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Association of Intensive Lifestyle Intervention, Fitness and Body Mass Index with Risk of Heart Failure in Overweight or Obese Adults with Type 2 Diabetes Mellitus: An Analysis from the Look AHEAD trial

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is associated with higher risk for heart failure (HF). The impact of a lifestyle intervention and changes in cardiorespiratory fitness (CRF), and body mass index (BMI) on risk for HF is not well-established.

Methods: Participants from the Look AHEAD (Action for Health in Diabetes) trial without prevalent HF were included. Time to event analyses were used to compare the risk of incident HF

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between the intensive lifestyle intervention (ILI) vs. diabetes support and education (DSE) groups. The associations of baseline measures of CRF estimated from a maximal treadmill test, BMI, and longitudinal changes in these parameters with risk of HF were evaluated using multivariable adjusted Cox models.

Results: Among the 5,109 trial participants, there was no significant difference in the risk of incident HF (n = 257) between the ILI vs. DSE groups [HR (95% CI) = 0.96 (0.75 to 1.23)] over a median follow-up of 12.4 years. In the most adjusted Cox models, the risk of HF was 39% and 62% lower among moderate fit [Tertile 2: HR (95% CI) = 0.61 (0.44 to 0.83)] and high fit [Tertile 3: HR (95% CI) = 0.38 (0.24 to 0.59)] groups, respectively (referent group: low fit, Tertile 1). Among HF subtypes, after adjustment for traditional CV risk factors and interval incidence of MI, baseline CRF was not significantly associated with risk of incident HFrEF. In contrast, the risk of incident HFpEF was 40% lower in moderate fit and 77% lower in the high fit groups. Baseline BMI was also not associated with risk of incident HF, HFpEF, or HFrEF after adjustment for CRF and traditional CV risk factors. Among participants with repeat CRF assessments (n = 3,902), improvements in CRF and weight loss over 4-year follow-up was significantly associated with lower risk of HF [HR (95% CI) per 10% increase in CRF = 0.90 (0.82 to 0.99), per 10% decrease in BMI = 0.80 (0.69 to 0.94)].

Conclusions: Among participants with T2DM in the Look AHEAD trial, the ILI did not appear to modify the risk of HF. Higher baseline CRF and sustained improvements in CRF and weight loss were associated with lower risk of HF.

Keywords

heart failure; risk; type 2 diabetes mellitus; overweight; obesity; body mass index; cardiorespiratory fitness

INTRODUCTION

Among adults with type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD) is the leading cause of death and heart failure (HF) accounts for 14% of the initial presentations of CVD [1–6]. In contrast to risk for myocardial infarction, optimal control of traditional cardiovascular (CV) risk factors such as blood pressure (BP), cholesterol, glycated hemoglobin (HbA1c), albuminuria, and smoking has not been proven to mitigate the risk of hospitalization for HF in T2DM [7]. These findings suggest that novel approaches, beyond targeting and managing traditional CV risk factors, are needed for prevention of HF among patients with T2DM.

Low cardiorespiratory fitness (CRF) and obesity are important risk factors for HF. Prior studies have demonstrated a consistent, graded association between lower CRF, higher body mass index (BMI), and increased risk of HF in the general population [8–12]. However, the independent associations of CRF and obesity with the risk of incident HF among those with T2DM, who have a higher burden of traditional CV risk factors and are at a higher baseline risk, are not well characterized. Furthermore, it is not known if lifestyle interventions and improvements in CRF and weight loss may modify risk of HF among patients with T2DM.

The Look AHEAD (Action for Health in Diabetes) randomized trial evaluated whether an intensive lifestyle intervention (ILI) would affect the risk of atherosclerotic cardiovascular disease (ASCVD) outcomes among patients with T2DM who are overweight or obese compared with diabetes support and education (DSE) and demonstrated no significant effect on the risk of ASCVD events with ILI [13, 14]. Of note, hospitalizations for new onset or worsened HF were adjudicated as part of a secondary composite outcome in the Look AHEAD trial. However, the original trial did not adjudicate events as HF with preserved ejection fraction (HFpEF) or HF with reduced ejection fraction (HFrEF). Accordingly, in this study, we re-adjudicated incident HF events into its subtypes, HFpEF and HFrEF, and extended the follow-up through December 2015 to evaluate the association of ILI with risk of incident HF and its subtypes[15]. We hypothesize that ILI (vs. DSE) would be associated with a lower risk of HF, particularly HFpEF, among participants of the Look AHEAD trial. We also evaluated the associations of baseline and longitudinal changes in CRF and BMI with risk of incident HF and its subtypes among Look AHEAD participants.

METHODS

The data and materials from the present study will not be made available by the authors for the purpose of reproducing the results.

Look AHEAD trial design and population

Look AHEAD trial design has been reported previously and the primary results were originally published in 2013 [13, 14]. From 2001 to 2004, the Look AHEAD trial enrolled overweight and obese adults (BMI ≥25 kg/m^2 or ≥27 kg/m^2 if taking insulin), aged 45 to 76 years, with T2DM (n = 5,145) who could complete a maximal exercise test and evaluated whether an ILI focused on weight loss would affect the risk for CV events compared with DSE. T2DM status was defined according to physician report, prevalent use of antihyperglycemic medication, or measured plasma glucose level. Participants who did not have a history of HF prior to enrollment and had available data on CRF and BMI at baseline were included in the present study (n = 5,109) (Supplemental Figure 1). Individuals unable to complete a maximal exercise test at baseline were excluded. The associations between change in CRF and BMI from baseline to 1- and 4-year follow-up with risk of incident HF were assessed among Look AHEAD participants who were free of HF at the time of the follow-up assessment and had follow-up CRF and BMI data (n = 4,380 and 3,902 for 1- and 4-year follow-up, respectively). The institutional review board at each participating site approved the study protocol. All participants provided written informed consent.

Treatment groups

Look AHEAD participants were randomly assigned to either an ILI or DSE group. As previously described, the ILI focused on achieving and maintaining at least 7% weight loss through group and individual counseling sessions (weekly for the initial 6 months followed by less frequent meetings), diet prescriptions, and encouragement to achieve physical activity goals [13, 14]. Participants in the ILI arm of the trial were prescribed a restricted caloric diet (1200 to 1800 kcal/day) and encouraged to achieve ≥ 175 minutes/week of

moderate-intensity physical activity. Participants randomized to 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. Both the ILI and DSE interventions were stopped after a median follow-up of 9.6 years in September 2012.

