Effect of Intensive Lifestyle Intervention on the Association between Weight Variability and Mortality and Cardiovascular Events in Overweight or Obese Adults with Type 2 Diabetes Mellitus

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Original investigation

Abstract

Background: The association among intensive lifestyle intervention (ILI), weight variability and the risks of death and cardiovascular events have limited data. We aimed to examine whether the weight variability is associated with all-cause mortality and cardiovascular events, and whether the intensive lifestyle intervention (ILI) will affect these associations in overweight or obese individuals with type 2 diabetes mellitus (T2DM).

Methods: Individuals from the Action for Health in Diabetes (Look AHEAD) trial who measured the weight variability based on 5 equally spaced medical measurements of within 4 years were enrolled. A multivariate-adjusted Cox regression models were used to evaluate the associations between weight variability and adverse outcomes including the all-cause mortality and primary cardiovascular disease (CVD) outcome, and the effects of ILI on these associations.

Results: Among the 3,859 participants with a median follow-up of 9.6 years, those with the highest quartile of weight variability experienced a double higher risk of death compared with those the lowest quartile (HR 2.25; 95% CI 1.44-3.52), but no difference was found in primary CVD outcome (HR 1.02; 95% CI 0.78-1.33). Moreover, the restricted cubic splines revealed that the risk of death grew with the increased weight variability. Of note, the association between weight variability and all-cause mortality was not observed in ILI arm (the highest vs. lowest quartile group, [HR 1.30; 95% CI 0.67-2.50]) and was just found in diabetes support and education (DSE) arm (the highest vs. lowest quartile group, [HR 3.31; 95% CI 1.84-5.95]).

Conclusions: Among the overweight or obese individuals with T2DM, the weight variability was independently associated with increased risks of all-cause mortality, but this association might be removed by ILI.

Trial registrations ClinicalTrials.gov identifiers: NCT00017953.

Background

Weight loss as an important treatment is recommended by clinical practice guideline for overweight or obese patients with type 2 diabetes mellitus (T2DM) [1]. Actually, the prescription of weight loss to individuals is often characterized with weight fluctuations [2, 3]. Most of individuals will partly regain the weight after successfully reducing it [2, 4], especially the patients with T2DM [5]. Of note, weight variability may be associated with cardiovascular outcomes and mortality in adults with T2DM [6, 7]. It was reported that approximately 90% of people with T2DM have overweight or obesity [8], but emerging evidence for the potential risks of higher weight variability in overweight or obese adults with T2DM remains limited. Therefore, it is meaningful to further assess the association between weight variability and cardiovascular outcomes and mortality in overweight or obese adults with T2DM.

Previous study supported that intensive lifestyle intervention (ILI) contributed to reducing the blood pressure, improving the lipid parameters and controlling the blood glucose [9]. The American Diabetes Association (ADA) also recommends the weight loss with high-intensity lifestyle interventions to achieve the optimal control of traditional cardiovascular risk factors in overweight or obese adults with T2DM [1], but it can be accompanied by weight fluctuations [2–4]. There is currently little evidence to illustrate whether the weight variability caused by high-intensity lifestyle interventions is also associated with cardiovascular outcomes and mortality.

Therefore, this study not just tests the associations between weight variability and mortality and cardiovascular events, but evaluates the effect of ILI on these associations in overweight or obese adults with T2DM using data from the Look AHEAD (Action for Health in Diabetes) randomized trial [10].

Methods

Study Design and Study Population

Look AHEAD trial was a multicenter randomized controlled clinical trial to evaluate the effects of ILI on the risk for cardiovascular events in comparison with diabetes support and education (DSE). Details of the design and methods have been described previously [10] and the trial was stopped early (median duration of follow-up 9.6 years) due to a futility analysis that found no significant difference on the primary cardiovascular events between ILI and DSE [9]. 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 (BMI ≥ 25 kg/m^2 or ≥ 27 kg/m^2 if taking insulin), aged 45 to 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 T2DM (n = 5,145) from 16 clinical centers in the USA [11], 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 primary analysis (Additional file 1: Figure S1). The Look Ahead trial obtained the 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 group. The ILI was designed to achieve and maintain at least 7% weight loss by changing their eating and physical activity levels. Participants in the ILI group (weekly group and individual counseling sessions in the first 6 months followed by less frequent meetings) were encouraged to achieve ≥ 175 minutes/week of moderate-intensity physical activity and prescribed a restricted caloric diet (1200 to 1800 kcal/day). Participants in the DSE group 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 [12, 13].

