Cardiovascular effects of intensive lifestyle intervention in adults with overweight/obesity and type 2 diabetes according to body weight time in range

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Summary

Background We aimed to assess whether the cardiovascular effects of intensive lifestyle intervention (ILI) vary for those who can maintain the lower body weight after weight loss through ILI.

Methods In the secondary analysis of the Look AHEAD trial, we identified the status of weight loss for the participants in the ILI arm based on body weight time in range (TIR). These participants were allocated to three groups according to body weight TIR: 0% (n = 727), >0% to 50% (n = 656), and >50% to 100% (n = 811). For each group, cardiovascular outcomes were compared with matched participants receiving diabetes support & education (DSE) using 1:1 propensity score matching and Cox regression.

Findings During a median of 9·5 years of follow-up, participants with TIR of >50% to 100% can effectively maintain their body weight after weight loss through ILI; participants with TIR of 0% or >0% to 50% do not achieve or maintain weight loss. Compared with the corresponding matched participants in the DSE arm, participants with TIR of >50% to 100% in the ILI arm had a 45% lower risk of the primary outcome (HR 0·55, 95% CI 0·40–0·76), and no significant effects were found on the risk of the primary outcome in participants with TIR of 0% (HR 1·12, 95% CI 0·86–1·46) or >0% to 50% (HR 1·14, 95% CI 0·85–1·52).

Interpretation In adults with overweight/obesity and type 2 diabetes, ILI might help in lowering the risk of cardiovascular events when the lower body weight is maintained after weight loss.

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Keywords: Body weight; Intensive lifestyle intervention; Obesity; Time in range; Type 2 diabetes

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Introduction

The marked growth of the dual epidemics of type 2 diabetes and obesity contributes directly to the increasing prevalence of cardiovascular disease (CVD) and represents one of the most important public health challenges worldwide.[1–4] Weight loss with intensive lifestyle intervention (ILI) has become a standard recommendation in the guidelines for the management of individuals with type 2 diabetes and comorbid obesity[5]; however, the level of evidence for such recommendations is only in "class B" because the evidence provided by randomized studies is limited.[5] The Look AHEAD (Action for Health in Diabetes) trial,[6] the largest trial to date of an ILI for adults with overweight/obesity and type 2 diabetes, did not show a significant reduction in

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Research in context

Evidence before the study

We searched PubMed with the search terms "obesity", "type 2 diabetes", "lifestyle intervention", and "cardiovascular disease" for reports published before 2 February 2022. Although weight loss with intensive lifestyle intervention (ILI) has become a standard recommendation for adults with overweight/obesity and type 2 diabetes, the evidence to support the cardiovascular benefits of ILI is limited. The Look AHEAD (Action for Health in Diabetes) trial, the largest trial to date of an ILI for adults with overweight/obesity and type 2 diabetes, did not show a significant reduction in cardiovascular morbidity or mortality.

Added value of the study

This secondary analysis of the Look AHEAD trial provides the new evidence supporting the cardiovascular benefits of ILI. In adults with overweight/obesity and type 2 diabetes, the ILI might help in lowering the risk of cardiovascular events when the lower body weight is maintained after weight loss.

Implications of all the available evidence

The available evidence showed that weight loss with ILI was an essential way of health management for individuals with type 2 diabetes and comorbid obesity. Of note, the management of body weight through ILI should focus not only on achieving weight loss, but also, and more importantly, on maintaining the lower body weight achieved.

cardiovascular morbidity or mortality. Of note, although the majority of the participants in the intervention group (55·1%) had achieved the study weight loss goal (Loss of ≥7% of baseline weight) at year 1,[7] they had not maintained this weight loss at the end of the trial due to weight regain.[6] Several studies have suggested that weight regain is associated with a deterioration of the cardiovascular benefits associated with weight loss.[8–11] Therefore, weight regain may represent an explanation for the absence of an effect of ILI on the incidence of cardiovascular events in the Look AHEAD trial. Furthermore, it may be that ILI reduces the long-term incidence of CVD in people who achieve and maintain their weight loss goal, but its benefits may be obscured in the population by individuals who do not successfully lose weight or maintain their weight loss. Therefore, we hypothesized that the achievement and maintenance of weight loss through ILI might help improve cardiovascular health.

To test this hypothesis, we conducted a *post-hoc* analysis of the Look AHEAD trial. According to body weight time in range (TIR), the participants in the ILI arm were classified into three groups (TIR = 0%; 0% < TIR ≤ 50%; 50% < TIR ≤ 100%) to characterize their clinical status of weight loss. We used doubly robust estimation, combining 1:1 propensity score matching and adjusted Cox regression analysis to compare the participants in each TIR group of the ILI arm with participants in the control group who had similar characteristics at baseline, to identify the effects of ILI, according to body weight TIR, on cardiovascular events.

