Prefecture, and Katsushika PHC of Tokyo), and Cohort II was drawn from residents aged 40–69 years in 6 areas (Mito PHC of Ibaraki Prefecture, Nagaoka PHC of Niigata Prefecture, Suita PHC of Osaka Prefecture, Chuo-higashi PHC of Kochi Prefecture, Kamigoto PHC of Nagasaki Prefecture and Miyako PHC of Okinawa Prefecture). The Cohort I data included 2,754 men and 4,940 women who were revisited in 1995 because their metabolic risk factors had not been measured at the first examination in 1990. The study was approved by the Ethical Committee of the National Cancer Center.

Measurements

Trained technicians measured BP using standard mercury sphygmomanometers. Body mass index (BMI, kg/m^2) was calculated as weight divided by the square of height in meters. Serum levels of total cholesterol, high-density lipoprotein-cholesterol (HDL-C) and triglycerides were measured in accredited laboratories with quality control certification from the Osaka Medical Center for Health Science and Promotion, a member of the Cholesterol Reference Method Laboratory Network (CRMLN)[10] The fasting condition for blood collection was defined as ≥8 h since the last meal. A self-administered questionnaire was conducted at baseline to assess medical history, smoking habit and regular alcohol consumption. The amount of ethanol per week was evaluated by measuring the weekly frequency of drinking and the typical dose of alcoholic beverage (beer, sake, whiskey, shochu or wine). A history of hypertension or diabetes was ascertained by the question, "Have the following conditions been diagnosed by physicians?" with hypertension, diabetes and other chronic diseases being listed as potential responses.

MetS was defined using both the modified Japanese criteria[6] and the National Cholesterol Education Program, ATP III[1] definition. Although both definitions require central obesity as defined by waist circumference, we used BMI values as we did not measure waist circumference in our study. The MetS of Japan definition includes waist circumference ≥85 cm in men and ≥90 cm in women as essential elements in the adapted IDF definition, corresponding to a BMI ≥25 kg/m^2.[11] Therefore, in the present study, MetS was defined as a BMI ≥25 kg/m^2 plus any 2 of the following factors: (1) dyslipidemia (high triglycerides [≥1.69 mmol/L, 150 mg/dl], and/or low HDL-C [<1.03 mmol/L, 40 mg/dl], and/or medication use), (2) raised BP (systolic BP ≥130 mmHg, diastolic BP ≥85 mmHg, and/or medication use), (3) raised plasma glucose (≥6.1 mmol/L (110 mg/dl) fasting, or ≥7.8 mmol/L (140 mg/dl) non-fasting, and/or medication use). The ATP III definition defines subjects with MetS having 3 or more of the following factors: (1) raised plasma glucose (≥5.6 mmol/L (100 mg/dl) fasting, or ≥7.8 mmol/L (140 mg/dl) non-fasting, and/or medication use), (2) raised BP, (3) high triglycerides, (4) low HDL-C <1.03 mmol/L (40 mg/dl) in men and <1.29 mmol/L (50 mg/dl) in women, and (5) BMI ≥25 kg/m^2. The values of raised BP and high triglycerides were the same as those used in the Japanese MetS definition.

Until 1995, the underlying cause of death was determined based on death certificates coded according to the criteria of the International Classification of Diseases, ninth revision (ICD-9). From 1995 onwards, the codes were translated into the corresponding ICD-10 codes. Deaths from cancer, IHD and stroke were defined as C00–97, I20–25 and I60–69 (ICD-10), respectively, with IHD and stroke combined as CVD in the analyses.

Statistical Analysis

The median period of follow-up was 12.3 years from

Table 2. Multivariate Adjusted HRs and 95%CI for the ATP III and Japanese Definitions of the MetS and Determinants for Specific Causes of Death in Men Aged 40–69 in the JPHC Study

