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Weight Change Since Age 20 and the Risk of Cardiovascular Disease Mortality: A Prospective Cohort Study

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Aim: Weight change could have many health outcomes. This study aimed to investigate the association between weight change and mortality risk due to total cardiovascular disease (CVD), ischemic heart disease (IHD), and stroke among Japanese.

Methods: We used Suita Study data from 4,746 people aged 30-79 years in this prospective cohort study. Weight change was defined as the difference between baseline weight and weight at age 20. We used Cox proportional hazards models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) of total CVD, IHD, and stroke mortality for 1) participants with a weight change (>10, 5 to 10, -5 to -10, and <-10 kg) compared to those with stable weight (-4.9 to 4.9 kg) and 2) participants who moved from one body mass index category (underweight, normal weight, or overweight) to another compared to those with normal weight at age 20 and baseline.

Results: Within a median follow-up period of 19.9 years, the numbers of total CVD, IHD, and stroke mortality were 268, 132, and 79, respectively. Weight loss of >10 kg was associated with the increased risk of total CVD mortality 2.07 (1.29, 3.32) and stroke mortality 3.02 (1.40, 6.52). Moving from normal weight at age 20 to underweight at baseline was associated with the increased risk of total CVD, IHD, and stroke mortality: 1.76 (1.12, 2.77), 2.10 (1.13, 3.92), and 2.25 (1.05, 4.83), respectively.

Conclusion: Weight loss, especially when moving from normal to underweight, was associated with the increased risk of CVD mortality.

Key words: Weight gain, Weight loss, Cardiovascular diseases, Stroke, Mortality, Japan

1. Introduction

The substantial decline of cardiovascular disease (CVD) mortality in Japan and high-income countries has been hailed as a public health success throughout previous decades[1-3]. However, recently, this decline has slowed[4] alongside the increasing overweight rates in these countries[5, 6].

Being overweight is an established risk factor for CVD morbidity and mortality in Japanese[7-12] and non-Japanese populations[13-17]. Being underweight is also associated with an increased risk of several CVD events[10, 11]. There are nationwide weight management services and programs in Japan and other high-income countries to reduce the CVD burden attributed to overweight and underweight[18-21].

Accumulating evidence, however inconclusive, has associated weight gain and weight loss with the

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risk of CVD events. For example, some studies showed increased CVD risk with weight gain but not weight loss[22-27], some studies with weight loss but not weight gain[28-33], some studies with both weight gain and weight loss[34-40], and some studies with neither weight gain nor weight loss[41-44]. In addition to the inconsistent results, most studies assessed weight change within a short period that might not be similar to weight change within a long period. While weight gain can increase CVD risk via inducing dyslipidemia, atherosclerosis, insulin resistance, and hypertension[45], muscle wasting, sarcopenia, and nutritional deficiencies related to weight loss can also increase that risk[17].

We conducted this prospective cohort study to investigate the association between weight gain and weight loss over a long period (from age 20 to baseline) and the future risk of mortality from total CVD, ischemic heart disease (IHD), and stroke among Japanese people aged 30-79 years from the urban city of Suita.

2. Methods

2.1. Study Population

The Suita Study is a prospective cohort study investigating sociodemographic, nutritional, lifestyle, and clinical risk factors for CVD. It included 8,360 Japanese middle-aged and older adults residing in Suita, an urban city in the South-West of Japan. Participants were randomly selected by their sex and 10-year age category. At baseline (between 1989 and 1998), participants filled out a questionnaire about their sociodemographic and clinical information and underwent a health check-up assessing several clinical characteristics. Then, participants were asked to return every two years for follow-up.

The current study excluded 3,614 people for the following reasons: having a history of IHD or stroke (n=367), being younger than 30 years or older than 79 years at the time of baseline survey (n=46), moving out (n=23), lacking data on weight at age 20 or baseline weight (n=2,039), having no data on CVD mortality (n=887), or being lost to follow-up (n=252) to leave a total of 4,746 people (2,066 men and 2,680 women) for analysis. Participants were followed up until the date of the outcome, death, or censoring, whichever came first.

2.2. Cardiovascular Mortality

Systematic reviews of death certificates, including the causes of death, were conducted. We defined mortality from total CVD, IHD, and stroke according to the International Classification of Diseases, ninth revision (ICD-9) until 1995 and tenth revision (ICD-10) from 1995 onwards. The ICD-9 and ICD-10 codes of total CVD mortality were 390-459 and I00-I99, IHD mortality 410-414 and I20-25, and stroke mortality 430-438 and I60-69.

