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Effect of intensive lifestyle intervention on the association between weight variability and major adverse cardiovascular events in overweight or obese adults with type 2 diabetes mellitus

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ABSTRACT

Aims/introduction: Weight variability is associated with cardiovascular outcomes in diabetic patients. However, whether the guideline-recommended intensive lifestyle intervention (ILI) will affect this association in overweight or obese adults with diabetes is not well established.

Materials and Methods: In 3,859 participants from the Action for Health in Diabetes (Look AHEAD) trial, the associations of 4 year weight variability measured by variability independent of the mean (VIM) with major adverse cardiovascular event (MACE) and secondary outcomes in ILI and diabetes support & education (DSE) arm were evaluated.

Results: During a median follow-up of 9.6 years, 255 (12.9%) participants in the ILI arm and 247 (13.2%) participants in the DSE arm developed MACE. Participants with the highest quartile of weight variability (VIM Q4) experienced a 2.23-fold higher risk of MACE compared with the lowest quartile (VIM Q1) in the DSE arm (hazard ratio [HR] 2.23; 95% CI 1.51–3.30). Compared with the lowest weight variability (VIM Q1), participants with the highest weight variability (VIM Q4) were associated with higher risks of secondary cardiovascular composite outcome (HR 1.88; 95% CI 1.20–2.95), all-cause mortality (HR 3.19; 95% CI 1.75–5.82), and myocardial infarction (HR 1.95; 95% CI 1.12–3.37) in the DSE arm.

Conclusions: Among the overweight or obese individuals with type 2 diabetes mellitus, rising weight variability was independently associated with increased MACE risks in the DSE arm. Therefore, a guideline-recommended ILI strategy for weight loss should be adopted to improve cardiovascular outcomes without worrying about the effect of weight fluctuations.

AIMS/INTRODUCTION

Weight loss as an essential treatment is recommended by the clinical practice guideline for overweight or obese patients with type 2 diabetes mellitus[1]. Substantial evidence also indicated that weight loss could reduce the risk of cardiovascular disease (CVD) and all-cause mortality[2,3]. Actually, a prescription of weight loss to individuals is often characterized by weight fluctuations[4,5]. Most individuals will partly regain the weight after successfully reducing it[4,6], especially patients with type 2 diabetes mellitus[7]. The higher weight variability, therefore, may be inexorable with the loss of body weight, even though proper weight can be maintained later. Interestingly, several large prospective cohort studies suggested that higher weight

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variability was associated with cardiovascular outcomes and mortality in adults with type 2 diabetes mellitus[8,9]. It may be a confusing problem that weight loss can reduce the risk of cardiovascular disease, but the higher weight variability caused by weight loss may increase the risk.

A prior study supported that intensive lifestyle intervention (ILI) contributed to reducing blood pressure, improving lipid parameters, and controlling blood glucose[10]. The American Diabetes Association (ADA) also recommends weight loss with ILI to achieve optimal control of traditional cardiovascular risk factors in overweight or obese adults with type 2 diabetes mellitus[1]. Based on this, we hypothesize that there might be heterogeneity for the effects of weight variability on the risk of cardiovascular disease in that the higher weight variability caused by ILI may not be associated with cardiovascular outcomes and mortality.

Therefore, the aim of this *post hoc* analysis of the Look AHEAD trial[11] is to evaluate whether ILI will affect the association between weight variability and a major adverse cardiovascular event (MACE) among overweight or obese adults with diabetes.

MATERIALS AND METHODS

Study design and study population

The Look AHEAD trial was a multicenter randomized controlled clinical trial to evaluate the effects of intensive lifestyle intervention on the risks for cardiovascular outcomes in comparison with diabetes support & education (DSE). Details of the design and methods have been described previously[11], and the trial was stopped early (median duration of follow-up 9.6 years) due to a futility analysis that found no significant difference in the primary cardiovascular outcomes between ILI and DSE[10]. The Look AHEAD trial is now continuing as a prospective observational cohort study.

From 2001 to 2004, the Look AHEAD trial recruited overweight and obese adults (body mass index [BMI] ≥25 kg/m^2 or ≥27 kg/m^2 if taking insulin), aged 45–76 years, systolic blood pressure (SBP) <160 mmHg, diastolic blood pressure (DBP) <100 mmHg, triglycerides (TGs) <600 mg/dL, glycosylated hemoglobin (HbA1c) ≤11% (97 mmol/mol), with type 2 diabetes mellitus (n = 5,145) from 16 clinical centers in the USA[12], of which 4,906 are available in the public access data sets, as those individuals participating from Native American sites are excluded, per consent limitations. Individuals with missing weight data at 1–4 years follow-up (n = 750) or who missed information on covariates (n = 292), or death data (n = 5) were excluded. Finally, 3,859 participants were included in the primary analysis (Figure S1). Compared with the included 3,859 participants, the excluded participants were more allocated to the DSE arm, more commonly identified as Hispanics, more previously diagnosed as having cardiovascular disease, and had fewer drinkers, lower education levels, and more insulin users (Table S1). The Look AHEAD trial obtained ethical approval from local institutional review boards, and all participants provided written informed consent.

Intervention

The participants were randomly assigned to either an ILI or DSE arm. The ILI was designed to achieve and maintain at least a 7% weight loss by changing their eating and physical activity levels. Participants in the ILI arm (weekly group and individual counseling sessions in the first 6 months followed by less frequent meetings) were encouraged to achieve ≥175 min/week of moderate-intensity physical activity and prescribed a restricted caloric diet (1,200–1800 kcal/day). Participants in the DSE arm received three educational group sessions per year during the first 4 years followed by an annual meeting focused on diet, exercise, and social support, but individualized behavioral support was not provided. The details of ILI and DSE have been described previously[13,14].

4 year weight variability

The 4 year weight variability was defined as intraindividual variability in weight for years 0 to 4, measured according to the standard deviation (SD), the average real variability (ARV), and the variability independent of the mean (VIM) calculated by the data of baseline and 1, 2, 3, and 4 years after baseline. We illustrated how each weight variability was calculated in Figure S2.

