Body Weight Variability and the Risk of Cardiovascular Outcomes and Mortality in Patients With Type 2 Diabetes: A Nationwide Cohort Study

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OBJECTIVE

Obesity and type 2 diabetes are risk factors for cardiovascular diseases and mortality, and they commonly result in weight variabilities. We aimed to investigate the association between body weight variability and risk of major cardiovascular outcomes and mortality in individuals with type 2 diabetes using large-scale, nationwide cohort data on the Korean population.

RESEARCH DESIGN AND METHODS

We enrolled 624,237 individuals with type 2 diabetes who underwent health examinations provided by the Korean National Health Insurance System between 2009 and 2010, with three or more body weight measurements within 5 years since enrollment and followed up until the end of 2017. We assessed body weight variability using four indices, including variability independent of the mean (VIM). A multivariate-adjusted Cox proportional hazards regression analysis was performed.

RESULTS

During the follow-up, 15,832, 25,038, and 44,716 cases of myocardial infarction (MI), stroke, and all-cause mortality, respectively, were recorded. Body weight variability was associated with increased risks of major cardiovascular outcomes after adjusting for confounding variables. Compared with the hazard ratios (HRs) of the lowest quartile group, the HRs (95% CIs) of the highest quartile group of VIM for body weight were 1.15 (1.10–1.20), 1.22 (1.18–1.26), and 1.58 (1.53–1.62) for MI, stroke, and all-cause mortality, respectively.

CONCLUSIONS

Body weight variability was associated with increased risks of MI, stroke, and all-cause mortality in patients with type 2 diabetes and may be a predictor of cardiovascular outcomes in such patients. Appropriate interventions to maintain stable weight could positively influence health outcomes in patients with type 2 diabetes.

Obesity is a widely accepted risk factor for cardiovascular diseases (CVDs) and mortality (1,2), and substantial evidence has shown the effects of body weight reduction in preventing diverse diseases in obese people (3). The public health recommendation to obese individuals, therefore, is that they should achieve proper body weight. The American Diabetes Association also recommends high-intensity

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interventions for regulating diet, physical activity, and behavior to reduce weight, followed by long-term comprehensive weight maintenance programs (4). However, it is common to regain body weight after successfully reducing it (5,6); ~80% of individuals who intentionally lose ≥10% of their body weight regain weight within 1 year (7). A previous study reported that individuals with diabetes regain their weight more rapidly and lose less weight than those without diabetes (8). Moreover, weight variability may lead to negative changes in body composition and adverse health outcomes (9–12).

Considering that obesity is one of the most important risk factors for type 2 diabetes, it is meaningful to assess the association between weight variability and subsequent health outcomes in patients with type 2 diabetes, especially given that type 2 diabetes is a very common metabolic disease across the world (13). The global prevalence of diabetes increased by 30%, from 333 million to 435 million individuals, between 2005 and 2015 (14). The prevalence of type 2 diabetes in Korea has increased from <1% in 1960 to 10.8% in 2013 (15). Although type 2 diabetes is a well-known risk factor for CVDs and mortality (16), there is extremely limited evidence supporting the association between weight variability and health outcomes in patients with type 2 diabetes. To our knowledge, only two epidemiological studies have investigated this issue. An Italian study conducted in older patients with type 2 diabetes suggests that body weight variability is associated with an increased risk of all-cause mortality (17). A study conducted in the U.S. reported that variabilities in body weight are associated with higher mortality and major cardiovascular events among patients with type 2 diabetes (18). However, this association was not observed in non-Western populations. Therefore, we aimed to investigate the association between body weight variability and risk of CVDs and mortality in patients with type 2 diabetes using large-scale, nationwide cohort data on a South Korean population.

RESEARCH DESIGN AND METHODS

Data Source and Study Population

This study was based on a data set provided by the National Health Insurance System (NHIS) of the National Health Insurance Corporation (NHIC) in South Korea. The South Korean NHIC is the only insurer managed by the South Korean government, and NHIS covers ~50 million people, accounting for 97% of the South Korean population. The NHIS data comprise various types of individual health information: eligibility (e.g., age, sex, and socioeconomic variables), disease diagnosis based on the ICD-10 Clinical Modification (ICD-10-CM), medical treatment and procedures, and health examination results (19). Individuals included in the NHIC are recommended to undergo a standardized medical examination at least every 2 years.

