Change in Weight and Body Mass Index Associated With All-Cause Mortality in Korea: A Nationwide Longitudinal Study

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Context: Many studies have reported conflicting evidence on the association between weight change and mortality.

Objective: We investigated the association between weight change and subsequent all-cause mortality, using a large-scale, population-based cohort from the National Health Insurance System health checkup data between 2005 and 2015.

Methods: A total of 11,524,763 subjects older than age 20 years were included. Weight was measured every 2 years and weight change over 4 years was divided into eight categories, from weight loss ≥15% to weight gain ≥20%, for every 5% of weight change. The hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality were analyzed using multivariable Cox proportional hazard models compared with the stable weight group (weight change <5%) after adjusting for age, sex, smoking, drinking, exercise, diabetes mellitus, hypertension, dyslipidemia, cancer, and income.

Results: Weight loss was associated with increased mortality rates compared with weight gain; the group with weight loss ≥15% had the highest HR for all-cause mortality (HR, 2.598; 95% CI, 2.537 to 2.659). The HR for all-cause mortality in the ≥20% weight gain group was 1.784 (95% CI, 1.695 to 1.877). Across all body mass index (BMI) categories, weight loss ≥15% was associated with increased mortality rates and the highest mortality rates were found in the BMI ≥30 kg/m^2 group (HR, 3.469; 95% CI, 2.236 to 5.381).

Conclusions: Weight change over 4 years showed a reverse J-shaped all-cause mortality curve, independent of BMI status. Weight loss was associated with a greater risk of mortality than was weight gain. ***(J Clin Endocrinol Metab* 102: 4041–4050, 2017)**

Obesity is a risk factor for cardiometabolic diseases, including diabetes mellitus (DM), hypertension (HTN), cardiovascular diseases, and some cancer types (1, 2). High body mass index (BMI) is associated with increased mortality rates, according to J-shaped (3, 4) or U-shaped curves (5, 6) as BMI increases. Both underweight

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Abbreviations: BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; HTN, hypertension; ICD-10, International Classification of Diseases, 10th Revision; NHIS, National Health Insurance System; Q, quartile; SD, standard deviation.

and obesity are associated with increased mortality, and obesity in mid adulthood or childhood is associated with increased all-cause mortality (7, 8). However, weight status changes continuously throughout a lifetime; therefore, changes in weight or BMI are also considered in the association between weight status and mortality.

Weight loss in overweight or obese people and weight gain in underweight people had beneficial effects on health, with lower mortality rates (9, 10). However, many studies have shown conflicting results regarding the association between weight change and mortality. Some studies showed that weight loss was associated with increased mortality, independent of BMI status (11–20), but some studies found no association (21, 22). The association between weight gain and mortality is also controversial, with some studies showing increased mortality (10, 12, 23, 24) and others showing no association (11–17, 21, 22).

Many studies have examined the association between weight change and mortality in the elderly population (9, 11, 13, 16, 17, 20). Some studies examined this association among white people (9, 13–15, 17, 18, 20, 22–24), Mexican Americans (11), and Asians (19, 21, 25). Many studies had relatively few participants (11, 13, 15, 18, 21, 23). However, to our knowledge, there are currently no large-scale studies involving the Korean population. Therefore, we investigated the association between weight change and subsequent all-cause mortality rates using a large-scale, population-based cohort derived from the National Health Insurance System (NHIS) health checkup data.

Materials and Methods

The NHIS database and NHIS health checkup program

The NHIS is a single insurer that manages the National Health Insurance program, with medical information on ~50 million Koreans. The NHIS includes patients' demographic data, such as age, sex, area of residence, medical use and transaction information, insurer payment coverage, and claims and deductions data. The source population of the NHIS is derived from the Health Insurance Review and Assessment service. The Health Insurance Review and Assessment database includes data on ~97.0% of the Korean population's health insurance claims; details of the NHIS database have been described elsewhere (26).

The National Health Insurance program provides a biannual health checkup program for all insured Koreans, except for employee subscribers who undergo yearly health checkups. The NHIS health checkup program consists of four areas: general health checkup, cancer checkup, lifetime transition-period health checkup, and baby/infant health checkup. Anthropometric measurements, such as weight, height, waist circumference, and systolic and diastolic blood pressures are measured by trained examiners. The NHIS health checkup also includes tests for visual and hearing acuity; laboratory tests, such as fasting blood glucose, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and serum creatinine levels; and urine analysis. Self-reported questionnaires for general health behaviors such as current smoking status, alcohol intake, and regular exercise were reviewed; The Korean Association of Laboratory Quality Control warranted the quality of the laboratory tests; the hospitals that performed the health checkups were certified by the NHIS.

Subjects

We used the NHIS health checkup database between 2005 and 2015 to select subjects older than 20 years who had health checkups over 4 years. A total of 11,676,522 subjects were followed up to 31 December 2015. The following were excluded: subjects with missing data (n = 71,148), those with a history of abrupt height loss ≥5 cm (n = 80,596), and subjects with unmatched mortality information (n = 15) over 4 consecutive years. Finally, 11,524,763 subjects were included in this study (n = 6,327,210 men; n = 5,197,553 women) and the mean observational time [± standard deviation (SD)] was 5.2 ± 1.2 years. This study was approved by the Institutional Review Board of the Korea National Institute for Bioethics Policy (No. P01–201603–21–005) and permission for the use of Health checkup data was granted by the NHIS (NHIS-2016-4-003).

