Published in final edited form as:

Prog Cardiovasc Dis. 2015 ; 58(1): 69–75. doi:10.1016/j.pcad.2015.04.002.

The Look AHEAD Trial: Implications for Lifestyle Intervention in Type 2 Diabetes Mellitus

Gareth R. Dutton, PhD and Cora E. Lewis, MD, MSPH

Division of Preventive Medicine, Department of Medicine, School of Medicine and Diabetes Research Center, University of Alabama at Birmingham, Birmingham, AL

Abstract

Given the array of adverse health consequences of obesity, including increased risk for type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD), the Look AHEAD trial (N=5,145) was conducted to test the hypothesis that an intensive lifestyle intervention (ILI) for weight loss would achieve significantly greater reductions in CVD morbidity and mortality than a control condition of diabetes support and education (DSE) among participants with T2DM. A number of significant and long-term improvements were observed for ILI, including body weight, physical fitness and physical function, glucose control, quality-of-life (QoL), and healthcare costs. However, ILI did not significantly reduce CVD-related morbidity/mortality (i.e., CVD death, non-fatal MI, non-fatal stroke, hospitalized angina) after nearly 10 years of follow-up. There was a suggestion of heterogeneity of response based on the history of prior CVD at baseline ($p=0.06$). Despite the overall lack of CVD risk reduction, ILI remains important for care of patients with T2DM, particularly when accompanied by medication management. In particular, ILI may be an appealing option for patients wanting to minimize medication intensification. Also, ILI carries with it other potential benefits important to patients (e.g., improvements in physical functioning and QoL). Based on data from other trials, intensive medication management, such as tight glycemic control, is not without potential risks, which should be weighed in making treatment decisions. Future research is needed to determine if results observed in this trial would be replicated among younger patients, those without established T2DM, and/or those with no pre-existing CVD.

Keywords

cardiovascular disease; type 2 diabetes mellitus; weight loss; lifestyle intervention

Corresponding author: Cora E. Lewis, MD, MSPH, Division of Preventive Medicine; 1717 11th Ave South; Birmingham, AL35205, celewis@uabmc.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of Interest: Dr. Lewis receives research grant support for her role as Principal Investigator (paid to the University of Alabama at Birmingham) from Novo Nordisk

Obesity, Cardiovascular Disease (CVD), and Type 2 Diabetes Mellitus (T2DM)

Obesity is associated with increased risk factors for CVD, including hypertension (HTN), dyslipidemia, and T2DM (1). In addition, obesity is associated with a variety of other clinical conditions and psychosocial outcomes, such as osteoarthritis, certain types of cancers, sleep apnea, depressive symptoms, diminished physical functioning, and reduced quality-of-life (QoL) (2–7). Obesity is related to increased overall mortality that is primarily driven by deaths attributable to CVD, cancers, and diabetes/kidney diseases (8). Finally, obesity is one of the key risk factors, along with poor diet, physical inactivity, and others, for the highly prevalent and expensive chronic disease burden in the United States (9).

There are numerous benefits of weight loss for the prevention and control of T2DM and other CVD risk factors (1). Modest reductions in body weight are associated with significant reductions in the incidence of HTN and T2DM (10–14). Results from the Diabetes Prevention Program (DPP) demonstrated a 58% reduction in T2DM risk with modest initial weight losses of approximately 7 kg (10). Modest weight loss is also associated with improvements in low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol, triglycerides, insulin level, and glycemic control (1, 15). Given the documented benefits of modest weight loss for the prevention and management of chronic health conditions and CVD risk factors, current clinical guidelines recommend 5–10% weight reduction for overweight and obese patients (1). In particular, the guidelines identify lifestyle modification targeting dietary changes, physical activity (PA), and other behavioral strategies to promote weight loss as an appropriate initial intervention for most overweight and obese patients (1).

