list of hypertension, diabetes and other chronic diseases as potential responses.

Weight change in cohort I was determined by the question, "Any changes of your weight (more than 5 kg) since the age of 20?", with potential responses of loss, no changes or gain. In cohort II, participants were asked, "What was your weight when you were 20 years old?" We computed the weight change from the difference between the weight reported at age 20 and at baseline. A total of 47 856 individuals (22 520 men and 25 336 women) from cohort I and 40 563 individuals (19 722 men and 20 841 women) from cohort II who reported that their weight had changed since age 20 were included in the analysis of weight change.

The following variables were used as covariates with dummy variables: non-smoker, light smoker (<20 cigarettes/day) and heavy smoker (≥20 cigarettes/day); sports and physical exercise (≥1 day/week, other); those who took drugs (hypertension, hyperlipidaemia, diabetes, gout); and those who had been diagnosed by a doctor (hypertension, diabetes, gastroduodenal ulcer, liver disease and kidney disease). Alcohol intake per week was estimated from the frequency and amount of alcohol consumed as defined by the ethanol concentration of major alcoholic beverages. These values were classified into categorical variables using a traditional portion in Japan: non-drinker, 1–23 g/day, 23–46 g/day, 46–69 g/day and ≥69 g/day.[16] These groups correspond to the categories related to incident cardiovascular disease (CVD) among Japanese. All variables were assessed with a self-administered questionnaire.

The underlying cause of death was determined based on death certificates and coded by the International Classification of Diseases, ninth revision (ICD-9) until 1995, and translated into the corresponding ICD-10 codes or coded by the ICD-10 after that. Deaths from cancer were defined as C00–C97, and deaths from CVD were defined as I20–25 and I60–69 (ICD-10).

Statistical analysis

With a median 12.9 years of follow-up from 1990 (cohort I) and 1993 (cohort II) to the end of 2005, person-years were calculated as the period from the date of the baseline to that of the first endpoint (death, emigration or loss) or to 31 December 2005. Among the participants, 25 moved out of Japan, one withdrew participation and 248 (0.3%) were lost to follow-up.

Weight change was classified into three comparable categories between cohorts I and II: loss (≥5 kg), stable (change <5 kg) and gain (≥5 kg). Furthermore, in the cohort II subjects, we reclassified weight change into five categories to analyse a dose–response relationship between weight change and mortality risk: loss ≥10 kg, loss 5–9 kg, stable (change <5 kg), gain 5–9 kg and gain ≥10 kg.

Sex-specific hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated after adjusting for age (continuous); current BMI; smoking status (non-smoker, <20 cigarettes/day and ≥20 cigarettes/day); ethanol intake (non-drinker, 1–23 g/day, 23–46 g/day, 46–69 g/day and ≥69 g/day); sports and physical exercise; medications or past history of hypertension and diabetes; and past history of liver disease and kidney disease as dummy variables, stratified by the JPHC communities and age groups of 40–49 years, 50–59 years and 60–69 years to adjust for an exposure period of weight change since age 20, using Cox's proportional hazard models. A test for linear trends was also carried out using a weight change variable (continuous) adjusted for the same covariates. Statistical significance was assumed at $p<0.05$. SAS software, V.9.1 (SAS Institute, Inc., Cary, North Carolina, USA), was used for all analyses.

RESULTS

During a median 12.9 years of follow-up, we documented 6494 deaths among 42 242 men and 46 177 women from combined cohorts I and II, including 2888 deaths from cancer, 1011 from CVD and 2595 from other causes. Figure 1 shows sex-specific mortality rates from all causes, cancer, CVD and other causes among individuals according to the category since age 20 by age group. It clearly illustrates high mortality rates from any cause for subjects with weight loss in each age group.

Table 1 shows population characteristics by weight change category and p values for differences among them. Those who reported weight loss ≥5 kg since age 20 indicated lower BMIs at baseline and higher BMIs at age 20; these data were available only for cohort II subjects. The percentages of smokers or those who had a past history of and had taken medication for diabetes were higher in men and women with weight loss. Significant differences between groups were recorded for most of the variables investigated, except for alcohol intake and gout in women.

