# U-Shaped Associations Between Body Weight Changes and Major Cardiovascular Events in Type 2 Diabetes Mellitus: A Longitudinal Follow-up Study of Over 1.5 Million Nationwide Cohort

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## OBJECTIVE

**Despite the benefits of weight loss on metabolic profiles in patients with type 2 diabetes mellitus (T2DM), its association with myocardial infarction (MI), ischemic stroke (IS), atrial fibrillation (AF), heart failure (HF), and all-cause death remains elusive.**

## RESEARCH DESIGN AND METHODS

**Using the National Health Insurance Service Database, we screened subjects who underwent general health checkups twice in a 2-year interval between 2009 and 2012. After identifying 1,522,241 patients with T2DM without a previous history of MI, IS, AF, and HF, we followed them until December 2018. Patients were stratified according to the magnitude of weight changes between two general health checkups: ≤ −10%, −10 to ≤ −5%, −5 to ≤5%, 5 to ≤10%, and >10%.**

## RESULTS:

**During the follow-up (median 7.0 years), 32,106 cases of MI, 44,406 cases of IS, 34,953 cases of AF, 68,745 cases of HF, and 84,635 all-cause deaths occurred. Patients with weight changes of −5 to ≤5% showed the lowest risk of each cardiovascular event. Both directions of weight change were associated with an increased cardiovascular risk. Stepwise increases in the risks of MI, IS, AF, HF, and all-cause death were noted with progressive weight gain (all $P < 0.0001$). Similarly, the more weight loss occurred, the higher the cardiovascular risks observed (all $P < 0.0001$). The U-shaped associations were consistently observed in both univariate and multivariate analyses. Explorative subgroup analyses also consistently showed a U-shaped association.**

## CONCLUSION

**Both weight loss and gain >5% within a 2-year interval were associated with an increased risk of major cardiovascular events in patients with T2DM.**


Type 2 diabetes mellitus (T2DM) is a prevalent disease worldwide, and its burden has progressively increased over the last decades (1). Numerous attempts have

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been made to improve the clinical outcomes of patients with T2DM because of its substantial contribution to cardiovascular morbidity and mortality (2). Pharmacologic and nonpharmacologic appr oaches have both been investigated (3,4) and have shown therapeutic benefits mainly by improving metabolic profiles and decreasing microvascular complications (5). Recently, sodium–glucose cotra nsporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP1) agonists have demonstrated their remarkable benefits in reducing major cardiovascular events in randomized controlled trials (6–8).

Obesity is a major risk factor for T2DM (9). Previous studies reported that weight loss in obese patients with T2DM can lead to a reduction in blood glucose, $HbA_{1c}$, and triglyceride levels (10–14). They also reported that weight loss is associated with improvements in regulating blood pressure and LDL and HDL cholesterol levels. However, these reports were based on a relatively small number of subjects and short-term follow-up duration and only showed improvements in metabolic profiles, but not in major cardiovascular events (10–14). In this regard, a paucity of data exists on whether weight loss could reduce major adverse cardiovascular outcomes in patients with T2DM. By contrast, recent studies have demonstrated that weight variability is associated with an increased risk of cardiovascular outcomes in patients with diabetes (15,16). Taken together, whether weight loss could improve major cardiovascular outcomes is unclear among overweight or obese pa tients with T2DM in the long-term follow-up. In addition, data regarding how underweight or normal-weight patients with T2DM should be managed in terms of their body weight are scarce (17).

Therefore, we aimed to investigate the association between weight changes and major cardiovascular outcomes, including myocardial infarction (MI), ischemic stroke (IS), atrial fibrillation (AF), heart failure (HF), and all-cause death in patients with T2DM by using a nationwide database.

## RESEARCH DESIGN AND METHODS

### Ethical Statement

The study was conducted in accordance with the Declaration of Helsinki. It was approved by our Institutional Review Board (IRB No. E-2107-013-1232). The need for informed consent was waived because anonymized data were used.

### Data Source and Study Population

This nationwide population-based cohort study used data from the Korean National Health Insurance Service (NHIS) database. A summary of the NHIS database has been previously reported (18,19). In brief, the NHIS is a single public insurer that covers the entire Korean population and encourages eligible Korean adults to receive general health checkups provided by the NHIS biannually. Therefore, the NHIS database includes individual demographic information, history of diagnoses, and results of health checkups. Individuals' history of diagnoses was coded according to the ICD-10-CM. We also obtained mortality data from Statistics Korea, as described previously (20).

The study design and flowchart of the selection of study subjects are shown in Fig. 1*A* and *B*. We identified 2,746,988 patients diagnosed with T2DM in general health checkups between 1 January 2009 and 31 December 2012. Patients who were newly diagnosed at health checkups and those who had been previously diagnosed with T2DM were included. This study included adult patients (age $\geq$20 years) who underwent both first and second general health checkups before 31 December 2012. We excluded subjects who had a previous history of MI, IS, AF, and/or HF before their second general health checkup. Patients with missing data during the general health checkups were also excluded. A total of 1,522,241 patients with T2DM were finally included and followed up until December 2018. The index date was the date of the second general health checkups, and data on baseline characteristics were collected from the index date.