Weight change and BMI

Weight change was calculated as the difference in body weight over 4 years, corresponding to the period between the first and third health checkup. For example, weight change over 4 years was checked during 2005 through 2009, 2006 through 2010, 2007 through 2011, and 2008 through 2012. Based on the study performed by Corrada *et al.* (20), we defined the weight stable group as weight change within 5%, and we categorized weight change into eight weight change groups by 5% increase or decrease as follows: weight loss ≥15%; loss ≥10% to <15%; loss ≥5% to <10%; weight change <5%; gain ≥5% to <10%; gain ≥10% to <15%; gain ≥15% to <20%; and gain ≥ 20%. The BMI was calculated as weight in kilograms divided by the square of the height in meters; BMI was also checked over 4 years, between the first and third health checkups. We defined obesity as a BMI ≥25 kg/m^2 and normal as 18.5 ≤ BMI < 23 kg/m^2, according to the World Health Organization recommendations for Asians (27).

General health behavior and sociodemographic variables

Smoking history was categorized as nonsmoker, ex-smoker, or current smoker. Alcohol drinking was categorized into imbibing zero, one to two, or three or more times per week. Regular exercise was defined as vigorous physical activity for at least 20 min/d, and categorized by frequency as follows: none, one to four, and five or more times per week. Income was divided by quartile (Q): Q1 (low income), Q2, Q3, and Q4.

Definition of chronic diseases

DM was defined as fasting plasma glucose levels ≥126 mg/dL (from the NHIS health checkup) or at least one claim per year for an antidiabetic medication prescription under the International Classification of Diseases, 10th Revision (ICD-10) codes E11–14.

HTN was defined by blood pressure ≥140/90 mm Hg or at least one claim per year for an antihypertensive medication prescription under ICD-10 codes I10–I15. Dyslipidemia was defined by total cholesterol level ≥240 mg/dL or at least one claim per year for an antihyperlipidemic medication prescription under ICD-10 code E78. Cardiovascular disease was identified when the subject gave an affirmative answer to the following question: "Do you have a history of stroke or acute myocardial infarction?" Cancer was defined by the presence of at least one claim per rare intractable disease meeting the specific diagnostic criteria for cancer, and diagnosed and certified by a physician.

All-cause mortality

The primary outcome was all-cause mortality between 1 January 2009 and 31 December 2015 in each participant, and the number of person-years of follow-up was counted. All-cause mortality was assessed as death during 5.2 years (±SD, 1.2 years) after the last recorded weight.

Statistical analysis

The general characteristics of subjects are expressed as mean ± SD for continuous variables and percentage (SD) for categorical variables, according to the eight weight-change categories. The hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality according to the eight weight-change categories were analyzed by multivariable Cox proportional hazard models, using the stable weight change (within ±5%) category as a reference group, after adjusting for age and sex in model 1; and age, sex, smoking, alcohol drinking, regular exercise, DM, HTN, dyslipidemia, cancer, and income (Q1) in model 2.The HRs and 95% CIs for mortality according to eight weight change categories were also obtained by constructing a multivariable Cox model for the following different subgroups: five BMI categories, age, sex, smoking status, drinking status, exercise, cancer, and the presence of at least one of the following cardiometabolic diseases: HTN, DM, and dyslipidemia. We also identified four categories of BMI changes over 4 years, as follows: group 1: normal to normal; group 2: obese to obese; group 3: normal to obese; and group 4: obese to normal. The HRs and 95% CIs for body mass change categories were obtained by a multivariable Cox proportional hazard models. Linear trend analysis was performed to determine the *P* for trend. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC), and $P < 0.05$ for two-tailed *t* tests was considered statistically significant.

Results

Baseline characteristics

Table 1 shows baseline characteristics of participants. We identified 212,704 deaths attributed to all-cause mortality. Compared with the weight loss groups, weight gain groups had greater proportions of men, smoking, and alcohol drinking. However, the following decreased as weight increased: age and the proportion of participants ≥60 years of age, low income (Q1), and chronic diseases (*i.e.*, DM, HTN, and cancer). A higher proportion of overweight participants (*i.e.*, $23 \leq \text{BMI} < 25\ \text{kg/m}^2$) was found in the weight stable groups. The highest death rate (8.67%) was found in the group with weight loss ≥15%, and the lowest death rate (1.3%) was observed in the group with weight gain between 5% and 10%. Among the three weight change groups (*i.e.*, weight loss, weight stable, and weight gain), the weight loss group had a higher proportion of patients with DM, HTN, dyslipidemia, and cancer (Supplemental Table 1). Because the prevalence of chronic diseases such as DM, HTN, and dyslipidemia decreased as weight increased, as shown in Table 1, we analyzed the odds ratio for the prevalence of chronic diseases after adjusting for age in the eight groups according to weight change (Supplemental Table 2). In contrast to the prevalence of DM and