Table 2 shows sex-specific multivariable-adjusted HRs for the cause of death comparing respondents with those with stable weight as a reference group. In men, an inverse association between weight gain and mortality was found for all-cause mortality, cancer mortality and other causes of mortality. HRs for all-cause mortality in the multivariable model were 1.44 (95% CI 1.32 to 1.56) and 0.89 (95% CI 0.82 to 0.97) for men with weight loss and weight gain, respectively. Those for all-cause mortality and other causes of mortality were likely to be high in the younger age group, and those for cancer mortality increased in older men. There was no increased risk of death among men with weight gain. In women, the multivariable model indicated an L-shaped association and an elevated risk of death for those with weight loss (1.33; 95% CI 1.17 to 1.52); however, risks of cancer and CVD were not increased significantly. Similar to men, the HRs for other causes of death were increased in younger women with weight loss. The association of weight gain with mortality was not clear. We analysed results after deletion of the first 5 years of follow-up and computed similar HRs for weight loss and gain (data not shown). Although each risk was somewhat attenuated, the elevated mortality risks for men and women with weight loss were almost the same.

In the subgroup analyses (table 3), as for the relationship of illnesses and smoking status with mortality, men and women with weight loss who were not ill and men and women with weight loss who smoked were at risk of mortality from all causes, cancer (men only) and other causes. Men who smoked or had illnesses were also at increased mortality risk.

Table 4 shows multivariable-adjusted HRs of weight change categories for death from all causes, cancer, CVD and other causes, stratified by baseline BMI (<18.5 kg/m^2, 18.5–24.9 kg/m^2 and ≥25 kg/m^2). The reference group was the 18.5–24.9 kg/m^2 baseline BMI group and stable weight change. In any group, HRs seemed to be increased significantly among individuals with weight loss. The highest HRs for all causes were found in persons with both baseline BMI <18.5 kg/m^2 and weight loss (≥5 kg).

Since we obtained self-reported weights at study entry and at age 20 from individuals in cohort II, we calculated multivariable-adjusted HRs for all-cause mortality classified into five weight change categories by BMI at age 20 (fig 2). Regardless of whether an individual was overweight at age 20, weight loss ≥10 kg was a risk factor for mortality. Among non-overweight