2.3. Weight Change

Trained nurses assessed the weights of all participants during the baseline check-up, and all participants reported their weight at age 20 in the baseline questionnaire. Therefore, weight change in this study was defined as the difference between baseline weight and weight at age 20.

In the primary analysis, participants were divided according to their weight change into 1) weight loss: −5 to −10 and < −10 kg, 2) stable weight −4.9 to 4.9 kg, and 3) weight gain: 5 to 10 and > 10 kg.

In a further analysis, we divided participants based on the change in their body mass index (BMI) from age 20 to baseline into 1) weight loss: normal weight at age 20 to underweight at baseline and overweight at age 20 to normal weight at baseline, 2) stable weight: normal weight at age 20 and baseline, and 3) weight gain: underweight at age 20 to normal weight at baseline and normal weight at age 20 to overweight at baseline. We did not add those who were underweight at age 20 and baseline (54 men and 135 women) or overweight at age 20 and baseline (100 men and 67 women) to the stable weight group in this analysis because underweight and overweight are, *per se*, risk factors for CVD[7, 15]. We also removed those who were overweight at age 20 and became underweight at baseline (1 man and 3 women) and those who were underweight at age 20 and became overweight at baseline (28 men and 36 women) because of their limited number. Underweight, normal weight, and overweight were BMI < 18.5, 18.5–24.9, and ≥ 25 kg/m^2.

2.4. Covariates

The following covariates were assessed using the baseline questionnaire: age, sex, smoking and drinking habits, physical activity, and perceived stress. The baseline health check-up assessed other covariates including height, weight, hypertension, diabetes, hypercholesterolemia, and chronic kidney disease. Hypertension was defined as blood pressure ≥ 140/90 mmHg or hypertension medication use. Diabetes was defined as fasting blood glucose ≥ 126 mg/dL or diabetes medication use. Hypercholesterolemia was defined as total cholesterol ≥ 240 mg/dL or statin use. Chronic kidney disease (CKD) was considered when the estimated glomerular filtration rate was ≤ 60 ml/min/1.73m^2.

Table 1. Sociodemographic and clinical characteristics of the participants distributed by their weight change since age 20

Characteristics	Weight change (kg)					*P*-value
	< -10	-5 to -10	-4.9 to 4.9	5 to 10	>10	
Frequency	140	367	2,024	1,150	1,065	---
Men, %	40.0	34.9	37.8	45.9	55.4	<0.001
Age (years)*	60.9 (11.3)	55.9 (13.1)	50.7 (12.7)	50.9 (11.8)	52.5 (10.9)	<0.001
Height (cm) *	157.1 (8.6)	157.4 (7.9)	158.5 (8.2)	159.5 (9.0)	161.5 (8.9)	<0.001
Weight at age 20 (kg) *	64.3 (11.8)	57.3 (8.5)	52.6 (7.8)	52.1 (8.1)	51.9 (8.2)	<0.001
Ever smoking, %	44.3	37.6	38.9	43.2	49.1	<0.001
Ever drinking, %	51.4	50.4	50.6	56.7	60.4	<0.001
Physical inactivity, %	59.3	57.5	56.2	53.1	60.2	0.010
High perceived stress, %	32.9	42.5	46.8	47.7	45.4	0.016
Hypertension, %	28.6	22.1	19.1	23.8	30.4	<0.001
Diabetes, %	11.4	3.3	2.8	3.6	6.6	<0.001
Hypercholesterolemia, %	14.3	13.4	16.0	20.4	23.8	<0.001
Chronic kidney disease, %	19.3	15.0	13.8	15.0	17.7	0.045

*Means ± standard deviations were calculated for such variables

2.5. Statistical Analyses

The Cox proportional hazards models were used to calculate the hazard ratios (HRs) and their 95% confidence intervals (CIs) of the total CVD, IHD, and stroke mortality for participants who experienced weight change (5 to 10, >10, −5 to −10, and <−10 kg) compared with those with stable weight (-4.9 to 4.9 kg). Then, we conducted a sensitivity analysis by measuring the association between weight change per year and the risk of total CVD mortality. In this approach, weight change per year was treated as a continuous variable. Weight change was calculated as weight difference/age difference. For example, if an individual was 65 kg at age 20 and became 70 kg at age 30, then his/her weight change per year would be 70–65/30–20=0.5. The differences in the proportions and mean values of the baseline characteristics across weight change groups were computed using the Chi-squared test for categorical variables and the one-way ANOVA test for continuous variables.