Exposure variables of interest

Cardiorespiratory fitness: Prior to randomization, all eligible participants underwent a symptom-limited graded maximal treadmill exercise test. The details of the exercise test protocol have been published previously and are described in further detail in the Supplemental Methods [16–18]. Briefly, trial participants performed a treadmill-based exercise stress test at a constant speed while grade was incrementally increased. Heart rate and rating of perceived exertion (RPE) were assessed throughout the trial. Exercise testing was terminated according to either standard stopping criteria or voluntary exhaustion. The American College of Sports Medicine metabolic equation for estimating peak oxygen consumption was used to estimate CRF [19]. Participants performed subsequent submaximal exercise treadmill tests at years 1 and 4. Changes in CRF at 1- and 4-years were calculated as the difference between estimated peak metabolic equivalents (METs) at baseline and the corresponding follow-up assessment as previously described [17, 20].

Body mass index: Research personnel blinded to participant group assignment measured baseline body weight and height in duplicate with a digital scale and stadiometer, respectively. Weight was evaluated annually during follow-up. BMI was calculated using the standard formula: [weight (kg)] / [height (meters)]^2.

Outcome of interest

The primary outcomes of interest were incidence of overall HF, HFpEF, and HFrEF. The original trial excluded individuals with New York Heart Association class III or IV HF. In the present study, we excluded Look AHEAD participants with any HF at baseline, and, therefore, adjudicated incident HF. As part of a Look AHEAD HF ancillary study, follow-up was extended with a median follow-up of 12.4 years and we further adjudicated incident HF hospitalizations into HFpEF and HFrEF using a previously validated approach to analyze longer-term HF outcomes and evaluate HF subtypes [15]. HF cases were first identified based on self-report and available ICD-9 codes from hospitalization records of participants on follow-up. Two physicians masked to trial-group assignment adjudicated HF hospitalizations. After clinical data (history, physical examination, test results, and medications) were reviewed, each case was classified into one of the following groups: definite or possible acute decompensated HF, chronic stable HF, HF unlikely, or unclassifiable. Incident HF was defined as definite or possible acute decompensated HF and only the first HF hospitalization was adjudicated. HF subtype (HFpEF and HFrEF) was based on left ventricular ejection fraction (LVEF) identified on echocardiography or cardiac ventriculography (catheterization or radionuclide) measured at the time of the incident HF hospitalization. HFpEF and HFrEF were defined as LVEF ≥50% or <50%, respectively.

Statistical analysis

The incidence of HF outcomes across the two randomized trial arms (ILI and DSE) were compared using cumulative incidence plots and log-rank tests. The risk of incident overall HF and its subtypes, HFpEF and HFrEF, associated with ILI (vs. DSE, referent group) were evaluated using Cox proportional hazard models.

Participants from both trial arms were pooled to evaluate the associations of baseline CRF and BMI with risk of incident HF. Baseline characteristics of trial participants were compared across tertiles of CRF and BMI using Jonckheere-Terpstra test for continuous variables and Cochran-Armitage test for categorical variables. The associations between categorical and continuous measures of baseline CRF, BMI, and risk of HF were assessed using multivariable-adjusted Cox proportional hazards models. Separate models were constructed for each outcome (overall HF, HFpEF, and HFpEF) with inclusion of the following covariates: *Model 1* included demographic characteristics (age, sex, ethnicity, education level, income), treatment group, and the exposure variable of interest (CRF or BMI in separate models); *Model 2* included variables in model 1 plus traditional CV risk factors (history of hypertension, systolic BP, smoking status, current alcohol use, history of CVD, HbA1c, glomerular filtration rate), and both exposure variables of interest (CRF and BMI in the same model); *Model 3* included variables in model 2 and interval myocardial infarction (MI) on follow-up as a time-updated covariate. Mortality and the other HF subtype (for HFrEF and HFpEF models) were treated as censoring events.

The associations between changes in CRF and BMI over short-term (1-year) and intermediate-term (4-year) follow-up and risk of incident HF were assessed in a subset of participants with available repeated measures of CRF and BMI who were free of HF at the time of repeat assessment. Baseline and follow-up characteristics of these participants were compared across categories of change in CRF and BMI over the specified follow-up period. Change in CRF from baseline to 1- or 4- year follow-up was categorized according to tertiles of change in METs over the specified follow-up period. For BMI change, previously described categories of change in BMI were used: gain (>2% gain), stable (≤2% gain to <5% loss), medium loss (≥5% loss to <10% loss), large loss (≥10% loss) [20]. Multivariable adjusted Cox models were constructed to evaluate the associations between longitudinal changes in CRF, BMI, and risk of incident overall HF, HFpEF, and HFrEF with sequential adjustment for covariates: Model 1 included baseline demographic characteristics (age, sex, ethnicity, education level, income), treatment group, baseline CV risk factors (history of hypertension, systolic BP, smoking status, current alcohol use, history of CVD, HbA1c, glomerular filtration rate), baseline CRF, baseline BMI, and the exposure variable of interest (change in CRF or BMI in separate models); Model 2 included the same covariates as Model 1 with both changes in CRF and BMI in the same model; Model 3 included variables in Model 2 plus changes in HbA1c and systolic BP from baseline to the year of follow-up (year 1 or 4). Interaction tests were performed to determine if the association between the study intervention and risk of HF were modified by baseline levels of CRF and BMI. Additional interaction tests were performed to evaluate if race (white vs. non-white) modified the associations of the study intervention, baseline CRF, and BMI with the risk of HF.

