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Editorial

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Does Weight Loss Increase the Risk of Death from and Incidence of Cardiovascular Disease even among Individuals with Overweight or Obesity at 20 Years of Age?

Yukako Tatsumi

Department of Hygiene and Public Health, Teikyo University School of Medicine, Tokyo, Japan

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In the current issue of the Journal of Atherosclerosis and Thrombosis, the association between weight change from 20 years of age to middle age or older and death from cardiovascular disease (CVD) was reported from a large and longitudinal Japanese cohort study, the Japan Collaborative Cohort (JACC) Study[1]. In that report, participants were classified as follows into exclusive categories based on weight change (in kg) from 20 years of age to baseline (age range, 40–79 years): –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 (reference), +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. During the follow-up period (median, 19.1 years), a significantly linearly increased risk of total CVD mortality was observed for all weight loss groups. The hazard ratio (HR) was 1.50 for the –12.5 kg or more weight loss group. Cause-specific HRs among this group were 1.48 for ischemic stroke and 1.74 for intracerebral hemorrhage. On the other hand, among all weight gain groups, only the +12.5 kg or more group had a significantly linearly increased risk for total CVD and ischemic heart disease, with HRs of 1.21 and 1.62, respectively.

Studies carried out in Japan[1-3], Sweden[4], and Norway[5] have reported an association between weight change from around 20 years of age to middle age or older and subsequent CVD mortality, and studies in Japan[6], Norway[7], and the USA[8] have reported an association with CVD incidence **(Table 1)**. Many of these studies have observed an increased risk of CVD among individuals following weight loss[1-7]. Although the degree of risk and CVD type differed among these studies, none reported that weight loss reduced the risk of CVD incidence and mortality. The participants with weight loss in these studies had relatively high weight, overweight, or obesity at around 20 years of age. Therefore, they might have been advised to lose weight to help prevent lifestyle diseases and CVD. Unfortunately, the Ohsaki Cohort Study reported that those with overweight at 20 years of age who lost weight until middle age or older were at a slightly increased risk of CVD mortality compared with those with overweight at 20 years of age who maintained a stable weight until middle age or older[2].

Why did those who lost weight have an increased risk of CVD mortality? Would it have been better not to lose weight? In a study involving White women in the USA, intentional weight loss reduced the risk of CVD mortality[9], which conflicts with previous studies. One possible explanation for this was an inverse cause-and-effect relation, in which weight loss might have predicted CVD death and incidence. However, this hypothesis is likely not valid because several studies that have excluded CVD incidence and mortality in the first several years of follow-up from their analyses reported similar results. A second reason could be that weight change during the follow-up period subsequent to a previous weight change might have affected CVD incidence and mortality. In our previous study investigating the association between change in waist circumference over a 5–10-year period and the subsequent incidence of type 2 diabetes, those who lost waist circumference gained waist circumference during the subsequent follow-up period[10]. A similar rebound in body weight might have increased the risk of CVD mortality and incidence. A third reason could be that the weight loss was the result of frailty and sarcopenia, which are risk factors for CVD, as discussed in the JACC Study.

The strengths of the JACC Study described in

Address for correspondence: Yukako Tatsumi, Department of Hygiene and Public Health, Teikyo University School of Medicine, 2–11–1, Kaga, Itabashi, Tokyo 173–8605, Japan E-mail: y.tatsumi@med.teikyo–u.ac.jp
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Table 1.