Later, while retaining the outcomes, we conducted a different analysis using Cox proportional hazards models. We analyzed the exposure groups representing those who moved from one BMI category at age 20 to another BMI category at baseline (underweight to normal weight, normal weight to underweight, normal weight to overweight, and overweight to normal weight) compared to those who had normal weight at age 20 and baseline. All associations were conducted overall, sex-specified, and age-specified (<65 and ≥ 65 years).

The associations were not conducted in categories with <3 incident cases. The HRs were adjusted for the following variables: age (continuous), smoking habits (ever or never), drinking behavior (ever or never), physical activity (yes or no), perceived stress (low, moderate, and high), hypertension (yes or no), diabetes (yes or no), hypercholesterolemia (yes or no), CKD (yes or no), and BMI at age 20 (underweight, normal weight, and overweight). SAS version 9.4 software (SAS Institute Inc, Cary, NC) was used for statistical analyses.

2.6. Ethical Consideration

The Institutional Review Board of the National Cerebral and Cardiovascular Center, Osaka, Japan approved the study protocol (M17-001). The study complied with the Declaration of Helsinki, and participants gave their informed consent before participation.

3. Results

Within 80,377 person-years (a median follow-up of 19.9 years) of 4,746 people (2,066 men and 2,680 women), we recorded 268 total CVD mortality (158 men and 110 women), 132 IHD mortality (75 men and 57 women), and 79 stroke mortality (49 men and 30 women).

3.1. Weight Change and Cardiovascular Mortality Risk

Compared to participants with stable weight, participants who lost weight >10 kg were older and had more hypertension and diabetes. Those who gained weight >10 kg had more hypertension and hypercholesterolemia (Table 1). Weight loss of >10

kg compared with stable weight was associated in the age-adjusted model with the increased risk of total CVD, IHD, and stroke mortality: HRs (95% CIs)= 2.13 (1.38, 3.30), 1.93 (1.01, 3.70), and 3.44 (1.72, 6.89), respectively. The associations remained significant in the fully adjusted model only with total CVD mortality 2.07 (1.29, 3.32) and stroke mortality 3.02 (1.40, 6.52). In the sex-specified analysis, weight loss of >10 kg, in the fully adjusted models, was associated with the increased risk of total CVD mortality in men 2.01 (1.04, 3.91) and women 2.20 (1.10, 4.38) and stroke mortality in men 3.13 (1.11, 8.78). In the age-specified analysis, the association between weight loss of >10 kg and the increased risk of total CVD and stroke mortality was significant among those ≥ 65 years; 2.44 (1.40, 4.26) and 3.95 (1.66, 9.39), respectively **(Table 2)**. In a sensitivity analysis, weight change per year was associated with the risk of total CVD in all models; 0.25 (0.17, 0.37), 0.22 (0.14, 0.33), and 0.23 (0.14, 0.36).

3.2. BMI Change and Cardiovascular Mortality Risk

Compared to participants with normal weight at age 20 and baseline, participants who moved from normal weight at age 20 to overweight at baseline were more likely to be physically inactive but had less hypertension, hypercholesterolemia, and CKD **(Table 3)**. Participants who moved from normal weight at age 20 to underweight at baseline had a higher risk of total CVD, IHD, and stroke mortality than those who had normal weight at age 20 and baseline in the fully adjusted models: 1.76 (1.12, 2.77), 2.10 (1.13, 3.92), and 2.25 (1.05, 4.83), respectively. Compared to women with normal weight at age 20 and baseline, women who moved from normal weight at age 20 to underweight at baseline and from overweight at age 20 to normal weight at baseline had a higher risk of total CVD mortality in the age-adjusted models: 2.02 (1.02, 3.99) and 2.74 (1.45, 5.16) and the fully adjusted models: 2.18 (1.08, 4.42) and 2.46 (1.29, 4.71), respectively. Also, women who moved from normal weight at age 20 to underweight at baseline and women who moved from overweight at age 20 to normal weight at baseline had a higher risk of IHD mortality in the age-adjusted model than women who had normal weight at age 20 and baseline: 2.87 (1.23, 6.71) and 2.66 (1.01, 6.99), respectively. However, in the fully adjusted model, the significant association remained only among women who moved from normal weight at age 20 to underweight at baseline: 2.86 (1.16, 7.06). Besides, women who moved from overweight at age 20 to normal weight at baseline had a higher risk of total stroke mortality in the age-adjusted model 4.40 (1.58, 12.26) and the fully adjusted model 4.06 (1.41, 11.69) than those who had normal weight at age 20 and baseline **(Table 4)**.

4. Discussion

Throughout the previous decades, Japan has witnessed increasing trends in both obesity and underweight[46]. These trends highlight the need for a better understanding of the potential impacts of weight change on health to efficiently provide weight management services in different healthcare settings across the country.