### Definitions of Diabetes and Body Weight Change

Patients with T2DM were defined as follows: *1*) having at least one claim per year for a prescription of antidiabetes medication under ICD-10-CM codes (i.e., E11–14) from the insurance claims data or *2*) having a fasting blood glucose (FBG) $\geq$126 mg/dL in the general health checkups without a prescription of oral hypoglycemic agents or insulin (21,22). Antidiabetes medications included metformin, sulfonylureas, meglitinides, dipeptidyl peptidase 4 inhibitors, thiazolidinediones, $\alpha$-glucosidase inhibitors, and insulin. Care was taken to exclude patients with type 1 diabetes (ICD-10-CM code E10). Medications were assessed at the index year, and T2DM duration was measured from the first diagnosis of T2DM up to the index date.

Body weight change was calculated as the difference in body weight between the first and second general health checkups (Fig. 1*A*). Patients were categorized into five groups according to body weight change between first and second general health checkups: severe weight loss group (weight change of $\leq -10\%$), moderate weight loss group (weight change of $-10$ to $\leq -5\%$), stable weight group (weight change of $-5$ to $\leq 5\%$), moderate weight gain group (weight change of 5 to $\leq 10\%$), and severe weight gain group (weight change of $>10\%$) (Fig. 1*B*).

### Definitions of Covariates and Clinical End Points

The date of the second general health checkup in each subject was designated as an index date. Demographic data, anthropometric data, and a previous history of hypertension, dyslipidemia, chronic kidney disease, peripheral artery disease, chronic obstructive pulmonary disease, cancer, and hyperthyroidism were obtained. In addition, data on lifestyle behaviors, T2DM duration, and use of insulin and/or oral hypoglycemic agents were collected. Data on alcohol consumption and physical activity were collected via a self-reported questionnaire. Specifically, average alcohol intake per day (g/day) was analyzed to evaluate alcohol consumption, and patients were subsequently categorized into non, mild ($<$30 g/day), and heavy ($\geq$30 g/day) drinkers. Regular physical activity was defined as moderate intensity exercise taken for $>$30 min and $\geq$5 days/week or vigorous intensity exercise taken for $>$20 min and $\geq$3 days/week. Examples of moderate or vigorous intensity exercise type were previously reported (20). Low income level was defined as the composite of the lowest quartile of yearly income in addition to Medicare beneficiaries.

We defined newly diagnosed cardiovascular events of MI, IS, AF, HF, and all-cause death as the study end points (Fig. 1*A*). These end points were defined based on the ICD-10-CM codes with additional conditions. Detailed definitions of comorbidities and study end points are provided in Supplementary Table 1. The date of death was also obtained from the NHIS