Of the 17,539,992 individuals who underwent health examinations provided by the South Korean NHIS between 1 January 2009 and 31 December 2010, we excluded those who underwent health examination fewer than two times within 5 years of enrollment (n = 9,163,132), aged <20 years (n = 106), with any missing variables (n = 165,191), without type 2 diabetes at the time of the first health examination (n = 7,508,386), and with prior diagnosis of myocardial infarction (MI) or stroke within 5 years of enrollment (n = 78,940). Finally, 624,237 individuals with type 2 diabetes (411,054 men and 213,183 women) and three or more available body weight measurements were enrolled in this study. The study participants were followed up until 31 December 2017. The mean follow-up duration was 7.6 ± 1.4 years for MI, 7.7 ± 1.3 years for stroke, and 7.8 ± 1.4 years for all-cause mortality. The flowchart of the study population is shown in Supplementary Fig. 1. This study protocol was approved by the Institutional Review Board of the Korea University Anam Hospital, Seoul, Korea (no. 2019AN0039). Informed consent was not obtained because deidentified and anonymous information was used in the analysis.

Definition of Type 2 Diabetes

Type 2 diabetes was defined as follows: *1*) at least one claim per year under ICD-10-CM codes E11–E14 and at least one claim per year for the prescription of antidiabetic medication or *2*) a fasting plasma glucose level ≥126 mg/dL.

Anthropometric Measurements and Indices of Body Weight Variability

Participants' height, body weight, and waist circumference were measured, and BMI was calculated as an individual's weight in kilograms divided by the square of their height in meters. We defined obesity as BMI ≥25 kg/m^2 based on the World Health Organization recommendations for Asian populations (20). A minimum of three body weight measurements made during 5 years prior to index date (including the examination at index date) were used in our analysis. Body weight variability was assessed using four indices: *1*) SD, *2*) coefficient of variation (CV), *3*) variability independent of the mean (VIM), and *4*) average real variability (ARV). VIM was calculated as $100 \times \mathrm{SD}/\mathrm{mean}^{\beta}$, where β is the regression coefficient, based on the ln of the SD over the ln of the mean. ARV is the average of the absolute differences between consecutive values and was calculated using the following formula: $\mathrm{ARV} = \frac{1}{n-1}\sum_{k=1}^{n-1}|Value_{k+1} - Value_k|$, where n denotes the number of anthropometric measurements. Change in body weight was calculated as the difference in weight within 5 years since enrollment. We defined <5% weight change as "stable weight" and categorized weight change into two groups: ≥5% weight loss and ≥5% weight gain.

Study Outcomes and Follow-up

Newly diagnosed MI, stroke, or all-cause mortality were the end points of this study. MI was defined as the recording of ICD-10-CM codes I21 or I22 during hospitalization or these codes being recorded at least twice. Stroke was defined as the recording of ICD-10-CM codes I63 or I64 during hospitalization with the application of brain MRI or brain computed tomography. Data on all-cause mortality were extracted from the Korean National Statistical Office. In this study, patients without MI or stroke during their follow-up periods were considered to have completed the study at the earlier occurrence of their cardiovascular events (MI or stroke) or on the date of all-cause death.

Definition of Covariates

A standardized self-reporting questionnaire was used to obtain demographic and lifestyle data. Smoking status was categorized as nonsmoker, former smoker, and current smoker. Individuals who consumed ≥30 g of alcohol per day were considered as heavy alcohol drinkers (21). Regular exercise was defined as performing strenuous physical activity for ≥20 min at least three times per week or moderate physical activity for ≥30 min at least five times per week. Income level was dichotomized into <25% or ≥25%. The South Korean NHIS provides health examinations

such as blood pressure (BP) and laboratory measurements. Systolic and diastolic BP was measured in the seated position after at least 5 min of rest. To measure serum glucose, lipid, and creatinine levels, blood samples were collected after an overnight fast. These health examinations were performed in hospitals certified by the NHIS and subjected to regular quality control. Baseline comorbidities were defined based on the combination of health examination results and ICD-10-CM diagnosis and prescription codes. Hypertension was defined as systolic/diastolic BP ≥140/90 mmHg or having claims for at least one prescription claim for antihypertensive medications per year under ICD-10-CM codes I10–I13 and I15. Dyslipidemia was defined as serum total cholesterol level ≥240 mg/dL or having at least one prescription claim of lipid-lowering medications per year under ICD-10-CM code E78. We defined estimated glomerular filtration rate <60 mL/min/1.73 m^2 as chronic kidney disease (22).