This study indicated that weight loss was associated with the increased risk of total CVD and stroke mortality, while weight gain was unrelated to total CVD, IHD, and stroke mortality. In terms of BMI, moving from normal weight at age 20 to underweight at baseline was associated with the increased risk of total CVD, IHD, and stroke mortality. Moving from overweight at age 20 to normal weight at baseline was associated with the increased risk of total CVD and stroke mortality in women.

To date, three previous national studies used prospective cohort designs to assess the risk of CVD mortality among those who experienced weight change from age 20 compared to those with stable weight. First, Saito *et al.*[30] used data of 42,242 men and 46,177 women, aged 40-69 years, from the Japan Public Health Center-based prospective study (JPHC). Within 12.9 years of follow-up, the risk of total CVD mortality increased by 34% among men with a weight loss of ≥ 5 kg but decreased by 19% among men with a weight gain of ≥ 5 kg. Women showed no excess CVD risk but did not benefit from losing or gaining weight[29]. Second, in the Ohsaki Cohort study[35], during 13.3 years of follow-up for 20,112 men and 21,252 women, aged 40-79 years, weight loss of ≥ 10 kg was associated with increased risk of total CVD mortality among men and women by 36% and 48%, respectively, and increased risk of IHD mortality among women by 92%. Weight gain of ≥ 10 kg, on the other hand, was associated with a 46% decreased risk of IHD mortality among men but a 48% increased risk of total CVD mortality among women[35]. Third, a recent study conducted on 69,681 people, aged 40-79 years, from the Japan Collaborative Cohort Study, showed that during 19.1 years of follow-up, weight losses of ≥ 12.5, 10-12.5, 7.5-9.9, 5-7.4, and 2.5-4.9 kg were associated with the increased risk of total CVD mortality by 50%, 45%, 20%, 15%, and 14% and IHD mortality by 33%, 48%, 40%, 30%, and 40%, respectively. The

Table 2. Hazard ratios and their 95% confidence intervals for the risk of CVD mortality by weight change since age 20