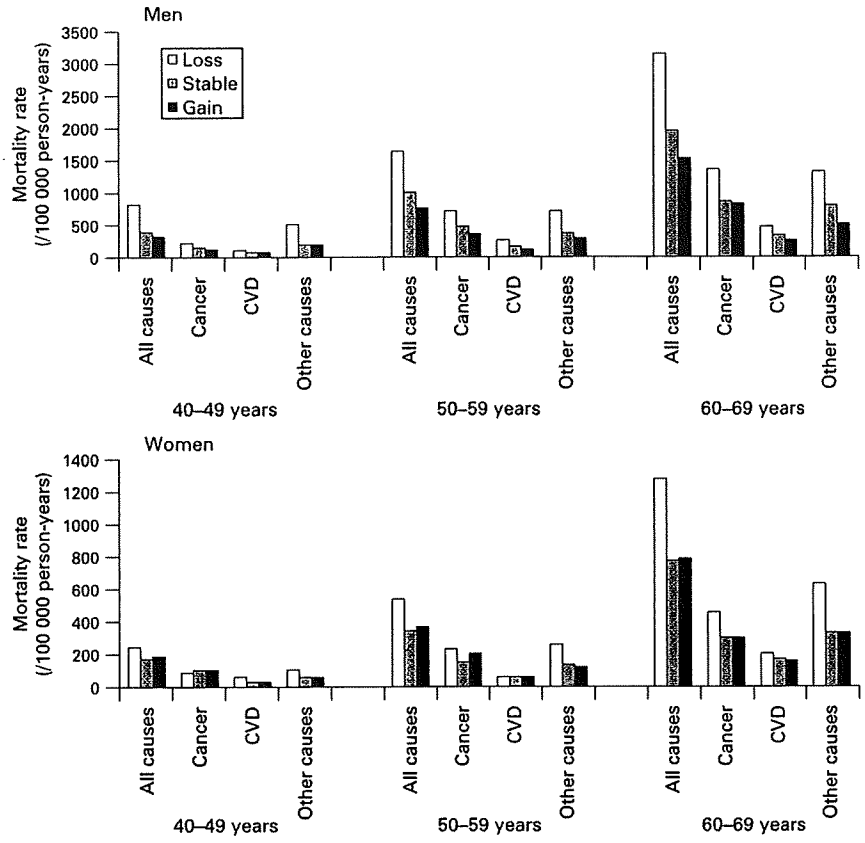

Figure 1 Sex-specific mortality rates from all causes, cancer, CVD and other causes among individuals with weight loss ≥5 kg, stable weight (change, <5 kg) and weight gain ≥5 kg since age 20 by age group.

Table 1 Population characteristics by sex and weight change categories since age 20

	Men				Women			
	Weight change since age 20				Weight change since age 20			
	Loss ≥5 kg	Stable, change <5 kg	Gain ≥5 kg	p Value	Loss ≥5 kg	Stable, change <5 kg	Gain ≥5 kg	p Value
Number	5159	14 338	22 745		5852	14 522	25 803	
Age, years	55.1	50.6	49.1	<0.001	52.1	49.4	49.9	<0.001
Baseline body mass index, kg/m²	21.5	22.0	25.0	<0.001	21.0	21.6	24.8	<0.001
Body mass index at 20,* kg/m²	24.4	21.8	21.0	<0.001	24.1	21.3	20.3	<0.001
Smoking status, %								
Non-smoker	35.5	41.0	52.4	<0.001	89.3	91.7	92.8	<0.001
<20 cigarettes/day	19.0	15.0	11.8		6.9	5.8	4.4	
≥20 cigarettes/day	45.5	43.9	35.9		3.8	2.5	2.8	
Alcohol intake, g/week	212.0	209.3	202.5	<0.05	18.0	18.1	19.7	0.189
Sports and physical exercise, %								
≥1 day/week	16.6	19.1	20.5	<0.001	15.7	19.7	18.8	<0.001
Persons who took drugs for, %								
Hypertension	13.8	8.8	12.3	<0.001	9.9	7.4	13.6	<0.001
Hyperlipidaemia	1.0	1.0	2.0	<0.001	1.7	1.5	2.4	<0.001
Diabetes	5.4	1.6	1.6	<0.001	2.1	0.8	1.2	<0.001
Gout	1.2	0.9	2.0	<0.001	0.4	0.2	0.3	0.054
Persons who had been diagnosed by a doctor with, %								
Hypertension	17.0	12.4	18.0	<0.001	10.6	9.2	16.5	<0.001
Diabetes	11.0	4.8	5.6	<0.001	3.6	1.7	2.8	<0.001
Liver disease	3.3	2.2	2.4	<0.001	1.1	0.8	0.9	<0.05
Kidney disease	2.8	2.1	1.9	<0.001	2.6	1.9	2.2	<0.001
Other illnesses†	23.8	18.6	17.3	<0.001	14.8	12.6	12.6	<0.001

*Data were available for 19 677 men and 20 786 women in cohort II.
†Includes any of asthma, allergy, stomach ulcer and gallstone.

Table 2 Sex- and age-specific number of deaths and multivariable-adjusted HRs of individuals with weight loss and weight gain since age 20 for death from all causes, cancer, CVD and other causes