Statistical Analysis

SAS (version 9.4; SAS Institute, Cary, NC) was used for statistical analyses. The baseline characteristics of the study participants according to VIM for body weight are presented as mean ± SD for continuous variables and number (percentage) for categorical variables; continuous variables were compared using ANOVA, whereas categorical variables were compared using a χ^2 test. The incidence rate of study outcomes (MI, stroke, and all-cause mortality) was calculated by dividing the number of events by 1,000 person-years. Kaplan-Meier curves were generated to determine incidence probabilities of these outcomes based on the quartile group of body weight variability (VIM for body weight), and the log-rank test was performed to compare differences in incidence probabilities between groups. Multivariate-adjusted Cox proportional hazards regression models were used to examine the association between quartiles of variabilities in body weight and the risk of study outcomes, and hazard ratios (HRs) and 95% CIs were calculated compared with the lowest quartile group. Model 1 was adjusted for age and sex, whereas model 2 was adjusted for age, sex, smoking status, alcohol consumption, physical activity, income, hypertension, dyslipidemia, chronic kidney disease, and antidiabetic medication (insulin use and number of oral antidiabetic agents used). In model 3, we further adjusted for baseline BMI on the index date in addition to the variables adjusted for in model 2. We also conducted a sensitivity analysis for the main outcomes by adding a lag time of 3 years, the duration between the date of first diabetes claim and indexed date, and insulin use to account for reverse causality. We performed subgroup analyses of age, sex, smoking status, baseline BMI, and weight change status, and we evaluated the associations between body weight variability and development of outcomes in these subgroups. *P* value for interaction was calculated using Cox regression analyses.

RESULTS

Baseline Characteristics

Table 1 shows the baseline characteristics of the study population (n = 624,237) based on the quartiles of VIM for body weight. The mean age of all the participants was 56.8 ± 11.7 years. The proportion of men was the highest in the Q1 group and the lowest in the Q4 group. The proportion of current smokers showed no trends. However, the proportions of heavy alcohol drinkers and regular exercisers were the highest in the Q1 group and decreased across the higher quartile groups of VIM for body weight. The mean values of cardiometabolic parameters such as weight, waist circumference, BMI, systolic and diastolic BP, total cholesterol, triglycerides, and LDL cholesterol were lower in the higher quartile groups of VIM for body weight. The mean values of HDL cholesterol and fasting glucose increased from the lowest to the highest quartile groups. The prevalence of hypertension and chronic kidney disease was significantly different, but that of dyslipidemia had no difference among the quartile groups. The proportions of antidiabetic medications and use of three or more oral hypoglycemic agents significantly increased in the higher quartile groups of VIM for body weight.

Association of Variability in Body Weight With Incidence and Risk of Study Outcomes

Supplementary Fig. 2 shows the Kaplan-Meier curves for incidence probabilities of MI, stroke, and all-cause mortality with respect to the quartiles of VIM for body weight. The incidence probabilities significantly increased in the higher quartile groups (all log-rank $P < 0.001$). Subsequent comparisons were performed using the Bonferroni post hoc test, and the differences among interquartile groups were significant (all $P < 0.001$). Table 2 shows the adjusted HRs (95% CIs) of MI, stroke, and all-cause mortality in the quartile groups of VIM for body weight. Even after adjusting for confounding variables, the HRs of MI, stroke, and all-cause mortality significantly increased in the higher quartile groups of VIM for body weight (all *P* for trend <0.001). In model 3, the HRs (95% CI) of the Q4 group were 1.15 (1.10–1.20) for MI, 1.22 (1.18–1.26) for stroke, and 1.58 (1.53–1.62) for all-cause mortality when compared with those of the Q1 group. These associations were also observed for other parameters of body weight variability (Supplementary Table 1). Results of the sensitivity analysis of a 3-year lag time (Supplementary Table 2), insulin use (Supplementary Table 3), and duration between the date of first diabetes claim and index date (Supplementary Table 4) were consistent with the main findings. In addition, we analyzed data after excluding patients who had been diagnosed with cancers and obtained results similar to the main findings (Supplementary Table 5). As observed in the findings regarding body weight variability, variabilities in the systolic and diastolic BP were positively associated with the risk of MI, stroke, and all-cause mortality; higher total cholesterol variability was significantly associated with the risk of all-cause mortality (Supplementary Table 6).

Subgroup Analyses

Table 3 presents a comparison of the HRs (95% CIs) of study outcomes between the Q4 group of VIM for body weight and Q1–Q3 groups in subgroups. There was a significant interaction with age in the association of VIM for body weight with MI and all-cause mortality (*P* for interaction = 0.009 and <0.001, respectively). The association between VIM for body weight and MI was more prominent in women than in men (*P* for interaction = 0.004), and the association between VIM for body weight and stroke was more prominent in nonsmokers than in current smokers (*P* for interaction = 0.031). The association between VIM for body weight and risk of MI and all-cause mortality was stronger in nonobese individuals than in obese individuals (*P* for interaction <0.001).