4-year Variability of Weight

The 4-year weight variability was defined as intraindividual variability in weight for years 0 through 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 the Figure S2 (Additional file 1).

Outcome Measures

We restricted the current analyses to the pre-specified outcomes in Look AHEAD trial including the primary cardiovascular disease (CVD) outcome and all-cause mortality, adjudicated by a masked outcomes committee. The primary CVD outcome was defined as first occurrence of non-fatal acute myocardial infarction or stroke, hospitalized angina, or CVD death.

Statistical Analyses

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

The risks of primary CVD outcome and all-cause mortality associated with ILI (vs. DSE, referent group) were evaluated using Cox proportional hazard models. Participants from both trial arms were pooled and further categorized the 4-year weight variability (SD for weight) into quartiles based on the sample distribution. A multivariate-adjusted Cox proportional hazards regression models were used to evaluate the associations of 4-year weight variability with the risk of primary CVD outcome and all-cause mortality and calculate the hazard ratios (HRs) and 95% CIs compared with the lowest quartile group. Separate models were constructed for the primary CVD outcome and all-cause mortality with 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 CVD, Insulin use at baseline, treatment arm; Model 3 adjusted for variables in model 2 and weight at baseline, rather than mean weight levels for 4 years due to the high correlation between weight at baseline and mean weight (Pearson's correlation r = 0.954; P< 0.001). A restricted cubic spline with 3 knots was also incorporated to determine the associations of 4-year weight variability as continuous variable with the risk of primary CVD outcome and all-cause mortality.

The subgroup analyses in ILI and DES groups were conducted to assess the effect of ILI on the risk of primary CVD outcome and all-cause mortality associated with 4-year weight variability. An interaction term between treatment arm and 4-year weight variability was individually added to the adjusted Cox model 3, and the P values and CIs for these associations were estimated. The subgroup analyses of other key variables (age, gender, race, weight, SBP, HbA1c, total cholesterol and serum creatinine) were also

performed to compare the risks of primary CVD outcome and all-cause mortality between the highest (SD Q4) and lowest quartile (SD Q1) of weight variability. In addition, the sensitivity analyses for 4-year weight variability defined by ARV and VIM were conducted through a multivariate-adjusted Cox regression model. Furthermore, the sensitivity analyses were also conducted in participants (n = 3643) without any outcomes occurred within 4 years when were used to define the weight variability. The 216 participants were excluded, of which 213 participants occurred the primary CVD outcome and 3 participants occurred death within 4 years.

A significance level of less than 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) and the R language (version 3.5.0.12).

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) with average 59 years old, 2,229 (57.8%) women and 2,609 (67.6%) white races. Compared with included participants in the study, the excluded participants (Additional file 1: Table S1) were more allocated to the ILI arm, more commonly identified as Hispanics, more previously diagnosed as CVD, and had fewer drinker, lower education level and more insulin user. During a mean follow-up of 9.6 (SD, 1.0) years, 601 incident primary CVD outcomes and 212 incident deaths occurred in included participants. The similar baseline demographic and clinical characteristics were found between the ILI and DSE groups (Additional file 1: Table S2) and there was no significant difference in the risk of primary CVD outcome (HR 1.05; 95% CI 0.89–1.24) and mortality (HR 0.81; 95% CI 0.62–1.07) between the ILI vs. DSE groups (Additional file 1: Table S3).

Association of Weight Variability with Mortality and Primary CVD Outcome

The ILI and DSE groups were pooled together to explore the association of weight variability with the risk of primary CVD outcome and mortality. The baseline characteristics of included participants based on the quartiles of SD of 4-year weight were showed in Table 1. Participants with the highest weight variability (SD Q4) were more allocated to the ILI arm, more previously diagnosed as hypertension, more likely white, and had higher weight and education level.

Table 1
Baseline characteristics of each group categorized by the SD of weight for 4 years.