Methods

Study design and population

Look AHEAD trial (trial registration NCT00017953) was a multi-centre, randomized controlled clinical trial that evaluated the effects of an ILI on the risk of cardiovascular events in comparison with diabetes support & education (DSE).[12,13] In accordance with the eligibility and exclusion criteria (The detailed description in Supplementary methods), the Look AHEAD trial included 5145 adults with overweight/obesity and type 2 diabetes, and randomly assigned them to the ILI (n = 2570) or control (n = 2575) groups, data for 4906 of whom are available in public access data sets. We excluded participants who had less than three body weight tests within the first 4 years (n = 262), and those with missing data regarding covariates (n = 327) or the primary outcome (n = 5). Finally, a total of 4312 participants (ILI: n = 2194; DSE: n = 2118) were included in the primary analysis (Figure S1) and had similar baseline characteristics to those who were excluded (Table S1). The Look AHEAD trial was approved by the local institutional review boards, and all participants provided written informed consent.

Body weight TIR in the ILI arm

Based on the design of the Look AHEAD trial,[12] the weight loss goal for participants in the ILI arm was a weight loss of at least 7% of baseline weight. Body weight TIR was defined as the percentage of time during which the body weight was within the Look AHEAD weight loss goal range (Loss of ≥7% of baseline weight), and estimated with linear interpolation[14,15] using at least three longitudinal measurements of body weight during years 0 to 4. The year 4 time point was chosen due to the more frequent individual supervision and group sessions for participants in the ILI arm at this time.

Body weight TIR was used to evaluate body weight management by participants in the ILI arm during the first 4 years of the study. The frequency distribution of body weight TIR was shown in Figure S2. To characterize their clinical status of weight loss, these participants were placed into three groups according to TIR. 1) TIR = 0% indicated that the participants did not achieve

the weight loss goal within 4 years (n = 727); 2) 0%< TIR ≤50% indicated that the participants did not maintain their lower body weight after effectively intended weight loss within 4 years (n = 656); and 3) 50% < TIR ≤ 100% indicated that the participants maintained their lower body weight after effectively intended weight loss within 4 years (n = 811).

Propensity score matching between each TIR group of the ILI arm and the DSE arm

We anticipated that demographic or clinical factors that affect cardiovascular risk would differ amongst the three TIR groups in the ILI arm. To account for potential confounding attributable to such differences, we used a propensity score to match participants of each TIR group in the ILI arm with participants in the DSE arm with similar baseline characteristics. To improve the quality of the matching, the analysis used matching with replacement,[16] such that a given participant in the DSE arm was eligible to be matched with a participant in each TIR group of the ILI arm, but not to multiple participants in one TIR group. The baseline characteristics considered for matching were key demographic characteristics (age, sex, and race) and cardiovascular risk factors (body mass index [BMI], systolic blood pressure [SBP], smoking status, low-density lipoprotein-cholesterol [LDL-c], fasting blood glucose, and serum creatinine). Greedy matching occurred 1:1 on the logit of a propensity score with a calliper of 0·2 × standard deviation (SD) that has been shown to substantially reduce initial bias.[17]

Study intervention

The ILI was aimed at achieving and maintaining weight loss of at least 7% by means of individual and group counselling sessions (weekly during the first 6 months, followed by less frequent meetings) and specific intervention strategies, including caloric restriction (1200 −1800 kcal/day) and greater physical activity (≥175 min/week of moderate-intensity physical activity). The DSE comprised three educational group sessions per year during the first 4 years, followed by annual meetings focused on nutrition, exercise, and social support. The details have been described previously.[13,18]

Primary and secondary outcomes

To ensure consistency with the Look AHEAD trial protocol,[12] we restricted the present analyses to the prespecified outcomes of the Look AHEAD trial, which were adjudicated by a blinded outcomes committee. The primary composite cardiovascular outcome was the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for angina. The following three secondary composite cardiovascular outcomes were also considered: death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke (Secondary outcome 1); death from any cause, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for angina (Secondary outcome 2); and death from any cause, non-fatal myocardial infarction, non-fatal stroke, hospitalization for angina, coronary-artery bypass grafting, percutaneous coronary intervention, hospitalization for heart failure, carotid endarterectomy, or peripheral vascular disease (Secondary outcome 3).

Statistical analysis

Descriptive statistics were used to analyse the baseline characteristics, which are presented as mean (SD) for continuous data and number (%) for categorical data. Furthermore, we graphically displayed the percent changes in body weight against baseline during the study period in the DSE arm and the three TIR groups of the ILI arm.

Cumulative incidences were estimated for each outcome for the ILI and DSE arms, the three TIR groups in the ILI arm, and the three propensity score-matched subgroups of the DSE arm using the Kaplan-Meier method. For all the participants, the risks of cardiovascular outcomes associated with the ILI (*vs.* the DSE arm) were evaluated using multivariate-adjusted Cox proportional hazard models. After propensity score matching, multivariate-adjusted Cox proportional hazards regression analysis was used to assess the cardiovascular effects of ILI in each TIR group compared to the corresponding propensity score-matched subgroups of the DSE arm. The Schoenfeld residuals test was used to check the Cox regression model for its fulfilment of the proportional hazard assumptions and confirmed that the assumption was met in each TIR group (Figure S3). Fully adjusted Cox regression models were generated for the primary and secondary outcomes, involving adjustment for age, sex, race, educational level, BMI, SBP, diastolic blood pressure (DBP), smoking status, drinking status, total cholesterol, high-density lipoprotein-cholesterol (HDL-c), LDL-c, triglyceride, fasting blood glucose, glycosylated haemoglobin (HbA1c), serum creatinine, history of hypertension and CVD, insulin use at baseline, mean body weight, and body weight variability. Body weight variability was adjusted in the fully model in that it was associated with CVD risks, and was assessed using SD of body weight.[19,20] Mean body weight and body weight variability were calculated as the mean and SD of all longitudinal measurements of body weight during years 0 to 4, respectively.

