HHS Public Access

Author manuscript

Lancet Diabetes Endocrinol. Author manuscript; available in PMC 2017 November 01.

Published in final edited form as:

Lancet Diabetes Endocrinol. 2016 November ; 4(11): 913–921. doi:10.1016/S2213-8587(16)30162-0.

Association of the Magnitude of Weight Loss and Physical Fitness Change on Long-term CVD outcomes: The Look AHEAD Study

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Abstract

Background—The Look AHEAD Study found no significant reduction in cardiovascular disease (CVD) incidence among adults with diabetes enrolled in an intensive weight loss intervention (ILI) compared to those randomized to diabetes support and education (DSE). We examined whether CVD incidence in Look AHEAD varied by weight or fitness change.

Methods—Among overweight or obese adults people aged 45–76 with type 2 diabetes in the Look AHEAD study, this observational analysis examined the association of magnitude of weight loss (N=4834) and fitness change (N=4406) over the first year with CVD incidence over a median 10.2 years of follow-up. The primary outcome was a composite of CVD death, myocardial infarction, stroke, or angina hospitalization; the secondary outcome included the same indices plus coronary–artery bypass grafting, carotid endartectomy, percutaneous coronary intervention, hospitalization for congestive heart failure, peripheral vascular disease, or total mortality. Analyses adjusted for baseline differences in weight or fitness, demographics and CVD risk factors.

Findings—In analyses of the full cohort combining ILI and DSE, persons who lost > 10% body weight in the first year had 21% lower risk of the primary outcome (HR=0.79, 95% CI, 0.64 to 0.98) and a 24% reduced risk of the secondary outcome (HR=0.76, 95% CI, 0.63 to 0.91) relative to those with stable weight/weight gain. Achieving a > 2 MET fitness change was associated with a significant reduction in the secondary outcome (HR=0.77, 95% CI, 0.61 – 0.96) but not the primary outcome (HR=0.78, 0.60 – 1.03). In analyses treating the DSE as the referent group, ILI participants with > 10% weight losses had a 20% lower risk of the primary outcome (HR=0.80 (95% CI, 0.65 – 0.99) and a 21% reduced risk of the secondary outcome (0.79 (95% CI, 0.66 – 0.95); fitness change was not significantly associated with either outcome.

Interpretation—This secondary analysis of Look AHEAD suggests an association between the magnitude of intentional weight loss and CVD incidence.

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Trial Registration clinical trials.gov identifier: NCT00017953

BACKGROUND

Observational studies have consistently associated obesity, physical inactivity, and low fitness with increased risk of cardiovascular disease (CVD) (1–3). Randomized controlled trials (RCTs) have shown that lifestyle interventions to reduce weight and increase physical activity levels lead to diverse metabolic benefits, including decreased levels of insulin resistance, blood pressure, and inflammatory markers, improved lipid profiles, decreased incidence of type 2 diabetes, and among persons with diabetes, improved glycemic control (4–9). However, whether these benefits lead to reduced CVD incidence, which remains the greatest single cause of morbidity and mortality for adults with diabetes, remains unclear. Observational studies of intentional weight loss have yielded mixed findings, ranging from modest benefit to harm (10). The Look AHEAD Study (Action for Health in Diabetes), the largest RCT to date of an intensive lifestyle-based weight loss intervention, led to numerous health benefits but had no significant effect on CVD morbidity and mortality (9, 11–13).

A variety of explanations have been offered for the lack of an effect of ILI on CVD outcomes in Look AHEAD. One possible explanation is that the weight losses achieved were not large enough to produce an impact on CVD outcomes. Behavioral responses to intensive weight loss interventions are notoriously heterogeneous, as some participants have a limited weight loss or fitness effect in the first year, and others achieve substantial changes in weight or fitness (14–16). It is conceivable that an intensive lifestyle intervention can reduce long-term CVD incidence for people with favorable behavioral and weight loss responses, but have its benefits obscured by people who are unsuccessful at weight loss. In these secondary analyses we examine the association between the magnitude of weight loss and physical fitness from baseline to one year and CVD incidence using 2 perspectives: First, we examine the association of weight change and fitness changes to CVD incidence for the full Look AHEAD cohort, combining both participants in ILI and DSE. Second, we compare CVD rates in ILI participants according to their weight change and fitness response, with participants from the DSE group.

METHODS

Study Design, Sample, and Inclusion Criteria

Look AHEAD was a multicenter, randomized controlled trial that tested the impact of an intensive lifestyle intervention on cardiovascular disease outcomes (17, 18). Overweight and obese adults aged 45 to 76 years with type 2 diabetes were recruited at 16 research centers and randomized to either an ILI aimed at achieving sustained weight loss and increased physical activity or to a diabetes support and education intervention (DSE). Eligibility required a body mass index > 25 kg/m^2 or > 27 kg/m^2 among those receiving insulin therapy. Diabetes status was verified by use of diabetes medication or physician report. Participants were excluded from Look AHEAD if they had hemoglobin A1c levels > 11%, systolic blood pressure >160 mm Hg, diastolic blood pressure > 100 mm Hg, or plasma triglyceride levels > 600 mg/dl, or were unable to complete a maximal graded exercise test or two weeks of diet and activity self-monitoring. These criteria led to a sample of 5145 adults with diabetes who were randomized equally to ILI or DSE. All participants signed a consent form approved by their local institutional review board.