	Model*	Underlying cause of death				
		All-cause	Cancer	IHD	Stroke	CVD
No. of deaths		1,240	573	71	106	177
MetS (Japan)	Model 1	1.04 (0.88–1.22)	0.98 (0.77–1.26)	2.17 (1.27–3.72)	1.48 (0.90–2.43)	1.74 (1.21–2.51)
	Model 2	1.07 (0.90–1.27)	1.06 (0.82–1.36)	1.91 (1.05–3.48)	1.31 (0.75–2.29)	1.54 (1.02–2.31)
ATP III MetS	Model 1	1.07 (0.94–1.23)	0.95 (0.77–1.17)	1.98 (1.21–3.25)	1.38 (0.89–2.14)	1.61 (1.16–2.23)
	Model 2	1.06 (0.92–1.23)	0.97 (0.78–1.20)	1.76 (1.03–3.01)	1.20 (0.74–1.94)	1.41 (0.99–2.02)
MetS elements						
Overweight	Model 1	0.86 (0.76–0.99)	0.92 (0.76–1.12)	1.88 (1.16–3.04)	0.93 (0.60–1.46)	1.27 (0.92–1.75)
	Model 2	0.92 (0.80–1.06)	1.02 (0.83–1.24)	1.98 (1.18–3.32)	0.76 (0.45–1.26)	1.16 (0.82–1.66)
Raised BP	Model 1	1.16 (1.03–1.32)	1.03 (0.86–1.23)	1.49 (0.87–2.55)	2.03 (1.25–3.30)	1.78 (1.24–2.54)
	Model 2	1.19 (1.04–1.35)	1.04 (0.87–1.25)	1.53 (0.87–2.70)	2.29 (1.35–3.87)	1.90 (1.30–2.79)
Dyslipidemia	Model 1	1.13 (1.01–1.28)	1.08 (0.90–1.29)	2.32 (1.44–3.73)	1.12 (0.75–1.69)	1.52 (1.12–2.05)
	Model 2	1.10 (0.97–1.24)	1.07 (0.89–1.28)	2.11 (1.27–3.49)	1.01 (0.66–1.56)	1.27 (0.91–1.77)
Raised plasma glucose	Model 1	1.19 (1.04–1.37)	1.04 (0.83–1.29)	1.96 (1.17–3.28)	1.45 (0.93–2.27)	1.64 (1.17–2.30)
	Model 2	1.22 (1.05–1.41)	1.07 (0.86–1.33)	1.92 (1.10–3.35)	1.27 (0.77–2.08)	1.51 (1.04–2.18)

*Model 1 was adjusted for the JPHC communities and age. Model 2 was further adjusted for fasting conditions at blood collection, smoking status (non-smoker, 1–19 cigarettes/day, and ≥20 cigarettes/day), alcohol consumption (g/week) and sports and physical exercise.
HRs, hazard ratios; CI, confidence interval; ATP III, National Cholesterol Educational Program, Adult Treatment Panel III in the US; JPHC, the Japan Public Health Center-based Prospective; IHD, ischemic heart disease; CVD, cardiovascular disease.

Table 3. Multivariate Adjusted HRs and 95%CI for the ATP III and Japanese Definitions of the MetS and Determinants for Specific Causes of Death in Women Aged 40–69 in the JPHC Study

	Model*	Underlying cause of death				
		All-cause	Cancer	IHD	Stroke	CVD
No. of deaths		800	374	38	89	127
MetS (Japan)	Model 1	1.25 (1.02–1.54)	1.26 (0.93–1.70)	2.52 (1.18–5.38)	0.86 (0.43–1.72)	1.28 (0.77–2.12)
	Model 2	1.24 (1.00–1.53)	1.27 (0.94–1.73)	2.56 (1.19–5.48)	0.88 (0.44–1.77)	1.31 (0.79–2.18)
ATP III MetS	Model 1	1.23 (1.05–1.44)	1.18 (0.93–1.50)	2.08 (1.07–4.01)	1.24 (0.77–1.98)	1.46 (1.00–2.13)
	Model 2	1.22 (1.03–1.43)	1.17 (0.92–1.49)	1.90 (0.97–3.74)	1.26 (0.79–2.03)	1.44 (0.98–2.11)
MetS elements						
Overweight	Model 1	0.99 (0.85–1.15)	1.07 (0.86–1.33)	1.97 (1.03–3.76)	1.03 (0.66–1.61)	1.26 (0.88–1.81)
	Model 2	0.99 (0.85–1.15)	1.07 (0.85–1.33)	2.03 (1.05–3.90)	1.07 (0.68–1.67)	1.30 (0.90–1.88)
Raised BP	Model 1	1.22 (1.05–1.42)	0.97 (0.78–1.21)	1.17 (0.58–2.35)	1.81 (1.10–2.97)	1.57 (1.05–2.36)
	Model 2	1.24 (1.06–1.44)	1.00 (0.83–1.25)	1.16 (0.55–2.26)	1.81 (1.10–2.98)	1.55 (1.03–2.33)
Dyslipidemia	Model 1	1.05 (0.90–1.23)	1.13 (0.90–1.42)	2.21 (1.15–4.23)	1.00 (0.62–1.60)	1.29 (0.88–1.88)
	Model 2	1.03 (0.87–1.21)	1.09 (0.87–1.38)	2.08 (1.06–4.05)	1.02 (0.63–1.64)	1.17 (0.79–1.73)
Raised plasma glucose	Model 1	1.70 (1.40–2.06)	1.33 (0.97–1.82)	2.76 (1.29–5.93)	1.23 (0.65–2.34)	1.64 (1.01–2.66)
	Model 2	1.70 (1.39–2.07)	1.42 (1.03–1.94)	2.80 (1.29–6.07)	1.23 (0.65–2.35)	1.64 (1.01–2.68)