RESULTS

Intensive lifestyle intervention & risk of incident HF

The present study included 5,109 participants from the Look AHEAD trial who were randomized to ILI vs. DSE. Over a median follow-up of 12.4 years (58,094 person-years), 257 incident HF events occurred [event rate per 1,000 person years (PY): 4.42], of which 50.2% (n = 129) were HFpEF (event rate per 1,000 PY: 2.23), 40.5% (n = 104) were HFrEF (event rate per 1,000 PY: 1.79), and 9.3% (n = 24) were HF with missing LVEF. There was no significant difference in the risk of incident HF between the ILI vs. DSE groups [HR (95% CI) = 0.96 (0.75 to 1.23)] (Figure 1). The risk of incident HF subtypes, HFpEF and HFrEF, were also not significantly different between the two randomized trial arms (Supplemental Table 1). The association between study intervention (ILI vs. DSE) and risk of HF, HFpEF, and HFrEF was not different among white vs. non-white participants (study intervention * race for risk of HF p-interaction = 0.38). Furthermore, the association between ILI and risk of HF was not modified by baseline CRF or BMI levels (study intervention * CRF p-interaction >0.5; study intervention * BMI p-interaction >0.5).

Baseline CRF & risk of incident HF

The ILI and DSE groups were pooled together to study the association of baseline and changes in CRF and BMI with risk of incident HF. Participants with higher CRF levels were younger, more commonly men, more likely white, and had lower burden of traditional CV risk factors and prevalent CVD (Table 1). Mean diastolic BP was higher among participants with higher CRF although within normal range and low-density lipoprotein cholesterol was similar across CRF groups.

In multivariable adjusted analysis, there was a significant, graded, inverse association between baseline CRF and risk of incident HF after adjustment for potential confounders including BMI, traditional CV risk factors, and interval MI on follow-up. Compared with low fit participants (Tertile 1, referent group), the risk of incident HF was 39% lower in moderate fit [Tertile 2: HR (95% CI) = 0.61 (0.44 to 0.83)] and 62% lower in the high fit groups [Tertile 3: HR (95% CI) = 0.38 (0.24 to 0.59)] (Table 2). Similar findings were observed when CRF was modeled as a continuous variable with 20% lower risk of incident HF per 1-MET higher CRF level [HR (95% CI) = 0.80 (0.72 to 0.88), Table 2]. The association between baseline CRF and risk of HF was similar among white vs. non-white participants (p-interaction = 0.86).

Among HF subtypes, there was graded inverse association between baseline CRF and risk of incident HFpEF with 40% and 77% lower risk of incident HFpEF among moderate fit [Tertile 2: HR (95% CI) = 0.60 (0.39 to 0.91)] and high fit [Tertile 3: HR (95% CI) = 0.23 (0.11 to 0.46)] individuals, respectively (referent group: Tertile 1, low fit; Table 2). In contrast, baseline CRF was not significantly associated with risk of incident HFrEF in the most adjusted model. Similar patterns of results were obtained when CRF was modeled as a continuous variable with a significant association between CRF and HFpEF but not HFrEF in the most adjusted model (Table 2).

Baseline BMI & risk of incident HF

Baseline characteristics of trial participants across categories of BMI are shown in Table 1. Participants with higher BMI at baseline were younger, more commonly women, more commonly white, had lower CRF levels, higher hypertension prevalence and systolic BP, higher HbA1c, and lower history of CVD.

In multivariable adjusted analyses, higher baseline BMI was significantly associated with higher risk of incident HF after adjustment for demographic characteristics and the treatment arm [HR (95% CI) Tertile 2 vs.1 = 1.64 (1.19 to 2.27), Tertile 3 vs.1 = 2.13 (1.53 to 2.95)]. However, this association was attenuated and no longer significant after further adjustment for CRF and traditional HF risk factors (Table 3). Similar findings were also observed when BMI was modeled as a continuous variable. There was no significant interaction between race (white vs. non-white) and baseline BMI for the risk of HF (p-interaction = 0.57). Among HF subtypes, continuous and categorical measures of BMI were not significantly associated with risk of incident HFpEF or HFrEF in the most adjusted models (Table 3).

Association between longitudinal changes in CRF & risk of incident HF

Association between longitudinal changes in CRF and risk of incident HF was assessed in a subset of participants who were free of HF and had a repeat assessment of CRF and BMI at year 1 (n = 4,380) and year 4 (n = 3,902) visits. Participants with greater improvements in CRF levels over short-term (1-year) or intermediate-term (4-year) follow-up were younger, more commonly assigned to the ILI arm, and had lower history of CVD at baseline (Supplemental Table 2, 3). Greater short-term and intermediate-term improvements in CRF were associated with significantly lower BMI, systolic BP, and HbA1c at follow-up.

In multivariable adjusted analyses, greater increase in CRF levels over short-term (1-year) follow-up was significantly associated with lower risk of incident HF (n = 199 events) after adjustment for baseline confounders [HR (95% CI) per 10% increase in CRF = 0.93 (0.87 to 0.99)]. However, this association was attenuated and no longer significant after further adjustment for changes in BMI [HR (95 % CI) = 0.96 (0.90 to 1.03)] (Table 4). In contrast, longitudinal improvements in CRF levels over intermediate-term follow-up (4-year) was significantly associated with lower risk of incident HF (n = 128 events) independent of baseline confounders as well as changes in BMI and other cardiometabolic parameters [HR (95% CI) per 10% increase in CRF = 0.90 (0.82 to 0.99)] (Table 4). The pattern of associations between changes in CRF and risk of incident HF subtypes were in the same direction as incident overall HF but were not consistently statistically significant.

Association between longitudinal changes in BMI & risk of incident HF

Participants with substantial weight loss over short-term (1-year) and intermediate-term (4-year) follow-up were more commonly white and more commonly assigned to the ILI group (Supplemental Table 4, 5). Greater weight loss over short-term and intermediate-term follow-up was associated with significant improvements in CRF, systolic BP, and HbA1c levels.

In multivariable adjusted analyses, a 10% decrease in BMI over short-term (1-year) follow-up was significantly associated with 31% lower risk of incident HF independent of baseline risk factors and changes in other parameters such as CRF, HbA1c, and systolic BP [HR (95% CI) = 0.69 (0.51 to 0.93)] (Table 5). Similarly, a 10% decrease in BMI over intermediate-term (4-year) follow-up was significantly associated with a 20% lower risk of incident HF in the most adjusted model [HR (95% CI) = 0.80 (0.69 to 0.94)]. The pattern of associations between changes in BMI and risk of incident HF subtypes were in the same direction to incident overall HF but were not consistently statistically significant for HFrEF in adjusted models (Table 5).