		Men						Women					
		Loss ≥5 kg		Stable, change <5 kg		Gain ≥5 kg		Loss ≥5 kg		Stable, change <5 kg		Gain ≥5 kg	
Cause of death	Age group	Deaths	HR* (95% CI)	Deaths	HR	Deaths	HR* (95% CI)	Deaths	HR* (95% CI)	Deaths	HR	Deaths	HR* (95% CI)
All causes	All	1148	1.44 (1.32 to 1.56)	1530	1.0	1747	0.89 (0.82 to 0.97)	418	1.33 (1.17 to 1.52)	563	1.0	1088	0.98 (0.87 to 1.10)
	40–49	125	1.61 (1.31 to 1.98)	355	1.0	527	0.89 (0.76 to 1.05)	72	1.21 (0.91 to 1.61)	164	1.0	302	0.84 (0.68 to 1.05)
	50–59	573	1.41 (1.26 to 1.58)	788	1.0	941	0.88 (0.79 to 0.98)	209	1.33 (1.10 to 1.61)	265	1.0	599	1.01 (0.86 to 1.19)
	60–69	450	1.35 (1.16 to 1.58)	387	1.0	279	0.92 (0.77 to 1.11)	137	1.36 (1.04 to 1.74)	134	1.0	187	1.11 (0.86 to 1.44)
Cancer	All	471	1.27 (1.12 to 1.44)	678	1.0	769	0.90 (0.80 to 1.02)	162	1.17 (0.96 to 1.44)	262	1.00	546	1.04 (0.88 to 1.23)
	40–49	33	1.20 (0.82 to 1.77)	129	1.0	188	0.92 (0.70 to 1.20)	25	0.80 (0.50 to 1.26)	89	1.0	154	0.97 (0.71 to 1.31)
	50–59	244	1.27 (1.07 to 1.50)	383	1.0	434	0.84 (0.72 to 0.98)	89	1.26 (0.95 to 1.67)	123	1.0	320	1.11 (0.88 to 1.40)
	60–69	194	1.34 (1.06 to 1.68)	166	1.0	147	1.13 (0.87 to 1.46)	48	1.44 (0.95 to 2.18)	50	1.0	72	0.95 (0.62 to 1.44)
CVD	All	169	1.34 (1.09 to 1.66)	233	1.0	281	0.81 (0.66 to 0.99)	63	1.22 (0.87 to 1.71)	92	1.0	173	0.82 (0.62 to 1.10)
	40–49	16	1.19 (0.68 to 2.09)	59	1.0	89	0.82 (0.55 to 1.21)	18	1.74 (0.92 to 3.27)	25	1.0	46	0.56 (0.33 to 0.96)
	50–59	86	1.37 (1.03 to 1.84)	111	1.0	148	0.82 (0.62 to 1.10)	24	1.02 (0.60 to 1.72)	39	1.0	90	0.93 (0.61 to 1.42)
	60–69	67	1.30 (0.89 to 1.90)	63	1.0	44	0.72 (0.46 to 1.13)	21	1.12 (0.60 to 2.07)	28	1.0	37	1.18 (0.66 to 2.12)
Other causes	All	508	1.66 (1.47 to 1.89)	619	1.0	697	0.92 (0.81 to 1.05)	193	1.56 (1.27 to 1.91)	209	1.0	369	0.97 (0.80 to 1.18)
	40–49	76	2.06 (1.56 to 2.72)	167	1.0	250	0.90 (0.72 to 1.14)	29	1.60 (1.00 to 2.56)	50	1.0	102	0.91 (0.62 to 1.33)
	50–59	243	1.60 (1.34 to 1.91)	294	1.0	359	0.97 (0.81 to 1.16)	96	1.53 (1.14 to 2.04)	103	1.0	189	0.91 (0.69 to 1.20)
	60–69	189	1.39 (1.10 to 1.76)	158	1.0	88	0.78 (0.57 to 1.06)	68	1.43 (0.98 to 2.10)	56	1.0	78	1.23 (0.83 to 1.85)

*HR was adjusted for age; current body mass index; smoking status (non-smoker, <20 cigarettes/day and ≥20 cigarettes/day); alcohol intake (non-drinker, 1–23 g/day, 23–46 g/day, 46–69 g/day and ≥69 g/day); sports and physical exercise; medications or past history of hypertension and diabetes; and past history of liver disease and kidney disease stratified by JPHC communities and age groups of 40–49 years, 50–59 years and 60–69 years (only for all age groups).
CVD, cardiovascular disease.

