

Weight Change and Mortality from Cardiovascular Diseases: The Japan Collaborative Cohort Study

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Aim: The aim of this study was to assess the association between weight change and mortality due to cardiovascular diseases (CVDs) in a Japanese population.

Methods: We used the data of a population-based prospective cohort study that was conducted from 1988 to 1990 in 45 areas throughout Japan. Among a total of 69,681 men and women aged 40–79 with no history of CVD or cancer at baseline, the association between weight change from 20 years of age to baseline and CVD-related mortality was evaluated.

Results: During a median follow-up period of 19.1 years, we observed 4,274 deaths from total CVD. After adjusting for age, sex, and other potential confounding factors, compared with participants with a weight change of <2.5 kg (stable weight), participants with a greater weight change (either loss or gain) had an increased risk of mortality from total CVD (U-shaped association). The hazard ratios for the total CVD risk in participants with a weight loss and a weight gain of ≥ 12.5 kg were 1.50 (95% confidence interval [CI], 1.30–1.72) and 1.21 (95% CI, 1.07–1.36), respectively. The associations between weight change and risk of mortality from ischemic heart disease or stroke showed similar trends. The risk of intracerebral hemorrhage was associated with weight loss only. Weight change was not associated with mortality from subarachnoid hemorrhage.

Conclusions: Weight loss or gain could be a risk factor for mortality from total or ischemic CVD, while weight loss could be a risk factor for intracerebral hemorrhage.

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Key words: Weight change, Ischemic coronary heart disease, Ischemic stroke, Intracerebral hemorrhage, Cohort study

Introduction

Body weight fluctuation has been suggested to be a risk factor for cardiovascular diseases (CVDs). Weight gain is a well-known risk factor for coronary heart disease and venous thromboembolism¹⁻⁴, while weight loss has been reported to be associated with heart failure⁵. Whether weight gain, loss, or both is associated with CVDs may depend on the type of CVD.

Previous studies on the association between weight change and CVD-related mortality are mainly from Western countries⁶⁻¹¹, and there is limited evidence in Asian populations¹², whose epidemiologic characteristics are different from those of Western populations. For example, hemorrhagic stroke is more common and ischemic heart disease is less common in Asian individuals than in Western individuals¹³⁻¹⁵. Obesity levels in the general population are also different, with overweight and obesity, defined as a body

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mass index (BMI) of 25 to <30 kg/m² and ≥ 30 kg/m², prevalence of 23.0% and 3.0% in Japan and 34.0% and 30.2% in the United States, respectively¹⁶.

Therefore, the aim of this study was to assess the association between weight change and mortality from total and type-specific CVD in a Japanese-population-based cohort study.

Methods

Study Population

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study), sponsored by the Ministry of Education, Culture, Sports, Science and Technology, conducted a baseline survey from 1988 to 1990 in 45 areas throughout Japan. Participants completed self-administered questionnaires concerning their lifestyle and history of CVD and cancer. Details of this survey have been described previously¹⁷. These participants comprised 110,585 individuals (46,395 men and 64,190 women) aged 40–79, of whom height and weight data were available for 73,466 (31,323 men and 42,143 women). A total of 3,785 participants (1,704 men and 2,081 women) with a history of CVD or cancer were excluded because of the potential influence of these comorbidities on the outcomes. Ultimately, 69,681 individuals (29,619 men and 40,062 women) were evaluated in this study. Informed consent was obtained from the individuals or mayors before participating in the study. The Ethics Committees of Nagoya University School of Medicine and Osaka University Graduate School of Medicine approved the study protocol.

Mortality Surveillance

Mortality surveillance was conducted systematically by reviewing death certificates, all of which were forwarded by the centers that serviced the individuals who died. Mortality data were then centralized at the Ministry of Health and Welfare, and the underlying causes of death were coded for the National Vital Statistics according to the International Classification of Diseases, 10th Revision (ICD-10). Registration of death is required by the Family Registration Law in Japan. Participants were followed up until death or the end of 2009, except for four areas in 1999, four areas in 2003, and two areas in 2008, where follow-up had been terminated. Deaths from various diseases were defined by ICD-10 codes as follows: CVD, I00 to I99; ischemic heart disease, I20 to I25; total stroke, I60 to I69; ischemic stroke, I63 or I69.3; intracerebral hemorrhage, I61 or I69.1; and subarachnoid hemorrhage, I60 or I69.0. The participants were treated as censored when moving from the community or at the

end of the follow-up for reasons other than death.