Although only a small minority of participants in the DSE arm have achieved body weight TIR more than 50% (n = 163), we still categorized the participants in the DSE arm into three body weight TIR subgroups in sensitivity analyses and estimated the cardiovascular

Baseline characteristics	TIR = 0%			0% < TIR ≤ 50%			50% < TIR ≤ 100%		
	ILI arm (*n* = 724)	Propensity score-matched DSE subgroup (*n* = 724)	*P* value	ILI arm (*n* = 656)	Propensity score-matched DSE subgroup (*n* = 656)	*P* value	ILI arm (*n* = 811)	Propensity score-matched DSE subgroup (*n* = 811)	*P* value
Age, years	58.0 (6.5)	57.9 (7.0)	0.806	58.6 (7.0)	58.5 (6.8)	0.914	59.8 (6.7)	59.7 (6.8)	0.736
Sex, No. (%)			0.747			0.609			0.727
Men	287 (39.6)	281 (38.8)		254 (38.7)	245 (37.3)		367 (45.3)	374 (46.1)	
Women	437 (60.4)	443 (61.2)		402 (61.3)	411 (62.7)		444 (54.7)	437 (53.9)	
Race, No. (%)			0.936			0.807			0.615
White	442 (61.0)	435 (60.1)		451 (68.8)	437 (66.6)		567 (69.9)	564 (69.5)	
Black (not Hispanic)	139 (19.2)	143 (19.8)		113 (17.2)	115 (17.5)		99 (12.2)	104 (12.8)	
Hispanic	112 (15.5)	118 (16.3)		64 (9.8)	72 (11.0)		120 (14.8)	126 (15.5)	
Other/Mixed	31 (4.3)	28 (3.9)		28 (4.3)	32 (4.9)		25 (3.1)	17 (2.1)	
Body weight, kg	99.6 (19.3)	99.6 (18.8)	0.977	101.8 (20.5)	101.8 (19.5)	0.992	101.2 (19.3)	102.1 (19.4)	0.200
BMI, kg/m^2	35.6 (6.0)	35.7 (5.6)	0.719	36.3 (6.3)	36.5 (6.1)	0.621	35.8 (5.8)	36.2 (5.8)	0.372
SBP, mm Hg	128.4 (17.5)	128.7 (16.8)	0.712	128.5 (17.4)	128.2 (17.1)	0.740	128.6 (17.2)	129.6 (17.4)	0.252
DBP, mm Hg	70.7 (9.7)	70.7 (9.6)	0.922	69.8 (9.3)	69.6 (9.4)	0.657	69.5 (9.7)	70.2 (9.8)	0.144
Total cholesterol, mg/mL	194.1 (38.4)	192.3 (35.4)	0.367	192.3 (38.1)	191.3 (36.9)	0.616	187.9 (36.9)	186.9 (35.6)	0.562
HDL-c, mg/mL	43.1 (12.0)	44.2 (11.7)	0.082	43.9 (12.2)	44.4 (12.3)	0.422	43.3 (11.8)	43.0 (11.5)	0.649
LDL-c, mg/mL	114.6 (32.0)	114.6 (32.6)	0.983	113.2 (32.7)	113.0 (31.3)	0.890	109.4 (31.3)	109.6 (31.4)	0.880
Triglyceride, mg/mL	186.6 (122.5)	172.5 (120.2)	0.027	180.4 (109.5)	174.3 (118.2)	0.327	179.4 (111.3)	175.6 (109.4)	0.480
Fasting glucose, mg/mL	156.4 (48.4)	156.4 (45.7)	0.974	152.7 (44.0)	150.8 (43.0)	0.433	146.9 (40.4)	145.6 (39.9)	0.529
HbA1c, %	7.4 (1.2)	7.4 (1.2)	0.444	7.2 (1.1)	7.2 (1.2)	0.846	7.1 (1.1)	7.1 (1.1)	0.130
Serum creatinine, mg/mL	0.8 (0.2)	0.8 (0.2)	0.738	0.8 (0.2)	0.8 (0.2)	0.750	0.8 (0.2)	0.8 (0.2)	0.843
History of CVD, No. (%)	120 (16.6)	83 (11.5)	0.005	77 (11.7)	72 (11.0)	0.664	118 (14.5)	111 (13.7)	0.618
History of hypertension, No. (%)	590 (81.5)	597 (82.5)	0.632	563 (85.8)	530 (80.8)	0.015	695 (85.7)	683 (84.3)	0.405
Education level, No. (%)			0.522			0.695			0.343
<13 years	143 (19.8)	138 (19.1)		110 (16.8)	107 (16.3)		180 (22.2)	173 (21.3)	
13–16 years	267 (36.9)	288 (39.8)		248 (37.8)	263 (40.1)		272 (33.5)	300 (37.0)	
>16 years	314 (43.4)	298 (41.2)		298 (45.4)	286 (43.6)		359 (44.3)	338 (41.7)	
Smoking, No. (%)			0.938			0.864			0.681
Never smoker	359 (49.6)	361 (49.9)		337 (51.4)	344 (52.4)		384 (47.3)	372 (45.9)	
Past smoker	326 (45.0)	327 (45.2)		295 (45.0)	286 (43.6)		394 (48.6)	410 (50.6)	
Current smoker	39 (5.4)	36 (5.0)		24 (3.7)	26 (4.0)		33 (4.1)	29 (3.6)	