Characteristics	Total	SD Q1	SD Q2	SD Q3	SD Q4	P value
No.	3859	965	966	963	965	
Treatment arm						< 0.001
Diabetes Support & Education	1876 (48.6)	688 (71.3%)	516 (53.4)	374 (38.8)	298 (30.9)	
Intensive Lifestyle Intervention	1983 (51.4)	277 (28.7%)	450 (46.6)	589 (61.2)	667 (69.1)	
Age, years	59.0 (6.8)	59.7 (6.9)	58.9 (6.8)	59.1 (6.7)	58.2 (6.6)	< 0.001
Sex, No. (%)						< 0.001
Men	1630 (42.2)	397 (41.1)	374 (38.7)	397 (41.2)	462 (47.9)	
Women	2229 (57.8)	568 (58.9)	592 (61.3)	566 (58.8)	503 (52.1)	
Race, No. (%)						< 0.001
White	2609 (67.6)	587 (60.8)	618 (64.0)	652 (67.7)	752 (77.9)	
Black (not Hispanic)	644 (16.7)	187 (19.4)	177 (18.3)	176 (18.3)	104 (10.8)	
Hispanic	469 (12.2)	144 (14.9)	132 (13.7)	104 (10.8)	89 (9.2)	
Other/Mixed	137 (3.6)	47 (4.9)	39 (4.0)	31 (3.2)	20 (2.1)	
Weight, kg	101.3 (19.1)	94.0 (16.4)	97.1 (17.6)	102.1 (18.2)	111.8 (19.4)	< 0.001
Systolic BP, mm Hg	128.8 (17.2)	128.6 (16.7)	129.7 (17.4)	128.4 (17.0)	128.5 (17.7)	0.339
Diastolic BP, mm Hg	70.1 (9.6)	70.6 (9.2)	70.7 (9.8)	69.7 (9.6)	69.5 (9.6)	0.006
HbA1c, %	7.23 (1.14)	7.24 (1.12)	7.28 (1.18)	7.25 (1.11)	7.17 (1.16)	0.186
Fasting Glucose, mg/mL	152.0 (44.6)	152.6 (44.4)	153.4 (45.5)	151.3 (43.0)	150.8 (45.3)	0.566

Characteristics	Total	SD Q1	SD Q2	SD Q3	SD Q4	P value
Total cholesterol, mg/mL	190.8 (37.5)	191.9 (36.7)	192.5 (39.0)	191.5 (38.0)	187.1 (36.0)	0.006
HDL-C, mg/mL	43.5 (11.9)	43.4 (11.9)	43.4 (12.1)	43.9 (11.9)	43.2 (11.8)	0.557
LDL-C, mg/mL	112.1 (32.1)	113.4 (31.2)	113.2 (33.1)	113.0 (33.0)	108.7 (30.8)	0.002
Triglyceride, mg/mL	180.4 (116.0)	178.6 (115.8)	185.9 (130.2)	177.2 (111.8)	180.1 (104.7)	0.372
Serum creatinine, mg/mL	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)	0.138
History of hypertension, No. (%)	3241 (84.0)	783 (81.1)	809 (83.7)	805 (83.6)	844 (87.5)	0.002
History of CVD, No. (%)	519 (13.4)	137 (14.2)	128 (13.3)	118 (12.3)	136 (14.1)	0.568
Insulin use, No. (%)	579 (15.0)	137 (14.2)	144 (14.9)	143 (14.8)	155 (16.1)	0.714
Education level, No. (%)						0.010
< 13 years	707 (18.3)	204 (21.1)	164 (17.0)	182 (18.9)	157 (16.3)	
13–16 years	1422 (36.8)	352 (36.5)	388 (40.2)	343 (35.6)	339 (35.1)	
> 16 years	1730 (44.8)	409 (42.4)	414 (42.9)	438 (45.5)	469 (48.6)	
Smoking, No. (%)						0.008
Current smoker	152 (3.9)	31 (3.2)	48 (5.0)	39 (4.0)	34 (3.5)	
Former smoker	1779 (46.1)	414 (42.9)	444 (46.0)	433 (45.0)	488 (50.6)	
Never smoker	1928 (50.0)	520 (53.9)	474 (49.1)	491 (51.0)	443 (45.9)	
Drinking, No. (%)						0.136
None/wk	2536 (65.7)	632 (65.5)	619 (64.1)	622 (64.6)	663 (68.7)	
≥1/wk	1323 (34.3)	333 (34.5)	347 (35.9)	341 (35.4)	302 (31.3)	
Mean of weight within 4 year	98.1 (18.8)	93.6 (16.6)	95.8 (18.2)	99.0 (19.1)	103.9 (19.6)	< 0.001