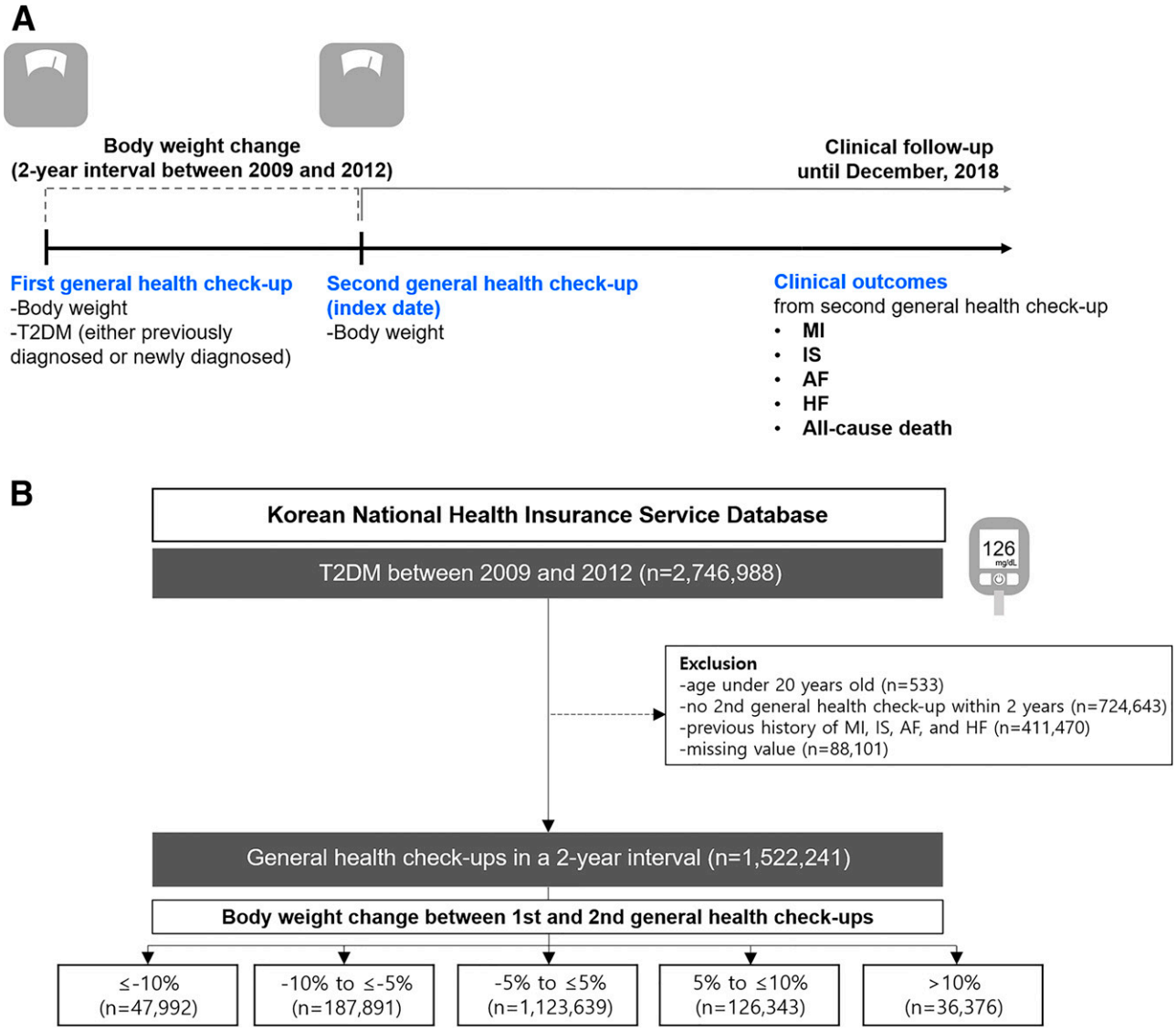


**Figure 1**—Study population. Study design (*A*) and flowchart of the selection of subjects (*B*).

database and Statistics Korea. Follow-up duration was defined as the interval between the index date and the first occurrence of the aforementioned study end points.

### Statistical Analysis

Data are presented as numbers and frequencies for categorical variables and as means ± SDs or medians with interquartile ranges for continuous variables. For categorical variables, the $\chi^2$ test or Fisher exact test was used, as appropriate. One-way ANOVA was used to analyze continuous variables between more than two groups. The annual event incidence rates (aIR) were calculated as the number of events per 1,000 person-years (PY). Multivariate Cox proportional hazard regression models were used to estimate hazard ratios (HRs) and corresponding 95% CIs for the associations between weight changes and cardiovascular outcomes. Patients with body weight changes of −5 to ≤5% were adopted as a reference group in multivariate analyses. The multivariable models were adjusted for covariates including age, sex, previous history of hypertension, dyslipidemia, cancer, hyperthyroidism, chronic kidney disease, peripheral artery disease, chronic obstructive pulmonary disease, income level, smoking status, drinking habit, regular physical activity, insulin medication, use of oral hypoglycemic agents, and obesity defined by BMI ≥25 kg/m$^2$. Subgroup analyses were separately conducted according to age, sex, obesity, T2DM duration, and T2DM medication using Cox models. A two-sided *P* value of $<0.05$ was considered statistically significant. All statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC).

### Data and Resource Availability

All raw data were accessible from designated terminals approved by the NHIS. For reasonable request, data are available through approval and oversight by the Korean NHIS.

## RESULTS

### Baseline Characteristics of the Study Population

In total, 1,522,241 patients with T2DM, but without a previous history of MI, IS, AF, and HF (mean age, 56.3 ± 12.0 years;

men, 969,118 [63.7%]), were analyzed. Hypertension was present in 787,078 patients (51.7%), dyslipidemia in 606,618 patients (39.9%), and chronic kidney disease in 122,128 patients (8.0%). With regard to medication for T2DM, 667,582 (43.9%) patients were free of antidiabetes medication, 839,513 (55.2%) patients took oral antihypoglycemic agents, and 100,238 (6.6%) patients were on insulin therapy.

Patients were categorized into five groups according to body weight change, and the baseline characteristics of each group are shown in Table 1. The weight gain groups were younger, had a higher BMI, and had a lower prescription rate of oral hypoglycemic agents than the weight loss groups. The weight loss groups showed better metabolic profile changes (i.e., decrease of blood pressure and improvement of lipid profiles).