*See footnote of Table 2. See Tables 1,2 for abbreviations.

either 1990 or 1995 (Cohort I) or 1993 (Cohort II) to the end of 2005. The person-years studied were calculated as the period from baseline to either the first endpoint (death, emigration) or December 31, 2005.

Cox proportional hazard models were used to calculate sex-specific hazard ratios (HR) and 95% confidence intervals (CI) after adjustment for age (continuous), JPHC communities (dummy variables) and fasting condition, smoking status (non-smoker, 1–19 cigarettes/day, or ≥20 cigarettes/day), alcohol consumption and sports and physical exercise (≥1 day/week, other). The risk estimations of all-cause and CVD mortality were calculated on data grouped according to the different MetS definitions, overweight category (BMI ≥25 kg/m^2 or <25 kg/m^2) or number of metabolic risk factors. A category-specific population attributable fraction (PAF) was computed as pd×(HR−1)/HR, where pd is the proportion of cases falling into the category and HR is the hazard ratio for that category![2] Statistical significance was assumed at $P<0.05$. SAS software, version 9.1 (SAS Institute, Inc, Cary, NC, USA) was used for all the analyses.

Results

The median follow up period was 12.3 years, during which we documented 2,040 deaths in the 12,412 men and 21,639 women of the combined Cohorts I and II, including 947 cancer and 304 CVD deaths. **Table 1** shows sex-specific population profiles according to the MetS criteria in Japan. The percentage of subjects aged 40–69 years classified as having the MetS was 14.1% in men and 9.3% in women. In the present study, the percentages of subjects with components of the MetS, including overweight, raised BP, dyslipidemia, and raised plasma glucose, were 29.2%, 59.0%, 36.7% and 16.6% in men and 29.7%, 50.6%, 24.4% and 8.0% in women, respectively.

Tables 2 and **3** list the multivariable adjusted HRs for the various MetS definitions and determinants for mortality from all-causes, cancer, IHD, stroke or CVD in men and women. In men, neither the MetS of Japan nor the ATP III MetS definition increased all-cause mortality risk. However, both classifications increased IHD and CVD mortality. For example, the HR for CVD mortality using the MetS criteria of Japan was 1.54 (95%CI, 1.02–2.31) in model 2. There

Table 4. Multivariate Adjusted HRs and 95% CIs for All-Cause and CVD Mortality According to the Number of Risk Factors and the Combination of Overweight and Other Risk Factors in Men

Categories	Population	All-cause			CVD		
		No. of deaths	Model*		No. of deaths	Model*	
			Model 1	Model 2		Model 1	Model 2
No. of risk factors**							
0	2,633	207	1.00	1.00	21	1.00	1.00
1	4,411	478	1.16 (0.98–1.36)	1.16 (0.98–1.38)	54	1.26 (0.76–2.09)	1.32 (0.79–2.22)
2	3,247	341	1.16 (0.97–1.38)	1.19 (0.99–1.43)	58	1.91 (1.16–3.15)	1.94 (1.16–3.26)
3	1,710	169	1.16 (0.95–1.42)	1.19 (0.96–1.47)	32	2.12 (1.22–3.68)	1.83 (1.01–3.32)
4	381	45	1.51 (1.10–2.09)	1.61 (1.15–2.25)	12	3.93 (1.93–8.01)	3.84 (1.79–8.27)
P for trend			0.041	0.017		<0.001	<0.001
Combination of overweight and 3 other risk factors							
Non-overweight and 0 risk factors	2,663	207	1.00	1.00	21	1.00	1.00
Non-overweight and 1 risk factor	3,923	461	1.23 (1.04–1.45)	1.22 (1.03–1.45)	53	1.36 (0.82–2.27)	1.42 (0.84–2.38)
Non-overweight and ≥2 risk factors	2,201	281	1.28 (1.07–1.54)	1.28 (1.06–1.54)	48	2.13 (1.27–3.58)	2.12 (1.24–3.63)
Overweight and 0–1 risk factors	1,869	124	0.86 (0.69–1.08)	0.94 (0.75–1.19)	18	1.21 (0.64–2.28)	1.21 (0.61–2.36)
Overweight and ≥2 risk factors	1,756	167	1.17 (0.96–1.44)	1.22 (0.99–1.52)	37	2.51 (1.46–4.29)	2.24 (1.26–3.98)