Table 1 *(Continued)*

Baseline characteristics	TIR = 0%			0% < TIR ≤ 50%			50% < TIR ≤ 100%		
	ILI arm (*n* = 724)	Propensity score-matched DSE subgroup (*n* = 724)	*P* value	ILI arm (*n* = 656)	Propensity score-matched DSE subgroup (*n* = 656)	*P* value	ILI arm (*n* = 811)	Propensity score-matched DSE subgroup (*n* = 811)	*P* value
Drinking, No. (%)			0.659			0.681			0.224
None / week	475 (65.6)	467 (64.5)		435 (66.3)	442 (67.4)		557 (68.7)	534 (65.8)	
≥ 1 / week	249 (34.4)	257 (35.5)		221 (33.7)	214 (32.6)		254 (31.3)	277 (34.2)	
Insulin use, No. (%)	126 (17.4)	111 (15.3)	0.287	96 (14.6)	118 (18.0)	0.100	115 (14.2)	124 (15.3)	0.528

Table 1: **Baseline characteristics of the participants in the three TIR groups of ILI arm and the corresponding propensity score-matched participants of the DSE arm after propensity score matching.** There are presented as mean (SD) for continuous variables and number (%) for categorical variables. DSE: diabetes support & education; ILI: intensive lifestyle intervention; TIR: time in range; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; HbA1c: glycosylated haemoglobin; CVD: cardiovascular disease; SD: standard deviation.

effects of ILI in different body weight TIR subgroups. Moreover, we also showed unmatched results through evaluating the risks of cardiovascular outcomes in each TIR group of the ILI arm compared with all participants in the DSE arm. To avoid the effect of CVD development before or at year 4 on the results, the analyses were repeated in participants who had no history of CVD at baseline and in whom the primary outcome had not occurred within the first 4 years (n = 3576). In addition, the E-value was used to assess the robustness of the identified cardiovascular effects of ILI in participants with a TIR of >50% to 100% (*vs.* the matched participants in the DSE arm) to potential unmeasured confounders. The detailed explanation of the E-value[21] was shown in Supplementary methods.

All analyses were performed using Stata Version 14 (College Station, TX, USA) and R language version 3·6·3, and a two-sided P value of less than 0·05 was regarded as being statistically significant.

Role of the funding sources
The study did not have any funders.

Results

Cardiovascular effects of ILI across all the participants
A total of 4312 participants in the Look AHEAD trial who were included in the ILI (n = 2194) and DSE (n = 2118) arms, with similar baseline characteristics (Table S2), were included in the analyses. Over a median follow-up period of 9·5 years (interquartile range 8·6–10·3 years), 352 participants in the ILI arm and 342 participants in the DSE arm experienced the primary outcome. Consistent with the findings of the previous study,[6] no significant differences were found in the risks of the primary outcome (hazard ratio [HR] 0·99; 95% confidence interval [CI] 0·85–1·15; P = 0·883) or the three secondary outcomes (all P > 0.05) between the ILI and DSE arms (Table S3).

Characteristics of the participants categorized by body weight TIR
Significant differences were observed in the baseline characteristics of the three TIR groups of the ILI arm (Table S4). Participants with TIR of >50% to 100% (n = 811) were characterized by older age, more frequently male and white, higher prevalence of hypertension and CVD, and lower fasting glucose and HbA1c. Participants with TIR of >0% to 50% (n = 656) were characterized by being more frequently white, higher body weight and BMI, higher prevalence of hypertension, and lower prevalence of CVD. Participants with TIR of 0% (n = 727) were characterized by younger age, higher fasting glucose and HbA1c, lower prevalence of hypertension, and higher prevalence of CVD. Of the

2118 participants who were eligible for analysis in the DSE arm, 724, 656, and 811 were matched to participants of the ILI arm in the TIR of 0%, >0% to 50%, and >50% to 100% groups, respectively. After propensity score matching, each TIR group in the ILI arm was well matched to an equal number of participants in the DSE arm with similar baseline characteristics (Table 1). In addition, the percent changes that occurred in body weight against baseline during the 10 years of follow-up in the DSE arm and the three TIR groups of the ILI arm are shown in Figure 1. As expected, participants with TIR of >50% to 100% in the ILI arm effectively maintained their body weight in the target range after intended weight loss during 10 years.