Characteristics	Total	SD Q1	SD Q2	SD Q3	SD Q4	*P* value
Variability of weight within 4 year						
SD	4.4 (3.3)	1.67 (0.5)	3.0 (0.4)	4.5 (0.5)	8.6 (3.8)	< 0.001
ARV	4.3 (2.9)	1.8 (0.7)	3.1 (0.9)	4.5 (1.2)	7.8 (3.5)	< 0.001
VIM	4.4 (3.1)	1.8 (0.5)	3.1 (0.6)	4.5 (0.8)	8.3 (3.6)	< 0.001
Continuous variables are presented as mean (SD), and categorical variables are presented as percentage. SD: standard deviation; BP: blood pressure; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; HbA1c: glycosylated hemoglobin; CVD: cardiovascular disease; ARV: average real variability; VIM: variability independent of the mean.						

In multivariable adjusted analysis, there was a significant, graded association between 4-year weight variability and all-cause mortality in overweight or obese adults with T2DM. Compared with the lowest weight variability participants (SD Q1, referent group), the risk of all-cause mortality was the double higher in the highest weight variability group (SD Q4: HR 2.25; 95% CI 1.44–3.52), 76% higher in the higher weight variability group (SD Q3: HR 1.76; 95% CI 1.16–2.68) and 30% higher in the moderate weight variability group (SD Q2: HR 1.23; 95% CI 0.85-2.00) (Table 2). Consistent with the analysis using quartiles of sample distribution, the restricted cubic splines revealed that the risk of deaths also grew with the increased weight variability (Fig. 1B). However, the association between weight variability and incident CVD event was not found. The risks of incident CVD event in the highest weight variability group (SD Q4) were similar to the lowest weight variability group (SD Q1) (HR 1.02; 95% CI 0.78–1.33) (Table 2). The results of restricted cubic splines also supported this finding (Fig. 1A).

Table 2

Association between 4-year weight variability defined by SD and primary CVD outcome and all-cause mortality in overweight or obese adults with type 2 diabetes mellitus.

Outcome	Model 1		Model 2		Model 3	
	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value
Primary CVD Outcome *						
SD Q1	1 (ref.)	-	1 (ref.)	-	1 (ref.)	-
SD Q2	1.21 (0.97−1.52)	0.092	1.18 (0.94−1.48)	0.161	1.18 (0.94−1.49)	0.146
SD Q3	1.08 (0.86−1.36)	0.494	1.12 (0.88−1.41)	0.366	1.13 (0.89−1.44)	0.309
SD Q4	0.99 (0.78−1.25)	0.919	0.99 (0.77−1.27)	0.934	1.02 (0.78−1.33)	0.883
All-Cause Mortality						
SD Q1	1 (ref.)	-	1 (ref.)	-	1 (ref.)	-
SD Q2	1.26 (0.82−1.92)	0.291	1.31 (0.85−2.01)	0.219	1.30 (0.85-2.00)	0.233
SD Q3	1.57 (1.05−2.35)	0.027	1.79 (1.18−2.70)	0.006	1.76 (1.16−2.68)	0.008
SD Q4	1.98 (1.33−2.94)	0.001	2.32 (1.53−3.54)	< 0.001	2.25 (1.44−3.52)	< 0.001

SD: standard deviation; CVD: cardiovascular disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL-C: high-density lipoprotein cholesterol; HbA1c: glycosylated hemoglobin.

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, treatment arm;

Model 3: adjusted for model 2 + weight at baseline.

* The primary cardiovascular disease outcome was defined as a composite of the first occurrence of death from cardiovascular causes, non-fatal acute myocardial infarction, stroke, or admission to hospital for angina.

The sensitivity analyses were conducted when the weight variability was measured according to ARV and VIM. The association between weight variability and risk of death was not modified, and the association between weight variability and risk of CVD was also not found (Additional file 1: Table S4 and Table S5). In the sensitivity analysis in participants without the primary CVD outcome or death occurred within 4 years, the results were unchanged (the highest weight variability group vs. the lowest weight variability group; [HR 2.19; 95% CI 1.34−3.58] for all-cause mortality, [HR 0.82; 95% CI 0.59−1.14] for primary CVD outcome) (Additional file 1: Table S6).