Intervention

Details of the intensive lifestyle intervention (ILI) have been described previously (18, 19). In brief, the ILI included weekly group and individual sessions in the first 6 months, followed by two group sessions and one individual session per month for the second 6 months, and two contacts per month (at least one in person) for years 2 through 4. The ILI aimed to reduce total caloric intake to 1200 to 1800 kcal/d based on initial weight and reduce total fat and saturated fat content to less than 30% and 10%, respectively, with support from calorie counting and provisions of meal replacements. Participants were counseled to achieve a goal of 175 minutes of physical activity per week, such as brisk walking. Behavioral strategies included self-monitoring, goal setting, and problem solving. Participants in the DSE were offered 3 group sessions each year focusing on diet, physical activity, and social support but individualized behavioral support was not provided and participants were not weighed during the sessions. Medical or pharmacological care for control of hyperglycemia, lipids, and blood pressure were provided by the participant's physician independent of the Look AHEAD study for both groups, with the exception of temporary changes in glucose-lowering medications that were made by study staff to reduce the risk of hypoglycemia in the ILI group.

Assessments

Participants attended a baseline clinic visit and annual follow-up visits, during which body weight and height were assessed using a digital scale and stadiometer, respectively. A maximal graded exercise test was administered at baseline and a submaximal exercise test conducted at years 1 and 4. Changes in fitness were computed as the difference between estimated metabolic equivalents at the point that the participants achieved or exceeded 80% of age-predicted maximal heart rate or a rating of perceived exertion of at least 16 at baseline and at the subsequent assessment (20, 21). Intervention response was based on the difference in weight and fitness between the baseline and first year clinic visit.

Outcomes

We restricted our analyses to the Look AHEAD pre-specified outcomes, adjudicated by a masked outcomes committee. The primary CVD outcome was defined as first occurrence of non-fatal acute myocardial infarction (AMI) or stroke, hospitalized angina, or CVD death. The secondary outcome included the same indices plus coronary–artery bypass grafting, carotid endartectomy, percutaneous coronary intervention, hospitalization for congestive heart failure, peripheral vascular disease, or total mortality. The median follow-up period was 10.2 years.

Statistical Analyses

For the analyses related to weight change, we excluded 246 persons (95 from ILI and 151 from DSE) lacking body weight measurements and 65 persons who had a primary event before the first annual clinic visit, leaving an analytic sample size of 4834. (Corresponding sample size for the secondary outcome was 4813). For the analyses related to fitness, we excluded 688 persons (278 from ILI and 398 from DSE) lacking fitness measurements, and

51 persons who had a primary event before the first annual clinic visit, leaving an analytic sample size of 4406. (The corresponding sample size for the secondary outcome was 4404).

Descriptive statistics were used to compare baseline characteristics of the DSE and the ILI groups according to 1-year weight loss and fitness responses from baseline to one-year of follow-up. Weight loss and fitness responses during the first year were examined as both continuous (expressed per standard deviation of weight loss and fitness increase) and categorical variables. We used the following cut points to assign categories of weight change: weight gain or weight stable (<2% weight loss or weight gain), small (> 2 to < 5% weight loss), moderate (> 5 to < 10 % loss), or large (> 10%) weight loss. We defined the large weight loss as > 10% because it corresponded with the intervention weight loss goal. Fitness change was categorized in terms of metabolic equivalents (METs) as fitness loss/ stable (fitness gain < 0.5 METS), small (>0.5 to <1.0), moderate (>1.0 to <2.0), or large (≥2.0 MET) change.

We conducted analyses from two distinct perspectives. First, we compared event rates across the categories of weight change and fitness change for the overall Look AHEAD study sample, with DSE and ILI groups combined, setting the stable weight group as the referent group. Second, we compared CVD rates in ILI participants according to their weight change and fitness response to lifestyle intervention, treating the DSE group as the referent group. The second analysis was undertaken to determine whether, compared to receiving DSE, receiving ILI and having a favorable response to ILI resultedresult in a reduced CVD incidence. In pharmacological trials, this analysis is sometimes referred to as a “per protocol” or “on treatment” analysis. We also tested interactions of randomization group by weight change and randomization group by fitness change on the primary outcome. For both analyses, we first calculated crude rates, then fit Cox proportional hazards regression models, adjusting for factors that varied across weight change or fitness change groups: age, sex, diabetes duration, insulin use, history of CVD, baseline smoking status, baseline weight, LDL cholesterol (LDL), systolic blood pressure (SBP) and diastolic blood pressure (DBP). We tested for non-linearity of the association of weight change and fitness change with CVD incidence and examined interactions of weight change and fitness change with the protocol-based pre-specified variables of age, CVD history, and race/ethnicity. All analyses were performed using SAS (Cary, NC). A two-sided p-value of less than 0.05 was considered statistically significant.

RESULTS

Between the baseline and first-year visits, 40% of the overall sample had stable weight or gained weight, whereas roughly 20% fell into each of the 3 weight loss categories: lost 2–5%, 5–10% or >10%. ILI participants represented only 18% of the weight stable/gain group, but 92% of those who lost >10% of weight. Participants with larger weight losses were older, more likely to be white, less likely to be taking insulin, and had lower LDL cholesterol and diastolic blood pressure than persons with stable weight or a weight gain (Table 1).

Fifty-two percent of the overall sample had a decline or no change in fitness between baseline and 1 year, whereas the remaining 48% fell roughly evenly into the 3 fitness change categories: gain 0.5 to 1.0 MET, 1.0 to 2.0 MET, > 2.0 MET (Table 1). ILI participants represented only 37% of those with no fitness improvement, increasing to 79% of persons with fitness gain > 2.0 MET. Similarly, persons with large fitness improvements were more likely to be men, white, of younger age, less likely to have CVD, have lower BMI, and have lower systolic blood pressure than those with no fitness improvement.

Analyses with ILI and DSE groups combined

In multivariate analyses (adjusting for adjusting for age, sex, baseline weight or baseline fitness, insulin use, diabetes duration, CVD history, LDL, SBP, DBP, smoking), combining participants in the DSE and ILI groups, those who lost at least 10% of body weight in the first year had a 21% lower risk of the primary outcome (HR=0.79, 95% CI, 0.64 to 0.98) and a 24% reduced risk of the secondary outcome (HR=0.76, 95% CI, 0.63 to 0.91) compared to those with stable weight/weight gain (Table 2). There was a significant association of weight change with CVD incidence across the full spectrum of weight loss groups for the secondary outcome (p for trend=0.006) but not the primary outcome (p for trend=0.17).