Study name or First auther, year published	*n*	Men (%)	Baseline year	Follow-up, years	Age at baseline	Outcome	Weight change categories	Body weight at 18-25 years old	Hazard ratios or relative risks (95% Confidence intervals)
JACC Study, 2020 [1]	69,681	42.5	1988-1990	median: 19.1	40-79	Death from CVD	Loss ≥ 12.5kg	27.2 (kg/m^2)	1.50 (1.30-1.72)
							Loss 10-12.4	24.7	1.45 (1.28-1.66)
							Loss 7.5-9.9	24.0	1.20 (1.03-1.39)
							Loss 5.0-7.4	23.4	1.15 (1.04-1.28)
							Loss 2.5-4.9	22.8	1.14 (1.02-1.29)
							Stable ± 2.4	21.9	reference
							Gain 2.5-4.9	21.4	0.92 (0.80-1.06)
							Gain 5.0-7.4	21.1	0.98 (0.87-1.10)
							Gain 7.5-9.9	20.9	0.91 (0.77-1.07)
							Gain 10-12.4	20.6	1.05 (0.92-1.21)
							Gain ≥ 12.5	20.0	1.21 (1.07-1.36)
Ohsaki Cohort Study, 2013 [2]	41,364	48.6	1994	13.3	40-79	Death from CVD		men, women	men, women
							Loss ≥ 10.0kg	26.1, 26.5 (kg/m^2)	1.52 (1.25-1.85), 1.62 (1.25-2.11)
							Loss 5.0-9.9	24.2, 24.4	1.04 (0.87-1.24), 1.52 (1.23-1.88)
							Stable ± 4.9	22.5, 22.4	reference
							Gain 5.0-9.9	21.7, 21.5	0.95 (0.78-1.16), 0.98 (0.77-1.24)
							Gain ≥ 10.0	21.1, 20.7	0.99 (0.80-1.21), 1.36 (1.09-1.69)
JPHC, 2009 [3]	88,419	47.8	1990-1993	median: 12.9	40-69	Death from CVD		men, women	men, women
							Loss ≥ 5kg	24.4, 24.1	1.34 (1.09-1.66), 1.22 (0.87-1.71)
							Stable ± 4.9	21.8, 21.3	reference
							Gain ≥ 5	21.0, 20.3	0.81 (0.66-0.99), 0.82 (0.62-1.10)
Rosengren A, 1999 [4]	6,874	100	1970-1973	mean: 19.7	47-55	Death from coronary disease	Loss > 4%	24.1 (kg/m^2)	1.84 (1.27-2.68)
							Stable ± 4	23.1	reference
							Gain 4-10	22.7	1.43 (1.04-1.97)
							Gain 10-15	22.5	1.62 (1.18-2.22)
							Gain 15-25	22.2	1.36 (1.00-1.84)
							Gain 25-35	21.6	1.73 (1.24-2.42)
							Gain > 35	20.6	1.86 (1.32-2.62)
Kjøllesdal MKR, 2020 [5]	148,021	78.4	1985-2003	mean: 19	40-50	Death from CVD	Loss ≥ 5.0kg	Not described	1.33 (0.87-2.03)
							Loss 2.5-5.0		1.14 (0.74-1.76)
							Stable ± 2.4		reference
							Gain 2.5-4.9		1.17 (0.88-1.55)
							Gain 5.0-9.9		1.03 (0.81-1.30)
							Gain 10.0-14.9		0.96 (0.76-1.22)
							Gain ≥ 15.0		0.98 (0.78-1.23)
JPHC, 2008 [6]	90,679	47.7	1990-1993	mean: 9.7	40-69	Incidence of CHD	Loss ≥ 10.0kg	26.2 (kg/m^2)	1.8 (0.9-3.5)
							Loss 5-10	23.8	0.9 (0.5-1.8)
							Stable ± 5.0	21.9	reference
							Gain 5-10	21.4	1.0 (0.6-1.8)
							Gain ≥ 10.0	20.9	1.3 (0.7-2.3)
Prestgaard E, 2020 [7]	2,014	100	1972-1975	median: 30.1	40-59	Incidence of stroke	Loss	Not described	1.46 (0.99-2.11)
							Gain 0-4.9 kg		reference
							Gain 5.0-9.9kg		1.46 (1.09-1.95)
							Gain ≥ 10		1.39 (1.03-1.87)
Willett WC, 1995 [8]	115,818	0	1976	14	30-55	Incidence of CHD	Loss ≥ 20kg	Not described	1.09 (0.53-2.21)
							Loss 11-19.9		1.15 (0.77-1.71)
							Loss 5-10.9		0.78 (0.57-1.06)
							Loss 4.9-Gain 4.9		reference
							Gain 5-7.9		1.25 (1.01-1.55)
							Gain 8-10.9		1.65 (1.33-2.05)
							Gain 11-19		1.92 (1.61-2.29)
							Gain ≥ 20		2.65 (2.17-3.22)

CHD, coronary heart disease; CVD, cardiovascular disease.

the current issue were the exclusive weight change categories, the large sample size, and the information on cause-specific CVD mortality. However, a notable limitation was the non-adjustment for lipid profiles, unlike the adjustment for hypertension. In the "metabolic domino" concept, which involves the progression of lifestyle-related diseases to CVD, both hypertension and dyslipidemia are in middle stream. It is well known that hypertension and dyslipidemia are strongly associated with ischemic stroke and ischemic heart disease, respectively. Therefore, to compare the impact of weight change on each CVD type, it is important to adjust for both hypertension and dyslipidemia, or neither. A previous study in the Sweden investigated the association between weight change from 20 years of age to middle age and subsequent mortality from coronary heart disease (CHD), adjusting for serum cholesterol levels, and reported a significantly higher risk of mortality from CHD due to both weight loss and weight gain[4]. A multivariable model was used, so estimates of the attenuation of risk by adjusting for serum cholesterol levels could not be made; however, it is speculated that the risks of weight loss and gain remained significantly high after adjusting for lipid profiles in the JACC Study.

The association between weight loss and CVD mortality and incidence remains unclear. Therefore, further studies are needed that observe weight change until specified end points, measure body composition, and investigate the causes, methods, and processes of weight loss.

Conflicts of Interests

None.

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