Weight Change and BMI

All participants provided information on weight at 20 years of age and weight and height at baseline using a self-administered questionnaire. Weight change was defined as the difference between the data from 20 years of age to baseline. BMI was calculated as weight (kg) divided by height squared (m²). The absolute value of weight change (kg) was categorized as follows: -12.5 or more, -10.0 to -12.4 , -7.5 to -9.9 , -5.0 to -7.4 , -2.5 to -4.9 , -2.4 to $+2.4$, $+2.5$ to $+4.9$, $+5.0$ to $+7.4$, $+7.5$ to $+9.9$, $+10.0$ to $+12.4$, and $+12.5$ or more. Participants with a weight change of <2.5 kg (stable weight) were considered the reference.

Statistical Analysis

The age- and sex-adjusted mean values and proportions of the baseline characteristics were compared across weight change groups using a linear regression analysis for continuous variables and a logistic regression analysis for categorical variables. The person-years of follow-up for each participant were calculated from the baseline in 1988 to 1990 to the first censoring.

The age-, sex-, and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards models. The adjusted variables included age (continuous), sex, alcohol intake (never, former, or current drinker with ethanol intake of 1–22, 23–45, 46–68, or ≥ 69 g per day), smoking status (never, former, or current smoker with 1–19 or ≥ 20 cigarettes per day), educational level (primary school, junior high school, high school, or college or higher), sleep duration (<6.0 , 6.0–6.9, 7.0–7.9, 8.0–8.9, or ≥ 9 h/day), walking (almost never, about 30, 30–60, or ≥ 60 min per day), and exercise (almost never, 1–2, 3–4, or ≥ 5 h/week) in Model 1 and, additionally, the history of diabetes (yes/no) and hypertension (yes/no) in Model 2. Hypertension was defined as ≥ 140 mmHg of reported systolic blood pressure, ≥ 90 mmHg of reported diastolic blood pressure, and/or antihypertensive medication use. We did not have information on the history of dyslipidemia. Because we found no statistically significant interaction between sex and exposure in relation to total and type-specific CVD mortality, analyses pooled across sexes were conducted. For sensitivity analysis, the models were rerun in the multivariable models further included BMI at the age of 20 years and after excluding participants who died within five years from baseline to avoid reverse causality.

Two-sided *P*-values of <0.05 were considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc.,

Table 1. Age- and sex-adjusted mean values and proportion of characteristics according to the quintile of weight change

	Weight change, kg											P for trend
	-12.5 or more	-10 to -12.4	-7.5 to -9.9	-5.0 to -7.4	-2.5 to -4.9	-2.4 to +2.4	+2.5 to +4.9	+5.0 to +7.4	+7.5 to +9.9	+10 or +12.4	+12.5 or more	
Number at risk	1,894	2,529	2,428	7,766	6,575	14,600	6,386	9,661	4,466	5,852	7,524	
Men, %	54.3***	49.5***	43.2*	45.5	40.9***	45.8	37.8***	39.3***	36.9***	41.4***	41.1***	<0.001
Age, years	65.5***	64.0***	61.8***	60.7***	57.9***	55.6	54.5***	54.6***	54.2***	54.6***	54.6***	<0.001
Body mass index at 20 ages, g/m ²	27.2***	24.7***	24.0***	23.4***	22.8***	21.9	21.4***	21.1***	20.9***	20.6***	20.0***	<0.001
Body mass index at baseline, kg/m ²	19.7***	20.3***	20.5***	21.0***	21.3***	21.9	22.8***	23.6***	24.3***	25.0***	27.0***	<0.001
Current smoker, %	37.9***	35.6***	33.3***	31.7***	28.4*	27.3	23.6***	23.6***	22.5***	22.7***	23.2***	<0.001
Current drinker, %	43.6*	44.0*	45.4	45.6	46.0	46.2	47.1	47.0	46.8	47.7*	46.6	<0.001
Hypertension, %	33.8***	33.9***	35.0**	37.6	37.2	38.6	41.9***	46.0***	49.2***	51.7***	59.4***	<0.001
History of diabetes, %	6.2**	5.0	4.3	4.9	4.1	4.3	4.8	4.9*	4.9	5.2**	7.2***	<0.001
Walking 30+ minutes/day, %	71.1	72.8	71.3	72.8	72.9	73.0	72.3	69.4***	67.9***	67.2***	64.2***	<0.001
Sports 1+ hours/week, %	24.9*	25.5*	27.0	26.0*	25.6**	27.5	29.7**	28.1	27.9	28.6	26.7	<0.001
High perceived mental stress, %	25.2***	23.3**	24.2***	22.0*	20.5	20.6	21.2	21.6	21.1	22.7**	24.3***	<0.05
College or higher education, %	11.8*	11.8**	11.7**	12.1***	12.6*	13.9	15.3*	15.8***	15.1	15.6**	14.4	<0.001