Greater increases in fitness were associated with a reduced incidence of CVD for both the primary outcome (p for trend=0.03) and the secondary outcome (p for trend=0.003). Specifically, a > 2 MET increase in fitness was associated with a reduced risk of the secondary outcome (HR=0.77, 95% CI, 0.61 – 0.96) but not the primary outcome (HR=0.78, 0.60 – 1.03). Analyses of the association of weight loss and fitness change with Look AHEAD's other pre-specified secondary outcomes (Appendix Table 3) were similar to the outcomes described above.

In analyses within DSE and ILI groups (Appendix Tables 1–2), HRs for the primary and secondary CVD outcomes associated with weight loss and fitness change were similar and there was no significant interactions of weight change or fitness change by intervention group with regard to their effect on the primary or secondary outcome. However, the associations of weight change and fitness change with CVD incidence were only significant for the ILI group, as there were more people in the large weight loss and fitness groups in ILI than in DSE, for which confidence intervals were broad.

Analyses Comparing ILI Weight and Fitness Change Groups to DSE as Referent

In multivariate analyses of the primary outcome (adjusting for age, sex, baseline weight or baseline fitness, insulin use, diabetes duration, CVD history, LDL, SBP, DBP, smoking), and treating the DSE group as the referent group, ILI participants with > 10% weight loss had a 20% reduced risk of the primary outcome (HR=0.80, 95% CI, 0.65 to 0.99) and a 21% reduced risk of the secondary outcome (HR=0.79, 95% CI, 0.66–0.95) (Table 3). Persons with a weight gain/stable weight had a 28% increased risk (HR=1.28, 95% CI, 1.01–1.64) of the secondary outcome (Table 3). Each SD of weight loss (about 7%) was associated with a 15% lower risk (HR =0.85, 95% CI, 0.76 – 0.95) of the primary outcome and 18% lower risk (HR=0.82, 95% CI, 0.74 – 0.90) of the secondary outcome compared to the DSE group (Table 2). Analyses of the association of weight loss and fitness change with Look

AHEAD's other pre-specified secondary outcomes were similar to the outcomes described above (Appendix Table 4).

Compared to persons in the DSE groups, there were no significant differences in risk of either the primary or secondary outcome according to the level of ILI-related fitness change. We also found no evidence of a non-linear relationship between weight change or fitness change and CVD incidence and no significant interactions between weight loss or fitness change and race/ethnicity, sex, or history of CVD at baseline.

DISCUSSION

In these secondary analyses of the overall cohort (ILI and DSE participants combined), achievement of a 10% weight loss or a 2 MET fitness increase in the first year was associated with an approximate 20% reduced CVD risk while there was no association of small or moderate weight loss with CVD risk. Analyses comparing ILI participants who met the 10% weight loss goal to the full group of DSE participants yielded a similar reduction in CVD incidence. As such, this is one of the first studies to-date, of either observational or randomized design, to observe an association of lifestyle-based weight loss with reduced CVD incidence. Significant reductions in CVD mortality reduction were observed in the Da Qing Diabetes Prevention Follow-up Study and reducing in CVD incidence from Mediterranean diet in the PREDIMED Study, although those trials were conducted in largely non-diabetic populations and achieved the effect with modest or no weight loss (22, 23).

There are subtle but important differences in interpretation between the two analyses presented, that may complement the original null ITT findings. The analyses of the combined cohort suggest that greater weight loss or fitness gain, achieved through possibly diverse pathways including the study intervention, self-driven behavior change, or other patient characteristics, is associated with reduced CVD risk. The comparison between ILI weight loss response groups and DSE indicates that individuals who respond well to intervention by meeting the first-year intervention goals, have a 20% reduction in the CVD incidence compared to persons not receiving the intervention. These findings should not be confused with the primary intent-to-treat analysis, which showed that weight loss intervention had no significant effect on either the primary outcome or secondary outcomes. Taken together, these analyses suggest that the ILI in Look AHEAD did not achieve a large enough weight loss or fitness change among enough people to affect CVD incidence. However, these findings highlight the variation of reponses to lifestyle intervention, and resulting outcomes, that may result from lifestyle interntion.

The amount of weight loss that was associated with benefit (≥10% weight loss) in the overall cohort analysis was achieved by almost 40% of the lifestyle intervention participants. Previous Look AHEAD analyses have shown that attainment of the weight loss goal was associated with more consistent attendance at intervention sessions, and with higher levels of reported physical activity, lower caloric intake, and more consistent self-monitoring (16). That study also found that among persons who met the one-year weight loss goal of 10%, 42 percent maintained at least 10% weight loss and 70% maintained at least 5% weight loss at four years. Previous studies have also shown that the amount of weight change is generally

associated with the dosage of behavioral support, with optimal efficacy observed when supported by a multidisciplinary team of specialists in nutrition, exercise, and behavior change (15).

These findings should be interpreted cautiously because of the potential for unmeasured confounding and selection bias that remain in secondary analyses. For example, ILI participants with large weight loss may have better underlying health or health behaviors to facilitate weight loss, or could have more actively sought or received preventive health care. The observation that intervention participants who had stable weight or a small weight gain (14% of the sample) had a higher rate of the secondary outcome than DSE participants may be further evidence of this. These types of biases have been reflected in previous studies showing that persons who adhere to a placebo have better health outcomes than those who do not (24). Given these concerns, our findings should not be considered a modification of the primary conclusions of Look AHEAD, and causality cannot be inferred from these findings. Instead they should stimulate closer examination of the characteristics and factors underlying persons who respond particularly well to lifestyle intervention and whether there are practical ways of identifying them for referral for lifestyle interventions (18, 25).

