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

Menghui Liu,a,b,1 Rihua Huang,a,b,1 Lin Xu,c Shaozhao Zhang,a,b Xiangbin Zhong,a,b Xiaohong Chen,d Yifen Lin,a,b Zhenyu Xiong,a,b Lichun Wang,a,b Xinxue Liao,a,b* and Xiaodong Zhuanga,b*

aDepartment of Cardiology, The First Affiliated Hospital, Sun Yat-sen University, 58 Zhongshan 2nd Rd., Guangzhou 510080, China
bNHC Key Laboratory of Assisted Circulation, Sun Yat-sen University, Guangzhou, China
cSchool of Public Health, Sun Yat-sen University, Guangzhou, China
dThe Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China

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.

Funding None.

Copyright © 2022 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

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

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; 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
Several studies have suggested that weight regain is associated with a deterioration of the cardiovascular health. We hypothesized that the achievement and maintenance of weight loss goal range (Loss of \( \geq \) 7% of baseline weight) at year 1, they had not maintained this weight loss at the end of the trial due to weight regain. Several studies have suggested that weight regain is associated with a deterioration of the cardiovascular benefits associated with weight loss. 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 \( \leq \) 30%; 30% < TIR \( \leq \) 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). 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, 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 \( \geq \) 7% of baseline weight), and estimated with linear interpolation 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) $0\% < \text{TIR} \leq 50\%$ indicated that the participants did not maintain their lower body weight after effectively intended weight loss within 4 years ($n = 636$); and 3) $50\% < \text{TIR} \leq 100\%$ 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, 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 at the logit of a propensity score with a calliper of $0.2 \times \text{standard deviation (SD)}$ that has been shown to substantially reduce initial bias.

### 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 ($\geq 175 \text{ min/week of moderate-intensity physical activity}$). 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.