	Weight change (kg)				
	<-10	-5 to -10	-4.9 to 4.9	5 to 10	>10
Overall					
Person-years	2,187	6,119	34,611	19,252	18,207
Total CVD mortality, n	25	41	106	46	50
Model I	2.13 (1.38, 3.30)	1.36 (0.95, 1.95)	1	0.90 (0.64, 1.28)	0.92 (0.66, 1.29)
Model II	1.93 (1.24, 3.01)	1.47 (1.02, 2.12)	1	0.90 (0.64, 1.28)	0.88 (0.63, 1.24)
Model III	2.07 (1.29, 3.32)	1.53 (1.05, 2.24)	1	0.89 (0.63, 1.26)	0.87 (0.61, 1.24)
IHD mortality, n	11	19	55	28	19
Model I	1.93 (1.01, 3.70)	1.21 (0.72, 2.04)	1	1.06 (0.67, 1.66)	0.70 (0.41, 1.18)
Model II	1.64 (0.84, 3.19)	1.32 (0.78, 2.24)	1	1.04 (0.66, 1.65)	0.65 (0.39, 1.11)
Model III	1.77 (0.88, 3.58)	1.38 (0.80, 2.40)	1	1.01 (0.64, 1.61)	0.62 (0.36, 1.06)
Stroke mortality, n	11	14	30	11	13
Model I	3.44 (1.72, 6.89)	1.68 (0.89, 3.18)	1	0.76 (0.38, 1.51)	0.80 (0.42, 1.54)
Model II	2.92 (1.44, 5.96)	1.77 (0.93, 3.37)	1	0.73 (0.37, 1.47)	0.77 (0.40, 1.49)
Model III	3.02 (1.40, 6.52)	1.80 (0.92, 3.53)	1	0.73 (0.36, 1.47)	0.77 (0.39, 1.52)
Men					
Person-years	842	2,093	13,174	8,791	10,059
Total CVD mortality, n	12	22	65	29	30
Model I	1.98 (1.07, 3.67)	1.15 (0.71, 1.87)	1	0.95 (0.61, 1.48)	0.78 (0.51, 1.21)
Model II	1.79 (0.95, 3.38)	1.25 (0.77, 2.04)	1	0.99 (0.64, 1.56)	0.76 (0.49, 1.18)
Model III	2.01 (1.04, 3.91)	1.34 (0.81, 2.22)	1	0.98 (0.62, 1.54)	0.76 (0.48, 1.21)
IHD mortality, n	5	8	34	18	10
Model I	1.79 (0.70, 4.58)	0.82 (0.38, 1.77)	1	1.12 (0.63, 1.98)	0.51 (0.25, 1.03)
Model II	1.59 (0.60, 4.22)	0.87 (0.40, 1.91)	1	1.18 (0.65, 1.12)	0.49 (0.24, 1.00)
Model III	1.58 (0.57, 4.38)	0.87 (0.39, 1.96)	1	1.17 (0.65, 2.13)	0.48 (0.23, 1.01)
Stroke mortality, n	6	9	19	6	9
Model I	3.09 (1.23, 7.77)	1.57 (0.71, 3.50)	1	0.68 (0.27, 1.72)	0.78 (0.35, 1.72)
Model II	2.63 (0.99, 6.96)	1.79 (0.79, 4.06)	1	0.74 (0.29, 1.89)	0.74 (0.33, 1.67)
Model III	3.13 (1.11, 8.78)	1.98 (0.85, 4.63)	1	0.73 (0.28, 1.88)	0.76 (0.33, 1.77)
Women					
Person-years	1,345	4,026	21,437	10,461	8,148
Total CVD mortality, n	13	19	41	17	20
Model I	2.32 (1.24, 4.33)	1.72 (1.00, 2.97)	1	0.83 (0.47, 1.47)	1.20 (0.70, 2.06)
Model II	2.19 (1.15, 4.16)	2.01 (1.15, 3.52)	1	0.79 (0.45, 1.41)	1.11 (0.64, 1.92)
Model III	2.20 (1.10, 4.38)	2.03 (1.14, 3.62)	1	0.79 (0.44, 1.40)	1.07 (0.60, 1.89)
IHD mortality, n	6	11	21	10	9
Model I	2.16 (0.87, 5.35)	1.94 (0.93, 4.03)	1	0.98 (0.46, 2.08)	1.10 (0.50, 2.40)
Model II	1.83 (0.71, 4.72)	2.14 (0.99, 4.60)	1	0.94 (0.43, 2.03)	0.95 (0.42, 2.13)
Model III	2.13 (0.79, 5.76)	2.40 (1.08, 5.34)	1	0.93 (0.43, 2.02)	0.84 (0.37, 1.95)
Stroke mortality, n	5	5	11	5	4
Model I	3.90 (1.35, 11.29)	1.77 (0.61, 5.10)	1	0.87 (0.30, 2.50)	0.86 (0.27, 2.69)
Model II	3.81 (1.25, 11.62)	1.89 (0.64, 5.57)	1	0.79 (0.27, 2.33)	0.83 (0.26, 2.66)
Model III	3.27 (0.92, 11.62)	1.75 (0.56, 5.47)	1	0.80 (0.27, 2.37)	0.77 (0.23, 2.62)
<65 years					
Person-years	1,493	4,469	29,349	16,959	15,737
Total CVD mortality, n	6	12	28	19	26
Model I	4.25 (1.76, 10.27)	3.01 (1.53, 5.93)	1	1.09 (0.61, 1.96)	1.51 (0.88, 2.60)
Model II	2.84 (1.15, 7.02)	2.96 (1.49, 5.88)	1	0.95 (0.53, 1.71)	1.21 (0.70, 2.10)
Model III	2.34 (0.88, 6.22)	2.77 (1.38, 5.58)	1	0.97 (0.54, 1.76)	1.26 (0.72, 2.21)
IHD mortality, n	4	4	12	10	9
Model I	6.63 (2.14, 20.56)	2.40 (0.77, 7.46)	1	1.32 (0.57, 3.06)	1.20 (0.50, 2.86)
Model II	3.42 (1.03, 11.42)	2.28 (0.72, 7.26)	1	1.08 (0.46, 2.53)	0.94 (0.39, 2.27)
Model III	4.01 (1.07, 15.00)	2.47 (0.76, 8.01)	1	1.04 (0.44, 2.46)	0.85 (0.34, 2.13)
Stroke mortality, n	2	4	9	6	8
Model I	---	3.12 (0.96, 10.15)	1	1.10 (0.39, 3.11)	1.54 (0.59, 4.04)
Model II	---	3.05 (0.93, 10.00)	1	1.00 (0.35, 2.83)	1.25 (0.47, 3.34)
Model III	---	2.07 (0.37, 11.53)	1	2.47 (0.72, 8.48)	1.06 (0.37, 3.00)

(Cont. Table 2)