The correlations among the mean of 4 year weight and each weight variability were analyzed by Pearson's correlation (Table S2). The SD and ARV of 4 year weight were correlated with mean weight in both the ILI and DSE arms (Pearson r = 0.236–0.280), but the VIM of 4 year weight was poorly correlated with mean weight (ILI: Pearson r = 0.004; DSE: Pearson r = 0.081) and had a strong correlation with SD and ARV (Pearson r = 0.883–0.978). Thus, to distinguish the impact of weight variability from that of mean weight on outcomes, the VIM was used to measure visit-to-visit weight variability in the primary analysis. The SD and ARV of weight were just used in the secondary analyses.

Primary and secondary outcomes

The primary outcome of interest was the incidence of MACE (composite of four endpoints), defined as the first occurrence of all-cause mortality, death from cardiovascular causes, or non-fatal acute myocardial infarction, stroke. Secondary cardiovascular composite outcome was defined as a composite outcome of the first occurrence of death from cardiovascular causes or non-fatal acute myocardial infarction, stroke. Other secondary outcomes included the four individual components of the primary outcome. All-cause mortality, cardiovascular death, myocardial infarction, and stroke events were classified by an Events Adjudication Committee, blinded to the treatment arm, that reviewed all pertinent medical records and death certificates to confirm these events.

Statistical analyses

Descriptive statistics are presented as mean (SD) for continuous variables or number (%) for categorical variables. Participants' characteristics were compared using the one-way ANOVA test, the Pearson χ^2 test, or the Kruskal-Wallis test, as appropriate.

Participants were categorized by the 4 year weight variability (VIM for weight) into quartiles based on the sample distribution in the ILI and DSE arms, respectively. The intervention-specific associations of 4 year weight variability with MACE and five secondary outcomes were examined using multivariate-adjusted Cox proportional hazard models. We further modeled 4 year weight variability (VIM for weight) as a continuous variable and rescaled the data by dividing by the SD (Per 1-SD: 3.14% in ILI; 2.83% in DSE). Separate models were constructed for MACE and five secondary outcomes with the inclusion of the following covariates: model 1 adjusted for age, sex, and race; model 2 adjusted for variables in model 1 plus education level, smoking status, drinking status, SBP, DBP, total cholesterol, high-density lipoprotein cholesterol (HDL-C), HbA1c, serum creatinine, prevalent hypertension, and cardiovascular disease, insulin use at baseline, and mean of 4 year weight. A restricted cubic spline with 3 knots was also incorporated to determine the intervention-specific associations of 4 year weight variability (VIM for weight) as a continuous variable with the risk of MACE.

Sensitivity analyses for the quartile of weight variability measured by ARV and VIM were conducted through a multivariate-adjusted Cox regression model. To mitigate potential reverse causation, we excluded 111 participants (ILI: n = 64; DSE: n = 47) those with MACEs occurring within 4 years when we measured the weight variability, and conducted the sensitivity analyses in the remaining participants (n = 3,748) without MACE occurring within 4 years. To distinguish the impact of weight variability from that of weight loss on outcomes, we conducted the sensitivity analyses in participants (N = 2,497) with weight loss in the fourth year.

In the secondary analyses, all included participants from both trial arms were pooled and further categorized into quartiles. To enhance the robustness of the intervention-specific association between weight variability and MACE risk, we examined the association of weight variability with the risk of MACE and five secondary outcomes, and conducted the subgroup analyses in the ILI and DES arms. An interaction term between treatment arm and weight variability was individually added to the adjusted Cox model, and the P values and CIs for these associations were estimated.

A significance level of <0.05 for 2-sided comparisons was considered statistically significant, and 95% CIs were reported where applicable. All analyses were conducted with the statistical program Stata Version 14 (StataCorp, College Station, Texas, USA) and the R language (version 3.5.0.12).

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, or in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results.

RESULTS

The present study included 3,859 participants from the Look AHEAD trial who were randomized to ILI (n = 1,983) vs DSE (n = 1,876), average 59 years old, 2,229 (57.8%) women and 2,609 (67.6%), white races. The characteristics of the participants in the two groups were similar at baseline (Table 1). During a median follow-up of 9.6 years (interquartile range [IQR], 8.9–10.3 years), 502 (13.0%) incident MACEs, 384 (10.0%)

Table 1 | Baseline characteristics of participants between the ILI and DSE arms

Characteristic	DSE arm	ILI arm	*P* value
No.	1876	1983	
Age, years	59.1 (6.8)	58.8 (6.8)	0.146
Sex, no. (%)			
Men	797 (42.5)	833 (42.0)	0.764
Women	1,079 (57.5)	1,150 (58.0)	
Race, no. (%)			
White	1,264 (67.4)	1,345 (67.8)	0.967
Black (not Hispanic)	318 (17.0)	326 (16.4)	
Hispanic	229 (12.2)	240 (12.1)	
Other/mixed	65 (3.5)	72 (3.6)	
Weight, kg	101.6 (18.8)	101.0 (19.4)	0.323
Systolic BP, mmHg	129.4 (17.0)	128.8 (17.4)	0.027
Diastolic BP, mmHg	70.3 (9.5)	70.1 (9.6)	0.358
Total cholesterol, mg/mL	191.0 (37.1)	190.5 (37.8)	0.682
HDL-C, mg/mL	43.5 (11.9)	43.4 (12.0)	0.815
LDL-C, mg/mL	112.8 (32.2)	111.4 (32.0)	0.191
Triglyceride, mg/mL	178.9 (116.2)	181.9 (115.9)	0.656
Fasting glucose, mg/mL	152.4 (44.5)	151.7 (44.7)	0.422
HbA1c, %	7.2 (1.2)	7.2 (1.1)	0.478
Serum creatinine, mg/mL	0.8 (0.2)	0.8 (0.2)	0.583
History of CVD, no. (%)	239 (12.7)	280 (14.1)	0.209
History of hypertension, no. (%)	1,563 (83.3)	1,678 (84.6)	0.270
Education level, no. (%)			
<13 years	336 (17.9)	371 (18.7)	0.204
13–16 years	718 (38.3)	704 (35.5)	
>16 years	822 (43.8)	908 (45.8)	
Smoking, no. (%)			
Never smoker	959 (51.1)	969 (48.9)	0.217
Past smoker	851 (45.4)	928 (46.8)	
Current smoker	66 (3.5)	86 (4.3)	
Drinking, no. (%)			
None/week	1,224 (65.2)	1,312 (66.2)	0.549
≥1/week	652 (34.8)	671 (33.8)	
Insulin use, no. (%)	276 (14.7)	303 (15.3)	0.622

Continuous variables are presented as mean (SD), and categorical variables are presented as percentage. BP, blood pressure; CVD, cardiovascular disease; DSE, diabetes support & education; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; ILI, intensive lifestyle intervention; LDL-C, low-density lipoprotein cholesterol.

incident secondary cardiovascular composite outcomes, 212 (5.5%) incident all-cause deaths, 60 (1.5%) incident cardiovascular deaths, 259 (6.7%) incident myocardial infarction, and 112 (2.9%) incident stroke occurred in the included participants.