Table 1. General Characteristics of Subjects

	Weight Change, %							
	≥ −15	<−15 to ≥−10	<−10 to ≥−5	<−5 to <5	≥5 to <10	≥10 to <15	≥15 to <20	≥20
No.	86,709	269,271	1,270,031	7,614,386	1,623,429	459,094	127046	74,797
Male sex, %	34,797 (40·1)	118,343 (44.0)	632,444 (49.8)	4,258,515 (55.9)	913,860 (56.3)	262,930 (57.3)	71,007 (55.9)	35,314 (47.21)
Age, y	55.6 ± 17.1	54.4 ± 15.6	53.6 ± 14.1	50.8 ± 13.1	46.5 ± 13.3	43.1 ± 13.7	41.1 ± 14.0	41.7 ± 15.2
Age ≥60 y, %	39,008 (45·0)	108,976 (40.5)	459,456 (36.2)	2,049,544 (26.9)	303,514 (18.7)	67,979 (14.8)	17,225 (13.6)	12,306 (16.45)
Height, cm	159.8 ± 9.6	160·8 ± 9.4	161.9 ± 9.2	163.6 ± 9.1	164.6 ± 9.3	165.4 ± 9.5	165.7 ± 9.5	164.3 ± 9.3
Weight, kg	53.9 ± 10.4	57.2 ± 10.5	60.0 ± 10.5	64.0 ± 11.1	66.7 ± 11.8	68.5 ± 12.4	70.5 ± 12.8	72.7 ± 13.3
Mean BMI, kg/m^2	21.0 ± 3.0	22.1 ± 2.9	22.8 ± 2.9	23.8 ± 3.0	24.5 ± 3.2	24.9 ± 3.3	25.6 ± 3.4	26.8 ± 3.9
BMI, kg/m^2								
<18.5	16,711 (19·3)	27,021 (10.0)	75,712 (6.0)	232,064 (3.1)	21,546 (1.3)	3762 (0.8)	604 (0.5)	183 (0.24)
≥18.5–<23	49,902 (57·6)	149,168 (55.4)	620,424 (48.9)	2,846,777 (37.4)	521,763 (32.1)	132,389 (28.8)	28,809 (22.7)	10,717 (14.33)
≥23–<25	12,094 (14·0)	53,371 (19.8)	309,699 (24.4)	2,002,102 (26.3)	419,031 (25.8)	115,924 (25.3)	31,502 (24.8)	15,597 (20.85)
≥25–<30	7488 (8·6)	36,799 (13.7)	245,378 (19.3)	2,312,095 (30.4)	575,857 (35.5)	172,853 (37.7)	53,032 (41.7)	33,834 (45.23)
≥30	514 (0.6)	2912 (1.1)	18,818 (1.5)	221,348 (2.9)	85,232 (5.3)	34,166 (7.4)	13,099 (10.3)	14,466 (19.34)
Smoker, %	15,208 (17.5)	54,053 (20.1)	276,354 (21.8)	1,747,419 (23.0)	402,143 (24.8)	122,487 (26.7)	34,580 (27.2)	17,314 (23.15)
Alcohol drinker, %	4099 (4.7)	15,182 (5.6)	81,599 (6.4)	565,655 (7.4)	127,110 (7.8)	37,090 (8.1)	10,403 (8.2)	5340 (7.14)
Regularly exercises, %	16,849 (19.4)	56,929 (21.1)	277,096 (21.8)	1,548,686 (20.3)	275,833 (17.0)	69,027 (15.0)	17,793 (14.0)	9906 (13.24)
Income, Q1, %	16,908 (19.5)	52,897 (19.6)	232,778 (18.3)	1,211,958 (15.9)	248,853 (15.3)	69,413 (15.1)	19,298 (15.2)	11,919 (15.94)
DM, %	15,335 (17.7)	44,798 (16.6)	185,615 (14.6)	733,027 (9.6)	107,690 (6.6)	27,905 (6.1)	7795 (6.1)	5510 (7.37)
HTN, %	31,164 (35.9)	90,899 (33.8)	410,114 (32.3)	2,226,627 (29.2)	403,444 (24.9)	100,258 (21.8)	26,379 (20.8)	17,145 (22.92)
Dyslipidemia, %	17,803 (20.5)	56,833 (21.1)	279,449 (22.0)	1,652,296 (21.7)	328,947 (20.3)	87,664 (19.1)	25,026 (19.7)	17,721 (23.69)
Cancer, %	7009 (8.1)	13,304 (4.9)	37,351 (2.9)	144,896 (1.9)	25,534 (1.6)	6487 (1.4)	1681 (1.3)	1043 (1.39)
Died, %	7521 (8.7)	14,035 (5.2)	38,159 (3.0)	122,236 (1.6)	21,045 (1.3)	6317 (1.4)	1885 (1.5)	1506 (2.01)

cancer, the prevalence of HTN and dyslipidemia increased as weight increased. When we calculated the prevalence of groups having more than one of the chronic diseases (among DM, HTN, and dyslipidemia), as weight increased, the risk of having more than one chronic disease increased.

All-cause mortality by weight change

The HR of all-cause mortality by weight change is shown in Table 2. All-cause mortality showed a reverse J-shaped mortality curve according to weight change. Compared with the weight stable group, after adjusting for all covariates, weight loss was associated with a greater mortality than weight gain per the same changes in weight. The group with weight loss ≥15% had the highest HR for all-cause mortality (HR, 2.598; 95% CI, 2.537 to 2.659) and the HRs for weight loss between 10% and 15% and weight gain ≥20% were 1.923 and 1.784, respectively.

All-cause mortality by weight change according to subgroups

We categorized participants by sex, age, smoking status, presence of more than one concomitant chronic disease (*i.e.*, DM, HTN, and dyslipidemia), and cancer. We also analyzed the HR for mortality in the eight weight change groups, setting the stable weight group as the reference group after adjusting for all covariates in Table 3. The HR for mortality was higher among men than among women, except for the groups with extreme weight change (*i.e.*, weight loss ≥15% and weight gain ≥20%). In the group younger than 60 years old, there was a higher HR for mortality among subjects with weight loss and a lower HR for mortality among subjects with weight gain, compared with the group of subjects ≥60 years old. Smoking and cancer groups had lower mortality HRs than those of the nonsmoking and noncancer groups, respectively, in all weight change criteria. The group of subjects with one or more chronic diseases had lower mortality HRs in weight loss, but higher mortality HRs in weight gain compared with the group with no chronic disease.