However, long-term data on weight loss, especially from controlled trials, are scarce. A recent systematic review and meta-analysis of lifestyle interventions for patients with or at risk for T2DM, including major results from Look AHEAD, concluded that there was no evidence of benefit on all-cause mortality, and insufficient evidence on CVD and microvascular outcomes (16). The authors noted that improvement in some secondary outcomes did not persist beyond the intervention phase and the clinical significance of findings was not clear. The secondary outcomes considered in this analysis were limited to body composition, metabolic variables, PA, and dietary intake. Other outcomes important to patients, such as QoL, were not examined.

The Look AHEAD Trial of Weight Loss in T2DM

Rationale

When the participating centers in Look AHEAD were initially funded in 1999, relatively short-term lifestyle interventions had been shown to improve CVD risk factors and obesity-related metabolic abnormalities. It was unknown whether these improvements could result in reductions in CVD-related morbidity or mortality, or whether long-term weight loss interventions could have adverse consequences (17). This was, and is, particularly relevant to patients with T2DM, who experience elevated CVD risk. To address this gap in the literature, the Look AHEAD trial was designed and conducted to examine the effects of

weight loss through behavioral means on CVD morbidity and mortality (18). Look AHEAD was designed to test the hypothesis that an intensive multi-component lifestyle intervention compared to diabetes support and education would reduce the incidence of CVD outcomes and improve other health parameters, including CVD risk factors, mortality, diabetes-related metabolic risk factors and complications, safety of interventions, indices of general health, QoL, and economic consequences among participants with T2DM (18).

Description

Participants—Details of the Look AHEAD protocol, intervention protocol, and sample characteristics have been described previously (18–20). Briefly, participants had T2DM and could be using any type of glucose-lowering medication, although the proportion of participants using insulin was limited to <30%. Participants with a history of certain types of CVD, including uncomplicated myocardial infarction (MI), coronary artery bypass surgery, percutaneous coronary intervention, and chronic stable angina pectoris, were included if the diagnosis or condition occurred at least 3 months prior to screening, in order to increase generalizability and to increase the expected event rate. There were extensive eligibility criteria, which are summarized in Table 1.

The study sample included 5,145 participants randomized to either an intensive lifestyle intervention (ILI) or diabetes support and education (DSE). The average age of participants was 58.7 years, 60% were women, 37% were racial/ethnic minorities, and the mean body mass index (BMI) was 36.0 kg/m² (20). The median duration of T2DM was 5 years, mean baseline A1c was 7.3%, and 14% of patients reported a history of CVD at baseline.

Outcomes—The primary outcome was a composite variable of CVD morbidity and mortality consisting of CVD death, non-fatal MI, non-fatal stroke, and hospitalized angina (21, 22). When the intervention was stopped in September 2012, the median follow-up was 9.6 years. In addition to the primary outcome of CVD events, Look AHEAD included additional composite CVD outcomes as well as numerous additional clinical outcomes, including body weight, physical fitness, glycated hemoglobin, lipids, BP, medication use, diabetes complications, and health care cost, among others.

Treatment conditions—The intervention protocol has been described in detail elsewhere (19). ILI aimed at achieving and maintaining at least a 7% weight loss by focusing on reduced caloric intake and increased PA. The program included frequent contact throughout the trial, with both group and individual sessions, a calorie goal of 1200–1800 kcal/day (<30% of calories from fat and >15% from protein), use of meal replacement products, and at least 175 minutes per week of moderate intensity PA. A toolbox of strategies was available for participants having difficulty achieving the weight loss or weight maintenance goals. The DSE condition included three group education sessions per year during years 1–4 focused on diet, exercise, and social support and one session annually in later years (18).

Main Findings

Weight loss—The ILI resulted in significantly greater weight loss than DSE throughout the course of the trial (21). Differences in mean weight loss between ILI and DSE were

greatest at one year (−8.6% vs. −0.7%, respectively). Averaged across the first four years of intensive treatment, mean weight losses for ILI and DSE were −6.15% vs. −0.88% (23). When study intervention ended due to a futility analysis on the primary outcome, the mean weight loss from baseline was −6.0% in ILI and −3.5% in DSE (21). Thus, ILI achieved remarkable sustained weight loss over an extended period of time. Moreover, weight loss was similar across baseline BMI categories (24), indicating similar efficacy in overweight to severely obese participants.