Table 3 Sex-specific multivariable-adjusted HRs of death from all causes, cancer, CVD and other causes among subgroups of people with and without illnesses; and smokers and non-smokers

	Men						Women					
	Loss ≥5 kg		Stable, change <5 kg		Gain ≥5 kg		Loss ≥5 kg		Stable, change <5 kg		Gain ≥5 kg	
Cause of death	Deaths	HR* (95% CI)	Deaths	HR	Deaths	HR* (95% CI)	Deaths	HR* (95% CI)	Deaths	HR	Deaths	HR* (95% CI)
Without illnesses†												
All causes	468	1.46 (1.29 to 1.64)	804	1.0	856	0.96 (0.86 to 1.08)	196	1.22 (1.02 to 1.47)	335	1.0	592	0.99 (0.85 to 1.16)
Cancer	206	1.34 (1.13 to 1.62)	361	1.0	401	1.00 (0.84 to 1.18)	85	1.01 (0.77 to 1.33)	177	1.0	320	1.00 (0.81 to 1.24)
CVD	58	1.18 (0.84 to 1.65)	118	1.0	107	0.72 (0.53 to 0.99)	22	1.20 (0.71 to 2.04)	43	1.0	83	0.91 (0.60 to 1.38)
Other causes	204	1.70 (1.41 to 2.05)	325	1.0	348	1.02 (0.85 to 1.22)	89	1.51 (1.13 to 2.02)	115	1.0	189	1.04 (0.80 to 1.36)
With illnesses†												
All causes	680	1.44 (1.29 to 1.61)	726	1.0	891	0.83 (0.74 to 0.94)	222	1.50 (1.24 to 1.82)	228	1.0	496	0.97 (0.81 to 1.16)
Cancer	265	1.20 (1.01 to 1.43)	317	1.0	368	0.82 (0.69 to 0.97)	77	1.46 (1.06 to 2.00)	85	1.0	226	1.10 (0.83 to 1.45)
CVD	111	1.52 (1.15 to 2.00)	115	1.0	174	0.93 (0.71 to 1.21)	41	1.21 (0.78 to 1.88)	49	1.0	90	0.81 (0.54 to 1.21)
Other causes	304	1.69 (1.43 to 2.00)	294	1.0	349	0.83 (0.69 to 0.99)	104	1.69 (1.26 to 2.26)	94	1.0	180	0.94 (0.70 to 1.25)
Non-smokers												
All causes	347	1.46 (1.27 to 1.69)	529	1.0	815	0.95 (0.84 to 1.08)	356	1.36 (1.18 to 1.57)	493	1.0	975	0.99 (0.87 to 1.12)
Cancer	128	1.31 (1.05 to 1.65)	224	1.0	371	1.00 (0.82 to 1.21)	141	1.20 (0.97 to 1.49)	233	1.0	503	1.06 (0.89 to 1.26)
CVD	50	1.37 (0.94 to 1.98)	79	1.0	133	0.86 (0.62 to 1.19)	46	1.14 (0.77 to 1.67)	76	1.0	148	0.86 (0.62 to 1.18)
Other causes	169	1.64 (1.32 to 2.03)	226	1.0	311	0.95 (0.77 to 1.16)	169	1.61 (1.29 to 2.01)	184	1.0	324	0.95 (0.78 to 1.17)
Smokers												
All causes	790	1.43 (1.29 to 1.58)	993	1.0	926	0.86 (0.77 to 0.95)	57	1.15 (0.79 to 1.66)	68	1.0	108	0.88 (0.61 to 1.25)
Cancer	337	1.24 (1.07 to 1.44)	452	1.0	395	0.84 (0.72 to 0.98)	19	0.99 (0.54 to 1.81)	27	1.0	40	0.92 (0.51 to 1.65)
CVD	118	1.34 (1.03 to 1.73)	150	1.0	146	0.78 (0.60 to 1.02)	15	1.41(0.68 to 2.90)	16	1.0	24	0.59 (0.28 to 1.23)
Other causes	335	1.71 (1.46 to 1.99)	391	1.0	385	0.91 (0.77 to 1.07)	23	1.15 (0.62 to 2.12)	25	1.0	44	1.10 (0.62 to 1.95)

*HR was adjusted for age; current body mass index; smoking status (non-smoker, <20 cigarettes/day and ≥20 cigarettes/day); alcohol intake (non-drinker, 1–23 g/day, 23–46 g/day, 46–69 g/day and ≥69 g/day); sports and physical exercise; medications or past history of hypertension and diabetes; and past history of liver disease and kidney disease stratified by JPHC communities and age groups of 40–49 years, 50–59 years and 60–69 years.
†Includes any of hypertension, diabetes, liver disease, kidney disease, asthma, allergy, stomach ulcer and gallstone.
CVD, cardiovascular disease.