Cardiovascular effects of ILI in participants categorized by body weight TIR

In the TIR of 0%, >0% to 50%, and >50% to 100% groups of the ILI arm, the cumulative incidences (95% CIs) of the primary outcome decreased progressively, from 19·5% (16·6–22·7%) to 18·9% (15·9–22·4%) and to 14·5% (12·0–17·5%). In the corresponding propensity score-matched subgroups of the DSE arm, the cumulative incidences (95% CIs) of the primary outcome were 15·7% (13·1–18·8%), 15·6% (12·9–18·9%), and 19·5% (16·7–22·6%), respectively (Table 2). The Kaplan-Meier survival function curves showed a higher cumulative incidence of the primary outcome in participants with TIR of >50% to 100% in the ILI arm compared with the corresponding propensity score-matched participants in the DSE arm (P = 0.005), and there was no difference between the participants with TIR of 0% (P = 0.080) or >0% to 50% (P = 0.209) in the ILI arm and the corresponding matched participants in the DSE arm (Figure S4).

In the fully adjusted model, participants with TIR of >50% to 100% in the ILI arm had a 45% lower risk of the primary outcome (HR 0·55; 95% CI 0·40–0·76; P < 0·001), a 59% lower risk of secondary outcome 1 (HR 0·41; 95% CI 0·28–0·61; P < 0·001), a 44% lower risk of secondary outcome 2 (HR 0·56; 95% CI 0·42–0·74; P < 0·001), and a 40% lower risk of secondary outcome 3 (HR 0·60; 95% CI 0·46–0·78; P < 0·001) compared with the corresponding propensity score-matched participants in the DSE arm (Table 2). No differences were found in the risks of the primary outcome in participants with TIR of 0% (HR 1·12, 95% CI 0·86–1·46; P = 0·389) or >0% to 50% (HR 1·14, 95% CI 0·85–1·52; P = 0·377) between the ILI arm and the corresponding matched participants in the DSE arm. The results for the three secondary outcomes were similar to those for the primary outcome in participants with TIR of 0% or >0% to 50% in the ILI arm (Table 2).

Sensitivity analyses

The 2118 participants in the DSE arm were also categorized into the TIR of 0% (n = 1539), >0% to 50% (n = 416), and >50% to 100% (n = 163) subgroups. In the TIR of >50% to 100% subgroup, participants in the ILI arm were still associated with the lower risks of the primary and three secondary outcomes compared with the participants in the DSE arm (Table S5). In the unmatched analysis, the results were similar to the primary findings from propensity score matching analysis (Table S6). Of the 4312 participants, 591 had a history of CVD at baseline and 145 experienced the primary

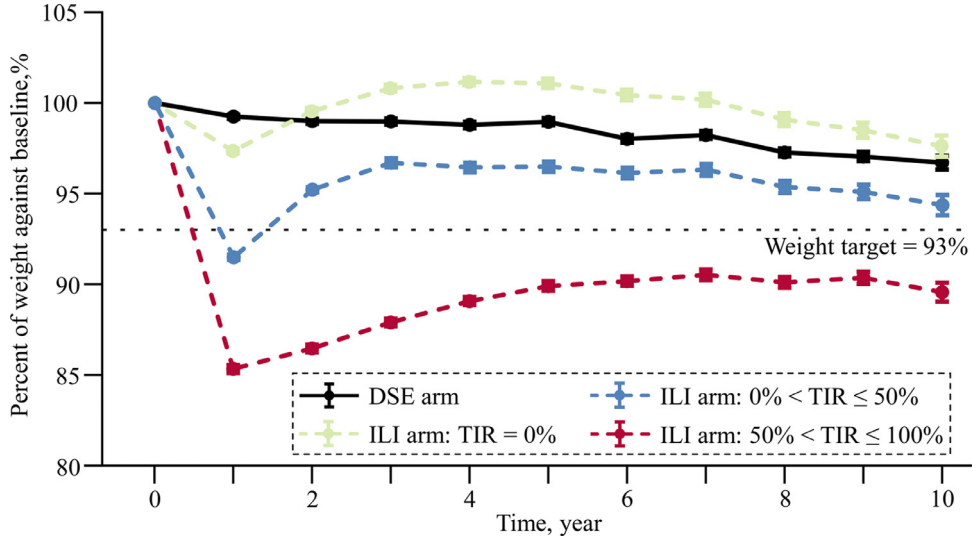

Figure 1. Percent changes in body weight against baseline during 10 years of follow-up amongst the DSE arm and the three TIR groups of the ILI arm. The percent of body weight against baseline is presented as mean (SEM). ILI: intensive lifestyle intervention; DSE: diabetes support & education; TIR: time in range; SEM: standard error of mean.