Table 1—Baseline characteristics of the study population with respect to the quartiles of VIM for body weight

	VIM				
	Q1 (N = 155,903)	Q2 (N = 156,007)	Q3 (N = 156,267)	Q4 (N = 156,060)	P value
Age (years)	57.0 ± 10.9	56.6 ± 11.2	56.5 ± 11.7	57.1 ± 13.0	<0.001
Sex (male)	108,463 (69.6)	105,683 (67.7)	102,626 (65.7)	94,282 (60.4)	<0.001
Current smoker	39,389 (25.3)	41,077 (26.3)	41,521 (26.6)	39,370 (25.2)	<0.001
Heavy alcohol drinker	16,321 (10.5)	15,825 (10.1)	15,304 (9.8)	13,857 (8.9)	<0.001
Regular exerciser	39,141 (25.1)	38,011 (24.4)	37,107 (23.8)	34,102 (21.9)	<0.001
Low income	35,440 (22.7)	36,220 (23.2)	37,170 (23.8)	38,166 (24.5)	<0.001
Height (cm)	164.0 ± 8.7	163.6 ± 8.9	163.3 ± 9.1	162.4 ± 9.5	<0.001
Weight (kg)	68.1 ± 10.5	67.1 ± 11.0	66.7 ± 11.4	65.4 ± 12.5	<0.001
Waist circumference (cm)	86.1 ± 7.8	85.4 ± 7.9	85.2 ± 8.2	84.7 ± 8.8	<0.001
BMI (kg/m^2)	25.3 ± 2.9	25.0 ± 3.0	24.9 ± 3.1	24.7 ± 3.6	<0.001
SD of weight	0.73 ± 0.31	1.4 ± 0.27	2.09 ± 0.38	3.86 ± 1.76	<0.001
CV of weight	1.06 ± 0.43	2.09 ± 0.27	3.14 ± 0.38	5.89 ± 2.57	<0.001
VIM of weight	0.69 ± 0.28	1.35 ± 0.17	2.03 ± 0.23	3.78 ± 1.64	<0.001
ARV of weight	0.86 ± 0.47	1.65 ± 0.55	2.41 ± 0.77	4.29 ± 2.32	<0.001
Systolic BP (mmHg)	128.9 ± 14.9	128.6 ± 14.9	128.4 ± 15.0	128.0 ± 15.5	<0.001
Diastolic BP (mmHg)	79.2 ± 9.8	79.1 ± 9.8	79.0 ± 9.8	78.5 ± 10.0	<0.001
Total cholesterol (mg/dL)	196.9 ± 39.8	196.9 ± 39.9	196.6 ± 40.4	195.4 ± 41.6	<0.001
Triglycerides (mg/dL)*	151.1 (150.7–151.5)	149.3 (148.9–149.7)	146.5 (146.0–146.9)	140.3 (139.9–140.7)	<0.001
HDL cholesterol (mg/dL)	51.3 ± 21.3	51.5 ± 20.5	51.9 ± 21.8	52.4 ± 21.4	<0.001
LDL cholesterol (mg/dL)	111.5 ± 44.5	111.5 ± 45.2	111.3 ± 45.3	110.9 ± 45.6	0.001
Fasting glucose (mg/dL)	142.1 ± 38.0	143.0 ± 40.2	143.8 ± 42.8	145.5 ± 49.6	<0.001
eGFR (mL/min/1.73 m^2)	83.7 ± 36.2	83.9 ± 35.5	84.3 ± 36.0	84.7 ± 37.1	<0.001
Hypertension	86,880 (55.7)	84,482 (54.2)	84,335 (54.0)	84,714 (54.3)	<0.001
Dyslipidemia	56,599 (36.3)	56,542 (36.2)	56,761 (36.3)	56,051 (35.9)	0.063
Chronic kidney disease	15,863 (10.2)	15,843 (10.2)	15,997 (10.3)	17,917 (11.5)	<0.001
Antidiabetic medication					
Insulin	8,653 (5.6)	9,328 (6.0)	10,760 (6.9)	15,234 (9.8)	<0.001
Sulfonylurea	73,971 (47.5)	74,004 (47.4)	75,461 (48.3)	76,803 (49.2)	<0.001
Metformin	71,967 (46.2)	72,015 (46.2)	74,537 (47.7)	78,479 (50.3)	<0.001
Meglitinide	3,574 (2.3)	3,593 (2.3)	3,939 (2.5)	4,825 (3.1)	<0.001
Thiazolidinedione	11,803 (7.6)	12,085 (7.8)	12,798 (8.2)	14,010 (9.0)	<0.001
DPP-4 inhibitor	11,350 (7.3)	11,206 (7.2)	12,095 (7.7)	13,182 (8.5)	<0.001
α-Glucosidase inhibitor	18,607 (11.9)	19,069 (12.2)	20,424 (13.1)	22,780 (14.6)	<0.001
Number of oral antidiabetic agents (≥3)	22,691 (14.6)	23,125 (14.8)	24,725 (15.8)	27,127 (17.4)	<0.001

Data are presented as mean ± SD or number (percentage) unless otherwise indicated. DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate. *Triglyceride levels are presented as median (interquartile range) using the Wilcoxon rank-sum test.