PA and physical fitness—The ILI focus on increasing PA resulted in improved fitness compared to DSE. Overall, fitness improved in ILI 21.0% and in DSE 5.7% at year 1, with significantly greater improvements seen in men than in women (25). Several other baseline factors were related to a lower increase in fitness, including higher baseline fitness, higher BMI, higher waist circumference, greater age, and baseline history of CVD.

Body composition—Over 1,000 participants were assessed with dual energy x-ray absorptiometry at baseline, and at years 1, 4 and 8 at four Look AHEAD centers to assess changes in body composition in the ILI and DSE groups (26). The ILI group lost more weight during follow-up than DSE. ILI experienced losses of both fat mass (5.6 ± 0.2 kg [mean $\pm$ SE]) and lean mass (2.3 ± 0.2 kg) at year 1, and increases in percent lean mass. Subsequently, ILI experienced losses of lean mass and gains of fat mass, with weight, fat mass and lean mass approaching but remaining significantly lower than in DSE at year 8. The mean weight loss in the DSE was approximately 0.23 kg/year of lean mass and approximately 0.1 kg of fat mass during the 8 years of follow-up.

CVD morbidity and mortality—There was no overall significant difference in the primary composite CVD outcome between the ILI and DSE groups after nearly 10 years of follow-up (21). More specifically, the composite outcome of CVD events occurred in 403 participants in the intervention group and 418 in the control group, which did not differ between conditions (1.83 and 1.92 events per 100 person-years, respectively; hazard ratio (HR) in the intervention group, 0.95; 95% confidence interval, 0.83–1.09; $P = 0.51$ [Table 2]).

There was a non-significant trend ($p=0.06$) for an interaction between treatment assignment and participants' baseline CVD status (21). Among participants with a history of CVD at baseline, those who received ILI had a numerically higher incidence of the composite CVD outcome which was not statistically different than those in DSE (HR for ILI, 1.13, 95% CI 0.90–1.42), while participants without a history of CVD at baseline had a numerically but not significantly lower incidence of the primary outcome (HR for ILI, 0.86, 95% CI 0.72–1.02). Thus, there were some preliminary indications that the ILI may have been more beneficial for individuals with no history of CVD, and little evidence of potential harm especially in those without a history of CVD.

Other clinical and patient reported outcomes—In addition to significant and sustained weight loss, the ILI had a number of other important benefits compared to DSE, including significantly improved glucose control throughout the trial and significant improvements in all other risk factors measured, except for LDL-C (21); greater likelihood

of partial remission of T2DM (27); reduced risk of developing clinically significant symptoms of depression and preserved physical health-related QoL (28); beneficial effects on renal outcomes (29); beneficial effects on urinary incontinence in men and women (30, 31); some evidence of improvement in erectile dysfunction in men (32); and fewer hospitalizations, fewer medications, and lower health-care costs over 10 years (33).

Overall, participants in the ILI experienced a significant improvement in the SF-36 physical function subscale at year 1 whereas DSE participants experienced a small decrease, resulting in significantly greater physical function scores at year 1 in ILI (34). Following year 1 in ILI, and in the entire 8 years of follow-up in DSE, physical function declined significantly as participants aged. However, the buffer created by the increased scores in ILI participants at year 1 was maintained, and differences in physical functioning were relatively constant between ILI and DSE across 8 years of follow-up. At year 8, an ILI participant with a baseline SF-36 subscale score of 48.5, the mean baseline score in Look AHEAD, had a physical function level that was equivalent to being 2.67 years younger than a DSE participant at year 8. On the other hand, the ILI participants who had CVD at baseline had lower baseline physical function scores than in ILI overall. Similar to ILI overall, ILI participants with pre-existing CVD experienced a benefit from ILI at year 1 with an increase in scores and benefit relative to DSE with pre-existing CVD, but then the ILI group lost all benefit relative to DSE by year 2. Subsequently, ILI participants with CVD at baseline did not experience a benefit of the intervention for physical functioning, and had similar scores to DSE from years 2 to 8 of follow-up.