Our study has some additional limitations. These analyses used one-year weight change because using a longer period of intervention response results in shorter follow-up after the period of intervention response assessment, considerably compromising statistical power. However, while one-year weight loss and fitness change are only proxies for sustained intervention response, shorter-term responses to intervention are highly correlated with longer-term responses term responses (26). These analyses were not intended to uncover the primary factors or covariates explaining the associations of weight change and fitness change with the study outcomes. In addition, our analyses did not adjust for randomization arm because of the high degree of collinearity between randomization arm and weight loss group, as 92% of the large weight loss group were ILI participants, and conversely 82% of the weight gain/weight stable group were DSE participants. However, our analyses adjusted for all variables that were observed to differ between the ILI and DSE groups, including CVD risk factors (blood pressure, lipid levels, smoking, CVD history) that have been consistently associated with CVD incidence. Of note, CVD history in this analysis was the most influential covariate, as its inclusion in the model strengthened the magnitude of association slightly by itself.

Although the current cohort study findings associate weight loss with reduced CVD incidence, they should not be interpreted to support 10% weight loss as a necessary target for lifestyle interventions in all settings. Previous RCTs have demonstrated large benefits on diabetes, hypertension, and disability with more modest weight loss (e.g., 5 to 7%) without major risks (6, 7, 11, 27, 28). Weight losses of 10% or greater may carry additional risk of adverse outcomes, including gallstone disease or bone loss in older adults (29) (30, 31). It is also noteworthy that the study sample had a very high baseline BMI (mean=36); although our analyses adjusted for baseline level of obesity, findings could conceivably differ in a leaner sample of adults with diabetes. Thus, recommendations related to the magnitude of weight loss should consider diverse factors, including the characteristics and needs of the participants, mode of weight loss, and the priority outcomes for prevention.

In summary, these secondary analyses, combined with the primary Look AHEAD study findings, lead to the following conclusions about the impact of intentional weight loss. First, as reported previously, the primary analyses using intention to treat indicate lifestyle intervention does not result in reduced CVD relative to DSE. However, analyses suggest that greater magnitude of weight loss was associated with lower CVD incidence in the total cohort and within ILI. These findings, combined with evidence for reduced incidence of diabetes, hypertension, disability, and other benefits indicate a need to continue to refine approaches to identify participants most likely to benefit from lifestyle interventions, and to develop strategies to improve the magnitude of sustained weight loss to lifestyle interventions (6, 11, 27).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding and Support

Funded by the National Institutes of Health through cooperative agreements with the National Institute of Diabetes and Digestive and Kidney Diseases: DK57136, DK57149, DK56990, DK57177, DK57171, DK57151, DK57182, DK57131, DK57002, DK57078, DK57154, DK57178, DK57219, DK57008, DK57135, and DK56992. Additional funding was provided by the National Heart, Lung, and Blood Institute; National Institute of Nursing Research; National Center on Minority Health and Health Disparities; NIH Office of Research on Women's Health; and the Centers for Disease Control and Prevention. This research was supported in part by the Intramural Research Program of the National Institute of Diabetes and Digestive and Kidney Diseases. The Indian Health Service (I.H.S.) provided personnel, medical oversight, and use of facilities. The opinions expressed in this paper are those of the authors and do not necessarily reflect the views of the I.H.S. or other funding sources.

Additional support was received from The Johns Hopkins Medical Institutions Bayview General Clinical Research Center (M01RR02719); the Massachusetts General Hospital Mallinckrodt General Clinical Research Center and the Massachusetts Institute of Technology General Clinical Research Center (M01RR01066); the University of Colorado Health Sciences Center General Clinical Research Center (M01RR00051) and Clinical Nutrition Research Unit (P30 DK48520); the University of Tennessee at Memphis General Clinical Research Center (M01RR0021140); the University of Pittsburgh General Clinical Research Center (GCRC) (M01RR000056), the Clinical Translational Research Center (CTRC) funded by the Clinical & Translational Science Award (UL1 RR 024153) and NIH grant (DK 046204); the VA Puget Sound Health Care System Medical Research Service, Department of Veterans Affairs; and the Frederic C. Bartter General Clinical Research Center (M01RR01346).

The following organizations have committed to make major contributions to Look AHEAD: FedEx Corporation; Health Management Resources; LifeScan, Inc., a Johnson & Johnson Company; OPTIFAST® of Nestle HealthCare Nutrition, Inc.; Hoffmann-La Roche Inc.; Abbott Nutrition; and Slim-Fast Brand of Unilever North America.

Some of the information contained herein was derived from data provided by the Bureau of Vital Statistics, New York City Department of Health and Mental Hygiene.

Appendix

Appendix Table 1

Primary and Secondary Outcomes Associated with Percent Weight Change, Stratified by Randomization Group

	Weight Change Groups (percent weight loss in first year)				
ILI Group	**Gain /Stable (<2% loss)**	**Small Loss (2 to 5%)**	**Medium Loss (5 to 10%)**	**Large Loss (≥10%)**	**Test for Trend**