Changes in the weight status showed an interaction effect only in the association between body weight variability and all-cause mortality (P for interaction = 0.038). The incidence rates of study outcomes were higher in the weight loss group than in the other groups (Supplementary Table 7).

Risk of Study Outcomes With Respect to Coexistence of Obesity and the Highest Quartile Group of VIM for Body Weight

Figure 1 presents the HRs (95% CIs) of MI, stroke, and all-cause mortality based on the coexistence of obesity and the highest quartile group of VIM for body weight. When compared with individuals who did not have either obesity or Q4 of VIM for body weight, those with only Q4 of VIM for body weight and those with both obesity and Q4 of VIM for body weight had significantly higher HRs for all three outcomes. The HRs were the highest in nonobese individuals with Q4 of VIM for body weight (for MI, HR 1.18 [95% CI 1.14–1.23]; for stroke, 1.19 [1.14–1.25]; and for all-cause mortality, 1.52 [1.49–1.56]). In addition, as for a combination of weight change status and weight variability degree, any weight variability groups combined with the weight stable group had the lowest HRs of study outcomes (Supplementary Table 8).

CONCLUSIONS

In this large-scale study of patients with type 2 diabetes, body weight variability was found to be associated with increased risks of MI, stroke, and all-cause mortality after adjusting for traditional cardiovascular risk factors. We also found that the highest degree (Q4) of body weight variability was independently associated with risk of all three outcomes both in obese and nonobese individuals. Our findings suggest that higher body weight variability is an important risk factor for adverse outcomes in patients with type 2 diabetes. Appropriate approaches to reduce body weight and maintain proper weight may help in

Table 2—HRs (95% CIs) of MI, stroke, and all-cause mortality with respect to quartiles of VIM for body weight among patients with type 2 diabetes

					HR (95% CI)		
	n	Events (*n*)	Person-years	Incidence rate*	Model 1†	Model 2‡	Model 3§
MI							
Q1	155,903	3,649	1,204,208	3.03	1 (reference)	1 (reference)	1 (reference)
Q2	156,007	3,744	1,208,056	3.10	1.05 (1.00–1.10)	1.04 (0.99–1.08)	1.03 (0.99–1.08)
Q3	156,267	3,998	1,203,225	3.32	1.13 (1.08–1.18)	1.09 (1.05–1.14)	1.09 (1.04–1.14)
Q4	156,060	4,441	1,177,268	3.77	1.24 (1.18–1.29)	1.15 (1.10–1.20)	1.15 (1.10–1.20)
P for trend					<0.001	<0.001	<0.001
Stroke							
Q1	155,903	5,625	1,197,883	4.70	1 (reference)	1 (reference)	1 (reference)
Q2	156,007	5,770	1,200,872	4.80	1.05 (1.02–1.09)	1.04 (1.00–1.08)	1.04 (1.00–1.08)
Q3	156,267	6,201	1,195,682	5.19	1.13 (1.09–1.18)	1.10 (1.07–1.15)	1.10 (1.06–1.14)
Q4	156,060	7,442	1,167,278	6.38	1.30 (1.25–1.35)	1.23 (1.18–1.27)	1.22 (1.18–1.26)
P for trend					<0.001	<0.001	<0.001
All-cause mortality							
Q1	155,903	8,767	1,215,904	7.21	1 (reference)	1 (reference)	1 (reference)
Q2	156,007	9,485	1,219,625	7.78	1.13 (1.10–1.17)	1.11 (1.08–1.14)	1.09 (1.06–1.12)
Q3	156,267	10,652	1,215,532	8.76	1.28 (1.24–1.31)	1.23 (1.20–1.27)	1.20 (1.17–1.24)
Q4	156,060	15,812	1,190,189	13.29	1.79 (1.75–1.84)	1.67 (1.62–1.71)	1.58 (1.53–1.62)
P for trend					<0.001	<0.001	<0.001

*Incidence per 1,000 person-years. †Model 1 was adjusted for age and sex. ‡Model 2 was adjusted for age, sex, smoking status, alcohol consumption, physical activity, income, hypertension, dyslipidemia, chronic kidney disease, insulin use, and number of oral antidiabetic agents used. §Model 3 was adjusted for age, sex, smoking status, alcohol consumption, physical activity, income, hypertension, dyslipidemia, chronic kidney disease, insulin use, number of oral antidiabetic agents used, and baseline BMI.

lowering the risk of adverse health outcomes in patients with type 2 diabetes.