All-cause mortality by weight change in five BMI categories

We also analyzed the HRs for all-cause mortality of weight change in the five BMI categories, after adjusting all covariates (Fig. 1). Across all BMI categories, weight loss ≥15% was associated with increased mortality rates. Among the weight loss ≥15% groups, the highest mortality rates were observed in subjects with BMI ≥30 kg/m^2 (HR, 3.469; 95% CI, 2.236 to 5.381) and the lowest mortality rates were observed in the subjects with BMI <18.5 kg/m^2 (HR, 1.830; 95% CI, 1.744 to 1.921). In underweight (BMI <18.5 kg/m^2), weight loss was associated with increased mortality rates, as were 5% to 10% and 10% to 15% weight gains, but weight gain of ≥15% was not associated with increased mortality rates. Compared with the normal BMI group, the overweight and obese groups had higher HRs for all-cause mortality for each weight change, and the weight loss group had higher HRs than weight gain group. In the BMI ≥30 kg/m^2 group, each weight loss had higher HRs, but each weight gain had lower HRs compared with the normal BMI group.

BMI category change and all-cause mortality

We also analyzed HRs for mortality by category of BMI change according to weight change (Fig. 2). Both the BMI stable group [*i.e.*, group 1 (normal to normal BMI) and group 2 (obesity to obesity BMI) together] showed a reverse J-shaped mortality curve. Compared with group 1, weight loss was associated with lower HR for mortality in group 2. In group 3 (obesity to normal BMI), increases in weight loss were associated with increased mortality rates. In group 4 (normal to obesity BMI), increases in weight gain were also associated with increased mortality

Table 2. Weight Change and All-Cause Mortality

				HR (95% CI)	
Weight Change, %	Died	Duration	Incidence	Model 1[a]	Model 2[b]
≥ −15	7521	426,389.83	17.6388	3.089 (3.017–3.163)	2.598 (2.537–2.659)
<−15 to ≥ −10	14,035	1,354,671.42	10.3604	2.160 (2.122–2.198)	1.923 (1.890–1.957)
<−10 to ≥ −5	38,159	6,527,906.6	5.8455	1.425 (1.408–1.441)	1.356 (1.365–1.371)
<−5 to <5	122,236	39,797,312.59	3.0715	1 (Ref)	1 (Ref)
≥5–<10	21,045	8,431,358.43	2.496	1.100 (1.084–1.116)	1.099 (1.083–1.115)
≥10–<15	6317	2,345,570.42	2.6932	1.407 (1.372–1.443)	1.388 (1.353–1.423)
≥15–<20	1885	641,186.72	2.9399	1.640 (1.567–1.716)	1.602 (1.531–1.677)
≥20	1506	375,348.2	4.0123	1.829 (1.739–1.925)	1.784 (1.695–1.877)

[a]Model 1 was adjusted for age and sex.

[b]Model 2 was adjusted for age, sex, smoking, drinking, exercise, DM, HTN, dyslipidemia, cancer, and income.