These self-reported findings are consistent with performance based measures obtained in an ancillary study 8–9 years post randomization (35). A subset of Look AHEAD centers participated in the Movement and Memory ancillary study and obtained the expanded short physical performance battery ([SPPB_{exp}] standing balance tasks, 4 m walk, repeated chair stands), and tests of usual walking speed (20 m), grip and knee extensor strength, and walking endurance (400 m). ILI participants, who had a mean weight loss of 6.0% at year 8, had significantly higher adjusted SPPB_{exp} scores, faster 20 m and 400 m walking speed than did DSE participants, who had experienced a 2.3% weight loss at year 8, while strength measures did not differ. Thus, there was better mobility and lower extremity physical performance, but no difference in upper or lower extremity strength, in the ILI group that experienced voluntary weight loss, compared to the DSE group.

Implications for Preventive Cardiology

These results from the Look AHEAD trial have important clinical implications relevant to lifestyle interventions and preventive cardiology. In terms of CVD, the 1.83 primary CVD events/100 person-years in ILI and the 1.92 events/100 person-years in DSE were not statistically different. However, the ILI achieved several other benefits, including weight reduction and increased PA. ILI also demonstrated improvements in glucose and CVD risk factor control with fewer medications (e.g., statins and insulin) than DSE. While both groups experienced medication intensification, DSE participants used more medications for control of glucose, LDL-C, and BP over time, and health-care costs were higher in DSE.

Treatment recommendations have included both lifestyle modification and medication for management of T2DM and CVD risk, tailored to patient preferences (36). The Look AHEAD results are consistent with these recommendations, and many ILI participants were on various medications for such management; however, intensive lifestyle modification could play a more central role depending on patient preferences. Some patients will be content with medication intensification, although others will prefer to minimize their need for additional medications. In the latter group of patients, lifestyle modifications to diet and exercise may be a more appealing option, and this carries with it other potential benefits important to patients.

Considerations influencing decisions about lifestyle modification and medication regimens may include clinical characteristics and patient history. In Look AHEAD, there were some indications of heterogeneity in response to ILI based on the history of CVD at baseline. Those participants with prior CVD did not experience the lasting overall ILI benefits on physical function experienced by ILI participants without CVD. There was a nonsignificant but suggestive interaction on the primary CVD outcome related to CVD history at baseline ($p=0.06$), with a suggestive but nonsignificant benefit of ILI on the primary outcome among those without CVD at baseline (HR 0.86 [95% CI 0.72–1.02]). Obviously, patients with T2DM, especially those with a history of CVD, should have ongoing and aggressive management of their risk factors with medications, such as statins, and this may obscure some of the benefits of lifestyle intervention on CVD (HR 1.13 [95% CI 0.90–1.42] for ILI vs DSE in the subgroup with baseline CVD). Specific aspects of the treatment response to lifestyle intervention among patients with CVD warrant additional investigation before more specific recommendations can be offered.

There are other important implications of Look AHEAD. For the many patients with T2DM managed primarily by medications, clinicians must consider the risks of this approach and the most appropriate treatment goals. Several recent trials of intensive vs more standard glucose control via medication management found that intensive control did not reduce the risk for CVD events or death (37, 38). However, intensive control was associated with more adverse events, including greater rates of hypoglycemic episodes (38). In addition, intensive control with medications was harmful, increasing total mortality in the ACCORD trial (39). Clearly, this treatment option is not without potential risks, which must be taken into consideration and carefully monitored.

For patients with T2DM who elect to pursue lifestyle modification and weight loss, with or without medication, Look AHEAD encouragingly demonstrates that long-term and clinically meaningful weight loss maintenance is possible with lifestyle interventions and may have several benefits. However, such programs should include ongoing contact that is intensive, comprehensive, and employs evidence-based behavioral principles. To achieve long-term success, it is important that interventions use evidence-based techniques to promote self-management for weight-control strategies and some level of ongoing contact. This intensity of treatment is clearly a challenge for many clinical settings, so referrals to evidence-based behavioral programs that provide long-term support to patients will be important to maximize the effects of this treatment option.