TIR groups of ILI arm	Matched DSE subgroup		ILI arm		Unadjusted		Fully adjusted	
	n/N	Cumulative Incidence, % (95% CI)	n/N	Cumulative Incidence, % (95% CI)	Hazard Ratio (95% CI)	*P* value	Hazard Ratio (95% CI)	*P* value
Primary outcome: Death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for angina								
TIR = 0%	107/724	15.7 (13.1−18.8)	132/724	19.5 (16.6−22.7)	1.26 (0.93−1.62)	0.081	1.12 (0.86−1.46)	0.389
0% < TIR ≤ 50%	96/656	15.6 (12.9−18.9)	114/656	18.9 (15.9−22.4)	1.19 (0.91−1.56)	0.209	1.14 (0.85−1.52)	0.377
50% < TIR ≤ 100%	147/811	19.5 (16.7−22.6)	106/811	14.5 (12.0−17.5)	0.70 (0.55−0.90)	0.006	0.55 (0.40−0.76)	< 0.001
Secondary outcome 1: Death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke								
TIR = 0%	65/724	9.5 (7.5−12.0)	88/724	13.5 (11.0−16.6)	1.39 (1.01−1.91)	0.046	1.29 (0.92−1.79)	0.138
0% < TIR ≤ 50%	68/656	11.2 (8.9−14.1)	77/656	13.3 (10.7−16.6)	1.13 (0.82−1.56)	0.466	1.06 (0.75−1.49)	0.760
50% < TIR ≤ 100%	106/811	14.3 (11.9−17.1)	65/811	8.7 (6.8−11.1)	0.60 (0.44−0.82)	0.001	0.41 (0.28−0.61)	< 0.001
Secondary outcome 2: Death from any cause, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for angina								
TIR = 0%	123/724	18.7 (15.7−22.1)	157/724	23.1 (20.0−26.6)	1.30 (1.03−1.65)	0.028	1.19 (0.94−1.52)	0.154
0% < TIR ≤ 50%	116/656	18.9 (15.9−22.3)	125/656	20.5 (17.4−24.1)	1.08 (0.84−1.39)	0.542	0.99 (0.76−1.29)	0.962
50% < TIR ≤ 100%	179/811	23.5 (20.6−26.9)	139/811	20.3 (17.0−24.0)	0.76 (0.61−0.94)	0.013	0.56 (0.42−0.74)	< 0.001
Secondary outcome 3: Death from any cause, non-fatal myocardial infarction, non-fatal stroke, hospitalization for angina, coronary-artery bypass grafting, percutaneous coronary intervention, hospital admission for heart failure, carotid endarterectomy, or peripheral vascular disease								
TIR = 0%	142/724	21.3 (18.2−24.9)	189/724	27.3 (24.1−30.8)	1.39 (1.11−1.71)	0.004	1.27 (1.01−1.59)	0.038
0% < TIR ≤ 50%	133/656	21.4 (18.3−25.0)	144/656	23.2 (20.0−26.7)	1.08 (0.86−1.37)	0.510	0.98 (0.77−1.26)	0.986
50% < TIR ≤ 100%	205/811	27.0 (23.8−30.4)	160/811	22.7 (19.4−26.5)	0.76 (0.62−0.93)	0.008	0.60 (0.46−0.78)	< 0.001

***Table 2*: Risk of primary and secondary composite cardiovascular outcomes in participants in the ILI arm categorized by body weight TIR compared to the corresponding propensity score-matched participants of the DSE arm.**

Cox proportional hazard models were fully adjusted for age, sex, race, education level, smoking status, drinking status, body mass index, systolic blood pressure, diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, fasting glucose, glycosylated haemoglobin, serum creatinine, history of hypertension and cardiovascular disease, status of insulin use at baseline, mean body weight, and body weight variability.

ILI: intensive lifestyle intervention; DSE: diabetes support & education; TIR: time in range; CI: confidence interval.

outcome within the first 4 years of the study. In a sensitivity analysis that excluded these 736 participants, the cardiovascular effects of ILI were similar to those identified in the primary analysis (Table S7). Furthermore, the E-values for the primary outcome and the three secondary composite cardiovascular outcomes were evaluated for the TIR of >50% to 100% group and compared to the HRs for the established cardiovascular risk factors for these outcomes. This comparison showed it would be unlikely that an unmeasured confounder exists that could account for the identified association between the ILI and the cardiovascular outcomes in the TIR of >50% to 100% group (Table S8).

Discussion

The secondary analysis of the Look AHEAD trial was performed for adults with overweight/obesity and type 2 diabetes to determine the risk of cardiovascular events in three body weight TIR groups in the ILI arm, compared to that of propensity score-matched subgroups in the DSE arm with similar baseline characteristics. After a median follow-up period of almost 10 years, the ILI was significantly associated with a lower risk of cardiovascular outcomes in participants with TIR of >50% to 100%, and the cardiovascular effects of the ILI were not observed in participants with TIR of 0% or >0% to 50% (Figure 2). These findings suggest that the ILI might help in lowering the risk of cardiovascular events when the lower body weight is maintained after weight loss in adults with overweight/obesity and type 2 diabetes. Therefore, the management of body weight through ILI should focus not only on achieving weight loss, but also, and more importantly, on maintaining the lower body weight achieved.

Two decades ago, a study conducted as part of the Diabetes Prevention Program identified the usefulness of lifestyle interventions to reduce the incidence of diabetes in individuals at high risk.[22] Secondary analyses of the Look AHEAD trial further suggested that an ILI can lead to the remission of type 2 diabetes,[23] as well as significant improvements in body weight, HbA1c, SBP, and HDL-c.[24] An epidemiological analysis of data from the combined cohort revealed that lifestyle intervention was associated with substantially lower risks of CVD and CVD-related mortality in 11,527 participants with type 2 diabetes.[25] These data imply that weight management through lifestyle intervention should be considered best practice for individuals with type 2 diabetes and drove the creation of recommendations regarding lifestyle intervention in the current guidelines.[5] However, to date, only limited evidence has been available from randomized trials to support this recommendation. Furthermore, in two large-scale clinical trials, the Diabetes Prevention Program trial and the Look AHEAD trial, lifestyle interventions did not significantly reduce the incidence of CVD in individuals at high risk of diabetes[26] or with type 2 diabetes.[6] Of note, these clinical trials did not take account of the adverse effects of weight regain after weight loss on the incidence of CVD events. The results of the present secondary analysis of the Look AHEAD trial emphasize the importance of avoiding the regain of lost body weight in individuals with type 2 diabetes undergoing ILI. This finding provides the new evidence to support the "class B" recommendation in the current guidelines that weight loss achieved and maintained through lifestyle intervention improves the cardiovascular health of individuals with type 2 diabetes.[5]