The Effect of ILI on the Association between Weight Variability and Mortality and Primary CVD Outcome

To determine whether the weight variability caused by ILI was also associated with the risks of mortality and CVD events, we first compared the risks of mortality and primary CVD outcome among the quartile groups in participants received ILI. Of note, the highest weight variability caused by ILI had no significant association with the risks of mortality (HR 1.30; 95% CI 0.67–2.50) and primary CVD outcome (HR 0.87; 95% CI 0.60–1.26) in comparison to the lowest weight variability (Fig. 2). In participants received DSE, the results consisted with the main findings. The association between weight variability and primary CVD outcome in DSE arm was not found (the highest weight variability group vs. the lowest weight variability group, [HR 1.22; 95% CI 0.82–1.83]), but the highest weight variability group was associated with a 3.31 times higher risk of mortality compared to the lowest weight variability group (HR 3.31; 95% CI 1.84–5.95) (Fig. 2). A significant interaction with the treatment arm in the association of the highest weight variability (SD Q4) with all-cause mortality (P for interaction = 0.005) was found, but not in the association of the highest weight variability with primary CVD outcome (P for interaction = 0.257) (Fig. 2). Additionally, the interaction with the treatment arm in the association of the higher weight variability (SD Q3) with primary CVD outcome was also significant (P for interaction = 0.034) (Fig. 2).

The similar results to previous finding were also found in sensitivity analyses that assessed the effect of treatment arm on the association between weight variability and mortality and primary CVD outcome when the weight variability was measured according to ARV (Additional file 1: Figure S3) and VIM (Additional file 1: Figure S4), and participants who occurred the primary CVD outcome or death within 4 years were excluded (Additional file 1: Figure S5).

Subgroup Analyses for Key Variables

Results of the comparison between the highest (SD Q4) and lowest (SD Q1) weight variability groups for primary CVD outcome and all-cause mortality stratified by age, gender, race, weight, SBP, HbA1c, total cholesterol and serum creatinine are shown in Figure S6 and Figure S7 respectively (Additional file 1). There was no association between weight variability and primary CVD outcome in key subgroups without a significant interaction (all $P > 0.05$) (Additional file 1: Figure S6). Moreover, although discrepant results were found when assessed the association between weight variability and all-cause mortality in age, race, SBP and total cholesterol subgroups, interaction testing revealed no heterogeneity (age: $P = 0.204$; race: $P = 0.282$; SBP: $P = 0.312$; total cholesterol: $P = 0.402$) (Additional file 1: Figure S7).

Discussion

In the current study of overweight or obese adults with T2DM, several important findings were observed. First, consistent with the findings from previous study [9], the ILI was not associated with lower risk of incident CVD or all-cause mortality on follow-up compared with DSE. Second, the rising weight variability was significantly associated with a higher risk of all-cause mortality independent of weight and traditional risk factors. In contrast, the weight variability was not associated with risk of incident CVD after adjustment for potential confounders. Third, these associations between weight variability and all-cause mortality were just observed in participants received DSE, but not in participants received ILI. Our findings suggested that higher weight variability was an important risk factor for death in overweight or

obese adults with T2DM, but the risk of death associated with weight variability might be removed by ILI. Therefore, weight loss and subsequent maintenance may be contributed to the lower risk of death in overweight or obese adults with T2DM, but the guideline-recommended ILI [1] to reduce weight may be still benefit even if the weight may be regained later.

Although the evidence about the effect of weight variability in overweight or obese adults with T2DM is limited, some data focused on the general population [14, 15] or the patients with T2DM [6, 7, 16] or coronary artery disease (CAD) [17] suggest that the higher weight variability was associated with higher mortality and a higher rate of cardiovascular events. A prospective cohort from Framingham Heart Study was the earlier study to explore the association between variability of body weight and health outcomes in community population about 30 years ago [14]. In analysis of 3,130 general participants, the relative risks of mortality and coronary heart disease (CHD) ranged from 1.27 to 1.93 in participants whose weight varied substantially compared with those with lower weight variability [14], with similar findings in the analysis of 6,748,773 subjects from Korea [15]. 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 CAD [17]. Recently, a prospective cohort study from U.S. of 6,408 subjects with T2DM 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) [6]. A Korean cohort of 624,237 subjects with T2DM 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 the individuals with the highest weight variability compared with those with the lowest weight variability [7]. In the present study, our data confirmed the association weight variability and all-cause mortality in overweight or obese adults with T2DM, which could be of additional value to further illustrate the effect of higher weight variability on all-cause mortality.