DISCUSSION

In this study, several important findings were observed. First, in a cohort of adults with T2DM who are overweight or obese from the Look AHEAD trial, the ILI was not associated with lower risk of incident HF or its subtypes on follow-up compared with DSE. Second, higher CRF was significantly associated with lower risk of incident HF independent of traditional risk factors and BMI. Among HF subtypes, a significant, graded inverse association was observed between CRF levels at baseline and risk of incident HFpEF independent of potential confounders. In contrast, baseline CRF was not associated with risk of incident HFrEF after adjustment for potential confounders. Third, significant associations were observed between changes in CRF, BMI and risk of incident HF during the study period such that improvements in CRF as well as greater weight loss over 4-year follow-up were independently associated with lower risk of incident HF. To our knowledge, the present study represents the first and most comprehensive evaluation of the association of ILI and longitudinal changes in CRF with the risk of HF subtypes.

Higher CRF and physical activity levels have been associated with lower risk of HF [21, 22]. Prior studies have demonstrated a graded association between CRF levels in young to middle age and risk of HF in older age [8, 11, 23–26]. However, most of these studies were limited by inclusion of a referral population with a clinical indication for CRF testing [24, 25] or low-risk participants with a lower burden of traditional HF risk factors such as T2DM [8, 9, 26]. Furthermore, these cohorts did not clinically adjudicate incident HF events and thus, it was not clear if the association of low CRF with HF is consistent for both HFpEF and HFrEF [8, 24–26]. Findings from the present study add to the existing literature by demonstrating a consistent graded, inverse association between CRF levels and risk of incident HF, particularly HFpEF in a higher risk cohort of patients with prevalent T2DM (Supplemental Table 6).

Prior studies have also evaluated the association of subjective measures of exercise capacity such as self-reported physical activity or walking speed with the risk of HF subtypes [12, 27, 28]. In a recent pooled analysis from 3 large cohorts, higher levels of physical activity were more consistently associated with lower risk of HFpEF but not HFrEF [12]. However, others have demonstrated consistent and similar patterns of association between physical activity levels and risk of HF subtypes [27, 28]. These discordant observations regarding physical activity associated risk of HF subtypes may be related to the subjective nature of the self-reported physical activity levels in these cohorts. Furthermore, physical activity

levels are more reflective of the habitual exercise behavior and only modestly associated with peak exercise capacity [29, 30]. In the present study, using CRF levels, an objective measure of peak exercise capacity, we demonstrated that higher CRF may modify the risk of HFpEF and HFrEF through potentially different mechanisms. A significant, graded inverse association was observed between CRF and risk of incident HFpEF independent of other risk factors suggesting a more direct effect of CRF on cardiac structure and function. In contrast, the association between CRF and risk of incident HFrEF was largely driven by differences in traditional risk factor burden and antecedent MI events prior to HF development.

The mechanism through which CRF may modify risk of HFpEF is not well established. Prior studies have demonstrated significant associations between low CRF levels and higher burden of diastolic dysfunction, a subclinical cardiac phenotype associated with development of HFpEF [31, 32]. Seminal studies have identified increased left ventricular (LV) stiffness, demonstrated by steeper LV pressure-volume loops and higher stiffness constant in invasive hemodynamic studies, as a key pathophysiologic abnormality in HFpEF [33–36]. Prior studies have also demonstrated a strong inverse association between lifelong exercise dose and LV stiffness among healthy participants [37]. These mechanistic findings corroborate the epidemiological observation of higher HFpEF risk among individuals who are low fit and highlight the independent and direct role of low CRF in development of HFpEF.

The present study also adds to the existing literature on CV effects of lifestyle interventions by evaluating its effects on the risk of HF and its subtypes, HFpEF and HFrEF. Despite the significant association between baseline CRF and risk of incident HF among participants of the Look AHEAD trial, the ILI did not appear to significantly modify the risk of incident HF compared with DSE. This is consistent with the negative results of the Look AHEAD trial for the primary CV outcome and may be related to the overall modest differences in the achieved weight loss and CRF improvements between the ILI vs. DSE groups during follow-up [average between-group difference in weight (ILI vs. DSE): −4 kg; average between-group difference in CRF (ILI vs. DSE): 0.6 METs] [14]. However, there were significant associations between changes in CRF and BMI during the trial period and risk of incident HF. Specifically, sustained improvements in CRF and weight loss over 4 years were each significantly associated with lower risk of incident HF independent of baseline confounders as well as changes in other relevant cardiometabolic parameters. In contrast with 4-year CRF changes, the association between short-term improvements in CRF at 1-year follow-up and lower risk of incident HF was largely driven by changes in BMI. It is plausible that early CRF improvements that were observed with ILI in the Look AHEAD trial were largely driven by weight loss and sustained improvements in CRF levels over longer-term follow-up may be more reflective of favorable changes in CV exercise reserve. Along these lines, recent exercise training trials have demonstrated that short-term exercise training (1-year duration) does not significantly modify LV stiffness, the key pathophysiologic abnormality associated with HFpEF, in sedentary, older individuals [38]. In contrast, high intensity exercise training over prolonged duration (2-year) in middle-age, sedentary individuals may significantly improve LV stiffness [39]. Future studies are needed to determine if implementation of more intense exercise training or weight loss interventions

aimed at promoting sustained improvements in CRF and body weight among young to middle-age patients with T2DM may significantly modify HF risk.

In contrast to the observed independent association between CRF and risk of HF, higher BMI associated risk of HF in the Look AHEAD cohort was largely driven by differences in the burden of CV risk factors and CRF levels. The lack of independent association between higher BMI and risk of HF may be related to the cohort characteristics which included only overweight and obese participants with T2DM. Furthermore, consistent with prior observations, adjustment for CRF in the present study may have substantially attenuated the relationship between higher BMI and risk of HF [11].