Two additional points about ILI deserve consideration here. First, ILI achieved comparable results regardless of patients' sex, race/ethnicity, or initial weight status (21). Thus, this approach may be beneficial for a broad and diverse group of patients with T2DM who are motivated and interested in this management option. Second, recent reports from the Look AHEAD research group indicate that participants' early response to treatment (i.e., weight loss within the first 1–2 months of the program) can serve as a very strong and reliable indicator of how well individuals will do during long-term follow-up (40). Therefore, it may be possible to initiate lifestyle interventions with a large number of patients and make clinical decisions relatively early regarding which patients are most likely to respond to this treatment option and should continue in the program, and which patients may be better served by discontinuing treatment and exploring other strategies as the principal approach for CVD risk reduction. This is an important point, as such decisions could reduce the unnecessary use of clinical resources for patients unlikely to benefit from treatment, and early discontinuation may reduce patients' frustration as well.

Future Directions

Although the Look AHEAD trial has provided novel and valuable insights about the relative benefits of ILI for a variety of clinical and patient-centered outcomes, many unanswered questions remain that warrant further investigation. One strength of the ILI was its comprehensive and intensive approach to promote behavior change. However, it is unclear exactly which components of treatment may be most important for improving long-term clinical outcomes. This issue is particularly relevant in the context of translating this intervention to applied clinical settings that have finite resources, which may require the 'un-packaging' and selection of particular components of the program to remain feasible for real-world implementation.

Also, Look AHEAD included older adults (>45 years-old) with diabetes, so the applicability of these findings for CVD risk reduction among younger patients and/or those without T2DM is unknown. Similarly, this trial included both participants with and without a history of CVD, and there is some indication that these two sub-groups responded somewhat differently to the intervention. Thus, one intriguing question is whether this treatment would demonstrate different results in CVD risk reduction specifically among patients with no pre-existing history of CVD (i.e., the primary prevention of initial events vs. the prevention of subsequent events). The Look AHEAD participants were screened and selected for their suitability and likely adherence to a long-term intensive lifestyle intervention program, and were evaluated with a maximal exercise test to insure safety of the intervention. Whether similar results would be obtained in a more general clinical population is unknown, as are the potential modalities that could be employed to promote adherence in real-world settings. Finally, long-term legacy effects of tight glucose control emerged over time with post-trial follow-up in UKPDS, resulting in benefits for acute MI and death from any cause despite early loss of glycemic differences (41). In ADVANCE, no long-term benefit of tight glycemic control was evident but benefits of tight BP control remained significant (42). Further observation of the participants in Look AHEAD will be required to determine whether such legacy effects will emerge.

Acknowledgements

Supported in part by U01-DK-57008, DK079626, and DK-081607

The views stated in this manuscript are those of the authors and not necessarily those of the Look AHEAD study group or its sponsors.

Abbreviations

BMI	Body mass index
BP	Blood pressure
CVD	Cardiovascular disease
DSE	Diabetes support and education
HTN	Hypertension
ILI	Intensive lifestyle intervention
LDL-C	Low-density lipoprotein cholesterol
MI	Myocardial infarction
PA	Physical activity
QoL	Quality of life
SPPB_{exp}	Expanded short physical performance battery
T2DM	Type 2 diabetes mellitus