The present findings link the cardiovascular benefits of lifestyle intervention with long-term weight management, and may encourage individuals with type 2 diabetes to manage their body weight more effectively over the long term. An estimated 42% of the world population tries to lose weight each year[27]; however, most individuals subsequently regain the lost body weight.[28,29] Specifically, approximately 79% of adults who achieve intentional weight loss regain the weight within 1 year.[29] Furthermore, individuals with type 2 diabetes regain this lost weight more rapidly than those without diabetes.[30] Previous systematic analysis suggested that a reduction in weight loss awareness (for example, disinhibition of eating, binge eating, or eating in response to negative emotions) may be the main factor driving weight regain.[31] The present findings highlight the need to maintain the lower body weight achieved through effective intentional weight loss. Emphasizing the cardiovascular benefits of ILI in long-term weight management may serve to motivate adults with overweight or obesity to become aware of and address their weight regain.

In the current study, the cardiovascular benefits of ILI were found in adults with overweight/obesity and type 2 diabetes when the lower body weight is maintained after weight loss. Of note, gradual weight regains, as observed in the previous study,[32] was common after lifestyle intervention. Thus, the introduction of modern methods to support weight loss maintenance, such as glucagon-like peptide-1 receptor agonist (GLP-1 RA) and bariatric surgery, might be needed for adults with overweight/obesity and type 2 diabetes. Semaglutide, a GLP-1 RA, was a Food and Drug Administration (FDA)-approved medication on the market for weight loss. In a 68-week trial, semaglutide was shown to significantly improve the maintenance of weight loss compared with placebo.[33] Moreover, bariatric surgery has been demonstrated to have substantially greater efficacy than lifestyle or pharmacological interventions for severe obesity (BMI ≥35 kg/m^2).[34] Based on the findings from the current study, a combination of the ILI and modern methods might help maintain the weight loss to gain the significant cardiovascular benefits.

To the best of our knowledge, this was the first study to use TIR to assess long-term body weight