To the best of our knowledge, only two studies in Western countries have examined the association between weight variability and major cardiovascular outcomes and mortality in patients with type 2 diabetes; their results were similar to those of our study. An Italian 10-year follow-up study of 1,319 older individuals with type 2 diabetes reported that variability in body weight predicted total mortality (HR 1.34 [95% CI 1.03–1.75]) independent of fasting plasma glucose. In this study, BMI was collected over a period of 3 years, and the CV of BMI was used to assess body weight variability (17). A U.S. study of 6,408 individuals with type 2 diabetes showed that body weight variability was positively associated with mortality (HR 1.16 [95% CI 1.10–1.22]; $P < 0.0001$), major cardiovascular outcomes (1.12 [1.04–1.20]; $P = 0.002$), and any cardiovascular events (1.08 [1.03–1.14]; $P = 0.0015$), independent of traditional

Table 3—HR (95% CI) of study outcomes with respect to body weight variability (Q4 vs. Q1–Q3 of VIM) in subgroups

	MI		Stroke		All-cause mortality	
Subgroup	HR (95% CI)*	*P* for interaction	HR (95% CI)*	*P* for interaction	HR (95% CI)*	*P* for interaction
Age (years)		0.009		0.279		<0.001
20–39	0.89 (0.71–1.10)		1.29 (0.99–1.69)		1.47 (1.22–1.77)	
40–64	1.07 (1.02–1.13)		1.18 (1.13–1.23)		1.52 (1.47–1.57)	
≥65	1.12 (1.07–1.18)		1.16 (1.12–1.20)		1.36 (1.33–1.40)	
Sex		0.004		0.178		0.160
Men	1.06 (1.02–1.11)		1.18 (1.14–1.22)		1.44 (1.40–1.47)	
Women	1.15 (1.09–1.22)		1.14 (1.09–1.19)		1.40 (1.35–1.45)	
Smoking status		0.056		0.031		0.502
Nonsmoker	1.13 (1.08–1.19)		1.16 (1.11–1.20)		1.44 (1.40–1.48)	
Former smoker	1.03 (0.95–1.12)		1.25 (1.17–1.33)		1.42 (1.36–1.49)	
Current smoker	1.06 (0.99–1.14)		1.12 (1.05–1.18)		1.41 (1.35–1.46)	
BMI (kg/m^2)		<0.001		0.093		<0.001
<25	1.16 (1.11–1.22)		1.20 (1.16–1.24)		1.53 (1.49–1.56)	
≥25	1.02 (0.96–1.07)		1.13 (1.08–1.18)		1.36 (1.31–1.40)	
Weight change (%)		0.072		0.302		0.038
≤−5	1.05 (0.98–1.12)		1.10 (1.04–1.16)		1.33 (1.28–1.38)	
−5 to 5	1.14 (1.07–1.22)		1.15 (1.09–1.22)		1.39 (1.34–1.44)	
≥5	1.00 (0.91–1.09)		1.14 (1.06–1.22)		1.29 (1.22–1.36)	

*HRs (95% CIs) were calculated using a multivariate Cox proportional hazards regression analysis after adjusting for age, sex, smoking status, alcohol consumption, physical activity, income, hypertension, dyslipidemia, chronic kidney disease, insulin use, number of oral antidiabetic agents used, and baseline BMI.