### U-Shaped Association Between Cardiovascular Events and Body Weight Change

During the median follow-up of 7.03 years (interquartile range 6.13–7.53), 32,106 cases of MI, 44,406 cases of IS, 34,953 cases of AF, 68,745 cases of HF, and 84,635 cases of all-cause death occurred. The aIRs of MI were 4.29, 3.62, 3.06, 3.19, and 3.59 per 1,000 PY for severe weight loss, moderate weight loss, stable weight, moderate weight gain, and severe weight gain groups, respectively. After adjusting for covariates, both weight loss (HR 1.24, 95% CI 1.17–1.32 for the severe weight loss group; HR 1.11, 95% CI 1.08–1.15 for the moderate weight loss group) and weight gain (HR 1.08, 95% CI 1.04–1.12 for the moderate weight gain group; HR 1.17, 95% CI 1.09–1.25 for the severe weight gain group) were significantly associated with an increased risk of MI compared with the stable weight group (Fig. 2*A* and Supplementary Table 2). With regard to IS, the aIRs were 6.21, 5.07, 4.23, 4.44, and 5.25 per 1,000 PY in groups of weight change of $\leq -10\%$, $-10$ to $\leq -5\%$, $-5$ to $\leq 5\%$ , 5 to $\leq 10\%$, and $>10\%$, respectively. Multivariate Cox regression analyses demonstrated a higher risk of IS in the weight loss groups (HR 1.20, 95% CI 1.14–1.26 for the severe weight loss group; HR 1.09, 95% CI 1.06–1.12 for the moderate weight loss group) and weight gain groups (HR 1.10, 95% CI 1.06–1.14 for the moderate weight gain group; HR 1.24, 95% CI 1.07–1.31 for the severe weight gain group) (Fig. 2*B* and Supplementary Table 2).

Similar associations with body weight changes were observed in AF and HF. The aIRs of AF were 4.53, 3.81, 3.38, 3.35, and 3.86 per 1,000 PY for the severe weight loss, moderate weight loss, stable weight, moderate weight gain, and severe weight gain groups, respectively. As body weight changed, either increasing or decreasing, the risk of AF progressively increased and showed a U-shaped association (HR 1.24, 95% CI 1.17–1.31 for the severe weight loss group; HR 1.09, 95% CI 1.06–1.13 for the moderate weight loss group; HR 1.03, 95% CI 0.99–1.08 for the moderate weight gain group; and HR 1.15, 95% CI 1.08–1.23 for the severe weight gain group) (Fig. 2*C* and Supplementary Table 2). HF also showed a U-shaped association with body weight changes (aIR 10.73, 7.95, 6.44, 7.00, and 8.77 per 1,000 PY across groups from severe weight loss to severe weight gain). The risks for HF were as follows: HR 1.41, 95% CI 1.36–1.47; HR 1.14, 95% CI 1.11–1.16; HR 1.13, 95% CI 1.10–1.16; and HR 1.35, 95% CI 1.30–1.42 in the severe weight loss, moderate weight loss, moderate weight gain, and severe weight gain groups, respectively, when the stable weight group was set as the reference (Fig. 2*D* and Supplementary Table 2).

Weight loss and gain were associated with higher risks of all-cause death. The aIRs of mortality were 19.04, 10.80, 7.35, 8.62, and 12.09 per 1,000 PY for severe weight loss, moderate weight loss, stable weight, moderate weight gain, and severe weight gain groups, respectively. Mortality risk was significantly increased in both weight loss (HR 1.87, 95% CI 1.82–1.92 and HR 1.26, 95% CI 1.24–1.29 for the severe weight loss and moderate weight loss groups, respectively) and weight gain groups (HR 1.23, 95% CI 1.20–1.27 and HR 1.63, 95% CI 1.57–1.70 for the severe weight gain and moderate weight gain groups, respectively) (Fig. 2*E* and Supplementary Table 2).

### Subgroup Analyses for Cardiovascular Events

To determine whether the prognostic effect of body weight changes is modified by baseline BMI status, we stratified the subjects into two groups: patients with BMI $<25$ kg/m$^2$ and those with BMI $\geq 25$ kg/m$^2$ (Supplementary Fig. 1). Regardless of baseline BMI status, both weight loss and weight gain were consistently associated with higher risks of MI, IS, AF, HF, and all-cause death; even weight gain in patients with BMI $<25$ kg/m$^2$ and weight loss in those with BMI $\geq 25$ kg/m$^2$ were associated with increased risks compared with the stable weight group. In addition to BMI, we performed explorative subgroup analyses, and the results for each of MI, IS, AF, HF, and all-cause death are provided in Supplementary Tables 3–7. Briefly, a U-shaped association between weight change and major cardiovascular events was again observed in all subgroups stratified by age, sex, T2DM duration, and use of antidiabetes medication.

## CONCLUSIONS

In this study, we investigated the association between body weight changes and major cardiovascular events in patients with T2DM, but without a previous history of major cardiovascular events, including MI, IS, AF, and HF. The main findings are summarized as follows. First, approximately one-fourth of the patients experienced weight loss or weight gain of $>5\%$ at 2 years of follow-up in a large nationwide population-based T2DM cohort. Second, U-shaped associations between body weight change and major cardiovascular events (i.e., MI, IS, AF, and HF), and all-cause death were observed (Fig. 3). Third, these U-shaped associations were consistently observed in explorative subgroup analyses according to age, sex, obesity, T2DM duration, and T2DM medication.