Participants were categorized by the weight variability into quartiles in the ILI and DSE arms, respectively. In the ILI arm, participants with the highest weight variability (VIM Q4) were more frequently white, had higher weight and lower HbA1c, were less likely to be drinkers, and had more history of hypertension (Table 2). In the DSE arm, participants with the highest weight variability (VIM Q4) were more frequently white or female, had higher weight, and were less likely to be drinkers (Table S5).

Intervention-specific association of weight variability with MACE

In the primary analysis, 255 participants (12.9%) in the ILI arm and 247 participants (13.2%) in the DSE arm developed MACE over the median follow-up of 9.6 years. In a multivariable-adjusted analysis, there was a significant, graded association between VIM of 4-year weight and MACE risks in DSE arm in overweight or obese adults with type 2 diabetes mellitus (P for trend <0.001) (Figure 1a). However, there was

Table 2 | Baseline characteristics of each group categorized by the VIM of weight for 4 years in the ILI arm

Characteristic	Total	VIM Q1	VIM Q2	VIM Q3	VIM Q4	*P* value
No.	1983	495	496	496	496	
Age, years	58.8 (6.8)	58.7 (6.6)	58.7 (7.0)	59.4 (6.7)	58.6 (6.7)	0.156
Sex, no. (%)						
Men	833 (42.0)	209 (42.2)	180 (36.3)	217 (43.8)	227 (45.8)	0.017
Women	1,150 (58.0)	286 (57.8)	316 (63.7)	279 (56.3)	269 (54.2)	
Race, no. (%)						
White	1,345 (67.9)	299 (60.4)	321 (64.7)	335 (67.5)	390 (78.6)	<0.001
Black (not Hispanic)	326 (16.4)	107 (21.6)	98 (19.8)	75 (15.1)	46 (9.3)	
Hispanic	240 (12.1)	64 (12.9)	58 (11.7)	67 (13.5)	51 (10.3)	
Other/mixed	72 (3.6)	25 (5.1)	19 (3.8)	19 (3.8)	9 (1.8)	
Weight, kg	101.0 (19.4)	97.9 (18.5)	98.8 (19.7)	100.3 (18.2)	106.9 (20.0)	<0.001
Systolic BP, mmHg	128.2 (17.4)	128.2 (17.5)	128.7 (16.8)	127.4 (17.3)	128.5 (17.8)	0.652
Diastolic BP, mmHg	70.0 (9.6)	70.9 (9.5)	70.5 (9.4)	69.4 (9.9)	69.0 (9.4)	0.006
HbA1c, %	7.2 (1.1)	7.4 (1.2)	7.3 (1.1)	7.2 (1.1)	7.0 (1.1)	<0.001
Fasting glucose, mg/mL	151.7 (44.7)	155.2 (47.0)	154.5 (45.4)	148.3 (41.2)	148.8 (44.7)	0.018
Total cholesterol, mg/mL	190.5 (37.8)	191.2 (38.7)	193.1 (38.1)	190.7 (38.5)	187.1 (35.9)	0.092
HDL-C, mg/mL	43.4 (12.0)	42.7 (12.2)	43.9 (12.1)	43.7 (11.8)	43.4 (11.8)	0.445
LDL-C, mg/mL	111.4 (32.0)	112.3 (31.9)	112.7 (32.6)	111.4 (32.5)	109.4 (30.9)	0.355
Triglyceride, mg/mL	181.9 (115.9)	185.1 (122.9)	186.7 (127.0)	181.6 (115.1)	174.2 (96.0)	0.327
Serum creatinine, mg/mL	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)	0.110
History of hypertension, no. (%)	1,678 (84.6)	408 (82.4)	413 (83.3)	416 (83.9)	441 (88.9)	0.021
History of CVD, no. (%)	280 (14.1)	83 (16.8)	56 (11.3)	70 (14.1)	71 (14.3)	0.104
Insulin use, no. (%)	303 (15.3)	86 (17.4)	70 (14.1)	83 (16.7)	64 (12.9)	0.160
Education level, no. (%)						
<13 years	371 (18.7)	93 (18.8)	79 (15.9)	100 (20.2)	99 (20.0)	0.119
13–16 years	704 (35.5)	185 (37.4)	173 (34.9)	188 (37.9)	158 (31.9)	
>16 years	908 (45.8)	217 (43.8)	244 (49.2)	208 (41.9)	239 (48.2)	
Smoking, no. (%)						
Current smoker	86 (4.3)	28 (5.7)	22 (4.4)	20 (4.0)	16 (3.2)	0.311
Former smoker	928 (46.8)	222 (44.8)	219 (44.2)	240 (48.4)	247 (49.8)	
Never smoker	969 (48.9)	245 (49.5)	255 (51.4)	236 (47.6)	233 (47.0)	
Drinking, no. (%)						
None/week	1,312 (66.2)	312 (63.0)	321 (64.7)	341 (68.8)	338 (68.1)	0.173
≥1/week	671 (33.8)	183 (37.0)	175 (35.3)	155 (31.3)	158 (31.9)	
Mean of weight within 4 year	95.7 (18.7)	96.4 (18.4)	95.6 (19.5)	94.9 (17.8)	95.8 (19.2)	0.694

Continuous variables are presented as mean (SD), and categorical variables are presented as percentage. BP, blood pressure; CVD, cardiovascular disease; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; ILI, intensive lifestyle intervention; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; VIM, variability independent of the mean.