### Primary and secondary outcomes

To ensure consistency with the Look AHEAD trial protocol, 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. 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 effects of ILI in each TIR group compared to the corresponding propensity score-matched subgroups of the DSE arm.
| Baseline characteristics | TIR = 0% | 0% < TIR ≤ 50% | 50% < TIR ≤ 100% |
|--------------------------|----------|-----------------|-----------------|
| **ILI arm** (n = 724)    | Propensity score-matched DSE subgroup (n = 724) | Propensity score-matched DSE subgroup (n = 656) | Propensity score-matched DSE subgroup (n = 811) |
| Age, years               | 58.0 (6.5) | 57.9 (7.0) | 58.6 (6.7) |
| Sex, No. (%)             | 0.747     | 0.609        | 0.736        |
| Men                      | 287 (39.6) | 281 (38.8) | 254 (38.7) |
| Women                    | 437 (60.4) | 443 (61.2) | 402 (61.3) |
| Race, No. (%)            | 0.936     | 0.648        | 0.615        |
| White                    | 442 (61.0) | 435 (60.1) | 451 (66.8) |
| Black (not Hispanic)     | 139 (19.2) | 143 (19.8) | 113 (17.2) |
| Hispanic                 | 112 (15.5) | 118 (16.3) | 64 (9.8)   |
| Other/Mixed              | 31 (4.3)  | 28 (3.9)    | 28 (4.3)   |
| Body weight, kg          | 99.6 (19.3) | 99.6 (18.8) | 101.8 (20.5) | 101.8 (19.5) | 101.2 (19.3) | 102.1 (19.4) | 0.092 | 0.992 | 0.200 |
| BMI, kg/m²               | 35.6 (6.0) | 35.7 (5.6) | 36.3 (6.3) |
| SBP, mm Hg               | 128.4 (17.5) | 128.7 (16.8) | 128.5 (17.4) | 128.2 (17.1) | 128.6 (17.2) | 129.6 (17.4) | 0.740 | 0.740 | 0.252 |
| DBP, mm Hg               | 70.7 (9.7)  | 70.7 (9.6) | 69.8 (9.3) |
| Total cholesterol, mg/mL | 194.1 (38.4) | 192.3 (35.4) | 192.3 (38.1) | 191.3 (36.9) | 191.3 (36.9) | 187.9 (36.9) | 0.367 | 0.616 | 0.562 |
| HDL-c, mg/mL             | 43.1 (12.0) | 44.2 (11.7) | 43.9 (12.2) |
| LDL-c, mg/mL             | 114.6 (32.0) | 114.6 (32.6) | 113.2 (32.7) | 113.0 (31.3) | 110.4 (31.3) | 109.6 (31.4) | 0.983 | 0.890 | 0.880 |
| Triglyceride, mg/mL      | 186.6 (122.5) | 172.5 (120.2) | 180.4 (109.5) | 174.3 (118.2) | 179.4 (111.3) | 175.6 (109.4) | 0.027 | 0.327 | 0.480 |
| Fasting glucose, mg/mL   | 156.4 (48.4) | 156.4 (45.7) | 152.7 (44.0) |
| HbA1c, %                 | 7.4 (1.2)   | 7.4 (1.2)   | 7.2 (1.1)   |
| Serum creatinine, mg/mL  | 0.8 (0.2)   | 0.8 (0.2)   | 0.8 (0.2)   |
| History of CVD, No. (%)  | 120 (16.6)  | 83 (11.5)   | 77 (11.7)   |
| History of hypertension, No. (%) | 590 (81.5) | 597 (82.3) | 563 (85.8) |
| Education level, No. (%) | 0.522       | 0.695        | 0.343        |
| <13 years                | 143 (19.8)  | 138 (19.1)  | 110 (16.8)  |
| 13–16 years              | 267 (36.9)  | 288 (39.8)  | 248 (37.8)  |
| >16 years                | 314 (43.4)  | 298 (41.2)  | 298 (45.4)  |
| Smoking, No. (%)         | 0.938       | 0.864        | 0.681        |
| Never smoker             | 359 (49.6)  | 361 (49.9)  | 337 (51.4)  |
| Past smoker              | 326 (45.0)  | 327 (45.2)  | 295 (45.0)  |
| Current smoker           | 39 (5.4)    | 36 (5.0)    | 24 (3.7)    | 26 (4.0)    | 33 (4.1)    | 29 (3.6)    |

**Table 1** (Continued)
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 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, 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 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.

www.thelancet.com Vol 49 Month July, 2022
| 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. Secondary analyses of the Look AHEAD trial further suggested that an ILI can lead to the remission of type 2 diabetes, as well as significant improvements in body weight, HbA1c, SBP, and HDL-c. 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. 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. 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 or with type 2 diabetes. 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.

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; however, most individuals subsequently regain the lost body weight. Specifically, approximately 79% of adults who achieve intentional weight loss regain the weight within 1 year. Furthermore, individuals with type 2 diabetes regain this lost weight more rapidly than those without diabetes. 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. 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, 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. Moreover, bariatric surgery has been demonstrated to have substantially greater efficacy than lifestyle or pharmacological interventions for severe obesity (BMI ≥35 kg/m²). 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, 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, 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.

Funding
None.

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.

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.

Declaration of interests
The authors declare no competing interests.

Acknowledgments
The authors thank the staff and participants of the Look AHEAD trial for their significant contributions, and Mark Cleasby, PhD from Liwen Bianji (Edanz) for editing the language of a draft of this manuscript.

Supplementary materials
Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101451.
13 Wadden TA, McPherson K, Marsh T, Gortmaker SL, Brown M. Health and economic burden of the projected obesity trends in the USA and the UK. Lancet. 2011;378(9793):315–25.

12 Ryan DH, Espeland MA, Foster GD, et al. Look AHEAD (action for health in diabetes): design and methods for a clinical trial of weight loss for the prevention of cardiovascular disease in type 2 diabetes. Arch Intern Med. 2010;170(7):616–23.