Table 3. Weight Change and All-Cause Mortality by Subgroup

Subgroup	Weight Change, %	No. of Subjects	Died	HR (95% CI) Model 1[a]	HR (95% CI) Model 2[b]
Men	≥−15	34,797	4114	2.985 (2.892–3·080)	2.472 (2.395–2.551)
	<−15 to ≥−10	118,343	8923	2.247 (2.198–2.297)	1.984 (1.940–2.028)
	<−10 to ≥−5	632,444	25,607	1.436 (1.416–1.456)	1.364 (1.345–1.383)
	<−5 to <5	4,258,515	86,951	1 (Ref)	1 (Ref)
	≥5–<10	913,860	14,832	1.109 (1.090–1.129)	1.108 (1.089–1.127)
	≥10–<15	262,930	4369	1.409 (1.367–1.453)	1.391 (1.349–1.434)
	≥15–<20	71,007	1254	1.624 (1.536–1.717)	1.591 (1.504–1.682)
	≥20	35,314	934	1.767 (1.657–1.885)	1.725 (1.618–1.840)
Women	≥−15	51,912	3407	3.155 (3.045–3.270)	2.725 (2.630–2.824)
	<−15 to ≥−10	150,928	5112	1.997 (1.939–2.057)	1.810 (1.757–1.864)
	<−10 to ≥−5	637,587	12,552	1.396 (1.367–1.424)	1.336 (1.309–1.363)
	<−5 to <5	3,355,871	35,285	1 (Ref)	1 (Ref)
	≥5–<10	709,569	6213	1.079 (1.05–1.109)	1.081 (1.052–1.111)
	≥10–<15	196,164	1948	1.398 (1.336–1.463)	1.382 (1.321–1.447)
	≥15–<20	56,039	631	1.657 (1.531–1.792)	1.616 (1.494–1.749)
	≥20	39,483	572	1.918 (1.766–2.083)	1.880 (1.731–2.042)
Age <60 y	≥−15	47,701	752	3.909 (3.636–4.202)	2.582 (2.400–2.777)
	<−15 to ≥−10	160,295	1902	2.625 (2.506–2.750)	2.056 (1.962–2.154)
	<−10 to ≥−5	810,575	6486	1.542 (1.501–1.584)	1.391 (1.354–1.430)
	<−5 to <5	5,564,842	28,902	1 (Ref)	1 (Ref)
	≥5–<10	1,319,915	5634	1.065 (1.035–1.096)	1.068 (1.038–1.099)
	≥10–<15	391,115	1605	1.317 (1.252–1.385)	1.291 (1.227–1.358)
	≥15–<20	109,821	451	1.590 (1.448–1.745)	1.518 (1.382–1.666)
	≥20	62,491	308	2.021 (1.806–2.261)	1.876 (1.676–2.099)
Age ≥60 y	≥−15	39,008	6769	2.915 (2.843–2.989)	2.508 (2.446–2.571)
	<−15 to ≥−10	108,976	12,133	2.055 (2.016–2.095)	1.856 (1.821–1.892)
	<−10 to ≥−5	459,456	31,673	1.390 (1.373–1.408)	1.332 (1.315–1.349)
	<−5 to <5	2,049,544	93,334	1 (Ref)	1 (Ref)
	≥5–<10	303,514	15,411	1.098 (1.080–1.117)	1.094 (1.076–1.113)
	≥10–<15	67,979	4712	1.398 (1.358–1.439)	1.373 (1.333–1.413)
	≥15–<20	17,225	1434	1.593 (1.512–1.678)	1.552 (1.473–1.635)
	≥20	12,306	1198	1.722 (1.626–1.823)	1.680 (1.587–1.778)
Nonsmoking	≥−15	71,501	6313	3.180 (3.099–3.263)	2.692 (2.624–2.763)
	<−15 to ≥−10	215,218	10,823	2.149 (2.106–2.192)	1.935 (1.897–1.975)
	<−10 to ≥−5	993,677	28,602	1.419 (1.400–1.438)	1.367 (1.349–1.386)
	<−5 to <5	5,866,967	90,713	1 (Ref)	1 (Ref)
	≥5–<10	1,221,286	15,963	1.126 (1.107–1.145)	1.123 (1.104–1.142)
	≥10–<15	336,607	4815	1.433 (1.392–1.475)	1.405 (1.365–1.447)
	≥15–<20	92,466	1451	1.669 (1.585–1.758)	1.627 (1.545–1.714)
	≥20	57,483	1213	1.890 (1.786–2.000)	1.847 (1.745–1.955)
Smoking	≥−15	15,208	1208	2.381 (2.248–2.523)	2.143 (2.022–2.270)
	<−15 to ≥−10	54,053	3212	1.971 (1.900–2.044)	1.866 (1.799–1.935)
	<−10 to ≥−5	276,354	9557	1.353 (1.322–1.385)	1.317 (1.287–1.348)
	<−5 to <5	1,747,419	31,523	1 (Ref)	1 (Ref)
	≥5–<10	402,143	5082	1.027 (0.997–1.058)	1.028 (0·998–1.059)
	≥10–<15	122,487	1502	1.321 (1.254–1.391)	1.320 (1.253–1.390)
	≥15–<20	34,580	434	1.508 (1.372–1.658)	1.503 (1.367–1.652)
	≥20	17,314	293	1.552 (1.384–1.742)	1.535 (1.368–1.722)
No chronic disease	≥−15	44,122	2149	3.301 (3.159–3.449)	2.509 (2.401–2.622)
	<−15 to ≥−10	141,031	4077	2.178 (2.108–2.250)	1.877 (1.817–1.939)
	<−10 to ≥−5	678,745	11,410	1.410 (1.380–1.439)	1.339 (1.311–1.368)
	<−5 to <5	4,356,108	38,717	1 (Ref)	1 (Ref)
	≥5–<10	1,011,038	6742	1.090 (1.063–1.119)	1.077 (1.049–1.105)
	≥10–<15	299,794	1976	1.378 (1.317–1.442)	1.337 (1.278–1.399)
	≥15–<20	82,830	558	1.602 (1.473–1.741)	1.555 (1.430–1.691)
	≥20	44,616	409	1.776 (1.611–1.957)	1.738 (1.577–1.916)

(*Continued*)

Table 3. Continued

Subgroup	Weight Change, %	No. of Subjects	Died	HR (95% CI)	
				Model 1[a]	Model 2[b]
Chronic disease	≥−15	42,587	5372	3.038 (2.955–3.124)	2.608 (2.536–2.682)
	<−15 to ≥−10	128,240	9958	2.169 (2.124–2.215)	1.934 (1.894–1.975)
	<−10 to ≥−5	591,286	26,749	1.438 (1.418–1.458)	1.361 (1.342–1.380)
	<−5 to <5	3,258,278	83,519	1 (Ref)	1 (Ref)
	≥5–<10	612,391	14,303	1.103 (1.084–1.123)	1.110 (1.090–1.130)
	≥10–<15	159,300	4341	1.419 (1.377–1.463)	1.410 (1.368–1.454)
	≥15–<20	44,216	1327	1.653 (1.565–1.745)	1.621 (1.535–1.711)
	≥20	30,181	1097	1.848 (1.741–1.961)	1.800 (1.696–1.911)
No cancer[c]	≥−15	79,700	6037	2.983 (2.906–3.062)	2.793 (2.721–2.868)
	<−15 to ≥−10	255,967	11,725	2.104 (2.064–2.145)	1.989 (1.951–2.028)
	<−10 to ≥−5	1,232,680	32,918	1.398 (1.381–1.416)	1.352 (1.336–1.369)
	<−5 to <5	7,469,490	108,202	1 (Ref)	1 (Ref)
	≥5–<10	1,597,895	18,810	1.113 (1.096–1.130)	1.117 (1.100–1.134)
	≥10–<15	452,607	5610	1.418 (1.381–1.457)	1.412 (1.374–1.450)
	≥15–<20	125,365	1675	1.651 (1.574–1.733)	1.625 (1.548–1.705)
	≥20	73,754	1375	1.883 (1.786–1.986)	1.836 (1.741–1.936)
Cancer[c]	≥−15	7009	1484	1.938 (1.837–2.045)	1.901 (1.802–2.006)
	<−15 to ≥−10	13,304	2310	1.602 (1.533–1.674)	1.566 (1.498–1.636)
	<−10 to ≥−5	37,351	5241	1.353 (1.310–1.396)	1.320 (1.278–1.362)
	<−5 to <5	144,896	14,034	1 (Ref)	1 (Ref)
	≥5–<10	25,534	2235	0.986 (0.943–1.031)	0.989 (0.946–1.034)
	≥10–<15	6487	707	1.262 (1.170–1.361)	1.257 (1.166–1.356)
	≥15–<20	1681	210	1.444 (1.260–1.654)	1.426 (1.244–1.634)
	≥20	1043	131	1.377 (1.159–1.635)	1.362 (1.147–1.618)