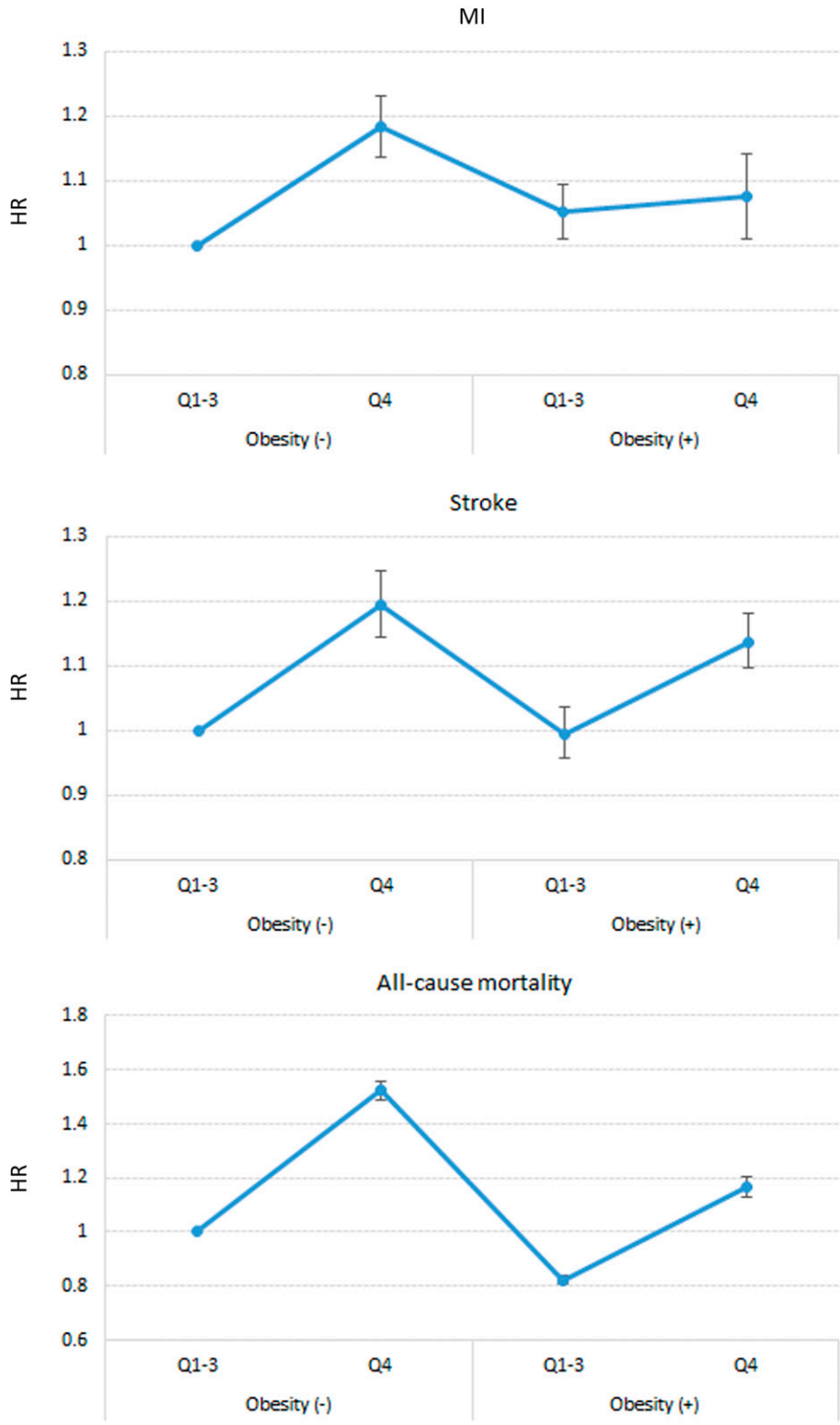

Figure 1—HRs (95% CIs) of MI, stroke, and all-cause mortality based on the coexistence of obesity and the highest quartile level (Q4) of VIM for body weight. When compared with individuals who did not have obesity or Q4 of VIM for body weight, those with only Q4 of VIM for body weight and those with both obesity and Q4 of VIM for body weight had significantly higher HRs for all three outcomes. The HRs were the highest in individuals with only Q4 of VIM for body weight.

cardiovascular risk factors (18). When compared with the lowest quintile group, the highest quintile group of body weight variability was associated with higher risks of mortality (82%), major coronary events (82%), and any cardiovascular events (75%). Besides being the first non-Western Asian population study, our study had a few strengths over previous studies. The Italian study only reported the association for the mortality of older patients (17). However, we found that the

association between body weight variability and MI and stroke was not limited to the elderly. The mean follow-up duration was 3.9–4.9 years in the U.S. study; the mean BMI of the study participants was 29 kg/m^2, and 85% of them were overweight or obese. In our study, the study participants were followed up for 7.6–7.8 years depending on the outcomes, and 73% of them were overweight and obese based on the Asian-Pacific criterion. In addition to longer follow-up durations, the lower mean BMI with diverse weight status necessitated that the outcomes be evaluated based on the coexistence of general obesity. Moreover, since the use of medications for type 2 diabetes might lead to weight gain through several mechanisms (23), adjusting for antidiabetic medications in our study is an additional strength over previous Western studies. Similar associations observed in patients with other comorbidities may strengthen our results. For instance, a study of individuals with coronary artery disease also reported that body weight variability was associated with higher rates of mortality and cardiovascular events (24). A similar trend was reported in studies conducted on the general population (25–27).