Prior studies in patients with T2DM have demonstrated the phenomenon of the obesity paradox whereby higher BMI in the overweight to obese range is associated with lower risk of mortality [40, 41]. It is noteworthy that the phenomenon of obesity paradox was not observed in the Look AHEAD cohort for development of HF. Furthermore, reduction in BMI was associated with lower risk of HF, highlighting the importance of weight loss to lower the risk of HF in overweight and obese adults with T2DM. These findings may suggest that the obesity paradox may not be applicable to non-fatal incident HF outcomes. However, patients with normal BMI were not included in the Look AHEAD trial limiting the evaluation of HF risk across a broader distribution of BMI.

The present study has several important public health and clinical implications. The burden of HF, particularly HFpEF, continues to increase in the community highlighting the need for novel approaches to its prevention [42]. Findings from our study demonstrate that low CRF may identify individuals with T2DM who are at increased risk for development of HF, particularly HFpEF. Furthermore, the low CRF associated risk of HF in this high-risk cohort of individuals with T2DM and overweight/obesity was modifiable with sustained improvements in CRF levels and weight loss. It is noteworthy that the ILI used in the Look AHEAD trial, which led to only modest improvements in CRF and weight loss as compared with the control arm, was not associated with significant reductions in HF risk. Similarly, prior studies of interventions that achieved modest improvement in functional capacity and/or weight loss have not demonstrated reductions in the risk of HF [43–45]. In contrast, therapeutic strategies such as bariatric surgery, which are associated with substantial weight loss, have been associated with lower risk of HF development in observational cohort studies (Supplemental Table 7) [46, 47]. Taken together, these findings highlight the need to test novel and effective interventions aimed at achieving substantial and sustained improvements in CRF levels and weight loss to modify the risk of HF, particularly HFpEF.

The strengths of the present study include the large sample size of the cohort, availability of adjudicated outcome events with HF subtype information, and availability of objective measures of CRF levels at baseline and follow-up. These analyses are not without limitations. First, there is a potential for unmeasured confounding and selection bias in this secondary analysis. This is particularly relevant for the associations between changes in CRF, BMI and risk of HF. Second, there is also a potential for reverse causation such that presence of subclinical heart disease at baseline may have contributed to lower CRF and observed associations between CRF and risk of incident HF. As a result, these findings

do not establish a causal association between CRF and risk of incident HF. Third, serum biomarkers with important prognostic implications for the risk of HF such as high-sensitivity cardiac troponin and/or N-terminal pro-B-type natriuretic peptide were not measured in the overall Look AHEAD cohort. Thus, we could not asses the association of ILI, CRF, and longitudinal changes in CRF with changes in these biomarkers. Finally, the present study findings may not be generalizable to patients with T2DM who would not have qualified for participation in the Look AHEAD trial owing to inability to participate in the ILI.

In conclusion, among individuals with T2DM who are overweight or obese, lower CRF is an independent and potentially modifiable risk factor for incident HF, particularly HFpEF. ILI implemented in the Look AHEAD trial did not significantly lower the risk of incident HF compared with DSE. However, intentional weight loss and sustained improvements in CRF may significantly lower the risk of incident HF. Future studies with more intense interventions targeting substantial weight loss and CRF improvement are needed to evaluate the role of lifestyle interventions in modifying HF risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

ASCVD	atherosclerotic cardiovascular disease
BMI	body mass index
CVD	cardiovascular disease
CRF	cardiorespiratory fitness
DSE	diabetes support and education
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
ILI	intensive lifestyle intervention
T2DM	type 2 diabetes mellitus

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CLINICAL PERSPECTIVE

What is new?

- In the Look AHEAD trial, an intensive lifestyle intervention among adults who are overweight or obese and have type 2 diabetes mellitus did not lower the risk of heart failure on follow-up.
- Among individuals with type 2 diabetes mellitus, high cardiorespiratory fitness was associated with lower risk of developing heart failure, particularly heart failure with preserved ejection fraction, independent of traditional risk factors.
- Sustained, long-term improvements in cardiorespiratory fitness and weight loss were associated with lower risk of heart failure development among adults with type 2 diabetes mellitus.

What are the clinical implications?

- Low cardiorespiratory fitness may identify individuals with type 2 diabetes mellitus who are at higher risk for developing heart failure and may benefit from strategies targeting substantial improvements in cardiorespiratory fitness and weight loss.
- Lifestyle intervention strategies with modest improvements in cardiorespiratory fitness and weight loss may not be sufficient to lower the risk of heart failure.