Abbreviation: Ref, reference.

[a]Model 1 was adjusted for age and sex.

[b]Model 2 was adjusted for age, sex, smoking, drinking, exercise, DM, HTN, dyslipidemia, cancer, and income.

[c]Cancer was not adjusted in model 2.

rates, but the HRs for mortality in group 4 were lower than those in group 3.

Discussion

In this study, weight change over 4 years was associated with increased all-cause mortality independent of BMI status, and weight loss was associated with higher mortality rates than was weight gain, overall, and in subgroup analysis. The HR for mortality with weight loss ≥15% was 2.598 (95% CI, 2.537 to 2.659), and with weight gain ≥20% was 1.784 (95% CI 1.695 to 1.877). Among the groups with weight loss ≥15%, BMI ≥30 kg/m^2 was associated with the highest mortality rates (HR, 3.469; 95% CI, 2.236 to 5.381).

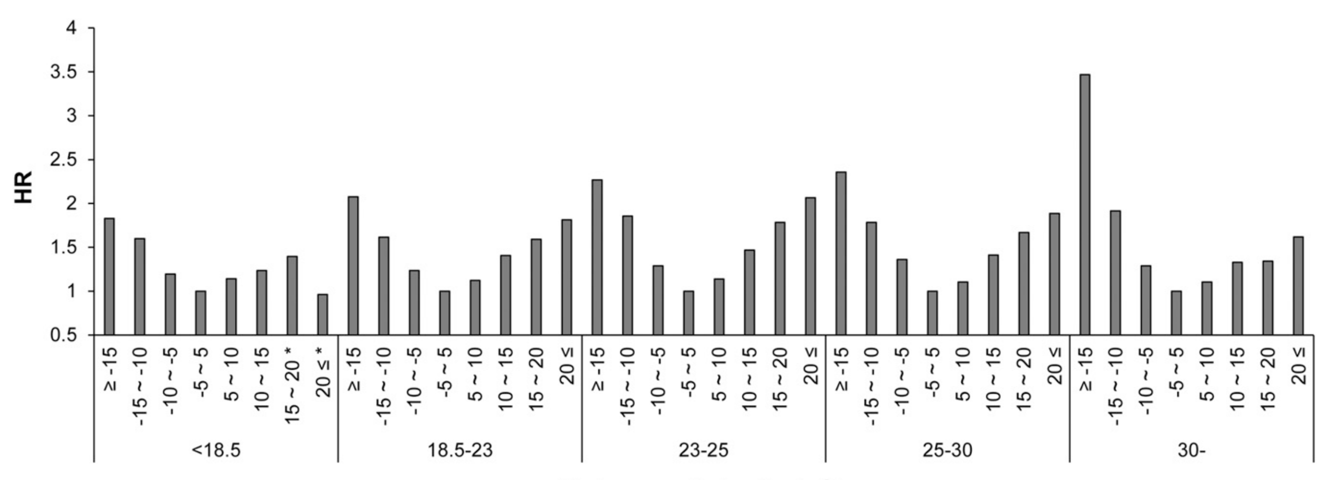

Figure 1. Weight change and all-cause mortality in the five BMI groups, adjusted for age, sex, smoking, drinking, exercise, DM, HTN, dyslipidemia, cancer, and income. *Not statistically significant.