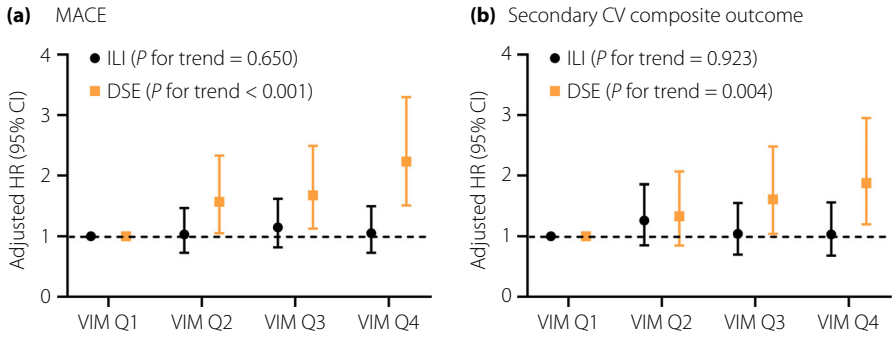

Figure 1 | Risks of a major adverse cardiovascular event (a) and secondary cardiovascular composite outcome (b) in different quartiles of 4 year weight variability measured by VIM, relative to the lowest quartile (reference group) in overweight or obese adults with type 2 diabetes mellitus. Adjusted HR (95% CI) are derived from Cox proportional hazard regression models adjusted for age, sex, race, education level, smoking status, drinking status, systolic blood pressure, diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, glycosylated hemoglobin, serum creatinine, prevalent hypertension, and cardiovascular disease, insulin use at baseline and mean 4 year weight. MACE was defined as a composite outcome of the first occurrence of all-cause mortality, death from cardiovascular causes or non-fatal acute myocardial infarction, stroke. Secondary CV composite outcome was defined as a composite outcome of the first occurrence of death from cardiovascular causes or non-fatal acute myocardial infarction, stroke. CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular event; VIM, variability independent of the mean.

no significant difference in the risk of MACE among the quartile groups of weight variability (P for trend = 0.650) (Figure 1a). Compared with the lowest weight variability participants (VIM Q1, reference group), those with the highest weight variability (VIM Q4) were at 2.23-fold greater risk of MACE in the DSE arm (HR 2.23; 95% CI 1.51–3.30), while no difference was found for the risk of MACE in the highest weight variability group (VIM Q4) in the ILI arm (HR 1.05; 95% CI 0.73–1.50) (Table 3).

In the further analysis with the VIM of 4 year weight as a continuous variable, each SD increase in VIM of 4 year weight (Per 1-SD: 3.14% in ILI; 2.83% in DSE) was associated with a 24% higher risk of MACE in the DSE arm (HR 1.24; 95% CI 1.11–1.37), but not in the ILI arm (HR 1.00; 95% CI 0.88–1.15; Table 4). The continuous associations between weight variability and the risk of MACE were examined using restricted cubic splines in the ILI and DSE arms, respectively. The results revealed that the risk of MACE also grew with the increased weight variability in the DSE arm (Figure 2b). Still, a continuous association was not found in the ILI arm (Figure 2a).

Intervention-specific association of weight variability with secondary outcomes

A secondary cardiovascular composite outcome occurred in 198 (10%) persons in the ILI arm (30 cardiovascular deaths, 126 myocardial infarctions, and 62 strokes) and 186 (9.8%) persons in the DSE arm (30 cardiovascular deaths, 133 myocardial infarctions, and 50 strokes). Death occurred in 102 persons in the ILI arm and 110 persons in the DSE arm.

In the ILI arm, the weight variability as a categorical variable or continuous variable did not affect the risks of secondary cardiovascular composite outcome, all-cause mortality, cardiovascular death, myocardial infarction, and stroke (Figure 1b; Figure S3; Table 4). Compared with the lowest weight variability participants (VIM Q1, reference group), those with the highest weight variability (VIM Q4) did not pose a risk for increase in secondary cardiovascular composite outcome, all-cause mortality, cardiovascular death, myocardial infarction, and stroke (all $P > 0.05$; Table 3). In the DSE arm, the weight variability was hierarchically associated with the risks of all secondary outcomes except cardiovascular death and stroke (Figure 1b; Figure S3). Compared with the lowest weight variability participants (VIM Q1, reference group), those with the highest weight variability (VIM Q4) were associated with higher risks of secondary cardiovascular composite outcome (HR 1.88; 95% CI 1.20–2.95), all-cause mortality (HR 3.19; 95% CI 1.75–5.82), and myocardial infarction (HR 1.95; 95% CI 1.12–3.37; Table 3). In the model with weight variability as a continuous variable, each SD increase in weight variability was associated with a higher rate of incident secondary cardiovascular composite outcome (HR 1.16; 95% CI 1.01–1.33), all-cause mortality (HR 1.41; 95% CI 1.24–1.61), and cardiovascular death (HR 1.42; 95% CI 1.05–1.92; Table 4).

Sensitivity analyses

Consistent with the results from primary analyses, intervention-specific associations of weight variability measured by SD (Table S3) and ARV (Table S4) with the risks of MACE and five secondary outcomes were also found. After excluding 111 participants (ILI: n = 64; DSE: n = 47), those with MACE occurring within 4 years, we also found the intervention-

Table 3 | Risk of MACE and five secondary outcomes for the highest (VIM Q4) vs lowest (VIM Q1) quartile of 4 year weight variability in ILI and DSE arms among overweight or obese adults with type 2 diabetes mellitus