	Weight change (kg)				
	<-10	-5 to -10	-4.9 to 4.9	5 to 10	>10
≥ 65 years					
Person-years	694	1,650	5,261	2,293	2,470
Total CVD mortality, n	19	29	78	27	24
Model I	2.07 (1.25, 3.43)	1.22 (0.80, 1.87)	1	0.87 (0.56, 1.35)	0.66 (0.42, 1.04)
Model II	1.98 (1.18, 3.31)	1.29 (0.84, 1.99)	1	0.89 (0.57, 1.38)	0.60 (0.38, 0.95)
Model III	2.44 (1.40, 4.26)	1.45 (0.93, 2.26)	1	0.86 (0.55, 1.34)	0.58 (0.36, 0.93)
IHD mortality, n	7	15	43	18	10
Model I	1.49 (0.67, 3.33)	1.17 (0.65, 2.11)	1	1.01 (0.58, 1.76)	0.51 (0.25, 1.01)
Model II	1.27 (0.55, 2.96)	1.18 (0.65, 2.13)	1	0.98 (0.56, 1.72)	0.44 (0.22, 0.89)
Model III	1.51 (0.61, 3.71)	1.30 (0.70, 2.41)	1	0.96 (0.55, 1.69)	0.43 (0.21, 0.89)
Stroke mortality, n	9	10	21	5	5
Model I	3.88 (1.77, 8.49)	1.59 (0.75, 3.38)	1	0.64 (0.24, 1.70)	0.49 (0.18, 1.28)
Model II	3.37 (1.49, 7.63)	1.71 (0.79, 3.72)	1	0.63 (0.23, 1.69)	0.41 (0.15, 1.11)
Model III	3.95 (1.66, 9.39)	1.96 (0.87, 4.39)	1	0.61 (0.22, 1.65)	0.40 (0.14, 1.13)

CVD: Cardiovascular diseases, IHD: Ischemic heart disease Model I: Adjusted for age and sex Model II: Adjusted further for smoking habits, drinking behavior, physical activity, perceived stress, hypertension, diabetes, hypercholesterolemia, and chronic kidney disease Model III: Adjusted further for body mass index at age 20

Table 3. Sociodemographic and clinical characteristics of participating men and women distributed by their body mass index change since age 20

Characteristics	Weight change (kg/m^2)					*P*-value
	Normal weight at age 20 and baseline	Underweight at age 20 to normal weight at baseline	Normal weight at age 20 to underweight at baseline	Normal weight at age 20 to overweight at baseline	Overweight at age 20 to normal weight at baseline	
Frequency	2,783	533	189	732	133	---
Men, %	44.6	35.8	28.6	51.0	41.4	<0.001
Age (years)*	51.3 (12.3)	50.6 (11.1)	53.3 (14.3)	53.1 (11.3)	60.9 (10.6)	<0.001
Height (cm) *	159.5 (8.4)	159.4 (8.7)	157.2 (7.5)	159.7 (9.3)	155.6 (8.2)	<0.001
Weight at age 20 (kg) *	53.3 (6.6)	44.8 (5.3)	50.1 (5.4)	55.6 (7.8)	64.7 (7.7)	<0.001
Ever smoking, %	42.9	40.7	40.2	41.8	39.9	0.384
Ever drinking, %	55.5	53.1	48.2	56.2	53.4	0.030
Physical inactivity, %	54.4	61.5	61.4	58.6	59.4	<0.001
High perceived stress, %	46.9	49.2	44.4	40.9	56.5	<0.001
Hypertension, %	20.0	22.3	15.9	34.0	32.3	<0.001
Diabetes, %	2.7	3.0	3.2	7.5	7.5	<0.001
Hypercholesterolemia, %	17.4	19.9	13.2	23.1	21.8	<0.001
Chronic kidney disease, %	15.2	11.2	12.7	16.8	21.8	<0.001

*Means ± standard deviations were calculated for such variables

highest two weight loss categories (≥ 12.5 and 10-12.5 kg) were associated with the increased risk of stroke mortality by 56% and 40%, respectively. Only the highest weight gain category (≥ 12.5 kg) was associated with the increased risk of total CVD mortality by 21% and IHD mortality by 62%[38].

Two other studies assessed the same association, but weight change was assessed during a shorter period. One study used data of 6,537 Japanese American men aged 45-68 years from the Honolulu Heart Program, a prospective cohort study. It detected a tendency toward a positive association between weight loss but not weight gain during six years and the risk of CVD mortality[47]. In the JPHC, weight gain in five years was associated with increased risk of CVD mortality in men and women, while weight loss during the same period was associated with increased risk of CVD mortality in women and a tendency to increased risk in men[48].