Primary Outcome					
Events / person years	58 / 3096	69 / 3766	114 / 6446	120 / 8257	
Crude rate/100 person years	1.87	1.83	1.77	1.45	
Unadjusted HR (95% C.I.)	REF	0.94 (0.66 – 1.33)	0.91 (0.66 – 1.25)	0.72 (0.52 – 0.99)*	0.03
Adjusted HR ≠ (95% C.I.)	REF	0.78(0.54 – 1.13)	0.89 (0.63 – 1.25)	0.61 (0.44 – 0.86)*	0.007
Secondary Outcome					
Events / person years	82 / 3018	108 / 3643	151 / 6335	173 / 8127	
Crude rate/100 person years	2.72	2.96	2.38	2.13	
Unadjusted HR (95% C.I.)	REF	1.04 (0.78 – 1.39)	0.84 (0.64 – 1.10)	0.73 (0.56 – 0.96)*	0.003
Adjusted HR ≠ (95% C.I.)	REF	0.90 (0.67 – 1.22)	0.79 (0.59 – 1.05)	0.61 (0.45 – 0.80)*	<0.0001
	Weight Change Groups (percent weight loss in first year)				
DSE Group	**Gain /Stable (<2% loss)**	**Small Loss (2 to 5%)**	**Medium Loss (5 to 10%)**	**Large Loss (≥10%)**	**Test for Trend**
Primary Outcome					
Events / person years	231 / 13978	72 / 4104	40 / 2124	8 / 685	
Crude rate/100 person years	1.65	1.75	1.88	1.17	
Unadjusted HR (95% C.I.)	REF	1.10 (0.84 – 1.43)	1.16 (0.82 – 1.62)	0.72 (0.35 – 1.45)	0.82
Adjusted HR ≠ (95% C.I.)	REF	1.17 (0.89 – 1.54)	1.26 (0.88 – 1.79)	0.71 (0.33 – 1.51)	0.51
Secondary Outcome					
Events / person years	340 / 13681	98 / 4014	52 / 2076	13 / 665	
Crude rate/100 person years	2.49	2.44	2.50	1.95	
Unadjusted HR (95% C.I.)	REF	1.02 (0.81 – 1.27)	1.03 (0.77 – 1.38)	0.80 (0.46 – 1.40)	0.76
Adjusted HR ≠ (95% C.I.)	REF	1.01 (0.79 – 1.27)	0.99 (0.73 – 1.35)	0.77 (0.42 – 1.42)	0.67

≠adjusted for sex, age, baseline weight(percent weight loss models), baseline fitness (fitness change models),CVD history, insulin use, diabetes duration, smoking status, LDL, SBP, DBP. Primary Outcome: (non-fatal MI, stroke, hospitalized angina, CVD death); Secondary Outcome: (non-fatal MI, stroke, hospitalized angina, CABG/PTCA, hospitalized CHF, carotid endarterectomy, PVD, total mortality)

Appendix Table 2

Primary and Secondary Outcomes Associated with Fitness Change, Stratified by Randomization Group.

	Fitness Change Groups (METs change in first-year)				
ILI Group	**Loss/Stable (<0.5)**	**Small Gain (0.5 to 1.0)**	**Medium Gain (1.0 to 2.0)**	**Large Gain (≥2.0)**	**Test for Trend**
Primary Outcome					
Events / person years	139 / 7731	53 / 3082	64 / 4744	59 / 4190	

Crude rate/100 person years	1.80	1.72	1.35	1.41	
Unadjusted HR (95% C.I.)	REF	0.93 (0.68 – 1.28)	0.74 (0.55 – 0.99)*	0.78 (0.57 – 1.07)	0.04
Adjusted HR ǂ (95% C.I.)	REF	0.91 (0.65 – 1.27)	0.74 (0.54 – 1.01)	0.80 (0.58 – 1.12)	0.08
Secondary Outcome					
Events / person years	197 / 7564	78 / 3041	92 / 4663	86 / 4111	
Crude rate/100 person years	2.60	2.57	1.97	2.09	
Unadjusted HR (95% C.I.)	REF	0.95 (0.73 – 1.24)	0.74 (0.58 – 0.95)*	0.79 (0.61 – 1.03)	0.02
Adjusted HR ǂ (95% C.I.)	REF	0.95 (0.72 – 1.25)	0.70 (0.54 – 0.91)*	0.80 (0.61 – 1.06)	0.02

	Fitness Change Groups (METs change in first-year)				
DSE Group	**Loss/Stable (<0.5)**	**Small Gain (0.5 to 1.0)**	**Medium Gain (1.0 to 2.0)**	**Large Gain (≥2.0)**	**Test for Trend**
Primary Outcome					
Events / person years	208 / 12266	42 / 3009	38 / 2439	13 / 1122	
Crude rate/100 person years	1.70	1.40	1.56	1.16	
Unadjusted HR (95% C.I.)	REF	0.80 (0.57 – 1.12)	0.89 (0.63 – 1.26)	0.65 (0.37 – 1.13)	0.09
Adjusted HR ǂ (95% C.I.)	REF	0.77 (0.54 – 1.10)	0.98 (0.68 – 1.40)	0.66 (0.37 – 1.17)	0.19
Secondary Outcome					
Events / person years	307 / 12032	53 / 2955	307 / 12032	14 / 1109	
Crude rate/100 person years	2.55	1.79	2.22	1.26	
Unadjusted HR (95% C.I.)	REF	0.68 (0.51 – 0.91)*	0.86 (0.64 – 1.16)	0.49 (0.28 – 0.83)*	0.003
Adjusted HR ǂ (95% C.I.)	REF	0.69 (0.51 – 0.93)*	0.90 (0.66 – 1.23)	0.54 (0.31 – 0.94)*	0.02

ǂ adjusted for sex, age, baseline weight(percent weight loss models), baseline fitness (fitness change models), CVD history, insulin use, diabetes duration, baseline fitness smoking status, LDL, SBP, DBP. Primary Outcome: (non-fatal MI, stroke, hospitalized angina, CVD death); Secondary Outcome: (non-fatal MI, stroke, hospitalized angina, CABG/PTCA, hospitalized CHF, carotid endarterectomy, PVD, total mortality

Appendix Table 3

Association of weight change and fitness change with additional Look AHEAD Pre-specified Secondary Outcomes.