Outcome	VIM Q1 (Reference) No./total no. (%)	VIM Q4 No./total no. (%)	Model 1		Model 2	
			Hazard ratio (95% CI)	*P* value	Hazard Ratio (95% CI)	*P* value
ILI arm (*N* = 1983)						
Primary outcome						
MACE	67/495 (13.5)	58/496 (11.7)	0.87 (0.61–1.25)	0.449	1.05 (0.73–1.50)	0.815
Secondary outcomes						
Secondary CV composite outcome	52/495 (10.5)	44/496 (8.9)	0.86 (0.57–1.29)	0.464	1.03 (0.68–1.56)	0.882
All-cause mortality	25/495 (5.1)	26/496 (5.2)	1.02 (0.58–1.78)	0.948	1.22 (0.69–2.15)	0.499
Cardiovascular death	8/495 (1.6)	8/496 (1.6)	0.97 (0.36–2.63)	0.957	1.29 (0.47–3.56)	0.627
Myocardial infarction	34/495 (6.9)	27/496 (5.4)	0.77 (0.46–1.28)	0.303	0.94 (0.56–1.59)	0.825
Stroke	17/495 (3.4)	14/496 (3.0)	0.95 (0.46–1.95)	0.889	1.02 (0.49–2.12)	0.960
DSE arm (*N* = 1876)						
Primary outcome						
MACE	40/469 (8.5)	74/469 (15.8)	2.32 (1.58–3.42)	<0.001	2.23 (1.51–3.30)	<0.001
Secondary outcome						
Secondary CV composite outcome	33/469 (7.0)	50/469 (10.7)	1.87 (1.20–2.91)	0.005	1.88 (1.20–2.95)	0.006
All-cause mortality	15/469 (3.2)	42/469 (9.0)	3.61 (2.00–6.52)	<0.001	3.19 (1.75–5.82)	<0.001
Cardiovascular death	5/469 (1.1)	11/469 (2.1)	3.12 (1.08–9.04)	0.036	2.68 (0.90–8.04)	0.078
Myocardial infarction	22/469 (4.7)	34/469 (7.2)	1.85 (1.08–3.17)	0.026	1.95 (1.12–3.37)	0.017
Stroke	9/469 (1.9)	13/469 (2.8)	1.72 (0.73–4.04)	0.215	1.60 (0.70–3.83)	0.290

MACE was defined as a composite outcome of the first occurrence of all-cause mortality, death from cardiovascular causes or non-fatal acute myocardial infarction, stroke. Secondary CV composite outcome was defined as a composite outcome of the first occurrence of death from cardiovascular causes or non-fatal acute myocardial infarction, stroke. Model 1: adjusted for age, sex, race at baseline; Model 2: adjusted for model 1 + education level, smoking status, drinking status, SBP, DBP, total cholesterol, HDL-C, HbA1c, serum creatinine, prevalent hypertension and CVD, insulin use at baseline, mean of 4 year weight. CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic blood pressure; DSE, diabetes support & education; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; ILI, intensive lifestyle intervention; MACE, major adverse cardiovascular event; SBP, systolic blood pressure; VIM, variability independent of the mean.

specific associations of weight variability with the risks of MACE and all-cause mortality, whereas weight variability was not associated with the risks of other secondary endpoints in both interventions (Table S5). In addition, analyses were repeated including only participants (n = 2,497) who gained weight loss in the fourth year. The results were similar to the primary analyses (Table S6).

Based on the findings from the previous study[10], we repeatedly assessed the effect of ILI on incident cardiovascular disease and found that the ILI was not associated with a lower risk of incident MACE or five secondary outcomes on follow-up compared with DSE (all $P > 0.05$; Table S7). Therefore, the ILI and DSE groups were pooled together to explore the association of weight variability with the risk of MACE or five secondary outcomes. The higher risks of MACE and all-cause mortality were observed in the highest weight variability (VIM Q4) compared with the lowest weight variability (VIM Q1), after adjusting for treatment arm and other covariates (Table S8). Of note, the association between weight variability and MACE was observed just in the DSE arm rather than in the ILI arm with a significant interaction (P for interaction = 0.005; Table S9).

DISCUSSION

In the current study, we examined intervention-specific associations of 4 year weight variability with the risks of MACE and secondary endpoints in overweight or obese adults with type 2 diabetes mellitus from the Look AHEAD trial. In the DSE arm of 1,876 participants, the rising weight variability was significantly associated with a higher risk of MACE, independent of mean weight and traditional risk factors. More importantly, the association of weight variability and the risk of MACE was not observed in the ILI arm. Our findings suggested that higher weight variability was a significant risk factor for cardiovascular outcomes in overweight or obese adults with type 2 diabetes mellitus, unless ILI caused it. Therefore, guideline-recommended ILI strategy for weight loss should be adopted to improve cardiovascular outcomes in overweight or obese adults with type 2 diabetes mellitus without worrying about the effect of weight fluctuations (Table 5).

To the best of our knowledge, it is the first large prospective study to assess the intervention-specific associations of weight variability with cardiovascular outcomes in overweight or obese adults with type 2 diabetes mellitus. Several prior studies, focused on the general population[15,16] or on patients with type

Table 4 | Association of 4 year weight variability (measured by VIM) as a continuous variable with the risk of MACE and five secondary outcomes in ILI and DSE arms among overweight or obese adults with type 2 diabetes mellitus

Outcome	Incidence, no. (%)	Model 1		Model 2	
		Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
ILI arm (*n* = 1983) (Per 1-SD [3.14%])					
Primary outcome					
MACE	255 (12.9)	0.95 (0.83–1.09)	0.485	1.00 (0.88–1.15)	0.951
Secondary outcome					
Secondary CV composite outcome	198 (10.0)	0.87 (0.73–1.03)	0.095	0.92 (0.78–1.09)	0.323
All-cause mortality	102 (5.1)	1.12 (0.93–1.35)	0.236	1.17 (0.97–1.40)	0.097
Cardiovascular death	30 (1.5)	0.90 (0.59–1.39)	0.643	0.98 (0.65–1.50)	0.936
Myocardial infarction	126 (6.4)	0.82 (0.66–1.02)	0.073	0.88 (0.71–1.09)	0.253
Stroke	62 (3.1)	0.96 (0.72–1.27)	0.768	0.98 (0.74–1.29)	0.860
DSE arm (*n* = 1876) (Per 1-SD [2.83%])					
Primary outcome					
MACE	247 (13.2)	1.24 (1.12–1.37)	<0.001	1.24 (1.11–1.37)	<0.001
Secondary outcome					
Secondary CV composite outcome	186 (9.9)	1.13 (0.99–1.30)	0.069	1.16 (1.01–1.33)	0.037
All-cause mortality	110 (5.9)	1.44 (1.27–1.63)	<0.001	1.41 (1.24–1.61)	<0.001
Cardiovascular death	30 (1.6)	1.39 (1.05–1.85)	0.020	1.42 (1.05–1.92)	0.023
Myocardial infarction	133 (7.1)	1.10 (0.93–1.30)	0.260	1.14 (0.96–1.35)	0.131
Stroke	50 (2.7)	1.12 (0.86–1.45)	0.424	1.12 (0.85–1.48)	0.420