References

1. Jensen MD, Ryan DH, Apovian CM, et al. AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Obesity Society. *J Am Coll Cardiol.* 2013; 63:2985–3023. [PubMed: 24239920]
2. Field, AE.; Barnoya, J.; Colditz, GA. Epidemiology and Health and Economic Consequences of Obesity. In: Wadden, TA.; Stunkard, AJ., editors. *Handbook of Obesity Treatment*. New York: The Guilford Press; 2002. p. 3-18.
3. National Heart Lung Blood Institute. Clinical Guidelines on the Identification, Evaluation, and treatment of overweight and bbesity in adults: the evidence report. NHLBI Obesity Education Initiative Expert Panel. , editor. NHLBI; 1998.
4. Coakley EH, Kawachi I, Manson JE, Speizer FE, Willet WC, Colditz GA. Lower levels of physical functioning are associated with higher body weight among middle-aged and older women. *Int J Obes Relat Metab Disord.* 1998; 22(10):958–965. [PubMed: 9806310]
5. Fine JT, Colditz GA, Coakley EH, et al. A prospective study of weight change and health-related quality of life in women. *JAMA.* 1999; 282(22):2136–2142. [PubMed: 10591335]
6. Petry NM, Barry D, Pietrzak RH, Wagner JA. Overweight and obesity are associated with psychiatric disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Psychosom Med.* 2008; 70(3):288–297. [PubMed: 18378873]
7. Zhao G, Ford ES, Dhingra S, Li C, Strine TW, Mokdad AH. Depression and anxiety among US adults: associations with body mass index. *Int J Obes (Lond).* 2009; 33(2):257–266. [PubMed: 19125163]
8. Flegal KM, Graubard BI, Williamson DF, Gail MH. Cause-specific excess deaths associated with underweight, overweight, and obesity. *JAMA.* 2007; 298(17):2028–2037. [PubMed: 17986696]

9. Bauer UE, Briss PA, Goodman RA, Bowman BA. Prevention of chronic disease in the 21st century: elimination of the leading preventable causes of premature death and disability in the USA. *Lancet*. 2014; 384(9937):45–52. [PubMed: 24996589]
10. 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. [PubMed: 11832527]
11. Pan XR, Yang WY, Li GW, Liu J. Prevalence of diabetes and its risk factors in China, 1994, National Diabetes Prevention and Control Cooperative Group. *Diabetes Care*. 1997; 20(11):1664–1669. [PubMed: 9353605]
12. Trials of Hypertension Prevention Collaborative Research Group. Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure. The trials of hypertension prevention, phase. II. The trials of hypertension prevention collaborative research group. *Arch Intern Med*. 1997; 157:657–667. [PubMed: 9080920]
13. Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med*. 2001; 344(18):1343–1350. [PubMed: 11333990]
14. Whelton PK, Appel LJ, Espeland MA, et al. Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). TONE Collaborative Research Group. *JAMA*. 1998; 279(11):839–846. [PubMed: 9515998]
15. Gregg, EW.; Williamson, DF. The relationship of intentional weight loss to disease incidence and mortality. In: Wadden, TA.; Stunkard, AJ., editors. *Handbook of Obesity Treatment*. New York, NY: The Guilford Press; 2002. p. 125-143.
16. Schellenberg ES, Dryden DM, Vandermeer B, Ha C, Korownyk C. Lifestyle interventions for patients with and at risk for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med*. 2013; 159(8):543–551. [PubMed: 24126648]
17. Yanovski SZ, Bain RP, Williamson DF. Report of a National Institutes of Health--Centers for Disease Control and Prevention workshop on the feasibility of conducting a randomized clinical trial to estimate the long-term health effects of intentional weight loss in obese persons. *Am J Clin Nutr*. 1999; 69(3):366–372. [PubMed: 10075318]
18. The Look AHEAD Research Group. 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. *Control Clin Trials*. 2003; 24(5):610–628. [PubMed: 14500058]
19. Look Ahead Research Group. Wadden TA, West DS, et al. The Look AHEAD study: a description of the lifestyle intervention and the evidence supporting it. *Obesity (Silver Spring)*. 2006; 14(5): 737–752. [PubMed: 16855180]
20. Look Ahead Research Group. Baseline characteristics of the randomized cohort from the Look AHEAD (Action for Health in Diabetes) study. *Diab Vasc Dis Res*. 2006; 3:202–215. [PubMed: 17160917]
21. Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med*. 2013; 369(2):145–154. [PubMed: 23796131]
22. Brancati FL, Evans M, Furburg CD, et al. Midcourse correction to a clinical trial when the event rate is underestimated: the Look AHEAD (Action for Health in Diabetes) Study. *Clin Trials*. 2012; 9(1):113–124. [PubMed: 22334468]
23. Look AHEAD Research Group. 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(17):1566–1575. [PubMed: 20876408]
24. Unick JL, Beavers D, Bond DS, Clark JM, Jakicic JM, Kitabchi AE, Knowler WC, Wadden TA, Wagenknecht LE, Wing RR. Look AHEAD Research Group. The long-term effectiveness of a lifestyle intervention in severely obese individuals. *Am J Med*. 2013; 126(3):236–242. [PubMed: 23410564]