P for difference in each category in reference to the middle category (-2.4 to +2.4 kg) (*, <0.05; **, <0.01; ***, <0.001).

Cary, NC, USA).

Results

Table 1 shows the distributions of the participants according to the weight change categories. Across the weight change categories from the extreme category of weight loss to the extreme category of weight gain, the participants were more likely to be younger, to have a lower BMI at 20 years of age and a higher BMI at baseline, to have an educational level of college or higher, and to be current alcohol drinkers, but they were less likely to be current smokers.

During a median follow-up of 19.1 years, we observed 4,274 deaths from total CVD, including 924 from ischemic heart disease, 1,849 from total stroke (1,018 from ischemic stroke, 498 from intracerebral hemorrhage, and 264 from subarachnoid hemorrhage), and 1,501 from other CVDs.

The cause-specific HRs for mortality after adjusting for age, sex, and other potential confounding factors are shown in **Table 2**. The age- and sex-adjusted model showed that, compared with participants with stable weight, participants with greater weight change (either loss or gain) had an increased risk of mortality from total CVD (U-shaped association). Further adjustments for other potential confounding factors did not alter the association. In the final model, the HRs for total CVD mortality in participants with a weight loss or gain of ≥ 10 kg were 1.45 (95% CI, 1.28–1.66) in the -10.0 to -12.4 kg group, 1.50 (95% CI, 1.30–1.72) in the -12.5 kg or more group,

1.05 (95% CI, 0.92–1.21) in the +10.0 to +12.4 kg group, and 1.21 (95% CI, 1.07–1.36) in the +12.5 kg or more group.

The association between weight change and the risk of mortality from ischemic heart disease also showed a U-shaped association. In the final model, the HRs for the risk of ischemic heart disease in participants with a weight loss or gain of ≥ 10 kg were 1.48 (95% CI, 1.10–1.99) in the -10.0 to -12.4 kg group, 1.33 (95% CI, 0.95–1.86) in the -12.5 kg or more group, 1.32 (95% CI, 0.99–1.77) in the +10.0 to +12.4 kg group, and 1.62 (95% CI, 1.26–2.08) in the +12.5 kg or more group.

The association between weight change and the risk of total stroke showed a reverse J-shaped pattern. In the final model, the HRs for total stroke mortality in participants with a weight loss of ≥ 10 kg were 1.40 (95% CI, 1.15–1.70) in the -10.0 to -12.4 kg group and 1.56 (95% CI, 1.27–1.91) in the -12.5 kg or more group. The association between weight change and mortality from ischemic stroke showed a U-shaped association, but the risk in participants with a weight gain was attenuated after adjusting for other potential confounding factors. The association between weight change and mortality from intracerebral hemorrhage showed statistical significance only in participants with a weight loss of ≥ 10 kg, with HRs of 1.41 (95% CI, 0.95–2.07) and 1.74 (95% CI, 1.17–2.59) in the -10.0 to -12.4 kg and -12.5 kg or more groups, respectively. Weight change was not associated with mortality from subarachnoid hemorrhage.

Table 2. Hazard ratios (HRs) and 95% confidence intervals (CIs) of mortality according to weight change at the baseline age from 20 years old