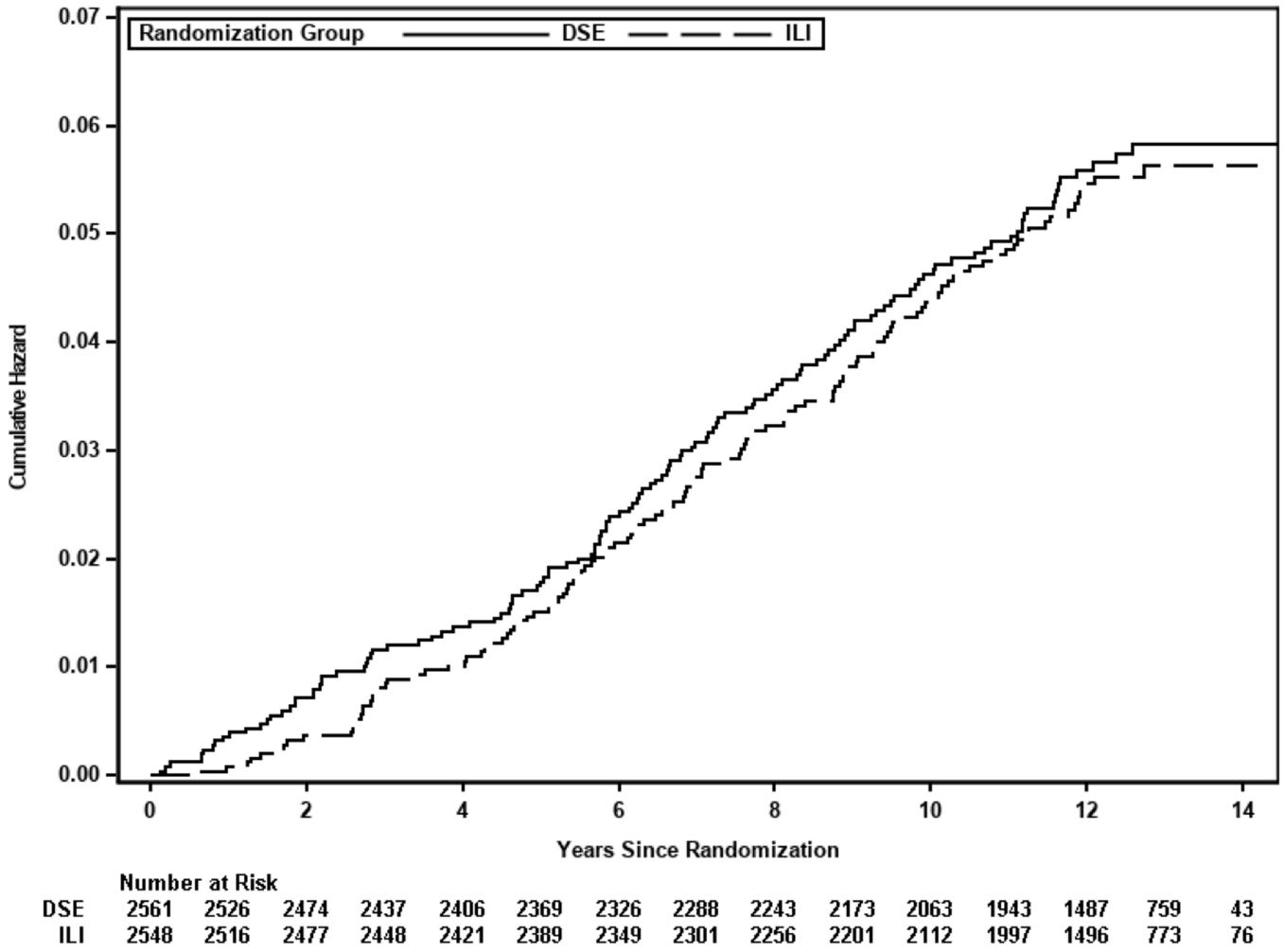

Figure 1. Cumulative incidence plot of overall incident HF risk according to treatment group

Abbreviations: DSE = diabetes support and education; HF = heart failure; ILI = intensive lifestyle

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Table 1.

Baseline and follow-up characteristics stratified by baseline BMI and CRF tertiles

	Cardiorespiratory fitness			Body mass index				
	Tertile 1 3.3–6.1 METs (n = 1,694)	**Tertile 2 6.2–7.8 METs (n = 1,786)**	**Tertile 3 7.9–16.7 METs (n = 1,629)**	**Tertile 1 24.53–32.60 kg/m^2 (n = 1,703)**	**Tertile 2 32.61–37.77 kg/m^2 (n = 1,703)**	**Tertile 3 37.78–63.53 kg/m^2 (n = 1,703)**	**P value for CRF tertiles**	**P value for BMI tertiles**
Baseline variables								
Estimated CRF, METs	5.2 (0.6)	7.0 (0.5)	9.5 (1.4)	8.1 (2.2)	7.3 (1.8)	6.2 (1.5)	<0.001	<0.001
BMI, kg/m^2	38.8 (6.7)	36.0 (5.1)	32.9 (4.0)	30.1 (1.8)	35.0 (1.5)	42.7 (4.2)	<0.001	<0.001
Age, years	60.8 (6.9)	58.3 (6.6)	57.1 (6.4)	60.2 (6.9)	58.8 (6.8)	57.2 (6.5)	<0.001	<0.001
Female, %	75.7	61.8	40.5	54.6	58.0	66.2	<0.001	<0.001
White, %	60.7	62.7	66.6	62.2	63.0	64.7	<0.001	<0.001
Education, %							<0.001	<0.001
<13 years	25.1	19.9	14.1	19.4	21.4	18.6		
13–16 years	41.2	37.8	32.7	33.9	36.5	41.5		
>16 years	31.5	39.8	51.1	44.3	39.6	38.2		
Missing	2.2	2.5	2.0	2.4	2.5	1.8		
Income, %							<0.001	0.007
<$20,000	15.6	11.7	6.8	11.7	11.2	11.2		
$20,000 to $39,999	26.6	18.3	12.4	18.0	19.8	19.7		
$40,000 to $59,999	19.1	19.2	17.3	18.1	18.0	19.4		
$60,000 to $79,999	12.9	15.0	15.9	12.5	14.6	16.6		
≥$80,000	14.6	25.9	39.7	29.5	26.3	23.8		
Missing	11.3	10.0	8.0	10.0	10.1	9.3		
Weight, kg	105.4 (21.1)	100.8 (18.9)	95.6 (16.1)	85.2 (11.2)	98.5 (12.3)	118.3 (16.8)	<0.001	<0.001
Systolic BP, mm Hg	132 (18)	129 (17)	126 (16)	126 (17)	129 (17)	132 (17)	<0.001	<0.001
Diastolic BP, mm Hg	69 (10)	70 (10)	72 (9)	70 (10)	70 (10)	70 (10)	<0.001	0.14
History of hypertension, %	89.9	84.1	75.0	78.1	83.2	88.0	<0.001	<0.001
History of CVD, %	16.9	12.0	10.7	14.2	14.3	11.2	<0.001	0.008
Insulin use, %	20.7	16.7	9.9	12.4	16.4	18.9	<0.001	<0.001

	Cardiorespiratory fitness			Body mass index				
	Tertile 1 3.3–6.1 METs (n = 1,694)	**Tertile 2 6.2–7.8 METs (n = 1,786)**	**Tertile 3 7.9–16.7 METs (n = 1,629)**	**Tertile 1 24.53–32.60 kg/m^2 (n = 1,703)**	**Tertile 2 32.61–37.77 kg/m^2 (n = 1,703)**	**Tertile 3 37.78–63.53 kg/m^2 (n = 1,703)**	**P value for CRF tertiles**	**P value for BMI tertiles**
Smoking, %							0.23	0.37
Never	50.7	51.4	48.6	50.3	49.4	51.0		
Past	44.4	44.3	47.5	45.4	45.4	45.2		
Current	4.9	4.4	3.9	4.3	5.2	3.8		
Alcohol, %							<0.001	<0.001
None / week	75.9	68.6	58.7	63.3	68.1	72.1		
1–3 / week	16.1	19.7	22.5	19.5	19.8	18.9		
4+ / week	8.1	11.8	18.8	17.3	12.2	9.0		
HbA1c, %	7.4 (1.2)	7.3 (1.2)	7.1 (1.1)	7.2 (1.1)	7.2 (1.2)	7.4 (1.2)	<0.001	<0.001
GFR, mL/min per 1.73 m^2	86.9 (17.5)	90.8 (15.6)	91.5 (14.3)	88.1 (15.3)	89.6 (16.0)	91.4 (16.5)	<0.001	<0.001
LDL-C, mg/dL	111 (33)	113 (32)	113 (32)	112 (33)	111 (31)	113 (33)	0.28	0.58
ILI treatment group, %	48.8	50.5	50.3	51.3	49.2	49.2	0.57	0.34
Follow-up variables								
Interval MI, %	1.1	0.4	0.2	0.7	0.7	0.3	<0.001	0.18