25. Jakicic JM, Jaramillo SA, Balasubramanyam A, et al. Effect of a lifestyle intervention on change in cardiorespiratory fitness in adults with type 2 diabetes: results from the Look AHEAD Study. *Internat J Obes*. 2009; 33:305–316.
26. Pownall HJ, Bray GA, Wagenknecht LE, et al. Changes in body composition over 8 years in a randomized trial of a lifestyle intervention: The Look AHEAD Study. *Obesity (Silver Spring)*. 2015; 23(3):565–572. [PubMed: 25707379]
27. 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. [PubMed: 23288372]
28. Rubin RR, Wadden TA, Bahnson JL, et al. Impact of intensive lifestyle intervention on depression and health-related quality of life in type 2 diabetes: the Look AHEAD Trial. *Diabetes Care*. 2014; 37(6):1544–1553. [PubMed: 24855155]
29. The Look AHEAD Research Group. Knowler WC, Bahnson JL, Bantle JP, Bertoni AG, Bray GA, et al. Effect of a long-term behavioural weight loss intervention on nephropathy in overweight or obese adults with type 2 diabetes: a secondary analysis of the Look AHEAD Randomised Clinical Trial. *Lancet Diabetes Endocrinol*. 2014; 2(10):801–809. [PubMed: 25127483]
30. Breyer BN, Phelan S, Hogan PE, et al. Intensive lifestyle intervention reduces urinary incontinence in overweight/obese men with type 2 diabetes: Results from the Look AHEAD Trial. *J Urol*. 2014; 192(1):144–1499. [PubMed: 24533998]
31. Phelan S, Kanaya AM, Subak LL, et al. Weight loss prevents urinary incontinence in women with type 2 diabetes: results from the Look AHEAD trial. *J Urol*. 2012; 187(3):939–944. [PubMed: 22264468]
32. Wing RR, Rosen RC, Fava JL, et al. Effects of weight loss intervention on erectile function in older men with type 2 diabetes in the Look AHEAD Trial. *J Sex Med*. 2010; 7(Pt 1):156–165. [PubMed: 19694925]
33. Espeland MA, Glick HA, Bertoni A, et al. Impact of an intensive lifestyle intervention on use and cost of medical services among overweight and obese adults with type 2 diabetes: the action for health in diabetes. *Diabetes Care*. 2014; 37(9):2548–2556. [PubMed: 25147253]
34. Rejeski WJ, Bray GA, Chen SH, et al. Aging and physical function in type 2 diabetes: 8 years of an intensive lifestyle intervention. *J Gerontol A Biol Sci Med Sci*. 2014; 70(3):343–351.
35. Houston DK, Leng X, Bray GA, et al. A long-term intensive lifestyle intervention and physical function: the Look AHEAD Movement and Memory Study. *Obesity (Silver Spring)*. 2015; 23(1):77–84. [PubMed: 25452229]
36. American Diabetes Association. Strategies for Improving care. *Diabetes Care*. 2015; 38(Supplement 1):S5–S7. [PubMed: 25537709]
37. ADVANCE Collaborative Group. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, et al. Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*. 2008; 358(24):2560–2572. [PubMed: 18539916]
38. Duckworth W, Abaira C, Moritz T, et al. Glucose Control and vascular complications in veterans with type 2 diabetes. *N Engl J Med*. 2009; 360(2):129–139. [PubMed: 19092145]
39. Action to Control Cardiovascular Risk in Diabetes Study Group. Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008; 358(24):2545–2559. [PubMed: 18539917]
40. Unick JL, Hogan PE, Neilberg RH, et al. Evaluation of early weight loss thresholds for identifying nonresponders to an intensive lifestyle intervention. *Obesity (Silver Spring)*. 2014; 22(7):1608–1616. [PubMed: 24771618]
41. Holman RR, Paul SK, Bethel A, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *New Engl J Med*. 2008; 359(15):1577–1589. [PubMed: 18784090]
42. Zoungas A, Chalmers J, Neal B, et al. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. *New Engl J Med*. 2014; 371(15):1392–1406. [PubMed: 25234206]

Table 1

Look AHEAD inclusion and exclusion criteria.