	Weight change, kg										
	-12.5 or more	-10.0 to -12.5	-7.5 to -9.9	-5.0 to -7.4	-2.5 to -4.9	-2.4 to +2.4	+2.5 to +4.9	+5.0 to +7.4	+7.5 to +9.9	+10.0 to +12.4	+12.5 or more
Person-years at risk	24,733	35,993	36,504	121,389	106,625	242,940	107,142	162,936	74,461	97,616	124,107
Total CVD											
No. of deaths	272	334	231	707	449	760	252	420	165	273	411
Age- and sex-adjusted HR	1.55 (1.35-1.79)	1.45 (1.27-1.65)	1.23 (1.06-1.43)	1.17 (1.06-1.30)	1.13 (1.01-1.27)	1.00	0.91 (0.79-1.06)	1.01 (0.89-1.13)	0.92 (0.78-1.09)	1.10 (0.96-1.27)	1.33 (1.18-1.50)
Multivariable HR ¹	1.45 (1.26-1.66)	1.38 (1.21-1.57)	1.17 (1.01-1.36)	1.14 (1.03-1.27)	1.13 (1.01-1.27)	1.00	0.95 (0.82-1.09)	1.02 (0.90-1.15)	0.95 (0.80-1.13)	1.12 (0.98-1.29)	1.34 (1.19-1.51)
Multivariable HR ²	1.50 (1.30-1.72)	1.45 (1.28-1.66)	1.20 (1.03-1.39)	1.15 (1.04-1.28)	1.14 (1.02-1.29)	1.00	0.92 (0.80-1.06)	0.98 (0.87-1.10)	0.91 (0.77-1.07)	1.05 (0.92-1.21)	1.21 (1.07-1.36)
Ischemic heart disease											
No. of deaths	45	63	50	149	104	147	58	99	35	66	108
Age- and sex-adjusted HR	1.39 (1.00-1.95)	1.48 (1.10-2.00)	1.45 (1.05-2.00)	1.32 (1.05-1.65)	1.39 (1.08-1.78)	1.00	1.10 (0.81-1.49)	1.24 (0.96-1.60)	1.02 (0.70-1.47)	1.38 (1.04-1.85)	1.82 (1.42-2.34)
Multivariable HR ¹	1.28 (0.92-1.80)	1.40 (1.04-1.88)	1.36 (0.99-1.88)	1.29 (1.03-1.62)	1.39 (1.08-1.79)	1.00	1.14 (0.84-1.54)	1.25 (0.97-1.61)	1.05 (0.72-1.51)	1.41 (1.05-1.89)	1.83 (1.42-2.35)
Multivariable HR ²	1.33 (0.95-1.86)	1.48 (1.10-1.99)	1.40 (1.01-1.93)	1.30 (1.03-1.64)	1.40 (1.09-1.80)	1.00	1.10 (0.81-1.49)	1.20 (0.93-1.55)	0.99 (0.69-1.44)	1.32 (0.99-1.77)	1.62 (1.26-2.08)
Total stroke											
No. of deaths	131	148	97	293	176	351	112	181	72	118	170
Age- and sex-adjusted HR	1.61 (1.32-1.98)	1.38 (1.14-1.68)	1.11 (0.89-1.40)	1.05 (0.90-1.23)	0.96 (0.80-1.15)	1.00	0.88 (0.71-1.08)	0.93 (0.78-1.12)	0.87 (0.67-1.12)	1.03 (0.83-1.27)	1.19 (0.99-1.43)
Multivariable HR ¹	1.50 (1.22-1.84)	1.33 (1.09-1.61)	1.06 (0.85-1.33)	1.02 (0.87-1.19)	0.96 (0.80-1.15)	1.00	0.91 (0.73-1.13)	0.95 (0.79-1.14)	0.89 (0.69-1.15)	1.05 (0.85-1.30)	1.19 (0.99-1.43)
Multivariable HR ²	1.56 (1.27-1.91)	1.40 (1.15-1.70)	1.09 (0.87-1.36)	1.03 (0.88-1.21)	0.97 (0.81-1.16)	1.00	0.88 (0.71-1.09)	0.91 (0.76-1.09)	0.85 (0.66-1.10)	0.98 (0.80-1.21)	1.07 (0.89-1.29)
Ischemic stroke											
No. of deaths	76	93	67	179	80	182	59	93	35	62	92
Age- and sex-adjusted HR	1.54 (1.18-2.02)	1.45 (1.13-1.87)	1.37 (1.03-1.81)	1.13 (0.92-1.39)	0.82 (0.63-1.06)	1.00	0.94 (0.70-1.26)	0.99 (0.77-1.27)	0.89 (0.62-1.27)	1.13 (0.84-1.50)	1.35 (1.05-1.74)
Multivariable HR ¹	1.42 (1.09-1.87)	1.40 (1.09-1.81)	1.30 (0.98-1.73)	1.09 (0.89-1.34)	0.82 (0.63-1.06)	1.00	0.99 (0.74-1.34)	1.00 (0.78-1.29)	0.92 (0.64-1.32)	1.16 (0.87-1.55)	1.37 (1.06-1.76)
Multivariable HR ²	1.48 (1.13-1.94)	1.50 (1.17-1.93)	1.33 (1.01-1.77)	1.11 (0.90-1.37)	0.83 (0.63-1.08)	1.00	0.96 (0.72-1.29)	0.96 (0.75-1.24)	0.88 (0.61-1.27)	1.09 (0.82-1.46)	1.23 (0.96-1.59)
Intracerebral hemorrhage											
No. of deaths	34	36	15	68	67	99	33	50	21	33	42
Age- and sex-adjusted HR	1.77 (1.19-2.63)	1.40 (0.95-2.06)	0.69 (0.40-1.19)	0.96 (0.70-1.31)	1.36 (0.99-1.85)	1.00	0.89 (0.60-1.32)	0.88 (0.63-1.24)	0.85 (0.53-1.37)	0.97 (0.66-1.45)	0.99 (0.69-1.42)
Multivariable HR ¹	1.67 (1.13-2.49)	1.34 (0.91-1.97)	0.66 (0.38-1.13)	0.94 (0.69-1.28)	1.37 (1.00-1.86)	1.00	0.91 (0.61-1.35)	0.90 (0.64-1.26)	0.87 (0.54-1.40)	0.99 (0.67-1.47)	0.98 (0.68-1.41)
Multivariable HR ²	1.74 (1.17-2.59)	1.41 (0.95-2.07)	0.67 (0.39-1.16)	0.95 (0.69-1.29)	1.38 (1.01-1.88)	1.00	0.89 (0.60-1.32)	0.86 (0.61-1.21)	0.83 (0.52-1.33)	0.92 (0.62-1.36)	0.88 (0.61-1.27)