Data presented as mean (standard deviation) or percentage. Comparison across groups performed using Cochran-Armitage test for categorical variables and Jonckheere-Terpstra test for continuous variables. Follow-up variables were assessed after the baseline visit.

BMI = body mass index; BP = blood pressure; CRF = cardiorespiratory fitness; CVD = cardiovascular disease; GFR = glomerular filtration rate; HbA1c = glycated hemoglobin; ILI = intensive lifestyle intervention; LDL-C = low density lipoprotein cholesterol; METs = metabolic equivalents; MI = myocardial infarction.

Table 2.

Multivariable adjusted association of categories and continuous measures of baseline CRF with risk of incident overall HF, HFpEF, and HFrEF

	Model 1		Model 2		Model 3	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Overall HF						
CRF categories (referent group: tertile 1)						
Tertile 2	0.47 (0.35, 0.64)	<0.001	0.54 (0.40, 0.73)	<0.001	0.61 (0.44, 0.83)	<0.001
Tertile 3	0.22 (0.15, 0.32)		0.31 (0.20, 0.48)		0.38 (0.24, 0.59)	
Continuous CRF measure						
Per 1 unit higher CRF	0.70 (0.64, 0.76)	<0.001	0.76 (0.69, 0.83)	<0.001	0.80 (0.72, 0.88)	<0.001
HFpEF						
CRF categories (referent group: tertile 1)						
Tertile 2	0.50 (0.34, 0.75)	<0.001	0.57 (0.38, 0.87)	<0.001	0.60 (0.39, 0.91)	<0.001
Tertile 3	0.14 (0.07, 0.27)		0.21 (0.10, 0.42)		0.23 (0.11, 0.46)	
Continuous CRF measure						
Per 1 unit higher CRF	0.68 (0.60, 0.77)	<0.001	0.74 (0.64, 0.86)	<0.001	0.75 (0.65, 0.87)	<0.001
HFrEF						
CRF categories (referent group: tertile 1)						
Tertile 2	0.56 (0.35, 0.91)	0.007	0.63 (0.38, 1.04)	0.14	0.71 (0.43, 1.19)	0.41
Tertile 3	0.44 (0.26, 0.77)		0.61 (0.33, 1.12)		0.75 (0.40, 1.41)	
Continuous CRF measure						
Per 1 unit higher CRF	0.80 (0.71, 0.91)	<0.001	0.85 (0.74, 0.98)	0.03	0.89 (0.77, 1.03)	0.12

Hazard ratio refers to the association of CRF categories / continuous measures of CRF with risk of incident overall HF, HFpEF, and HFrEF. Separate models were constructed for each HF outcome (overall, HFpEF, and HFrEF). Tertile 1 was the referent group in the categorical analysis.

Model 1 included age, sex, ethnicity, education level, income, treatment group, baseline CRF

Model 2 included Model 1 covariates plus baseline BMI, history of hypertension, systolic BP, smoking status, current alcohol use, history of CVD, HbA1c, GFR

Model 3 included Model 2 covariates plus interval MI on follow-up.

BP = blood pressure; BMI = body mass index; CI = confidence interval; CRF = cardiorespiratory fitness; CVD = cardiovascular disease; GFR = glomerular filtration rate; HbA1c = glycated hemoglobin; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HR = hazard ratio; MI = myocardial infarction.

Table 3.

Multivariable adjusted association of categories and continuous measures of baseline BMI with risk of incident overall HF, HFpEF, and HFrEF

	Model 1		Model 2		Model 3	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Overall HF						
BMI categories (referent group: tertile 1)						
Tertile 2	1.64 (1.19, 2.27)	<0.001	1.30 (0.94, 1.81)	0.29	1.36 (0.97, 1.90)	0.12
Tertile 3	2.13 (1.53, 2.95)		1.20 (0.84, 1.72)		1.42 (0.99, 2.06)	
Continuous BMI measure						
Per 1 unit higher BMI	1.05 (1.03, 1.07)	<0.001	1.00 (0.98, 1.03)	0.81	1.01 (0.99, 1.04)	0.27
HFpEF						
BMI categories (referent group: tertile 1)						
Tertile 2	1.43 (0.89, 2.29)	0.001	1.04 (0.64, 1.69)	0.79	0.99 (0.61, 1.61)	0.64
Tertile 3	2.28 (1.45, 3.60)		1.18 (0.71, 1.94)		1.21 (0.73, 2.00)	
Continuous BMI measure						
Per 1 unit higher BMI	1.06 (1.03, 1.09)	<0.001	1.01 (0.97, 1.04)	0.75	1.01 (0.98, 1.04)	0.62
HFrEF						
BMI categories (referent group: tertile 1)						
Tertile 2	1.75 (1.07, 2.85)	0.06	1.56 (0.94, 2.57)	0.20	1.66 (0.99, 2.76)	0.16
Tertile 3	1.71 (1.01, 2.88)		1.23 (0.69, 2.19)		1.43 (0.79, 2.59)	
Continuous BMI measure						
Per 1 unit higher BMI	1.03 (0.997, 1.07)	0.07	1.01 (0.97, 1.05)	0.81	1.01 (0.97, 1.06)	0.51

Hazard ratio refers to the association of BMI categories / continuous measures of BMI with risk of incident overall HF, HFpEF, and HFrEF. Separate models were constructed for each HF outcome (overall, HFpEF, and HFrEF). Tertile 1 was the referent group in the categorical analysis.