Several studies have shown metabolic profile improvement in patients with T2DM who experienced weight loss during follow-up. In particular, the United Kingdom Prospective Diabetes Study included 3,044 patients with T2DM and showed an association between weight loss and decreased $HbA_{1c}$ and FBG levels after a 3-month follow-up (13). Franz et al. (23) reported that in 179 patients with T2DM with only 6 months of follow-up, patients who experienced proper nutrition treatment could receive benefits, including weight loss and improvement in FBG, $HbA_{1c}$, and serum lipid levels. Several meta-analyses also showed that weight loss in patients with T2DM is associated with metabolic profile improvement (24,25). Based on

**Table 1—Clinical characteristics according to body weight change in patients with diabetes**

| | Body weight change | | | | | |
|---|---|---|---|---|---|---|
| | ≤ −10% | −10 to ≤ −5% | −5 to ≤ 5% | 5 to ≤10% | >10% | |
| | *n* = 47,992 | *n* = 187,891 | *n* = 1,123,639 | *n* = 126,343 | *n* = 36,376 | *P* value |
| Demographics | | | | | | |
| Age, years | 58.4 ± 13.5 | 57.6 ± 12.0 | 56.3 ± 11.7 | 54.4 ± 12.9 | 53.9 ± 14.3 | <0.0001 |
| Sex | | | | | | <0.0001 |
| Male | 24,075 (50.2) | 107,484 (57.2) | 735,633 (65.5) | 79,974 (63.3) | 21,952 (60.4) | |
| Female | 23,917 (49.8) | 80,407 (42.8) | 388,006 (34.5) | 46,369 (36.7) | 14,424 (39.7) | |
| BMI, kg/m$^2$ | 22.7 ± 3.4 | 23.9 ± 3.2 | 25.0 ± 3.2 | 25.7 ± 3.6 | 26.2 ± 4.0 | |
| Comorbidities | | | | | | |
| Hypertension | 24,180 (50.4) | 95,500 (50.8) | 584,997 (52.1) | 64,025 (50.7) | 18,376 (50.5) | <0.0001 |
| Dyslipidemia | 18,256 (38.0) | 74,958 (39.9) | 448,569 (39.9) | 50,274 (39.8) | 14,561 (40.0) | <0.0001 |
| Chronic kidney disease | 4,807 (10.0) | 15,812 (8.4) | 87,559 (7.8) | 10,460 (8.3) | 3,490 (9.6) | <0.0001 |
| Peripheral artery disease | 1,791 (3.7) | 6,593 (3.5) | 36,079 (3.2) | 3,963 (3.1) | 1,156 (3.2) | <0.0001 |
| COPD | 4,816 (10.0) | 16,164 (8.6) | 84,196 (7.5) | 9,901 (7.8) | 3,020 (8.3) | <0.0001 |
| Cancer | 4,568 (9.5) | 11,787 (6.3) | 53,764 (4.8) | 6,165 (4.9) | 1,905 (5.2) | <0.0001 |
| Hyperthyroidism | 1,001 (2.1) | 2,391 (1.3) | 10,155 (0.9) | 1,562 (1.2) | 774 (2.1) | <0.0001 |
| Social history | | | | | | |
| Low income level | 10,851 (22.6) | 40,346 (21.5) | 227,863 (20.3) | 27,422 (21.7) | 8,280 (22.8) | <0.0001 |
| Smoking | | | | | | <0.0001 |
| Nonsmoker | 29,714 (61.9) | 107,436 (57.2) | 581,722 (51.8) | 65,299 (51.7) | 19,521 (53.7) | |
| Former smoker | 7,169 (14.9) | 31,838 (16.9) | 235,819 (21.0) | 26,501 (21.0) | 7,129 (19.6) | |
| Current smoker | 11,109 (23.2) | 48,617 (25.9) | 306,098 (27.2) | 34,543 (27.3) | 9,726 (26.7) | |
| Alcohol consumption | | | | | | <0.0001 |
| Nondrinker | 32,101 (66.9) | 111,507 (59.4) | 578,162 (51.5) | 65,598 (51.9) | 20,386 (56.0) | |
| Mild drinker | 12,651 (26.4) | 60,254 (32.1) | 429,860 (38.3) | 48,142 (38.1) | 12,719 (35.0) | |
| Heavy drinker | 3,240 (6.8) | 16,130 (8.6) | 115,617 (10.3) | 12,603 (10.0) | 3,271 (9.0) | |
| Regular physical activity | 10,501 (21.9) | 43,237 (23.0) | 256,253 (22.8) | 25,205 (20.0) | 6,628 (18.2) | <0.0001 |
| Antidiabetes medication | | | | | | |
| Medication-naïve | 18,068 (37.7) | 73,220 (39.0) | 499,739 (44.5) | 60,154 (47.6) | 16,401 (45.1) | <0.0001 |
| Oral hypoglycemic agent | 29,239 (60.9) | 112,819 (60.0) | 613,730 (54.6) | 64,494 (51.1) | 19,231 (52.9) | <0.0001 |
| Insulin | 5,285 (11.0) | 14,269 (7.6) | 66,693 (5.9) | 9,979 (7.9) | 4,012 (11.0) | <0.0001 |
| Metabolic profile changes between 1st and 2nd general health checkups | | | | | | |
| Blood pressure | | | | | | |
| Systolic, mmHg | −4.6 ± 17.8 | −3.0 ± 16.9 | −0.3 ± 16.3 | 2.3 ± 16.7 | 3.1 ± 17.6 | <0.0001 |
| Diastolic, mmHg | 2.9 ± 11.9 | −2.0 ± 11.4 | −0.5 ± 11.1 | 0.9 ± 11.3 | 1.3 ± 11.8 | <0.0001 |
| Total cholesterol, mg/dL | −15.2 ± 53.5 | −10.2 ± 47.6 | −5.0 ± 44.5 | −1.6 ± 45.9 | −0.8 ± 52.6 | <0.0001 |
| Triglyceride, mg/dL | −43.9 ± 146.7 | −33.8 ± 136.7 | −9.4 ± 135.2 | 12.4 ± 137.8 | 15.2 ± 148.0 | <0.0001 |