(Cont. Table 2)

	Weight change, kg										
	-12.5 or more	-10.0 to -12.5	-7.5 to -9.9	-5.0 to -7.4	-2.5 to -4.9	-2.4 to +2.4	+2.5 to +4.9	+5.0 to +7.4	+7.5 to +9.9	+10.0 to +12.4	+12.5 or more
Subarachnoid hemorrhage											
No. of deaths	11	14	11	33	23	62	19	32	12	20	27
Age- and sex-adjusted HR	1.11 (0.58-2.12)	1.02 (0.57-1.83)	0.86 (0.45-1.64)	0.82 (0.54-1.26)	0.75 (0.46-1.21)	1.00	0.73 (0.43-1.21)	0.80 (0.52-1.23)	0.67 (0.36-1.24)	0.84 (0.51-1.40)	0.89 (0.57-1.40)
Multivariable HR ¹	1.02 (0.53-1.95)	0.95 (0.53-1.71)	0.82 (0.43-1.56)	0.79 (0.52-1.21)	0.74 (0.46-1.20)	1.00	0.74 (0.44-1.25)	0.82 (0.54-1.26)	0.69 (0.37-1.29)	0.86 (0.52-1.43)	0.92 (0.58-1.45)
Multivariable HR ²	1.05 (0.55-2.02)	0.99 (0.55-1.78)	0.84 (0.44-1.61)	0.79 (0.52-1.21)	0.75 (0.46-1.21)	1.00	0.73 (0.43-1.21)	0.78 (0.51-1.20)	0.65 (0.35-1.21)	0.79 (0.48-1.31)	0.81 (0.51-1.28)
Other CVD											
No. of deaths	96	123	84	265	169	262	82	140	58	89	133
Age- and sex-adjusted HR	1.56 (1.23-1.97)	1.51 (1.22-1.87)	1.27 (1.00-1.63)	1.25 (1.05-1.49)	1.22 (1.01-1.48)	1.00	0.86 (0.67-1.11)	0.97 (0.79-1.19)	0.94 (0.71-1.25)	1.05 (0.82-1.33)	1.26 (1.02-1.55)
Multivariable HR ¹	1.45 (1.14-1.84)	1.43 (1.15-1.78)	1.21 (0.95-1.55)	1.22 (1.02-1.45)	1.22 (1.01-1.48)	1.00	0.89 (0.69-1.14)	0.98 (0.80-1.21)	0.97 (0.73-1.30)	1.06 (0.83-1.35)	1.26 (1.03-1.56)
Multivariable HR ²	1.50 (1.19-1.91)	1.50 (1.21-1.87)	1.24 (0.97-1.59)	1.23 (1.04-1.46)	1.24 (1.02-1.50)	1.00	0.87 (0.68-1.11)	0.95 (0.77-1.17)	0.94 (0.70-1.25)	1.00 (0.79-1.28)	1.16 (0.94-1.43)

CVD, cardiovascular disease.