Besides focusing on the overweight or obese adults with T2DM, our study had a few strengths over previous studies. The finding from the Chicago Western Electric Company study [18] indicated that the length of the follow-up period may influence the observable effect of weight variability. In previous studies focused on the patients with T2DM, the mean follow-up period was 3.9−4.9 years in the U.S. study [6] and 7.6−7.8 years in Korean cohort study [7]. However, our study comprised a longer follow-up period with 9.6 years for the analysis of survival. In addition, a prospective cohort study of 6,537 middle-aged Japanese American men from the Honolulu Heart Program [19] shown that the association between weight fluctuation and mortality were partially explained by the presence of pre-existing disease. Thus, this association might be better demonstrated in the population with fewer comorbidities. Compared with previous observational studies [6, 7], our study population enrolled in clinical trial (Look AHEAD trial) tend to be less comorbidities and heterogeneity than those in the community.

As mentioned above, the weight loss often accompanied by weight fluctuations, which was defined as "yo-yo effect" by Kelly D. Brownell at Yale University [20]. Some data shown that approximately 79% of adults who intentionally achieve successful weight loss will regain the weight within 1 year [4]. According

to the findings from previous studies [6, 7, 14–17] and our study, the weight cycling (higher weight variability) was associated with the higher risks of death. 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 recommendation hardly can be created due to the risks of CVD and death secondary to obesity. Therefore, a strategy that not only can lose the body weight but also is able to avoid the risks of death associated with weight fluctuations is particularly important for the overweight or obese adults. Of note, the findings presented herein supported that achieving weight loss by ILI might be able to avoid the risks of death associated with the high weight variability, and further provided the information for making decisions about the benefits of ILI. Although this finding was considered exploratory, such information contributed to strengthening the recommendation from 2020 ADA guideline that supported the ILI was used to achieve the weight loss in overweight or obese adults with T2DM [1].

The strengths of this investigation are worth note. We had a large sample size of the cohort focused on the overweight or obese adults with T2DM 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 = 3643) without any outcomes occurred within 4 years and found the 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 clinical trial (Look AHEAD trial). Moreover, the consistency of results in several sensitivity analyses and subgroup analyses for key variables (age, gender, race, weight, SBP, HbA1c, total cholesterol and serum creatinine) supported the robust findings. Third, due to the non-interventional observational study, the findings are unable to make a causality but are merely hypotheses-generating. Therefore, the interpretation of the findings should be cautious. Finally, although the study population had the multiethnic diversity, the findings might not be generalizable to the overweight or obese adults with T2DM who would not have qualified for taking part in the Look AHEAD trial.

Conclusions

Among the overweight or obese individuals with T2DM, the weight variability was independently associated with increased risks of all-cause mortality, but not for cardiovascular event. Of note, the risk of death associated with weight variability might be removed by ILI. Therefore, weight loss and subsequent maintenance are needed to reduce the risks of death, but weight loss by the guideline-recommended ILI may be still benefit even if the weight may be regained later.

List Of Abbreviations

ILI
intensive lifestyle intervention; Look AHEAD trial:Action for Health in Diabetes trial; DSE:diabetes support and education; T2DM:type 2 diabetes mellitus; CVD:cardiovascular disease; ADA:American Diabetes

Association; SBP:systolic blood pressure; DBP:diastolic blood pressure; TGs:triglycerides; HbA1c:glycosylated hemoglobin; SD:standard deviation; ARV:average real variability; VIM:variability independent of the mean; HRs:hazard ratios; CAD:coronary artery disease; CHD:coronary heart disease; TNT trial:Treating to New Targets trial.

Declarations

Authors' contributions

M.L. and X.C. researched data and wrote the manuscript. M.L., X.C., X.L. and X.Zhu. conceived the research idea and designed the study. S.Z. and D.Y. conducted all data analyses. Y.L., Z.X., Y.H., X.Zho. and L.W. contributed to discussion and reviewed and edited the manuscript. Each author read and approved the final manuscript. X.L. and X.Zhu. are 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 the accuracy of the data analysis.

Availability of data and materials

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure because of human subjects' restrictions. However, interested investigators can contact the Look AHEAD study Coordinating Center to request overall access to Look AHEAD study data.