Inclusion
• 45–74 years old
• BMI 25.0 kg/m ² (27.0 if currently taking insulin)
• Type 2 diabetes mellitus determined by self-report with objective verification (including fasting glucose 126 mg/dL, etc)
Exclusion
• Inadequate control of comorbid conditions
• HbA1C > 11%
• Blood pressure 160/100 mm Hg
• Fasting triglycerides 600 mg/dL
• Factors that may limit adherence to interventions or affect conduct of the trial: Unable or unwilling to give informed consent or communicate with study staff; hospitalization for depression in past 6 months; self-report of alcohol or substance abuse within the past 12 months; travel plans that limit participation; lack of support from primary care provider or family members; failure to complete run-in for dietary intake and physical activity monitoring tasks; weight loss > 10 lb in previous 3 months; history of bariatric surgery, small bowel resection, or extensive bowel resection; chronic treatment with systemic corticosteroids; another member of household is participant or staff member of Look AHEAD; weight > 350 lb or ability to complete exercise test; current diagnosis of schizophrenia, other psychotic disorders, or bipolar disorder; current use of weight loss medication; inability to walk 2 blocks; amputation of lower limb for non-traumatic cause; other medical, psychiatric, or behavioral limitations that may interfere with participation
• Underlying diseases likely to limit life span and/or affect the safety of the interventions: Currently pregnant or nursing; cancer requiring treatment in past 5 years unless prognosis is excellent; self-report of HIV infection, or active tuberculosis; CVD event within 3 months; documented history of pulmonary embolus within 6 months; various CVD manifestations (including unstable angina, history of cardiac arrest, complex ventricular arrhythmia at rest or with exercise, , New York Heart Association Class III or IV congestive heart failure, clinically significant aortic stenosis, aortic aneurysm repair, resting heart rate < 45 or > 100 beats per minute, maximum exercise stress test showing unsafe to participate in lifestyle intervention etc); renal disease (urine dipstick protein 4+, serum creatinine 1.4 mg/dL (women) or 1.5 mg/dL (men), or currently receiving dialysis); chronic obstructive pulmonary disease that would limit ability to follow protocol; self-reported chronic hepatitis B or C, inflammatory bowel disease requiring treatment in past year, Cushings syndrome, acromegaly self-report or clinical diagnosis, any major organ transplant; moderate or high risk for cardiac complications during exercise and/or inability to self-regulate activity, or understand recommended activity level

Table 2

Frequency and event rate for the primary outcome* overall and by prespecified subgroups

	Diabetes Support and Education Number (%/year)	Intensive Lifestyle Intervention Number (%/year)	HR (95% CI)	p- value (interaction)
Overall	418 (1.92)	403 (1.83)	0.95 (0.83–1.09)	
CVD history				0.06
No	274 (1.42)	240 (1.23)	0.86 (0.72–1.02)	
Yes	144 (5.92)	163 (6.56)	1.13 (0.90–1.42)	
Sex				0.73
Men	245 (2.94)	232 (2.72)	0.93 (0.78–1.11)	
Women	173 (1.29)	171 (1.26)	0.97 (0.79–1.20)	
Race/Ethnicity				0.17
African American	46 (1.32)	63 (1.82)	1.34 (0.91–1.96)	
American Indian	13 (1.18)	10 (0.86)	0.74 (0.31–1.76)	
Asian/Pacific Islander	3 (1.67)	1 (0.38)	0.71 (0.06–8.28)	
Non-Hispanic white	303 (2.19)	286 (2.06)	0.94 (0.80–1.11)	
Other	10 (2.35)	12 (2.96)	1.15 (0.45–2.89)	
Hispanic	43 (1.54)	31 (1.06)	0.66 (0.41–1.05)	

* Primary outcome: CVD death, non-fatal MI, non-fatal stroke, hospitalized angina Adapted from (21)