	Weight Change Groups (percent weight loss in first year)				
	Gain /Stable (<2% loss)	**Small Loss (2 to 5%)**	**Medium Loss (5 to 10%)**	**Large Loss (≥10%)**	**Test for Trend**
Secondary Outcome 1					
Events / person years	198 / 17563	87 / 8139	113 / 8785	76 / 9171	
Crude rate/100 person years	1.13	1.07	1.29	0.83	
Unadjusted HR (95% C.I.)	1.0	0.96 (0.75 – 1.24)	1.16 (0.92 – 1.46)	0.71 (0.55 – 0.93)*	0.12

Adjusted HR ǂ (95% C.I.)	1.0	0.94 (0.73 – 1.22)	1.24 (0.97 – 1.57)	0.69 (0.53 – 0.91) *	0.12
Secondary Outcome 2					
Events / person years	369 / 17076	175 / 7870	179 / 8570	167 / 8941	
Crude rate/100 person years	2.16	2.22	2.09	1.87	
Unadjusted HR (95% C.I.)	1.0	1.04 (0.87 – 1.25)	0.98 (0.82 – 1.17)	0.85 (0.71 – 1.02)	0.11
Adjusted HR ǂ (95% C.I.)	1.0	1.03 (0.86 – 1.24)	1.03 (0.86 – 1.24)	0.80 (0.66 – 0.97) *	0.06
	Fitness Change Groups (METs change in first-year)				
	Loss/Stable (<0.5)	**Small Gain (0.5 to 1.0)**	**Medium Gain (1.0 to 2.0)**	**Large Gain (≥2.0)**	**Test for Trend**
Secondary Outcome 1					
Events / person years	239 / 20579	65 / 6240	69 / 7335	37 / 5461	
Crude rate/100 person years	1.16	1.04	0.94	0.68	
Unadjusted HR (95% C.I.)	1.0	0.88 (0.67 – 1.15)	0.80 (0.61 – 1.04)	0.56 (0.40 – 0.80) *	0.0008
Adjusted HR ǂ (95% C.I.)	1.0	0.86 (0.64 – 1.14)	0.85 (0.64 – 1.12)	0.59 (0.41 – 0.85) *	0.0051
Secondary Outcome 2					
Events / person years	778 / 19997	119 / 6091	123 / 7184	85 / 5312	
Crude rate/100 person years	2.23	1.95	1.71	1.60	
Unadjusted HR (95% C.I.)	1.0	0.86 (0.70 – 1.05)	0.75 (0.62 – 0.92) *	0.70 (0.55 – 0.88) *	0.0002
Adjusted HR ǂ (95% C.I.)	1.0	0.85 (0.69 – 1.05)	0.77 (0.62 – 0.94) *	0.73 (0.57 – 0.93) *	0.0013

ǂ adjusted for sex, age, baseline weight(weight change models), baseline fitness (fitness change models),CVD history, insulin use, diabetes duration, smoking status, LDL, SBP, DBP.

* P< 0.05

Secondary Outcome 1: (MI, stroke, CVD Death); Secondary Outcome 2: (non-fatal MI, stroke, hospitalized angina, CVD death, total mortality)

Appendix Table 4

Association of weight change and fitness change with additional Look AHEAD Pre-specified Secondary Outcomes. Comparison of DSE Condition (Referent Group) with ILI weight loss and fitness change groups.

		ILI Weight Change Groups (percent weight loss in first year)					
	Overall DSE	**Gain /Stable (<2% loss)**	**Small Loss (2 to 5%)**	**Medium Loss (5 to 10%)**	**Large Loss (≥10%)**	**HR per SD weight change**	**P value**
Secondary Outcome 1							
Events / person years	239 / 21478	38 / 3203	46 / 3872	81 / 6617	70 / 8488		

Crude rate/100 person years	1.11	1.19	1.19	1.22	0.82		
Unadjusted HR (95% C.I.)	1.0	1.08 (0.76 – 1.53)	1.08 (0.79 – 1.48)	1.18 (0.87 – 1.44)	0.72 (0.55 – 0.94)*	0.87 (0.76 – 0.99)	0.03
Adjusted HR ǂ(95% C.I.)	1.0	1.15 (0.80 – 1.65)	1.06 (0.77 – 1.46)	1.22 (0.94 – 1.59)	0.70 (0.54 – 0.92)*	0.85 (0.74 – 0.98)	0.03
Secondary Outcome 2							
Events / person years	449 / 20892	69 / 3088	86 / 3766	132 / 6447	154 / 8266		
Crude rate/100 person years	2.15	2.23	2.28	2.05	1.86		
Unadjusted HR (95% C.I.)	1.0	1.07 (0.83 – 1.38)	1.07 (0.85 – 1.35)	0.96 (0.79 – 1.17)	0.85 (0.71 – 1.02)	0.90 (0.81 – 0.99)	0.02
Adjusted HR ǂ(95% C.I.)	1.0	1.22 (0.93 – 1.58)	1.04 (0.82 – 1.32)	1.02 (0.84 – 1.25)	0.80 (0.66 – 0.97)*	0.86 (0.78 – 0.95)	0.003