Multivariable HR¹ were adjusted for age, sex, smoking, drinking, education level, walking, sports, sleep duration, and perceive mental stress.Multivariable HR² were further adjusted for hypertension and history of diabetes.

Only weight loss was associated with an increased risk of other CVDs, with HRs of 1.50 (95% CI, 1.21–1.87) in the –10.0 to –12.4 kg group and 1.50 (95% CI, 1.19–1.91) in the –12.5 kg or more group. Within these other CVDs, the corresponding HRs for mortality from heart failure, defined with an ICD-10 code of I50, were 1.39 (95% CI, 1.02–1.89) in the –10.0 to –12.4 kg group and 1.37 (95% CI, 0.98–1.91) in the –12.5 kg or more group (data not shown).

When we additionally adjusted for the BMI at 20 years of age, the HRs for total CVD were almost the same: 1.51 (1.30–1.75) in the –12.5 kg or more group and 1.20 (1.06–1.36) in the +12.5 kg or more group (**Supplemental Table 1**). These associations were not substantially altered when deaths within five years were excluded from the analysis (data not shown in Table).

Discussion

We investigated the association between weight change and mortality from CVD and type of CVD in a Japanese-population-based prospective cohort study and found that weight loss, gain, or both was associated with an increased risk of CVD, depending on the type of CVD. There were U-shaped associations for

mortality from total CVD, ischemic heart disease, and ischemic stroke; an inverse J-shaped association for mortality from total stroke; and an evident association in weight loss categories only for intracerebral hemorrhage.

The association between weight change and total CVD showed a U-shaped association, which mainly reflected the associations of weight change with ischemic heart disease and probably ischemic stroke. Our study extended the current evidence regarding the association between weight change and CVD mortality using more refined categories of weight change by 2.5 kg compared with a previous report using categories of weight change by 5.0 kg⁵. Previous studies reported the associations of weight gain with the risk of coronary heart disease^{2, 4} and ischemic stroke¹⁸. However, there has been no report on the long-term effect of weight loss on the risk of ischemic heart disease and stroke. Only the short-term effects have been reported, which suggest a positive association².

Weight gain in addition to high blood pressure, high cholesterol level, and high glucose level is a known risk factor for fatal or nonfatal CVDs, including ischemic heart disease and stroke¹⁹. As for the association between weight loss and total CVD mortality, our result is consistent with previous studies^{6, 7}. The presence of weight loss might indicate muscle loss

according to aging rather than body fat loss (i.e., frailty and sarcopenia), which has been suggested to be a risk factor for CVD²⁰).

The reverse J-shaped association between weight change and total stroke mortality probably reflects the mixed pattern of the increased risk of mortality from intracerebral hemorrhage seen only in weight loss categories and the U-shaped association of weight change with ischemic stroke mortality. Weight loss could be associated with low cholesterol level, which has been reported to be a potential risk factor for intracerebral hemorrhage²¹).

The association between weight loss and other CVDs may reflect the increased risk of mortality from heart failure, as we previously reported⁵). A previous cohort study of middle-aged men and women in Norway supported the higher risk of heart failure events in patients with weight loss compared with stable weight after adjusting for the BMI²²). Studies on patients with heart failure showed that the BMI is inversely associated with the risk of total mortality during hospital admission²³), 30-day and one-year follow-up²⁴), and two-year follow-up²⁵). Although we excluded participants with a history of CVD and those who experienced early death from this analysis, we cannot completely negate the possibility of reverse causality.