Data are presented as mean ± SD or *n* (%). COPD, chronic obstructive pulmonary disease.

these reports, the current guidelines recommend weight loss in patients with T2DM who are overweight or obese (17). However, no data are available directly showing associations between weight loss in patients with T2DM and reduction in cardiovascular morbidities and mortality. This issue is of clinical value, because improvement in surrogate markers, such as FBG, $HbA_{1c}$, and serum lipid profiles, is not always translated into improvement in hard clinical end points. To deal with this important issue, a long-term follow-up period may be required. Proving the benefits of hyperglycemia control on major cardiovascular events requires a prolonged follow-up period compared with those on microvascular complications (5,26). In this regard, the aforementioned studies had insufficient follow-up duration to evaluate the association between body weight loss and major cardiovascular events. Moreover, as the clinical implication of weight changes in underweight patients with T2DM has rarely been investigated (27), this issue remains unclear in the current practice guidelines (17). The Korean nationwide database provides a good opportunity to unveil the association between body weight changes and cardiovascular events because of the large number of unselected participants with T2DM and long-term follow-up period.

Increasing risks of cardiovascular events in association with weight gain are in line with previous reports (28,29), but increasing risks of cardiovascular events in relation to weight loss, even with blood pressure reduction and lipid profiles improvement, could be counterintuitive and surprising. These observations have several plausible explanations. Weight loss is associated with a reduction in fat mass and lean mass (30). Caloric restriction and weight loss could lead to incident hypoglycemic events and frailty in patients with T2DM (31). Body weight variability, regardless of weight gain or loss, has been reported to have an effect on increased risks of various