MACE was defined as a composite outcome of the first occurrence of all-cause mortality, death from cardiovascular causes or non-fatal acute myocardial infarction, stroke. Secondary CV composite outcome was defined as a composite outcome of the first occurrence of death from cardiovascular causes or non-fatal acute myocardial infarction, stroke. Model 1: adjusted for age, sex, race at baseline; Model 2: adjusted for model 1 + education level, smoking status, drinking status, SBP, DBP, total cholesterol, HDL-C, HbA1c, serum creatinine, prevalent hypertension and CVD, insulin use at baseline, mean of 4 year weight. CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic blood pressure; DSE, diabetes support & education; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; ILI, intensive lifestyle intervention; MACE, major adverse cardiovascular event; SBP, systolic blood pressure; SD, standard deviation; VIM, variability independent of the mean.

2 diabetes mellitus[8,9,17] or coronary artery disease (CAD)[18], demonstrated that higher weight variability was associated with higher mortality and a higher rate of cardiovascular events. A prospective cohort from Framingham Heart Study was the earliest study to explore the association between variability of body weight and health outcomes in the community population about 30 years ago[15]. In an analysis of 3,130 general participants, the relative risks of mortality and coronary heart disease ranged from 1.27 to 1.93 in participants whose weight varied substantially compared with those with lower weight variability[15] with similar findings in the analysis of 6,748,773 subjects from Korea[16]. In a *post hoc* analysis of the Treating to New Targets (TNT) trial, the fluctuation in body weight was associated with an 85% higher risk of cardiovascular event and a 124% higher risk of death compared with the lowest variation in body weight among the 9,509 patients with coronary artery disease[18]. Recently, a prospective cohort study from the USA of 6,408 subjects with type 2 diabetes mellitus demonstrated that weight variability was positively associated with an increase in the risk of death (HR 1.16; 95% CI 1.10–1.22) and any cardiovascular event (HR 1.08; 95% CI 1.03–1.14)[8]. A Korean cohort of 624,237 subjects with type 2 diabetes mellitus also reported a significant higher risk of all-cause mortality (HR 1.58; 95% CI 1.53–1.62), myocardial infarction (HR 1.15; 95% CI 1.10–1.20), and stroke (HR 1.22; 95% CI 1.18–1.26) among individuals with the highest weight variability compared with those with the lowest weight variability[9]. The present study extended those findings and provided additional information, showing that the association of weight variability with MACE was also observed in overweight or obese adults with type 2 diabetes mellitus. More importantly, we found heterogeneity in the effects of weight variability on cardiovascular outcomes. The higher weight variability caused by ILI was not a risk factor for cardiovascular outcomes. Therefore, the reasons leading to increase weight variability should be considered in future studies to explore the effects of weight variability on cardiovascular outcomes.

As mentioned above, weight loss often accompanied by weight fluctuations was defined as the 'yo-yo effect' by Kelly D. Brownell at Yale University[19]. Some data have shown that approximately 79% of adults who intentionally achieve successful weight loss will regain the weight within 1 year[6]. According to the findings from previous studies[8,9,15–18] and our study, weight cycling (higher weight variability) was associated with

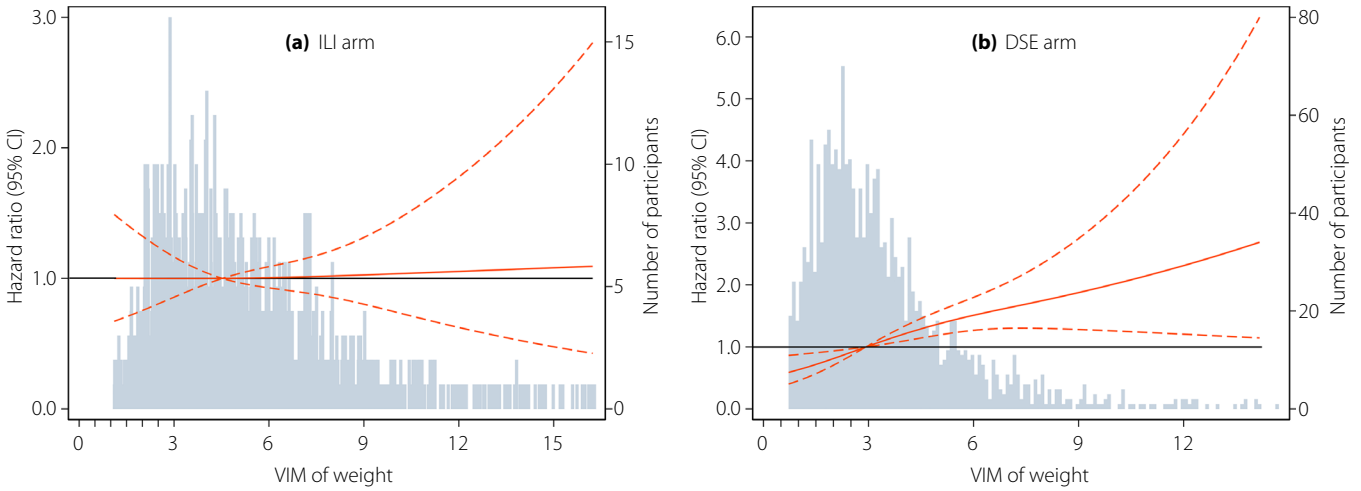

Figure 2 | Adjusted hazard ratios (95% CI) for the association of 4 year weight variability measured by VIM with MACE in ILI (a) and DSE (b) arms among overweight or obese individuals with type 2 diabetes mellitus. Hazard ratios (indicated by a red solid line) and 95% CIs (red dotted lines) are derived from Cox proportional hazard regression models adjusted for age, sex, race, education level, smoking status, drinking status, systolic blood pressure, diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, glycosylated hemoglobin, serum creatinine, prevalent hypertension and cardiovascular disease, insulin use at baseline and mean 4 year weight. VIM values of weight were centered at the sample median and modeled using a restricted cubic spline with knots at the 5th, 50th, and 95th percentiles. Black solid line is the reference line as hazard ratio = 1. Histograms represent the frequency distribution of 4 year weight variability (VIM). Participants with extreme VIM values (in the bottom first and top 99th percentile) were excluded from these analyses. DSE, diabetes support & education; ILI, intensive lifestyle intervention; MACE, major adverse cardiovascular event; VIM, variability independent of the mean.