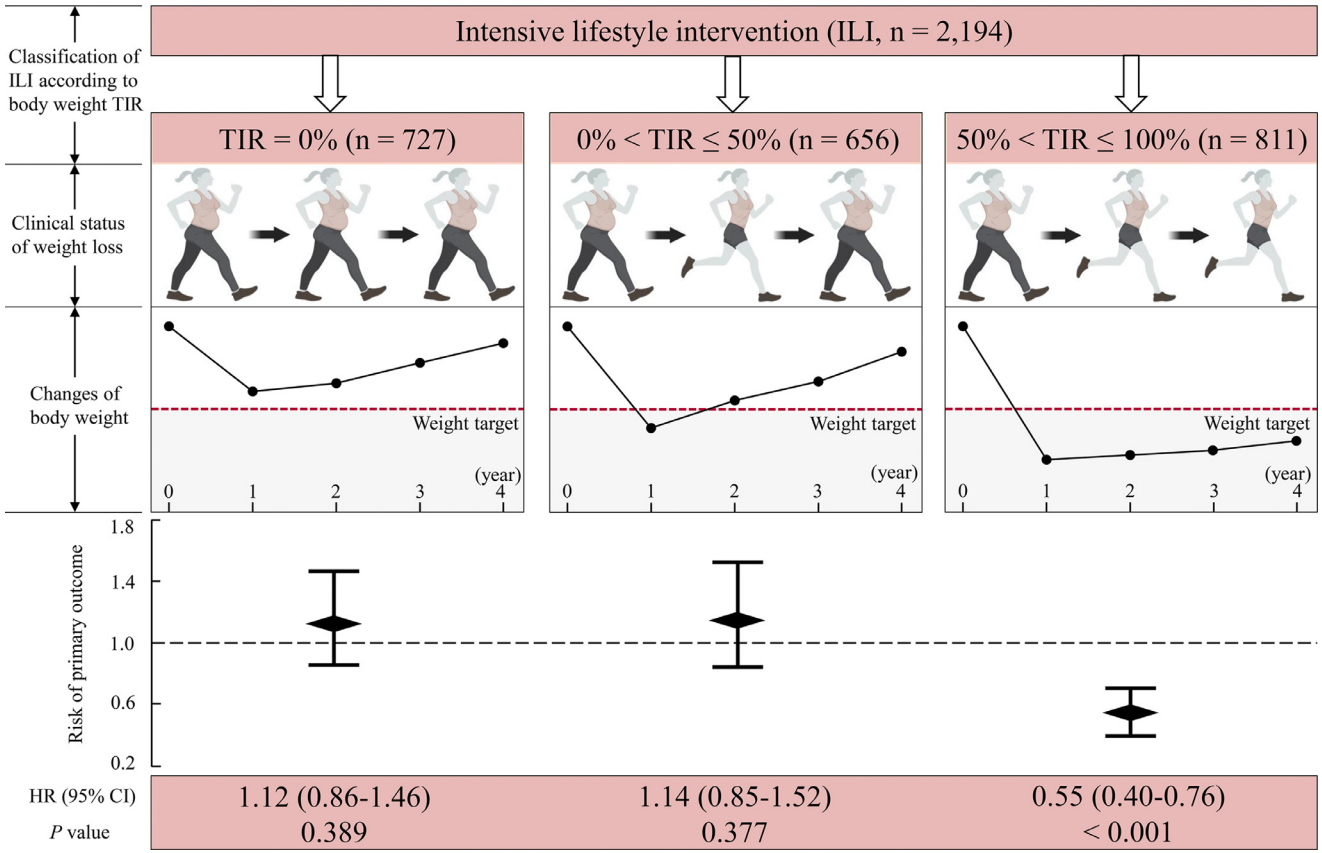

Figure 2. Risk of the primary composite cardiovascular outcome in participants in the ILI arm, categorized according to body weight TIR, compared to the corresponding propensity score-matched participants of the DSE arm. TIR = 0% indicated that the participants did not achieve the weight loss goal within 4 years; 0%< TIR ≤50% indicated that the participants did not maintain their lower body weight after effectively intended weight loss within 4 years; 50%< TIR ≤100% indicated that the participants maintained their lower body weight after effectively intended weight loss within 4 years. Weight target was the prespecified weight loss goal in the Look AHEAD trial that was a body weight loss of at least 7% of baseline weight. In the Look AHEAD trial, the majority of participants still had overweight or obesity after losing body weight by the ILI even in the subgroup with TIR of >50% to 100%. ILI: intensive lifestyle intervention; DSE: diabetes support & education; TIR: time in range; HR: hazard ratio; CI: confidence interval.

management. Previous studies have used the proportion of body weight lost at a single time point to evaluate the effect of body weight management,[8] but long-term changes in body weight cannot be assessed in this way. Body weight TIR may represent a useful surrogate outcome for the characterization of the long-term effect of body weight management during clinical trials of weight loss interventions. This approach may also be useful for clinicians, because it provides a more holistic, long-term view of an individual patient's body weight management, and can therefore be used to inform decisions regarding body weight interventions. In the present study, participants in the ILI arm were allocated to three groups according to body weight TIR, to compare the clinical status of patients with varying degrees of weight loss and regain, and reference to these categories may be of use in clinical practice.

The present study had several strengths. The analysis used data from a multi-centre, randomized controlled trial with a large sample size that focused on the adults with overweight/obesity and type 2 diabetes and it involved a long follow-up period of almost 10 years. However, this study also had several limitations. First, we could not exclude the influence of residual measured or unmeasured confounders, owing to this being a secondary analysis of the clinical trial. However, we did exclude the effects of key confounders by using a doubly robust estimation that combined propensity score matching and outcome regression. Furthermore, the analysis of the E-value supported that the unmeasured confounders are unlikely to eliminate the identified association between ILI and cardiovascular events in participants with TIR of >50 to 100%. In addition, similar results of several sensitivity analyses further supported the robustness of primary findings. Second, bias may have been introduced by some participants experiencing cardiovascular events before their body weight TIR was calculated. Therefore, we conducted a sensitivity analysis after excluding participants who had a history of CVD at baseline or in whom the primary outcome occurred within the first 4 years of the study, which generated consistent results with the primary analyses. Third, maintaining the lower body weight after achieving weight loss might be largely dependent on the individual psychological factors and the support of social networks and this might lead to the selection bias of participants in three TIR groups of the ILI arm. Although we used the propensity score matching to ensure the homogeneity between the intervention and control groups, the differences among the participants in the three TIR groups should be noted. Fourth, in this secondary analysis of the clinical trial, inferences cannot be made regarding causality. However, as weight loss and gain invariably are affected by many individual and metabolic factors,[35,36] it is almost impossible to randomize participants to the group which can maintain the lower body weight after achieving weight loss through ILI. Therefore, the rigorous observational analysis such as the one presented here may be the main source of evidence for this question.

In conclusion, among adults with overweight/obesity and type 2 diabetes, cardiovascular effects of ILI are not apparent if they have TIR of 0% to 50%, whereas those with TIR of >50% to 100% are at significantly lower risk of cardiovascular events compared with the matched participants who undergo DSE. Thus, the ILI might help in lowering the risk of cardiovascular events when the lower body weight is maintained after weight loss. These findings provided the new evidence for the recommendations contained in the current guidelines and emphasized the importance of maintaining the lower body weight after achieving weight loss through improvements in diet and physical activity.

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Data sharing statement
Data from the Look AHEAD trial is available on application at National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Repository.

Contributors
ML, RH, XL and XZhu conceived and designed the study, interpreted the data and wrote the manuscript. LX, SZ, XZho, XC, YL, ZX and LW interpreted the data and revised the manuscript draft for important intellectual content. All authors agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript. XL and XZhu had full access to all data in the study and assumed final responsibility for the decision to submit the manuscript for publication.

Declaration of interests
The authors declare no competing interests.

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