*See the footnote of Table 2. **Indicates the 4 elements of overweight, raised BP, dyslipidemia and raised plasma glucose.
See Table 2 for abbreviations.

Table 5. Multivariate Adjusted HRs and 95% CIs for All-Cause and CVD Mortality According to the Number of Risk Factors and the Combination of Overweight and Other Risk Factors in Women

Categories	Population	All-cause			CVD		
		No. of deaths	Model*		No. of deaths	Model*	
			Model 1	Model 2		Model 1	Model 2
No. of risk factors**							
0	6,938	171	1.00	1.00	19	1.00	1.00
1	7,502	285	1.10 (0.90–1.33)	1.07 (0.88–1.31)	43	1.33 (0.77–2.29)	1.27 (0.73–2.21)
2	4,973	211	1.10 (0.89–1.35)	1.08 (0.88–1.34)	40	1.66 (0.95–2.90)	1.62 (0.93–2.84)
3 (≥3 for CVD)	1,965	110	1.41 (1.10–1.80)	1.37 (1.07–1.77)	25	2.27 (1.23–4.19)	2.27 (1.23–4.20)
4	261	23	2.02 (1.30–3.14)	2.04 (1.31–3.17)	–	–	–
P for trend			0.002	0.003		0.005	0.005
Combination of overweight and 3 other risk factors							
Non-overweight and 0 risk factors	6,938	171	1.00	1.00	19	1.00	1.00
Non-overweight and 1 risk factor	6,022	248	1.14 (0.93–1.39)	1.12 (0.91–1.37)	38	1.36 (0.78–2.37)	1.30 (0.74–2.28)
Non-overweight and ≥2 risk factors	2,248	125	1.33 (1.05–1.69)	1.30 (1.02–1.66)	23	1.88 (1.01–3.50)	1.81 (0.96–3.39)
Overweight and 0–1 risk factors	4,423	146	0.98 (0.78–1.23)	0.97 (0.77–1.22)	29	1.63 (0.91–2.93)	1.63 (0.91–2.92)
Overweight and ≥2 risk factors	2,008	110	1.38 (1.08–1.77)	1.34 (1.04–1.73)	18	1.83 (0.95–3.54)	1.84 (0.95–3.55)

*See the footnote of Table 2. **Indicates the 4 elements of overweight, raised BP, dyslipidemia and raised plasma glucose.
See Table 2 for abbreviations.

was no relationship between cancer mortality and the MetS or any of its determinants, whereas raised BP and increased plasma glucose were significant predictors of all-cause mortality after adjustment for potential confounders. Raised BP and plasma glucose levels were also both significant risk factors for CVD deaths, whereas being overweight, hypertensive or dyslipidemic doubled the risk of IHD mortality.

As shown in **Table 3**, multivariable adjusted HRs for all-cause mortality in women were increased for both the MetS classifications of Japan and ATP III. The Japanese MetS criteria also predicted IHD mortality, but not CVD mortality when combined with stroke. Women with high BP and raised plasma glucose levels had greater risk of all-cause mortality. We found a close association between IHD mortality and subjects who were overweight and dyslipidemic with a raised plasma glucose level. In contrast, the risk of stroke mortality was increased by raised BP only. Raised BP and increased plasma glucose levels were also significant predictors for CVD mortality.