The mechanism behind the association between increased body weight variability and adverse cardiovascular events and mortality remains unclear. Fat mass seems to reduce the lean mass during weight loss and increase it during weight regain (28,29). This may lead to increases in fat mass after body weight variabilities, resulting in an increase in adipose tissues. After weight gain followed by initial weight loss, rapid adipose tissue growth and hyperplasia occur owing to metabolic shifts that favor lipid storage. Adipose tissue, which is metabolically active, can increase the production of leptin, cytokines, and adiponectin, potentially leading to adverse outcomes (30). In a study on Japanese male workers, individuals with greater weight variability appeared to have higher fasting insulin levels (31). The increased insulin level likely reflects a change in adiposity, including increases in total fat and visceral fat mass. Weight variability could also be associated with abdominal fat accumulation, likely resulting in a preference for visceral fat (32). Visceral fat can negatively affect insulin levels and cause inflammation (33,34). Moreover, the ATTICA study revealed that visceral adiposity is independently associated with an elevated 10-year CVD risk, with inflammation as a possible explanatory factor (35). In studies using weight-cycling mice, weight variability also increased the number of CD4+ and CD8+ T cells in adipose tissues (36). In the study, elevation of multiple T-helper-1–associated cytokine levels increased subsequent to weight variabilities. These exaggerated adaptive immune responses in adipose tissues may indicate metabolic dysfunction associated with weight variability.

Some interesting results arose from the subgroup analyses. There were significant interactions with BMI in the association between weight variability and outcomes. The associations of weight variability with MI and all-cause mortality were stronger in nonobese individuals than in obese individuals. The highest quartile group of body weight variability was associated with the risk of all three outcomes both in obese and nonobese individuals; the HRs were the highest in nonobese individuals with the highest body weight variability. This suggests that weight variability is also an important risk factor of adverse outcomes in nonobese individuals. There was a significant interaction with sex in the association between weight variability and development of MI. It has been shown that women are at higher risk of developing CVDs than men, owing to cardiovascular risk factors such as common disorders of pregnancy, gestational hypertension and diabetes, and endocrine disorders, which only occur in women of reproductive age (37,38). Weight variability may, thus, be a stronger risk factor of major cardiovascular outcomes and mortality in women. However, further studies are warranted to confirm these associations.

Our study has several notable strengths. We had a large sample size of >620,000 individuals and a long follow-up period of >7 years. We believe this is the first study to investigate the association between weight variability and CVDs and mortality risk in patients with type 2 diabetes using nationwide cohort data. Various subgroup analyses were possible using this data, which provided interesting conclusions. The analyses were performed after adjusting for substantial confounding variables, including baseline BMI and antidiabetic medications, such as insulin, that may cause weight changes. Because the Korean society is a single ethnic society, it was possible to involve a homogeneous group in a nationwide study. Despite these advantages, our study also had limitations. First, there may be reverse causation in our results because of the retrospective cohort design. However, we considered the washout period when assessing study outcomes to address this issue. Our sensitivity analyses results with a 3-year lag time and possible severity indices of type 2 diabetes (such as insulin use and duration between the date of first diabetes claim and index date) were consistent with our main findings. Second, we could not determine whether the weight loss was intentional or unintentional. Intentional weight loss may be associated with a reduction in cardiovascular events and mortality when it is induced to improve health status (39,40). Third, we could not take into account the exact severity of type 2 diabetes based on duration of disease and glycated hemoglobin levels due to lack of data in Korean NHIS. Sicker patients had to alter their diabetes medications more extensively, resulting in more weight variabilities. Nevertheless, the main findings persisted in the groups classified based on insulin use and the date of first diabetes claim, and hence, we used these parameters as proxy indicators of the severity of type 2 diabetes. Fourth, because the analytic sample was limited to Korean individuals, additional studies in other ethnic groups are required to generalize our results.

In conclusion, this nationwide, population-based study conducted in South Korea found that body weight variability was independently associated with increased risks of MI, stroke, and all-cause mortality in patients with type 2 diabetes. Our findings suggest that body weight variability may be a predictor of CVD and all-cause mortality in patients with type 2 diabetes. Overall, appropriate interventions for stable body weight are needed to prevent future adverse health outcomes in patients with type 2 diabetes.

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concept and design; acquisition, analysis, and interpretation of the data; and critical revision of the manuscript. C.-w.L., Y.K., B.H., S.P., J.-H.P., Y.-H.K., D.-H.K., S.M.K., Y.S.C., and K.H.C. contributed to the acquisition and interpretation of the data and critical revision of the manuscript. All authors gave final approval of the version to be published. Y.G.P. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of data analysis.

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