higher risks of cardiovascular outcomes. Dr William Kannel joked that once you are fat, you better stay fat, when he made a presentation for Framingham study regarding weight cycling. Of course, such recommendations can hardly be created due to the risks of cardiovascular disease and death secondary to obesity. Therefore, a strategy that can lose body weight and avoid the risks of cardiovascular disease associated with weight fluctuations is essential for overweight or obese adults. The findings presented herein support that achieving weight loss by ILI might avoid higher risks of cardiovascular outcomes associated with the increased weight variability. Therefore, the prescription of ILI for weight loss was adopted by clinicians to manage overweight or obese adults with type 2 diabetes mellitus without worrying about the effect of weight fluctuations. Such information contributed to strengthening the recommendation from 2020 ADA guideline supporting the use of ILI to achieve weight loss in overweight or obese adults with type 2 diabetes mellitus[1], and providing evidence to the development of the subsequent guidelines and clinical decisions on the strategy of weight loss to prevent cardiovascular outcomes.

The mechanism lying behind weight variability and cardiovascular outcomes remains attractive. Obesity is a well-established cause of increased inflammatory burden[20]. On the other hand, adverse cardiac events are also associated with elevated inflammatory markers[21]. Thus, weight variation might trigger MACEs *via* increased inflammation. Indeed, altered metabolic/inflammatory predictors have been reported in various conditions that are associated with cardiovascular diseases, such as hypertension[22], type 2 diabetes mellitus[23], diabetic kidney disease[24], metabolic syndrome[23], and hepatosteatosis[25]. Recent studies also figure out the relationship between chronic, systemic tissue inflammation and diabetes in obese patients[26]. However, whether weight and weight variability causes cardiovascular events through similar or totally different mechanisms remains unclear. Further studies comparing the differences between inflammation profiles among high weight variability and low weight variability groups may tell us the answer.

The finding from the Chicago Western Electric Company study[27] indicated that the length of the follow-up period might influence the observable effect of weight variability. Previous studies focused on patients with type 2 diabetes mellitus, the mean follow-up period was 3.9–4.9 years in the U.S. study and 7.6–7.8 years in the Korean cohort study[8,9]. However, our study comprised a longer follow-up period with 9.6 years for the analysis of cardiovascular outcomes. In addition, a prospective cohort study of 6,537 middle-aged Japanese American men from the Honolulu Heart Program[28] showed that the association between weight fluctuation and mortality was partially explained by the presence of pre-existing disease. Thus, this association might be better demonstrated in a population with fewer comorbidities. Compared with previous observational studies[8,9], our study population enrolled in the clinical trial (Look AHEAD trial) tended to have fewer comorbidities and heterogeneity than those in the community.

The strengths of this investigation are worth noting. We had a large sample size of the cohort focused on overweight or obese

Table 5 | Baseline characteristics of each group categorized by the VIM of weight for 4 years in the DSE arm

Characteristic	Total	VIM Q1	VIM Q2	VIM Q3	VIM Q4	*P* value
No.	1876	469	469	469	469	
Age, years	59.1 (6.8)	59.8 (6.9)	59.3 (6.7)	59.1 (6.7)	58.5 (6.8)	0.032
Sex, no. (%)						
Men	797 (42.5)	227 (48.4)	198 (42.2)	199 (42.4)	173 (36.9)	0.005
Women	1,079 (57.5)	242 (51.6)	271 (57.8)	270 (57.6)	296 (63.1)	
Race, no. (%)						
White	1,264 (67.4)	310 (66.1)	303 (64.6)	313 (66.7)	338 (72.1)	0.392
Black (not Hispanic)	318 (17.0)	88 (18.8)	78 (16.6)	83 (17.7)	69 (14.7)	
Hispanic	229 (12.2)	56 (11.9)	68 (14.5)	57 (12.2)	48 (10.2)	
Other/mixed	65 (3.5)	15 (3.2)	20 (4.3)	16 (3.4)	14 (3.0)	
Weight, kg	101.6 (18.8)	99.4 (17.7)	99.3 (18.4)	101.4 (18.5)	106.1 (20.0)	<0.001
Systolic BP, mmHg	129.4 (17.0)	128.5 (16.0)	130.4 (16.8)	130.4 (17.9)	128.5 (17.1)	0.119
Diastolic BP, mmHg	70.3 (9.5)	70.6 (9.0)	71.1 (9.7)	70.2 (9.8)	69.1 (9.4)	0.013
HbA1c, %	7.2 (1.2)	7.2 (1.1)	7.2 (1.1)	7.3 (1.2)	7.3 (1.2)	0.090
Fasting glucose, mg/mL	152.4 (44.5)	152.9 (43.2)	150.6 (41.3)	152.9 (45.4)	153.0 (47.8)	0.802
Total cholesterol, mg/mL	191.0 (37.1)	187.7 (35.9)	195.2 (37.8)	192.5 (38.5)	188.6 (35.9)	0.006
HDL-C, mg/mL	43.5 (11.9)	42.5 (11.2)	43.1 (11.3)	43.6 (12.3)	44.8 (12.5)	0.025
LDL-C, mg/mL	112.9 (32.2)	110.3 (31.7)	116.7 (32.1)	114.9 (33.1)	109.4 (31.6)	0.001
Triglyceride, mg/mL	178.9 (116.2)	179.3 (109.6)	182.7 (123.7)	176.6 (126.8)	177.1 (103.3)	0.851
Serum creatinine, mg/mL	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)	0.056
History of hypertension, no. (%)	1,563 (83.3)	380 (81.0)	393 (83.8)	395 (84.2)	395 (84.2)	0.493
History of CVD, no. (%)	239 (12.7)	54 (11.5)	72 (15.4)	65 (13.9)	48 (10.2)	0.082
Insulin use, no. (%)	276 (14.7)	70 (14.9)	54 (11.5)	74 (15.8)	78 (16.6)	0.130
Education level, no. (%)						
<13 years	336 (17.9)	84 (17.9)	88 (18.8)	91 (19.4)	73 (15.6)	0.649
13–16 years	718 (38.3)	180 (38.4)	180 (38.4)	183 (39.0)	173 (37.3)	
>16 years	822 (43.8)	205 (43.7)	201 (42.9)	195 (41.6)	221 (47.1)	
Smoking, no. (%)						
Current smoker	66 (3.5)	13 (2.8)	16 (3.4)	19 (4.1)	18 (3.8)	0.786
Former smoker	851 (45.4)	203 (43.3)	221 (47.1)	211 (45.0)	216 (46.1)	
Never smoker	959 (51.1)	253 (53.9)	232 (49.5)	239 (51.0)	235 (50.1)	
Drinking, no. (%)						
None/week	1,224 (65.2)	304 (64.8)	297 (63.3)	295 (62.9)	328 (69.9)	0.090
≥1/week	652 (34.8)	165 (35.2)	172 (36.7)	174 (37.1)	141 (30.1)	
Mean of weight within 4 year	100.6 (18.6)	99.3 (17.8)	99.2 (18.6)	100.9 (18.9)	103.0 (18.9)	0.006