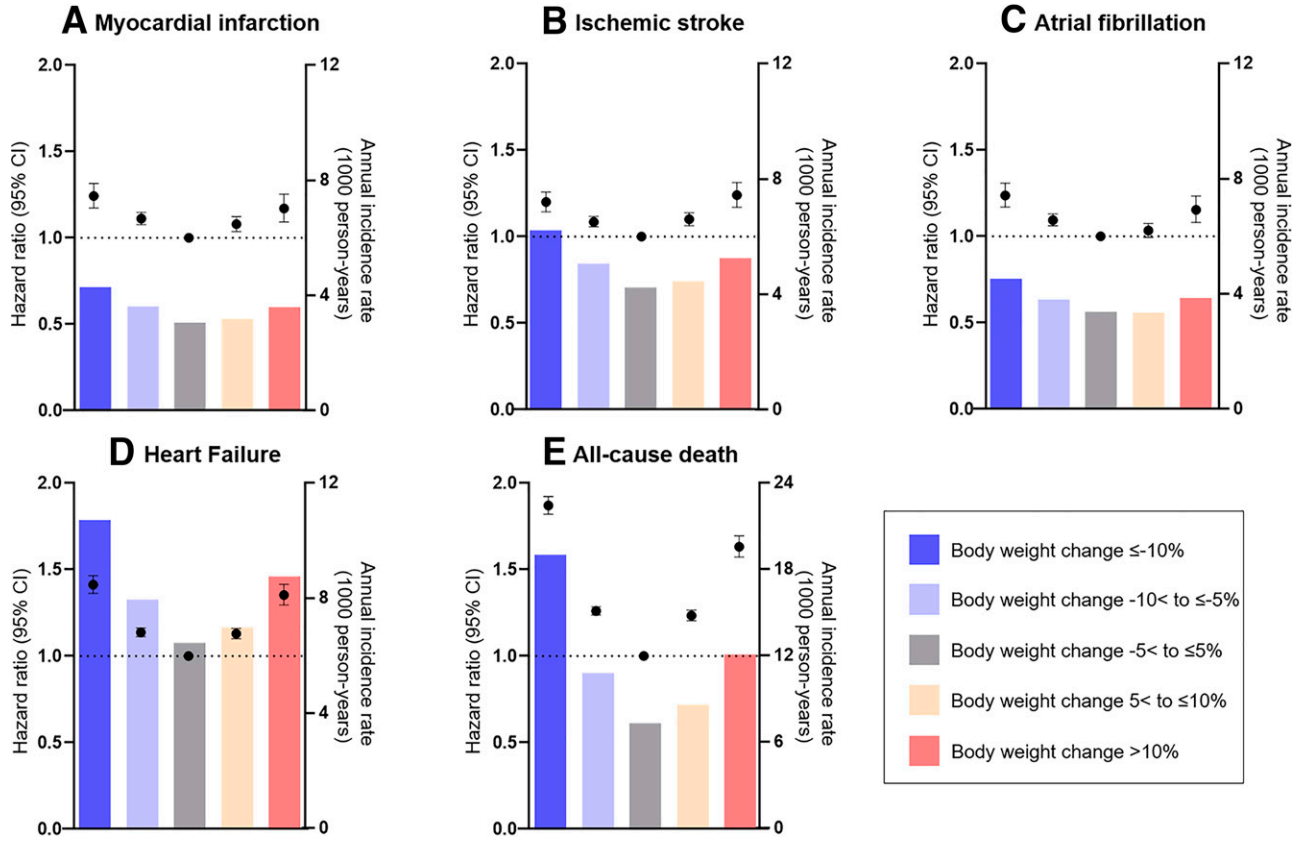


**Figure 2**—Risks for each of MI (*A*), IS (*B*), AF (*C*), HF (*D*), and all-cause death (*E*) according to body weight change. HRs with 95% CIs are presented as dot and whisker plots after adjusting for covariates (adjusted for age, sex, previous history of hypertension, dyslipidemia, cancer, hyperthyroidism, chronic kidney disease, peripheral artery disease, chronic obstructive pulmonary disease, income level, smoking status, drinking habit, regular physical activity, insulin medication, use of oral hypoglycemic agents, and obesity defined by BMI ≥25 kg/m$^2$). The aIRs for each cardiovascular event are denoted by bars.

cardiovascular events (15,16,22). Taken together, the longer-term association between weight loss and cardiovascular events in patients with T2DM is possibly more complicated than we have expected based only on simple metabolic profile improvement with relatively limited follow-up duration.

Meticulous and intensive care with medical nutrient education is difficult to perform in a real-world clinical setting; however, this has been performed in previous randomized controlled trials (10,11,13). In addition, intentional versus unintentional weight loss could not be easily distinguished in the current study. Unintentional weight loss is prevalent and has been known to have harmful effects on clinical prognosis (32–34). Therefore, weight loss in patients with T2DM observed in the clinic might not necessarily reflect metabolic improvement.

Although weight loss was associated with improvement in the metabolic profiles in patients with T2DM (13,23–25), it has been unclear whether weight loss could also improve clinical outcomes in patients with T2DM. To our knowledge, this study is the first to show comprehensive relationships between body weight change and major cardiovascular events in a sizable T2DM cohort with a long-term follow-up. This study has two main strengths. First, it was based on a nationwide prospective database officially managed by the Korean government. Although a randomized controlled trial is the best to prove any hypothesis, an ethical issue may arise in a trial demanding weight gain or weight loss. Therefore, a well-designed observational study including a large number of subjects with a long-term follow-up period is the best alternative and could provide valuable information. Second, we performed several statistical analyses and showed that the interaction between body weight change and cardiovascular outcomes in patients with T2DM was consistent in univariate and multivariate analyses to minimize bias. This was also true in the multiple exploratory subgroup analyses.

This study also has several limitations. First, this was an observational study. Despite a large and well-controlled study, we could not exclude the possibility of unmeasured confounding factors contributing to a U-shaped association between body weight changes and major cardiovascular events. In particular, information on the family history of T2DM and/or cardiovascular events was not available in the NHIS database.

Second, for the purpose of statistical analysis, this study categorized all participants into five groups according to body weight change based on general health checkups between 2009 and 2012. This time point was before the introduction of SGLT2 inhibitors and GLP1 analogs in Korea, both of which proved substantial cardiovascular risk reduction. In addition, as the use of SGLT2 inhibitors and GLP1 analogs resulted in significant weight loss, extrapolating the study results to patients taking these two classes of antidiabetes medication is not reasonable.