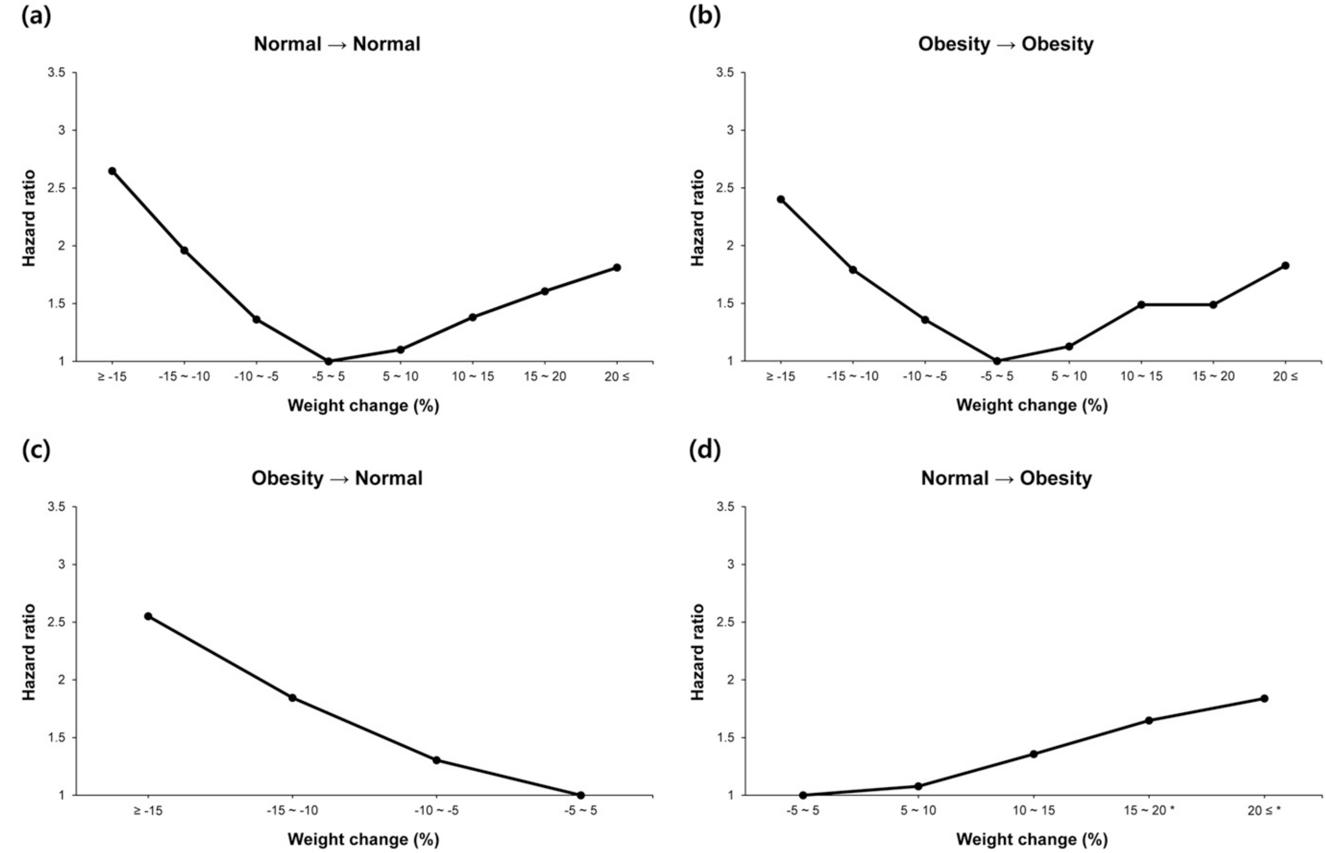

Figure 2. Graphs indicating results of change in BMI by category, and all-cause mortality according to weight change. (a) Normal to normal BMI change group. (b) Obese to obese BMI change group. (c) Obese to normal BMI change group. (d) Normal to obese BMI change group. Data were adjusted for age, sex, smoking, drinking, exercise, DM, HTN, dyslipidemia, cancer, and income. *Not statistically significant.

Weight loss was associated with increased mortality rates (11–20) even after excluding subjects with coexisting morbidity (13, 14, 17–19, 23). In this study, weight loss caused more deaths than did weight gain and this association was still maintained in subgroup analysis in the group without chronic disease and no-cancer group. In the first National Health and Nutrition Examination Survey, with a 5-year follow-up, weight loss ≥15% increased mortality by twofold compared with weight loss <5% in men and women (28). In a large-scale Japanese cohort study over 8.7 years, a reverse J-shaped association between weight change during a 5-year period and all-cause mortality was observed, and weight loss was associated with a greater HR for all-cause mortality than was weight gain (25). However, other studies showed no association between weight loss and mortality in healthy Japanese-American men (21) and Dutch women older than age 50 years (22).

The mechanism underlying the association between weight loss and mortality is unclear, although changes in body composition, such as muscle mass decline, particularly among the elderly, has been considered (29). Weight loss, particularly among the elderly, is associated with frailty, which correlates with morbidity, falls, disability, hospitalization, and mortality (30). Weight loss is associated with oxidative DNA damage, which is hypothesized to exert a carcinogenic effect (31) and may also weaken the immune system (32), increasing the incidence of cancer and cancer-related mortality. In underweight individuals, weight loss ≥5% and a 5% to 15% weight gain were associated with increased mortality. In a Swiss national cohort study, the underweight group had increased mortality risk (33). Moreover, in a US population study, the underweight participants who lost >5% of their weight had a 1.87 times increased risk for all-cause mortality (20). However, the effect of weight gain in the underweight subjects' mortality is controversial. Weight gain of 5% to 15% was not associated with increased mortality rate in the US population study, but >15% weight gain was associated with decreased mortality in underweight elderly people (20). Moreover, one study found a beneficial effect of weight gain on mortality (34). In this study, weight gain ≥15% in underweight individuals was not associated with decreased mortality (34). This result may be due to the small number of underweight individuals gaining ≥15% of their weight. Moreover, the Japanese study (25) reported the highest mortality rates among patients with weight loss ≥5 kg, particularly in the BMI <22 kg/m^2 group (HR, 2.85 in men and 3.62 in women). However, our study shows conflicting results, with the highest HR for mortality in the BMI ≥30 kg/m^2 group with weight loss ≥15% compared with the group with BMI <18.5 kg/m^2 and weight loss ≥15%. This difference may be due to the effects of the different exclusion criteria. The Japanese study excluded subjects with BMI <14 kg/m^2 and ≥40 kg/m^2, and chronic diseases, such as cancer, cerebrovascular disease, chronic liver disease, and myocardial disease. Moreover, different effects of weight and BMI on mortality or morbidity in Korean and Japanese subjects may also have different effects (35). Further research, including genomic studies, is required to evaluate the differences among ethnicities (36).