Multivariable adjusted HRs for all cause and CVD mortality are shown for men (**Table 4**) and women (**Table 5**), grouped according to the number of metabolic risk factors present and body weight range. In men, there was a linear relationship between the HRs for all-cause and CVD mortality and an increase in the number of risk factors. Stratification of the data according to the overweight category showed men who were not overweight with 1 or ≥2 risk factors had a higher risk for all-cause mortality than overweight men with the same number of factors. Regarding CVD death, men with ≥2 risk factors, were at approximately 2-fold greater risk than men with no risk factors, regardless of whether or not they were overweight. The calculations of PAF in non-overweight and overweight men with ≥2 risks factors were 9.4% and 7.8%, respectively.

Similar analyses in women showed the HRs for all-cause and CVD mortality both increased in a linear manner. Multivariable adjusted HRs for all-cause mortality in non-overweight and overweight women with ≥2 risk factors were almost the same. Significant increases in HRs were not seen in model 2, although overweight and non-overweight women with ≥2 risk factors were likely to have a relatively higher risk of CVD mortality.

Figure shows the multivariable adjusted HRs for CVD mortality for the combination of raised BP, increased plasma

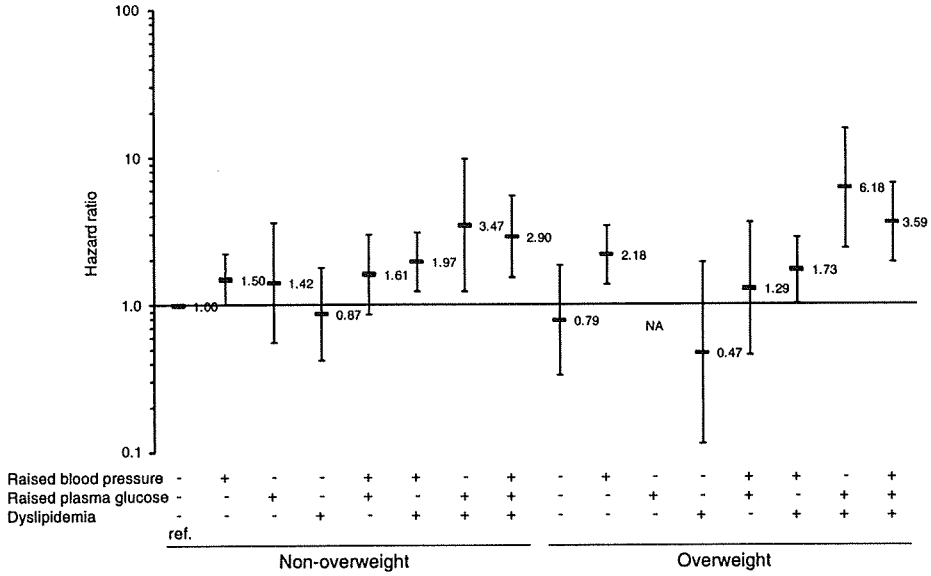

Figure. Multivariate adjusted hazard ratios for cardiovascular disease mortality of clustering of metabolic components in the combined data of men and women, grouped according to overweight category. The hazard ratios were calculated using subjects who were not overweight with no risks as the reference group.

glucose and dyslipidemia stratified according to the overweight category ranges in the combined data of men and women. The HRs increased significantly in subjects who had raised BP alone or those who had raised BP and/or raised plasma glucose combined with dyslipidemia, regardless of being overweight or not.

Discussion

This large prospective study confirmed that MetS has a moderate impact on all-cause and CVD mortality. We found the HRs for both types of mortality were increased not only in individuals with MetS, but also in non-overweight individuals with a constellation of risk factors compared with non-overweight individuals with no risk factors. Mortality risk increased in a linear manner according to the number of MetS factors present, including being overweight. We therefore do not agree with the recent proposal that the presence of the MetS identifies all individuals with a high risk of CVD mortality.