Overall, the results of the Suita Study were consistent with the previous national studies regarding detecting a positive association between weight loss

Table 4. Hazard ratios and their 95% confidence intervals for the risk of CVD mortality by changes in body mass index between age 20 and baseline

	Weight change (kg/m^2)				
	Normal weight at age 20 and baseline	Underweight at age 20 to normal weight at baseline	Normal weight at age 20 to underweight at baseline	Normal weight at age 20 to overweight at baseline	Overweight at age 20 to normal weight at baseline
Overall					
Person-years	47,404	9,028	3,158	12,504	2,173
Total CVD mortality, n	146	20	22	39	20
Model I	1	0.97 (0.61, 1.55)	1.79 (1.14, 2.80)	1.00 (0.70, 1.43)	1.53 (0.96, 2.45)
Model II	1	0.92 (0.58, 1.48)	1.76 (1.12, 2.77)	0.93 (0.65, 1.33)	1.43 (0.89, 2.30)
IHD mortality, n	68	10	12	21	10
Model I	1	1.05 (0.54, 2.04)	2.11 (1.14, 3.91)	1.13 (0.69, 1.84)	1.56 (0.80, 3.04)
Model II	1	1.00 (0.51, 1.95)	2.10 (1.13, 3.92)	1.03 (0.63, 1.69)	1.43 (0.73, 2.80)
Stroke mortality, n	43	6	8	9	7
Model I	1	0.95 (0.40, 2.22)	2.41 (1.13, 5.13)	0.78 (0.38, 1.60)	1.95 (0.87, 4.34)
Model II	1	0.93 (0.39, 2.21)	2.25 (1.05, 4.83)	0.74 (0.36, 1.54)	1.90 (0.84, 4.27)
Men					
Person-years	20,969	3,363	873	6,302	904
Total CVD mortality, n	98	10	12	18	8
Model I	1	0.80 (0.42, 1.54)	1.69 (0.92, 3.08)	0.72 (0.44, 1.19)	0.93 (0.45, 1.92)
Model II	1	0.72 (0.37, 1.40)	1.63 (0.88, 3.00)	0.72 (0.43, 1.19)	0.92 (0.44, 1.92)
IHD mortality, n	45	4	5	9	5
Model I	1	0.67 (0.24, 1.86)	1.65 (0.65, 4.16)	0.76 (0.37, 1.55)	1.14 (0.45, 2.90)
Model II	1	0.62 (0.22, 1.74)	1.54 (0.60, 3.98)	0.73 (0.36, 1.51)	1.24 (0.48, 3.18)
Stroke mortality, n	29	3	6	5	2
Model I	1	0.76 (0.23, 2.50)	3.03 (1.26, 7.31)	0.65 (0.25, 1.69)	---
Model II	1	0.79 (0.23, 2.68)	3.32 (1.32, 8.31)	0.70 (0.27, 1.84)	---
Women					
Person-years	26,435	5,665	2,285	6,202	1,269
Total CVD mortality, n	48	10	10	21	12
Model I	1	1.29 (0.65, 2.55)	2.02 (1.02, 3.99)	1.52 (0.91, 2.54)	2.74 (1.45, 5.16)
Model II	1	1.23 (0.61, 2.45)	2.18 (1.08, 4.42)	1.29 (0.76, 2.19)	2.46 (1.29, 4.71)
IHD mortality, n	23	6	7	12	5
Model I	1	1.79 (0.73, 4.44)	2.87 (1.23, 6.71)	1.82 (0.91, 3.66)	2.66 (1.01, 6.99)
Model II	1	1.71 (0.68, 4.27)	2.86 (1.16, 7.06)	1.44 (0.69, 2.99)	2.13 (0.78, 5.83)
Stroke mortality, n	14	3	2	4	5
Model I	1	1.28 (0.37, 4.47)	---	1.05 (0.35, 3.19)	4.40 (1.58, 12.26)
Model II	1	1.26 (0.35, 4.50)	---	0.90 (0.28, 2.86)	4.06 (1.41, 11.69)
< 65 years					
Person-years	40,436	8,014	2,536	10,485	1,360
Total CVD mortality, n	46	11	1	19	5
Model I	1	1.29 (0.67, 2.48)	---	1.53 (0.90, 2.62)	3.35 (1.33, 8.44)
Model II	1	1.21 (0.62, 2.35)	---	1.35 (0.78, 2.32)	2.98 (1.17, 7.59)
IHD mortality, n	16	5	1	10	2
Model I	1	1.70 (0.62, 4.64)	---	2.30 (1.04, 5.07)	---
Model II	1	1.52 (0.55, 4.20)	---	2.04 (0.91, 4.57)	---
Stroke mortality, n	15	4	0	5	2
Model I	1	1.41 (0.47, 4.24)	---	1.28 (0.46, 3.52)	---
Model II	1	1.43 (0.47, 4.33)	---	1.14 (0.41, 3.21)	---
≥ 65 years					
Person-years	6,968	1,014	622	2,019	812
Total CVD mortality, n	100	9	21	20	15
Model I	1	0.63 (0.32, 1.25)	2.45 (1.53, 3.92)	0.73 (0.45, 1.18)	1.36 (0.79, 2.34)
Model II	1	0.62 (0.31, 1.23)	2.59 (1.60, 4.19)	0.63 (0.39, 1.03)	1.29 (0.74, 2.25)
IHD mortality, n	52	5	11	11	8
Model I	1	0.67 (0.27, 1.67)	2.68 (1.40, 5.13)	0.75 (0.39, 1.44)	1.38 (0.66, 2.91)
Model II	1	0.63 (0.25, 1.58)	2.80 (1.44, 5.47)	0.65 (0.34, 1.26)	1.20 (0.55, 2.63)
Stroke mortality, n	28	2	8	4	5
Model I	1	---	3.60 (1.64, 7.91)	0.52 (0.18, 1.47)	1.66 (0.64, 4.32)
Model II	1	---	3.66 (1.64, 8.19)	0.46 (0.16, 1.34)	1.82 (0.68, 4.84)