Many studies have reported the association between weight gain and increased mortality (12, 23, 24). However, some studies found no association between weight gain and mortality (11–17, 21, 22, 37). The conflicting findings may result from study design, subject age, duration of weight change or observation period, and cause of death. Weight gain also increases the risk of DM, HTN, and cardiovascular disease risk factors (38–40), with a resulting increase in inflammation, which may increase mortality (41). Obesity-related cancers, including colorectal, prostate, and breast cancer, are more common in the obese population and weight gain is associated with increased cancer-related mortality (42, 43). Nevertheless, weight gain increases mortality to a lesser extent than weight loss, and this may be explained by weight tolerance associated with aging. People tend to gain weight over the life span (44, 45), so people have some tolerance to weight gain and, therefore, there may be a decreased effect of weight gain, compared with weight loss, on mortality (24). Moreover, weight loss with concomitant chronic diseases is largely due to loss of lean body mass, which is replaced by fat mass, resulting in greater increases in mortality in the weight loss group than in the weight gain group (24). However, in two studies including the reanalysis of Framingham Heart Study and the Tecumseh Community Health Study data, authors suggested that weight loss via fat mass may reduce mortality (46). Therefore, the lower mortality rates in the subjects in the group who had one or more chronic diseases than in subjects without chronic diseases may be explained by intentional weight loss, although we could not know intention of weight change in this study. More precisely designed studies are needed to reveal this result.

We also examined the categorical BMI change and all-cause mortality according to weight change. In the Ohsaki study, change from normal BMI (*i.e.*, 18.5 to 24.9 kg/m^2) to overweight BMI (*i.e.*, 25 to 29.9 kg/m^2) was associated with decreased all-cause mortality (HR, 0.87), but change from normal BMI to obese BMI was associated with increased all-cause mortality (HR, 1.38), and stable obese BMI was also associated with increased all-cause mortality (HR, 2.21) (47). In our study, increased mortality was observed in the normal to obese BMI group, consistent with the Ohsaki study, although, the same weight change was associated with a greater increase in mortality in the obese to normal BMI group than in the normal to obese BMI group. Moreover, stable normal weight subjects had an increased mortality rate compared with stable obese subjects with the same weight loss. These results suggest that normal-weight people may be more sensitive to weight loss than obese subjects, and weight loss may be more harmful than weight gain, contrary to popular belief, even in obese subjects. A Swedish study found that overweight or obese people had increased rates of noncancer mortality after weight loss; therefore, we postulated that increased mortality in obese subjects may be caused by noncancer mortality in this weight loss group (48), although we did not know the cause of death in this study. Another potential explanation is that in persons who are obese and maintain obese status for a long time, the sustained effect of excess weight and fat mass or weight change become less harmful (49).

Although we could not examine the cause of death in this study, we analyzed the association between weight change and mortality in subgroup analysis. Some studies have found that BMI values at younger ages have a greater predictive power with respect to mortality than BMI values at older ages (50, 51). Moreover, weight loss in the elderly mainly results from preexisting or new onset of disease, and weight gain may cause few adverse effects on mortality in the elderly (49). This is explained by the fact that cumulative body mass has already exerted an effect on mortality from early adulthood; therefore, weight gain in later life has little effect on mortality (24). Weight change resulted in greater increases in mortality in the noncancer group than in the cancer group. This implies that substantial weight change in individuals without cancer reflects development of a new condition not captured or reflected in their data; for example, the effect of educational interventions about weight change in patients with cancer. The effects of weight change on mortality were also greater among nonsmokers than among smokers in this study. A similar association was also reported in a Japanese study (25) and in Western studies (13–15, 17–19, 23); therefore, we postulated that smoking may modify the weight change effect on mortality such that the cumulative effect of smoking supersedes the effect of weight change.

This study has several limitations. First, we did not know whether weight change was intentional or unintentional. Intentional weight loss to improve health is associated with lower mortality (9, 10). The exclusion of participants losing weight intentionally may affect these results, particularly for obese participants. Second, we did not assess body composition. Weight loss involving muscle mass will increase mortality to a greater extent than weight loss involving fat mass (29); however, the measurement of body composition in large cohort studies is challenging. Third, we were not able to design this study to assess time and duration of comorbidities, which also affect weight status. Fourth, the duration of weight change and the mean observational time were too short to fully assess the association between weight change and mortality. Fifth, we did not know the cause of death; studies on causes of death according to weight change are required. Sixth, this study only included Korean participants and results cannot be generalized to other ethnicities. The effect of weight may be different by cancer type and ethnicity. Stomach and esophageal cancer are common in Korea and Japan but not in Western countries, and are more prevalent in low-BMI populations (52).

Nevertheless, this study has important strengths. To the best of our knowledge, this is the first study to examine weight change and all-cause mortality in a large population of Korean adults. Second, we conducted a nationwide study involving a homogeneous participant group. Furthermore, we analyzed various subgroups, adjusting for covariates potentially affecting mortality.

In conclusion, weight change over 4 years showed a reverse J-shaped all-cause mortality curve independent of BMI status. Both weight loss and weight gain were associated with increased mortality and weight loss was associated with a greater mortality risk, particularly in the BMI ≥30 kg/m^2 group. Further research is required to establish the association between weight change and mortality by taking into account the intentional elements of weight loss and body composition. Moreover, studies on cause-specific mortality according to weight change are also required to determine the underlying mechanisms.

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