14 Schmitt L, Speckman J, Ansell J. Quality assessment of anticoagulation management: comparative evaluation of measures of time-in-therapeutic range. J Thromb Thrombolysis. 2003;15(3):211–16.

15 Prentice JC, Mohr DC, Zhang L, et al. Increased hemoglobin A1c time in range reduces adverse health outcomes in older adults with diabetes. Diabetes Care. 2011;34(8):1750–56.

16 Deheja RH, Wahla S. Propensity score-matching methods for nonexperimental causal studies. Rev Econ Stat. 2002;84(1):151–61.

17 Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat. 2011;10(2):150–61.

18 Wesche-Thobaben JA. The development and description of the comparison group in the Look AHEAD trial. Clin Trials. 2011;8(3):320–329.

19 Nam GE, Kim W, Han K, et al. Body weight variability and the risk of cardiovascular outcomes and mortality in patients with type 2 diabetes: a nationwide cohort study. Diabet Care. 2020;43(9):2234–2241.

20 Kaze AD, Santhiapan P, Erqou S, Ahima RS, Bertoni AG, Echouffo-Tcheugui JB. Body weight variability and risk of cardiovascular outcomes and death in the context of weight loss intervention among patients with type 2 diabetes. JAMA Netw Open. 2022;5(2):e220055.

21 VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med. 2017;167(4):268–274.

22 Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346(6):393–403.

23 Gregg EW, Chen H, Wagenknecht LE, et al. Association of an intensive lifestyle intervention with remission of type 2 diabetes. JAMA. 2012;308(23):2489–2496.

24 Wing RR. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. Arch Intern Med. 2010;170(7):616–23.

25 Liu G, Li Y, Hu Y, et al. Influence of lifestyle on incident cardiovascular disease and mortality in patients with diabetes mellitus. J Am Coll Cardiol. 2018;71(21):2867–2876.

26 Diabetes Prevention Program Research Group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the diabetes prevention program outcomes study. Lancet Diabetes Endocrinol. 2015;3(11):866–875.

27 Santos I, Sniehotta FF, Marques MM, Carraça EV, Teixeira PJ. Prevalence of personal weight control attempts in adults: a systematic review and meta-analysis. Obes Rev. 2017;18(1):92–103.

28 Anderson JW, Konz EC, Frederick RC, Wood CL. Long-term weight-loss maintenance: a meta-analysis of US studies. Am J Clin Nutr. 2005;74(3):579–584.

29 Wing RR, Phelan S. Long-term weight loss maintenance. Am J Clin Nutr. 2005;82(1):228–235. Suppl.

30 Norris SL, Zhang X, Avenell A, Gregg E, Schmid CH, Lau J. Meta-analysis of US randomized trials of weight-loss maintenance: a meta-analysis of US studies. Am J Clin Nutr. 2005;74(3):579–584.

31 Elfhag K, Rössner S. Who succeeds in maintaining weight loss? A conceptual review of factors associated with weight loss maintenance and weight regain. Obes Rev. 2005;6(1):67–85.

32 Foster GD, Wyatt HR, Hill JO, et al. Weight and metabolic outcomes after 2 years on a low-carbohydrate versus low-fat diet: a randomized trial. Ann Intern Med. 2010;153(11):747–757.

33 Wadden TA, Bailey TS, Billings LK, et al. Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: the STEP 3 randomized clinical trial. JAMA. 2021;325(14):1403–1413.

34 Pareek M, Schauer PR, Kaplan LM, Leiter LA, Ruhino F, Bhatt DL. Metabolic surgery: weight loss, diabetes, and beyond. J Am Coll Cardiol. 2018;71(6):670–687.

35 Anastassiadis CA, Karlapoulou E, Yannakoulia M. Weight regaining: from statistics and behaviors to physiology and metabolomics. Metabolism. 2015;64(11):1395–1407.

36 Sumithran P, Proietto J. The defence of body weight: a physiological basis for weight regain after weight loss. Clin Sci. 2013;124(4):237–241. (Lond).