Model 1 included age, sex, ethnicity, education level, income, treatment group, baseline BMI

Model 2 included Model 1 covariates plus baseline CRF, history of hypertension, systolic BP, smoking status, current alcohol use, history of CVD, HbA1c, GFR

Model 3 included Model 2 covariates plus interval MI on follow-up.

BP = blood pressure; BMI = body mass index; CI = confidence interval; CRF = cardiorespiratory fitness; CVD = cardiovascular disease; GFR = glomerular filtration rate; HbA1c = glycated hemoglobin; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HR = hazard ratio; MI = myocardial infarction.

Table 4.

Multivariable adjusted association of changes in CRF from baseline to 1- and 4-year follow-up with risk of incident overall HF, HFpEF, and HFrEF

			Model 1		Model 2		Model 3	
	Person-years	**Event Rate per 1,000 person years**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Per 10% increase in CRF from baseline to 1-year follow-up								
Overall HF	51,159	3.89	0.93 (0.87, 0.99)	0.02	0.96 (0.90, 1.03)	0.26	0.97 (0.90, 1.04)	0.37
HFpEF	51,037	1.86	0.89 (0.81, 0.99)	0.02	0.93 (0.84, 1.03)	0.16	0.94 (0.85, 1.004)	0.20
HFrEF	51,037	1.69	0.95 (0.86, 1.05)	0.32	1.00 (0.90, 1.11)	0.96	1.01 (0.91, 1.11)	0.92
Per 10% increase in CRF from baseline to 4-year follow-up								
Overall HF	47,408	2.70	0.86 (0.79, 0.94)	0.001	0.88 (0.80, 0.97)	0.009	0.90 (0.82, 0.99)	0.03
HFpEF	47,324	1.23	0.85 (0.74, 0.97)	0.02	0.88 (0.77, 1.01)	0.07	0.90 (0.78, 1.03)	0.14
HFrEF	47,324	1.27	0.86 (0.75, 0.98)	0.02	0.87 (0.76, 0.998)	0.047	0.88 (0.77, 1.01)	0.07

HR refers to the association of 10% increase in CRF with risk of incident overall HF, HFpEF, and HFrEF included in separate Cox proportional hazards models. Separate models were constructed for each HF outcome (overall, HFpEF, and HFrEF). Separate models were created with sequential adjustment for confounders.

Model 1 included age, sex, ethnicity, education level, income, treatment group, history of hypertension, systolic BP, smoking status, current alcohol use, history of CVD, HbA1c, GFR, baseline BMI, baseline CRF, change in CRF.

Model 2 included age, sex, ethnicity, education level, income, treatment group, history of hypertension, systolic BP, smoking status, current alcohol use, history of CVD, HbA1c, GFR, baseline BMI, baseline CRF, change in CRF and change in BMI (both included in the same model).

Model 3 included age, sex, ethnicity, education level, income, treatment group, history of hypertension, systolic BP, smoking status, current alcohol use, history of CVD, HbA1c, GFR, baseline BMI, baseline CRF, change in CRF and change in BMI (both included in the same model), % change in A1c, % change in systolic BP.

BP = blood pressure; BMI = body mass index; CI = confidence interval; CRF = cardiorespiratory fitness; CVD = cardiovascular disease; GFR = glomerular filtration rate; HbA1c = glycated hemoglobin; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HR = hazard ratio.

Table 5.

Multivariable adjusted association of changes in BMI from baseline to 1- and 4-year follow-up with risk of incident overall HF, HFpEF, and HFrEF

			Model 1		Model 2		Model 3	
	Person-years	**Event rate per 1,000 person years**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Per 10% decrease in BMI from baseline to 1-year follow-up								
Overall HF	51,159	3.89	0.61 (0.47, 0.80)	<0.001	0.65 (0.48, 0.86)	0.003	0.69 (0.51, 0.93)	0.01
HFpEF	51,037	1.86	0.57 (0.38, 0.84)	0.005	0.63 (0.42, 0.96)	0.03	0.64 (0.42, 0.98)	0.04
HFrEF	51,037	1.69	0.54 (0.36, 0.83)	0.005	0.55 (0.35, 0.85)	0.008	0.59 (0.37, 0.93)	0.02
Per 10% decrease in BMI from baseline to 4-year follow-up								
Overall HF	47,408	2.70	0.76 (0.66, 0.86)	<0.001	0.79 (0.68, 0.92)	0.002	0.80 (0.69, 0.94)	0.006
HFpEF	47,324	1.23	0.71 (0.60, 0.84)	<0.001	0.74 (0.62, 0.89)	0.001	0.76 (0.63, 0.91)	0.003
HFrEF	47,324	1.27	0.81 (0.64, 1.02)	0.07	0.86 (0.64, 1.15)	0.30	0.89 (0.64, 1.22)	0.46

HR refers to the association of 10% decrease in BMI with risk of incident overall HF, HFpEF, and HFrEF included in separate Cox proportional hazards models. Separate models were constructed for each HF outcome (overall, HFpEF, and HFrEF). Separate models were created with sequential adjustment for confounders.

Model 1 included age, sex, ethnicity, education level, income, treatment group, history of hypertension, systolic BP, smoking status, current alcohol use, history of CVD, HbA1c, GFR, baseline BMI, baseline CRF, change in BMI.

Model 2 included age, sex, ethnicity, education level, income, treatment group, history of hypertension, systolic BP, smoking status, current alcohol use, history of CVD, HbA1c, GFR, baseline BMI, baseline CRF, change in BMI and change in CRF (both included in the same model).

Model 3 included age, sex, ethnicity, education level, income, treatment group, history of hypertension, systolic BP, smoking status, current alcohol use, history of CVD, HbA1c, GFR, baseline BMI, baseline CRF, change in BMI and change in CRF (both included in the same model), % change in A1c, % change in systolic BP.

BP = blood pressure; BMI = body mass index; CI = confidence interval; CRF = cardiorespiratory fitness; CVD = cardiovascular disease; GFR = glomerular filtration rate; HbA1c = glycated hemoglobin; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HR = hazard ratio.