Table 4 Sex-specific multivariable-adjusted* HRs for deaths from all causes, cancer, CVD and other causes, according to weight change category since age 20 stratified by baseline BMI

			Baseline BMI, <18.5 kg/m²			Baseline BMI, 18.5–24.9 kg/m²			Baseline BMI, ≥25 kg/m²		
			Weight change since age 20			Weight change since age 20			Weight change since age 20		
Sex	Cause of death		Loss ≥5 kg	Stable, change <5 kg	Gain ≥5 kg	Loss ≥5 kg	Stable, change <5 kg	Gain ≥5 kg	Loss ≥5 kg	Stable, change <5 kg	Gain ≥5 kg
Men	All causes	Deaths	178	67	6	883	1352	920	77	100	811
		HR* (95% CI)	2.40 (2.04 to 2.82)	1.30 (1.01 to 1.68)	1.59 (0.71 to 3.56)	1.35 (1.23 to 1.47)	1.00	0.83 (0.76 to 0.90)	1.36 (1.08 to 1.72)	0.76 (0.62 to 0.94)	0.80 (0.73 to 0.88)
	Cancer	Deaths	67	25	3	374	597	410	24	48	354
		HR* (95% CI)	1.84 (1.41 to 2.39)	1.14 (0.76 to 1.70)	1.75 (0.56 to 5.45)	1.23 (1.08 to 1.41)	1.00	0.86 (0.76 to 0.98)	0.96 (0.63 to 1.44)	0.83 (0.61 to 1.13)	0.84 (0.74 to 0.97)
	CVD	Deaths	13	11	1	145	211	139	10	11	139
		HR* (95% CI)	1.18 (0.67 to 2.08)	1.32 (0.70 to 2.49)	–†	1.34 (1.07 to 1.68)	1.00	0.75 (0.60 to 0.94)	0.96 (0.51 to 1.83)	0.47 (0.25 to 0.89)	0.78 (0.62 to 0.98)
	Other causes	Deaths	98	31	2	364	544	371	43	41	318
		HR* (95% CI)	3.60 (2.88 to 4.50)	1.47 (1.01 to 2.14)	–†	1.49 (1.29 to 1.71)	1.00	0.83 (0.72 to 0.95)	1.96 (1.43 to 2.68)	0.81 (0.58 to 1.12)	0.77 (0.67 to 0.89)
Women	All causes	Deaths	79	52	9	307	462	517	26	46	554
		HR* (95% CI)	2.12 (1.66 to 2.70)	1.61 (1.21 to 2.16)	2.46 (1.22 to 4.95)	1.26 (1.08 to 1.46)	1.00	0.91 (0.80 to 1.04)	1.29 (0.86 to 1.94)	0.84 (0.62 to 1.14)	1.04 (0.91 to 1.18)
	Cancer	Deaths	29	20	6	117	220	271	13	20	265
		HR* (95% CI)	1.71 (1.15 to 2.55)	1.31 (0.83 to 2.07)	3.15 (1.30 to 7.66)	1.06 (0.84 to 1.33)	1.00	1.00 (0.83 to 1.20)	1.56 (0.89 to 2.75)	0.82 (0.52 to 1.31)	1.11 (0.92 to 1.34)
	CVD	Deaths	7	6	1	50	78	74	6	8	98
		HR* (95% CI)	1.07 (0.49 to 2.34)	0.98 (0.40 to 2.44)	–†	1.16 (0.80 to 1.68)	1.00	0.77 (0.55 to 1.07)	1.36 (0.55 to 3.39)	0.82 (0.39 to 1.71)	1.02 (0.74 to 1.39)
	Other causes	Deaths	43	26	2	140	164	172	7	18	191
		HR* (95% CI)	3.16 (2.24 to 4.46)	2.34 (1.54 to 3.54)	–†	1.56 (1.24 to 1.97)	1.00	0.86 (0.69 to 1.07)	0.96 (0.45 to 2.06)	0.87 (0.53 to 1.42)	0.95 (0.75 to 1.19)