		ILI Fitness Change Groups (METs change in first-year)					
	Overall DSE	**Loss/Stable (<0.5)**	**Small Gain (0.5 to 1.0)**	**Medium Gain (1.0 to 2.0)**	**Large Gain (≥2.0)**	**HR per SD fitness change**	**P value**
Secondary Outcome 1							
Events / person years	208 / 19521	104 / 8257	35 / 3172	39 / 4856	31 / 4312		
Crude rate/100 person years	1.07	1.26	1.10	0.80	0.72		
Unadjusted HR (95% C.I.)	1.0	1.20 (0.95 – 1.52)	1.03 (0.72 – 1.47)	0.75 (0.53 – 1.05)	0.66 (0.45 – 0.96)	0.83 (0.72 – 0.97)	0.02
Adjusted HR ǂ(95% C.I.)	1.0	1.22 (0.96 – 1.56)	1.04 (0.72 – 1.51)	0.79 (0.55 – 1.12)	0.69 (0.47 – 1.03)	0.82 (0.70 – 0.97)	0.02
Secondary Outcome 2							
Events / person years	385 / 19026	183 / 8025	69 / 3081	77 / 4744	72 / 4190		
Crude rate/100 person years	2.02	2.28	2.24	1.62	1.72		
Unadjusted HR (95% C.I.)	1.0	1.15 (0.97 – 1.37)	1.09 (0.85 – 1.41)	0.80 (0.62 – 1.02)	0.84 (0.65 – 1.08)	0.90 (0.81 – 0.99)	0.047
Adjusted HR ǂ(95% C.I.)	1.0	1.16 (0.97 – 1.39)	1.11 (0.85 – 1.44)	0.79 (0.62 – 1.02)	0.87 (0.67 – 1.14)	0.90 (0.80 – 1.01)	0.08

ǂadjusted for sex, age, baseline weight(weight change models), baseline fitness (fitness change models), CVD history, insulin use, diabetes duration, smoking status, LDL, SBP, DBP. Secondary Outcome 1: (MI, stroke, CVD Death); Secondary Outcome 2: (non-fatal MI, stroke, hospitalized angina, CVD death, total mortality).

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Appendix: Look AHEAD Research Group at End of Intervention

Updated 08/11/2015

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Research in context

Evidence before this study

Randomized controlled trials (RCTs) have shown that lifestyle interventions lead to diverse benefits among persons with diabetes, improved glycemic control (4–9) but the Look AHEAD Study found no significant effect on CVD morbidity and mortality (9, 11–13). It remains unclear, however, whether the impact of the intervention depends upon the magnitude of weight loss, fitness change, or response to the intervention. Authors searched PubMed for randomized controlled trials and quasi-experimental studies from 1990 to 2016 as background data.

Added value of this study

These secondary analyses of the Look AHEAD study found that achievement of a 10% weight loss or a 2 MET fitness increase in the first year was associated with an approximate 20% reduced CVD risk while there was no association of small or moderate weight loss with CVD risk. Analyses comparing ILI participants who met the 10% weight loss goal to the full group of DSE participants yielded a similar reduction in CVD incidence. These analyses suggest that greater magnitude of weight loss was associated with lower CVD incidence, and that Look AHEAD did not achieve a large enough weight loss or fitness change among enough people to affect CVD incidence.

Implications of all the available evidence

These findings, combined with evidence for reduced incidence of diabetes, hypertension, disability, and other benefits indicate a need to continue to refine approaches to identify participants most likely to benefit from lifestyle interventions, and to develop strategies to improve the magnitude of sustained weight loss to lifestyle interventions.

Lancet Diabetes Endocrinol. Author manuscript; available in PMC 2017 November 01.

Table 1

Comparison of Baseline Characteristics According to Magnitude of First-year Weight Change and Fitness Change in the Overall Look AHEAD Sample.

	Weight Change Groups (percent weight loss in first year)				
	Gain /Stable (<2% loss)	**Small Loss (2 to 5%)**	**Medium Loss (5 to 10%)**	**Large Loss (>10%)**	**P Value**
N (%)	1972 (40.3)	914 (18.7)	1000 (20.4)	1013 (20.7)	
ILI Group (%)	18.2	47.4	74.9	92.0	
Men (%)	40.5	39.2	38.7	43.9	0.07
Non-white (%)	38.7	41.9	37.4	26.7	<0.0001
Age (mean years)	58.4	58.9	58.7	59.3	0.004
History of CVD (%)	14.3	14.0	12.2	13.8	0.46
Using Insulin (%)	17.9	15.7	12.9	13.9	0.002
Smoking: Never (%)	52.2	50.7	50.4	47.5	0.11
Current (%)	3.7	5.4	4.7	4.1	
Duration of Diabetes (mean years)	6.8	6.9	6.6	6.8	0.45
BMI (mean kg/m^2)	35.9	35.8	35.8	36.1	0.34
LDL Cholesterol (mean mg/DL)	112.7	113.9	110.8	110.3	0.03
SBP (mean mm/Hg)	128.6	129.7	128.7	128.4	0.12
DBP (mean mm/Hg)	70.2	70.8	70.4	69.1	0.004
1-y Change in weight (mean %)	1.6	−3.5	−7.3	−15.8	NA
1-y fitness change (mean METs)	0.1	0.4	0.7	1.5	<0.0001
	Fitness Change Groups (METs change in first-year)				
	Loss/Stable (<0.5)	**Small Gain (0.5 to 1.0)**	**Medium Gain (1.0 to 2.0)**	**Large Gain (>2.0)**	**P Value**
N (%)	2306 (52.3)	701 (15.9)	812 (18.4)	591 (13.4)	
ILI Group (%)	36.9	51.5	65.6	79.4	
Men (%)	37.8	38.8	43.1	52.8	<0.0001
Non-white (%)	38.6	36.2	31.5	30.3	<0.0001
Age (mean years)	59.4	58.3	58.2	57.4	<0.0001
History of CVD (%)	14.6	14.3	10.7	10.8	0.008

Using Insulin (%)	15.4	16.3	15.8	11.2	0.05
Smoking: Never (%)	52.0	53.2	47.7	47.0	0.06
Current (%)	3.7	4.6	4.7	3.6	
Duration of Diabetes (mean years)	6.8	7.0	6.4	6.4	0.18
BMI (mean kg/m^2)	35.9	36.0	36.0	34.9	0.001
LDL Cholesterol (mean mg/DL)	112.0	112.3	112.5	110.3	0.50
SBP (mean mm/Hg)	128.7	129.4	129.1	126.4	0.01
DBP (mean mm/Hg)	69.8	70.5	70.2	70.8	0.11
1-y Change in weight (mean %)	−2.4	−5.2	−7.4	−11.3	<0.0001
1-y fitness change (mean METs)	−0.3	0.7	1.4	2.9	NA

* P-values obtained using the Kruskal-Wallis test for continuous variables and Chi-square test for categorical variables.