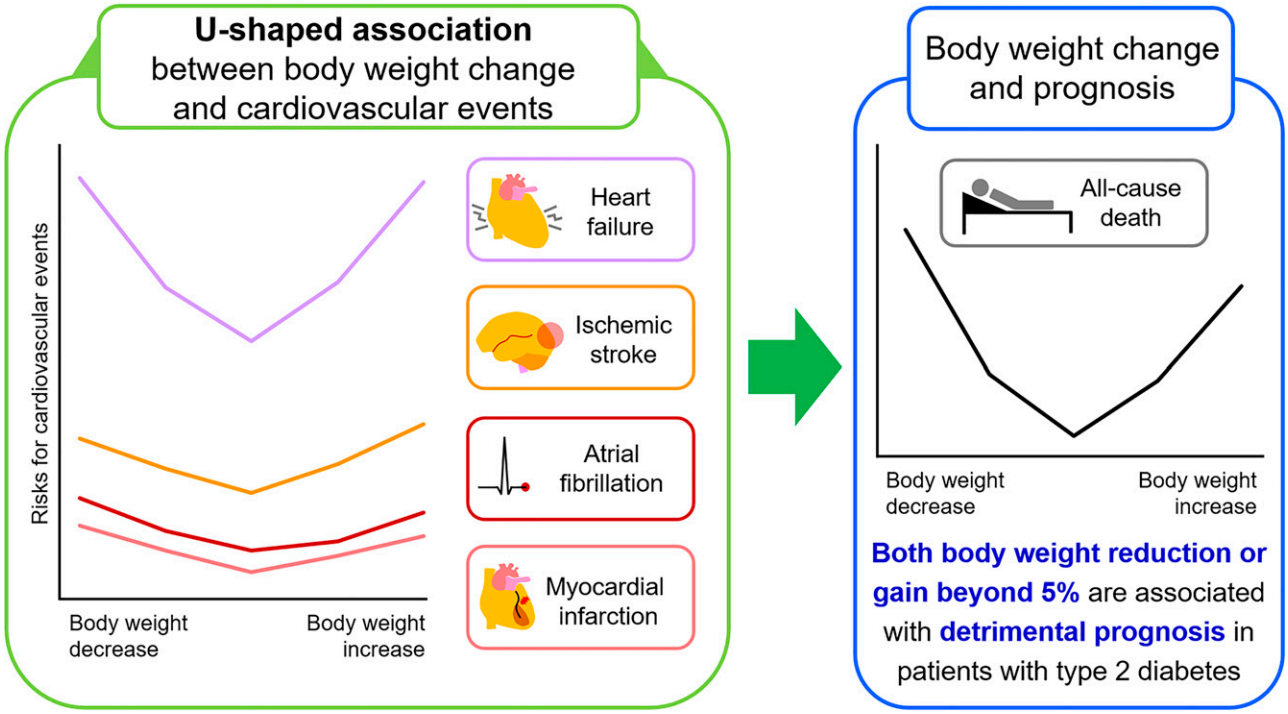


**Figure 3**—U-shaped associations between body weight change and major cardiovascular events were consistently observed. Weight gain and loss were significantly associated with increased risks of MI, AF, IS, HF, and all-cause death.

Third, apart from antidiabetes medication issues, body weight and metabolic profiles might have changed during the follow-up after the second general health checkup, information of which is not available. In addition, we could not sophisticatedly identify the reason of weight changes in each subject (35).

Fourth, we did not assess changes in cardiorespiratory fitness and had only crude assessment of physical activity. Cardiorespiratory fitness is known to be significantly reduced in T2DM and obesity (9). Given the close association of greater cardiorespiratory fitness with overall improved clinical outcomes, some interventions, such as enhanced physical activity, exercise training, and healthy diet, have been proposed as effective therapeutic strategies to prevent adipose tissue remodeling and eventually modify prognosis (36–38).

Lastly, the study results were derived from patients with T2DM. Thus, the results of the current study are not generalizable to other populations.

Despite all of the above limitations, this nationwide cohort enabled us to provide a notably large number of subjects with long-term follow-up that effectively reflected the phenomenon observed in real-world practice.

## Conclusion

In this large nationwide cohort study, a U-shaped association was found between body weight change and major cardiovascular event risks such as MI, IS, AF, HF, and all-cause death.

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**Author Contributions.** C.S.P contributed to the conception and design of the work, data interpretation and analysis, and drafting of the manuscript. Y.-J.C., T.-M.R., H.J.L., H.-S.L., J.-B.P., and Y.-J.K. contributed to the conception and design of the work and critically revised the manuscript. K.-D.H. contributed to the conception, design, data acquisition, and analysis and critical revision of the manuscript. H.-K.K. contributed to conception, design, data acquisition and interpretation, and critical revision of the manuscript. K.-D.H. and H.-K.K. and are guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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