Ethics approval and consent to participate

The Look Ahead trial obtained the ethical approval from local institutional review boards, and all participants provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures
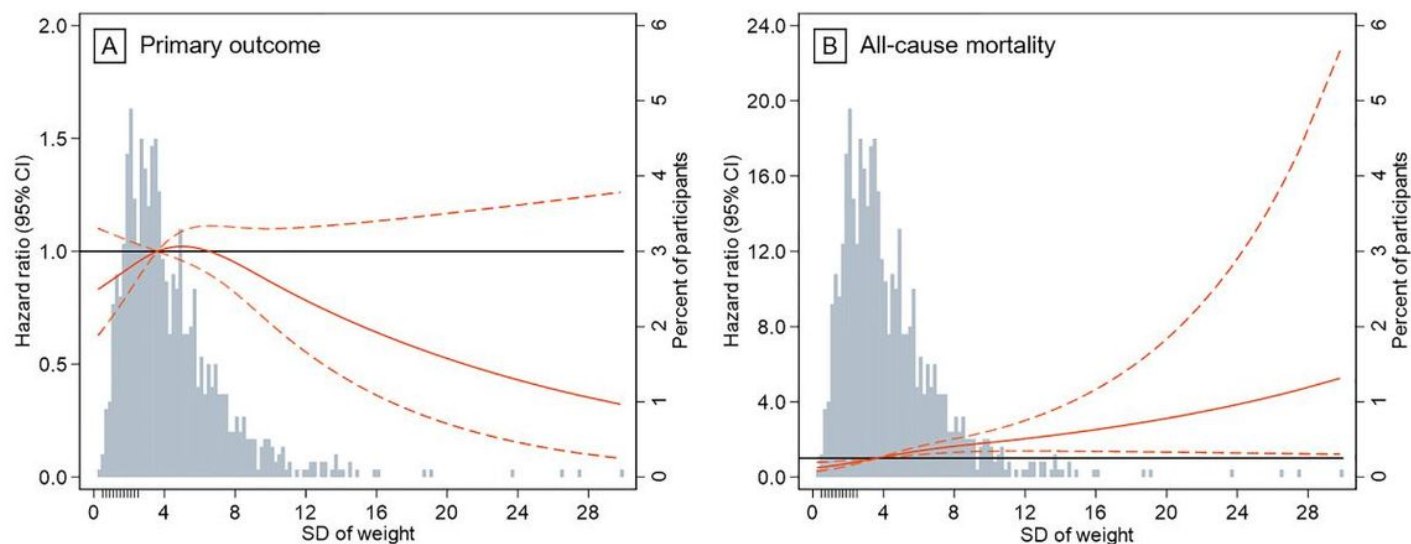
Figure 1

Adjusted hazard ratios (95% CI) for the association of 4-year variability of weight with incident primary cardiovascular event (A) and death (B) in 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, treatment arm, and weight at baseline. Standard deviation (SD) 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 weight variability (SD).

Weight Variability (SD)	Intensive Lifestyle Intervention			Diabetes Support & Education			P for interaction
	Hazard Ratio (95%CI)	P Value		Hazard Ratio (95%CI)	P Value		
Primary CVD outcome							
SD Q2	0.97 (0.67, 1.39)	0.862		1.36 (1.01, 1.82)	0.041		0.134
SD Q3	0.89 (0.62, 1.26)	0.505		1.52 (1.09, 2.11)	0.014		0.034
SD Q4	0.87 (0.60, 1.26)	0.470		1.22 (0.82, 1.83)	0.326		0.257
All-cause mortality							
SD Q2	0.87 (0.44, 1.73)	0.691		1.48 (0.85, 2.56)	0.165		0.159
SD Q3	1.14 (0.61, 2.16)	0.677		2.09 (1.19, 3.65)	0.010		0.085
SD Q4	1.30 (0.67, 2.50)	0.440		3.31 (1.84, 5.95)	< 0.001		0.005

Figure 2

Association between weight variability defined by SD and mortality and primary CVD outcome in ILI arm and DSE arm in overweight or obese individuals with T2DM. The lowest quartile of weight variability (SD Q1) is reference group. Hazard ratios and 95% CIs 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 CVD, insulin use, and weight at baseline, except the treatment arm. SD: standard deviation; CVD: cardiovascular disease; ILI: intensive lifestyle intervention; DSE: diabetes support and education; T2DM: type 2 diabetes mellitus.

Supplementary Files

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- Additionalfile1.pdf