Continuous variables are presented as mean (SD), and categorical variables are presented as percentage. BP, blood pressure; CVD, cardiovascular disease; DSE, diabetes support & education; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; VIM, variability independent of the mean.

adults with type 2 diabetes mellitus and defined the 4 year weight variability based on five equally spaced medical measurements. Our study is not without limitations. First, as in all observational studies, there may be a potential for reverse causation. Therefore, we conducted a sensitivity analysis in participants (n = 3,748) without MACE occurring within 4 years and found consistent results with our main findings. Second, the residual measured or unmeasured confounders were difficult to exclude, although the effect of various confounding factors had been adjusted in the Cox regression model and the study population had a lower heterogeneity due to enrolling in the clinical trial (Look AHEAD trial). Moreover, the consistency of results in several sensitivity analyses supported the robust findings. Third, due to the observational study, the findings are unable to show causality but are merely hypotheses-generating. The actual association between weight variability and MACEs can be complex. For example, whether weight variation triggers MACEs *via* increased inflammation remains unclear. Therefore, the interpretation of the findings should be made with caution. Finally, although the study population had a multiethnic diversity, the findings might not be generalizable to overweight or obese adults with type 2 diabetes mellitus who would not have qualified for taking part in the Look AHEAD trial.

CONCLUSIONS

Among overweight or obese individuals with type 2 diabetes mellitus, the effects of weight variability on MACE showed large differences between the ILI and DSE arms. High weight

variability was independently associated with increased risks of MACE in the DSE arm but not in the ILI arm. Such information supported that guideline-recommended ILI strategy for weight loss should be adopted to improve cardiovascular outcomes in overweight or obese adults with type 2 diabetes mellitus without worrying about the effect of weight fluctuations.

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DISCLOSURE

The authors declare no conflict of interest.
Approval of the research protocol: The Look Ahead trial obtained the ethical approval from local institutional review boards, and all participants provided written informed consent.
Registry and the registration no. of the study/trial: N/A.
Informed consent: N/A.
Animal studies: N/A.

DATA AVAILABILITY STATEMENT

Data are available upon request to the Look AHEAD study Coordinating Center.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Characteristics of the included and excluded participants at baseline.

Table S2 | Correlations among mean of 4 year weight and different measures of 4 year weight variabilities.

Table S3 | Risk of MACE and five secondary outcomes for the highest (SD Q4) vs lowest (SD Q1) quartile of 4 year weight variability in the intensive lifestyle intervention and diabetes support & education arms among overweight or obese adults with type 2 diabetes mellitus (N = 3,859).

Table S4 | Risk of MACE and five secondary outcomes for the highest (ARV Q4) vs lowest (ARV Q1) quartile of 4 year weight variability in the intensive lifestyle intervention and the diabetes support & education arms among overweight or obese adults with type 2 diabetes mellitus (N = 3,859).

Table S5 | Risk of MACE and five secondary outcomes for the highest (VIM Q4) vs lowest (VIM Q1) quartile of 4 year weight variability in the intensive lifestyle intervention and the diabetes support & education arms among overweight or obese adults with type 2 diabetes mellitus without MACE occurred within 4 years (N = 3,748).

Table S6 | Risk of MACE and five secondary outcomes for the highest (VIM Q4) vs lowest (VIM Q1) quartile of 4 year weight variability in the intensive lifestyle intervention and the diabetes support & education arms among overweight or obese adults with type 2 diabetes mellitus with weight loss in the fourth year (N = 2,497).

Table S7 | Risk of MACE and five secondary outcomes for the intensive lifestyle intervention vs the diabetes support & education arms among overweight or obese adults with type 2 diabetes mellitus (N = 3,859).

Table S8 | Risk of MACE and five secondary outcomes for the highest (VIM Q4) vs lowest (VIM Q1) quartile of 4 year weight variability in all included participants (N = 3,859).

Table S9 | Risk of MACE and five secondary outcomes for the highest (VIM Q4) vs lowest (VIM Q1) quartile of 4 year weight variability in treatment arm subgroup in all included participants (N = 3,859).

Figure S1 | Study flowchart with detailed study exclusion information.

Figure S2 | The calculating formula of standard deviation (SD), average real variability (ARV), and variability independent of the mean (VIM).

Figure S3 | Risk of four secondary individual outcomes (all-cause mortality, cardiovascular death, myocardial infarction, and stroke) in different quartiles of 4 year weight variability measured by variability independent of the mean, relative to the lowest quartile (reference group) in overweight or obese adults with type 2 diabetes mellitus.