The prevalence of MetS in the present study was 14.1% in men and 9.3% in women aged 40–69 years. These percentages are almost similar to those reported in other investigations in which BMI was adopted for the MetS definition[13,14] The Japan National Health and Nutrition Survey documented the prevalence using waist measurements and showed 22.8% of men and 8.7% of women had MetS[15]

Various committees have proposed criteria for the IDF and Japanese definitions of MetS, both of which require central obesity plus any 2 of the metabolic risk factors[5] A small number of studies have reported that the ATP III definition of MetS clearly predicted stroke occurrence in the Japanese population,[16] whereas the Japanese classification did not[17] The recent concept requiring central obesity as an essential component was seemingly based on the pathogenesis of MetS[4,18] However, to date this requirement has not been supported by epidemiological evidence at the population level. With regard to detecting those at high risk, a European study was critical of the IDF definition because the criteria did not identify high-risk individuals[8]

Not surprisingly, it has been reported that the association between obesity and mortality is very weak in Japanese subjects[19] Instead, high mortality rates from all-cause and CVD deaths were found in individuals with lower BMI or weight loss since age 20, with inverse, L-shaped or U-shaped associations being observed between these variables[20] Although our study did not assess central obesity by measuring waist circumference, being overweight did not have a major role in identifying individuals at high risk of all-cause and CVD mortality.

The main finding of our study was that in the general Japanese population there were more non-overweight individuals with a constellation of risk factors than overweight individuals with the same constellation, with both groups having a similar mortality risk. When waist circumference was assessed, these unbalanced proportions for Japanese were confirmed,[17] and were quite different from proportions seen in a European population[8] Because of this, the PAF was greater in non-overweight individuals with 2 or more risk factors than in overweight individuals with the same number of risk factors. This finding suggests that strategies for preventing CVD may not be sufficient in people with MetS.

Hypertension and diabetes are strong predictors of all-cause and CVD mortality in the Japanese population. Prospective studies in Japan report that elevated plasma glucose is a major contributor to CVD mortality,[21] and that non-obese participants with clustering of risk factors are at increased mortality risk regardless of obesity[13] Those results are in general agreement with our findings. Furthermore, it has been documented that HRs of incident stroke in Japan are nearly the same between non-central and centrally obese individuals with 1 and ≥2 metabolic components[17] Our data also demonstrated that people with all the components of

Mets did not have increased HRs for CVD mortality, and regardless of them being overweight, this ratio was lower than in people with the 2 MetS components of raised plasma glucose and dyslipidemia. Although we are unable to explain the reason for this finding, a possible explanation may be that individuals with more serious conditions tend to need medication and were therefore excluded from participating in this study. Alternatively, smoking is a well-established risk factor for CVD mortality. In the present study, detailed analysis of data stratified by smoking habits was carried out and verified that metabolic risks had a similar effect on all-cause and CVD mortality in both smokers and non-smokers.

Although the JPHC study has the major advantages of including several large cohorts throughout Japan and the rich variability in health practices among these regions, several limitations of the study need to be taken into account. Firstly, we did not measure waist circumference. Several studies in Japan have used BMI values in the MetS definition, with Japanese guidelines recommending a BMI $\geq 25\,kg/m^2$ as representing obesity![1] This value corresponds to a cut-off point for visceral fat area of $100\,cm^2$, regarded as the gold standard for defining central obesity. Correlation coefficients of visceral fat area with BMI were reported to be 0.61 in men and 0.63 in women,[11] values that were almost equal to the correlations we observed with waist circumference. Secondly, fasting blood samples were collected from only 54% of the subjects. Although we used different cut-off points for fasting and non-fasting plasma glucose levels, it is possible misclassification of the MetS may have occurred because we used non-fasting blood samples. The prevalence of the MetS in fasting and non-fasting subjects was 13.1% and 15.5% in men and 6.6% and 11.8% in women, respectively. People who had blood samples taken in the non-fasting state were more likely to have dyslipidemia and to be taking antihypertensive medication. Thirdly, although clustering of risk factors was not a significant predictor for CVD mortality in non-overweight and overweight women, this relationship nearly reached statistical significance ($P< 0.1$). Because of the smaller number of CVD deaths in women, it is likely beta errors were relatively high. Finally, subjects in the study were selected if they had undergone a health checkup and were therefore not randomly recruited from the general population. A previous study in this cohort showed mortality was relatively low compared with that in the general population?[22] This may limit extrapolation of our findings to the general population.

In conclusion, although our study has several limitations, such as not assessing waist circumference, we showed that the presence of MetS increased all-cause and CVD mortality. We also showed that MetS definitions requiring obesity as an essential criterion certainly overlook non-overweight high risk individuals who have a high mortality risk and, in the present study, were greater in number than subjects with MetS. Indeed, a further large prospective study is needed to clarify the association of central obesity and MetS with CVD mortality in the Japanese population.

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Appendix 1

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