*HR was adjusted for age; current body mass index; smoking status (non-smoker, <20 cigarettes/day and ≥20 cigarettes/day); alcohol intake (non-drinker, 1–23 g/day, 23–46 g/day, 46–69 g/day and ≥69 g/day); sports and physical exercise; medications or past history of hypertension and diabetes; and past history of liver disease and kidney disease stratified by JPHC communities and age groups of 40–49 years, 50–59 years and 60–69 years.
†Not represented because of fewer cases.
BMI, body mass index, CVD, cardiovascular disease.

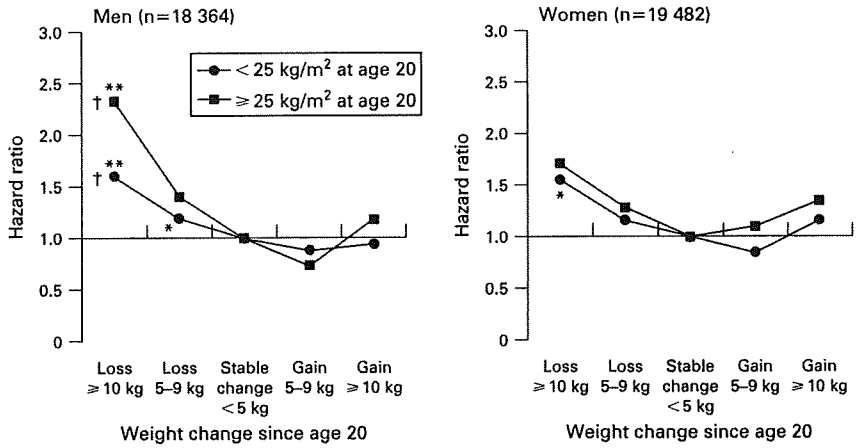

Figure 2 Multivariable-adjusted HRs of all-cause mortality according to weight change category by body mass index (BMI) at age 20 in cohort II. Covariate variables were the same as in table 2. *p<0.05; **p<0.001 for difference versus stable change group. †p<0.001 for linear trends.

and overweight men, an inverse linear association between weight gain and mortality was found (p for trend <0.001).

DISCUSSION

This large prospective cohort study confirmed a strong association between weight loss after early adulthood and all-cause mortality, death from cancer (men only), CVD (men only) and other causes. These findings applied to middle-aged Japanese men and women, regardless of whether they had illnesses, were smokers or were overweight. The HR for all-cause mortality increased with weight loss in each age group and for other causes of death, and was higher in the younger bracket for men and women with weight loss. Further, when subjects were stratified by BMI at baseline or age 20, the association between weight loss and death was the same. On the contrary, weight gain seemed to be protective against mortality in men. These findings remained unchanged after exclusion of the first 5 years of follow-up, which was done to avoid a potential effect of latent diseases. The previous JPHC study reported that both overweight and underweight subjects at baseline had an increased risk of death, representing a U-shaped association. Furthermore, mortality was higher for individuals who were underweight rather than overweight when considered with weight change.[12]

Of interest, weight gain did not predict CVD mortality in the JPHC cohort. Compared with Caucasians, mean BMI is very low in Japanese individuals, leading to a low level of high-sensitivity C-reactive protein,[17] a low grade of atherosclerosis,[18] and one-quarter the mortality from coronary heart disease.[19] Recently, data from this cohort documented that men with high BMIs or with weight gain ≥10 kg who were relatively lean (<21.7 kg/m²) at age 20 were at risk for coronary heart disease,[20] although there were no linear trends between weight gain and risk. Given these previous findings and the significant association between weight loss and death as seen in the present study, it may be hypothesised that obesity-induced atherosclerosis may be rather uncommon in Japan. Instead, we believe that hypertension is an essential factor for atherosclerosis more than other traditional risk factors, as pathological studies have documented.[21 22] These data support our results and suggest two different pathogenic mechanisms of atherosclerosis in Japanese and Caucasians.