CVD: Cardiovascular diseases, IHD: Ischemic heart disease Model I: Adjusted for age and sex Model II: Adjusted further for smoking habits, drinking behavior, physical activity, perceived stress, hypertension, diabetes, hypercholesterolemia, and chronic kidney disease

and increased risk of CVD mortality. Yet, the association between weight gain and the risk of CVD mortality was inconsistent across the national studies.

Of note, muscle wasting and sarcopenia associated with aging could explain the positive association between weight loss and the risk of CVD [17, 49]; however, in this study, the associations did not significantly change by age category (<65 or ≥ 65 years). Also, we found that weight change from overweight to normal weight in women and participants <65 years was associated with the increased risk of CVD mortality, suggesting that muscle wasting and sarcopenia cannot fully explain this association. Other CVD risk factors might have confounded our results, yet most findings did not materially change after adjusting for potential CVD risk factors. One more explanation was that weight loss could include loss of not only the harmful abdominal and ectopic fat mass but the beneficial peripheral subcutaneous fat mass and lean body mass as well [50].

Although this study posed several strengths, such as the long follow-up period, the random selection of the included subjects, standardized methods to ascertain baseline weight and outcomes, and control for most potential confounders, some limitations should be mentioned. First, the Suita Study was conducted on an urban study population. Given that the prevalence of overweight and underweight differs between urban and rural areas in Japan [46], generalizing our results to populations in rural areas should be done cautiously. Second, more than 40% of the original sample was deleted for different reasons. The included sample was younger and had a lower prevalence of hypertension and CKD than the original sample. Nevertheless, our results adjusted for age, blood pressure, and CKD, and stratifying results by age group did not materially affect the conclusion. Third, data on weight at age 20 was collected from the Suita baseline questionnaire, making it vulnerable to recall bias. Yet, a meta-analysis of 15 studies concluded that the self-reported early-life weight could be a valid measure used in epidemiological studies [51]. Fourth, it was not clear whether weight loss was intentional or unintentional. A previous meta-analysis of 26 prospective studies showed that unintentional weight loss was associated with a high mortality risk while intentional weight loss was not [52]. Fifth, the limited number of populations in some weight change and BMI categories was another limitation. Sixth, we did not adjust our results for depression, a confounder that could be independently associated with each of weight loss and CVD [53, 54]. However, we adjusted our results for stress, another affective disorder that is known to be strictly related to depression [55]. Seventh, weight change was defined based on the weight difference between baseline and age 20; thus, we could not know whether the weight change was sustained or fluctuated during this period. One study showed that 15% of participants experienced weight fluctuations during eight years of follow-up; however, weight fluctuations (gain-loss or loss-gain) had the same cardio-pathogenic impact as sustained weight loss [28]. When weight change was treated as a continuous variable in a sensitivity analysis, the results did not materially change.

In conclusion, weight loss >10 kg since age 20 was associated with the increased risk of total CVD and stroke mortality. Moving from normal weight at age 20 to underweight at baseline was associated with the increased risk of total CVD, IHD, and stroke mortality. On the other hand, weight gain was not associated with the risk of total CVD, IHD, and stroke mortality. The results did not significantly change by sex or age group. Future studies aiming to compare between intentional and unintentional weight loss are warranted.

Conflict of interest

None to declare.

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