There are several limitations in this study. First, weight change was calculated on the basis of a self-reported questionnaire, which might have led to an underestimation of weight and an overestimation of height. However, as self-reported height and weight are highly correlated with measured height and weight in the Japanese population²⁶), the misclassification of weight change might be small. Second, we used recalled data regarding weight at 20 years of age. However, a high correlation between recalled weight at 25 years of age and the actual measured weight was shown in a validation study ($r=0.85$)²⁷). Third, weight reflects not only fat mass, but also lean body mass and muscle mass, and we could not evaluate which body component changes affected the association with CVD risk. Fourth, our results showed that weight change in either direction (loss or gain) could affect the risk of CVD mortality in the Japanese population. Potential mediators such as hypertension and history of diabetes were less likely to affect our findings because the adjustment for these factors did not alter the HRs substantially. Finally, we did not have information on dyslipidemia, which may be a potential confounding or intermediate factor. Further studies are needed to justify the biological mechanisms that explain the association between weight loss and CVD outcomes, especially considering the different CVD profiles and body weight (BMI) distributions between

Japanese and western populations²⁸).

In conclusion, our prospective cohort study suggested that weight loss or gain could be a risk factor for mortality from total and ischemic CVD, whereas weight loss could be a risk factor for intracerebral hemorrhage.

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Conflicts of Interest

The authors declare no conflict of interest.

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Supplement Table 1. Hazard ratios (HRs) and 95% confidence intervals (CIs) of mortality according to weight change at the baseline age from 20 years old

	Weight change, kg										
	-12.5 or more	-10.0 to -12.5	-7.5 to -9.9	-5.0 to -7.4	-2.5 to -4.9	-2.4 to +2.4	+2.5 to +4.9	+5.0 to +7.4	+7.5 to +9.9	+10.0 to +12.4	+12.5 or more
Multivariable HR											
Total CVD	1.51 (1.30-1.75)	1.46 (1.28-1.67)	1.20 (1.04-1.40)	1.16 (1.04-1.28)	1.15 (1.02-1.29)	1.00	0.92 (0.80-1.06)	0.98 (0.87-1.10)	0.91 (0.76-1.07)	1.05 (0.92-1.21)	1.20 (1.06-1.36)
Ischemic heart disease	1.26 (0.89-1.79)	1.43 (1.06-1.94)	1.38 (0.99-1.90)	1.28 (1.02-1.61)	1.39 (1.08-1.79)	1.00	1.10 (0.81-1.49)	1.21 (0.93-1.56)	1.00 (0.69-1.45)	1.34 (1.00-1.79)	1.65 (1.28-2.13)
Total stroke	1.62 (1.30-2.02)	1.43 (1.17-1.75)	1.10 (0.88-1.39)	1.05 (0.89-1.22)	0.97 (0.81-1.17)	1.00	0.88 (0.71-1.09)	0.90 (0.75-1.08)	0.84 (0.65-1.09)	0.97 (0.79-1.20)	1.05 (0.87-1.27)
Ischemic stroke	1.45 (1.09-1.92)	1.48 (1.14-1.92)	1.32 (1.00-1.76)	1.10 (0.90-1.36)	0.82 (0.63-1.07)	1.00	0.96 (0.72-1.29)	0.97 (0.75-1.24)	0.89 (0.62-1.27)	1.10 (0.82-1.47)	1.25 (0.97-1.61)
Intracerebral hemorrhage	2.00 (1.30-3.07)	1.52 (1.02-2.27)	0.71 (0.41-1.23)	0.99 (0.72-1.35)	1.41 (1.03-1.92)	1.00	0.88 (0.59-1.30)	0.84 (0.60-1.19)	0.80 (0.50-1.29)	0.88 (0.59-1.32)	0.83 (0.57-1.20)
Subarachnoid hemorrhage	1.35 (0.67-2.69)	1.14 (0.62-2.09)	0.94 (0.49-1.81)	0.86 (0.55-1.32)	0.78 (0.48-1.26)	1.00	0.70 (0.42-1.18)	0.75 (0.49-1.16)	0.61 (0.33-1.14)	0.74 (0.44-1.23)	0.72 (0.45-1.15)
Other CVD	1.52 (1.19-1.96)	1.52 (1.21-1.89)	1.24 (0.97-1.60)	1.24 (1.04-1.47)	1.24 (1.02-1.51)	1.00	0.87 (0.68-1.11)	0.95 (0.77-1.16)	0.93 (0.70-1.24)	1.00 (0.78-1.27)	1.15 (0.93-1.42)

CVD, cardiovascular disease.

Multivariable HR were adjusted for age, sex, smoking, drinking, education level, walking, sports, sleep duration, and perceive mental stress, hypertension, history of diabetes, and BMI at age 20 years.