The underlying mechanism responsible for the association between weight loss and the risk of death is not fully understood. In general, weight loss is considered to be caused by several physical conditions, such as nutrient deficiency related to liver disease, heavy alcohol drinking, smoking and worsening diabetes. Therefore, even though we adjusted for these confounders in the analysis of multivariable models, the associations still remained. Also, a British study emphasised the effect of smoking on weight change and mortality.[23] In the present study, when subjects were stratified by smoking conditions (current smokers or others), there was an increased risk of death for those with weight loss regardless of smoking habits and no interactions between smoking and weight loss with mortality. People who lost weight may have had underlying health problems or illnesses related to weight loss, although we evaluated several illnesses in this study.

The JPHC study has the advantage of providing large cohorts and assesses the effects of numerous variables on health practices. However, several limitations should be noted. First, we calculated BMIs according to self-reported weight and height values. When analysed in the subgroup in which health check-up data were available, measured BMI almost corresponded to self-reported BMI (r = 0.89 in men and 0.91 in women), as described elsewhere.[12] Second, weight at age 20 was not validated in our study, in spite of the high rank correlation coefficient for self-reported weight; however, a previous study in Japan validated the use of recalled weight for epidemiological studies.[24] Because men with higher BMI tended to underestimate their weights at age 25, a bias for weight change was expected to be large for those individuals. This potential classification bias may weaken the association between weight gain and risk of death among obese people. Third, covariates in our study might not be sufficient to explain the association between weight loss and mortality, because weight change, especially weight loss, is thought to be related to several conditions of illness or an unfavourable lifestyle. Furthermore, we did not exclude people with intentional weight loss in our analysis. Fourth, the specific cause of death was not validated in this study. Validation studies in Japan indicated that diagnoses of death from cancer and stroke were generally correct, but those of death from coronary heart disease were not.[25] Therefore, potential diagnostic bias on death certificates for coronary heart disease was real in the present study.

In conclusion, although there is no doubt that weight gain elevates the risks of atherosclerosis and CVD,[26] we found an inverse relationship in men and an L-shaped association in

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 ($\geq$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.

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Conflict of interest: none.

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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-

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

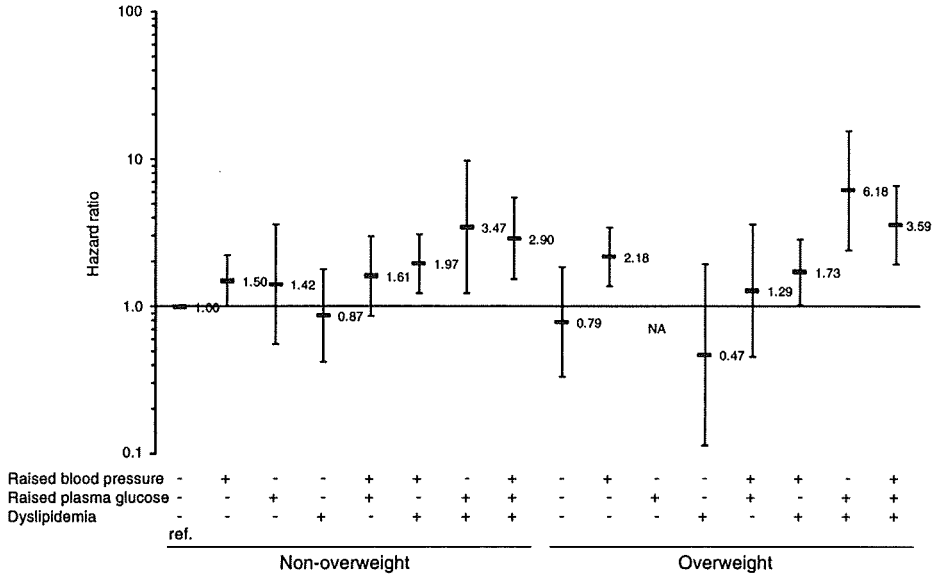

Figure. Multivariate adjusted hazard ratios for cardiovascular disease mortality of clustering of metabolic components in the combined data of men and women, grouped according to overweight category. The hazard ratios were calculated using subjects who were not overweight with no risks as the reference 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![11] 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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