Table 2

Primary and Secondary Outcomes Associated with Percent Weight Change and Fitness Change: Overall Sample (ILI and DSE Combined)

	Weight Change Groups (percent weight loss in first year)				
	Gain /Stable (<2% loss)	**Small Loss (2 to 5%)**	**Medium Loss (5 to 10%)**	**Large Loss (≥10%)**	**Test for Trend**
Primary Outcome					
Events / person years	289 / 17075	141 / 7870	154 / 8570	128 / 8942	
Crude rate/100 person years	1.69	1.79	1.80	1.43	
Unadjusted HR (95% C.I.)	1.0	1.07 (0.88 – 1.31)	1.07 (0.88 – 1.31)	0.83 (0.67–1.02)	0.21
Adjusted HR ǂ (95% C.I.)	1.0	1.08 (0.88 – 1.33)	1.16 (0.95 – 1.42)	0.79 (0.64–0.98) *	0.17
Secondary Outcome					
Events / person years	422 / 16699	206 / 7657	203 / 8411	186 / 8792	
Crude rate/100 person years	2.53	2.69	2.41	2.12	
Unadjusted HR (95% C.I.)	1.0	1.08 (0.91– 1.27)	0.96(0.81– 1.13)	0.83 (0.70 – 0.99) *	0.04
Adjusted HR ǂ (95% C.I.)	1.0	1.05 (0.88 – 1.25)	0.97 (0.82 – 1.16)	0.76 (0.63 – 0.91) *	0.006
	Fitness Change Groups (METs change in first-year)				
	Loss/Stable (<0.5)	**Small Gain (0.5 to 1.0)**	**Medium Gain (1.0 to 2.0)**	**Large Gain (≥2.0)**	**Test for Trend**
Primary Outcome					
Events / person years	347 / 19997	95 / 6091	102 / 7183	72 / 5312	
Crude rate/100 person years	1.74	1.56	1.42	1.36	
Unadjusted HR (95% C.I.)	1.0	0.88 (0.70 – 1.10)	0.80 (0.64 – 1.00)	0.76 (0.59 – 0.98) *	0.009
Adjusted HR ǂ (95% C.I.)	1.0	0.87 (0.68 – 1.10)	0.83 (0.66 – 1.05)	0.78 (0.60 – 1.03)	0.03
Secondary Outcome					
Events / person years	504 / 19596	131 / 5996	145 / 7056	100 / 5220	
Crude rate/100 person years	2.57	2.18	2.05	1.92	
Unadjusted HR (95% C.I.)	1.0	0.83 (0.69 – 1.01)	0.79 (0.65 – 0.95) *	0.73 (0.59 – 0.91) *	0.0005
Adjusted HR ǂ (95% C.I.)	1.0	0.84 (0.69 – 1.02)	0.79 (0.65 – 0.96) *	0.77 (0.61 – 0.96) *	0.0031

≠ adjusted for sex, age, baseline weight (weight change models), baseline fitness (fitness change models),CVD history, insulin use, diabetes duration, smoking status, LDL, SBP, DBP. Primary Outcome: (non-fatal MI, stroke, hospitalized angina, CVD death); Secondary Outcome: (non-fatal MI, stroke, hospitalized angina, CABG/PTCA, hospitalized CHF, carotid endarterectomy, PVD, total mortality);

* $P < 0.05$

Table 3

Primary and Secondary Outcomes Associated with Percent Weight Loss and Fitness Change over the First Year: Comparison of DSE Condition (Referent Group) with ILI weight loss and fitness change groups.

		ILI Weight Change Groups (percent weight loss in first year)					
	Overall DSE	**Gain /Stable (<2% loss)**	**Small Loss (2 to 5%)**	**Medium Loss (5 to 10%)**	**Large Loss (>10%)**	**HR per SD weight change**	**P value**
Primary Outcome							
Events / person years	351 / 20891	58 / 3087	69 / 3766	114 / 6446	120 / 8266		
Crude rate/100 person years	1.68	1.88	1.83	1.77	1.45		
Unadjusted HR (95% C.I.)	1.0	1.14 (0.86– 1.51)	1.09 (0.85 – 1.42)	1.06 (0.86 – 1.31)	0.84 (0.68 – 1.04)	0.88 (0.79 – 0.98)	0.02
Adjusted HR ǂ (95% C.I.)	1.0	1.29 (0.96 – 1.72)	1.04 (0.80 – 1.36)	1.15 (0.92 – 1.43)	0.80 (0.65 – 0.99)*	0.85 (0.76 – 0.95)	0.006
Secondary Outcome							
Events / person years	503 / 20436	82 / 3009	108 / 3643	151 / 6335	173 / 8136		
Crude rate/100 person years	2.46	2.72	2.96	2.38	2.13		
Unadjusted HR (95% C.I.)	1.0	1.14 (0.90 – 1.44)	1.22 (0.99 – 1.50)	0.97 (0.81 – 1.17)	0.85 (0.72 –1.02)	0.86 (0.78 – 0.94)	0.0007
Adjusted HR ǂ (95% C.I.)	1.0	1.28 (1.01 – 1.64)*	1.19 (0.96 – 1.47)	1.02 (0.84 – 1.23)	0.79 (0.66 – 0.95)*	0.82 (0.74 – 0.90)	<0.0001
		ILI Fitness Change Groups (METs change in first-year)					
	Overall DSE	**Loss/Stable (<0.5)**	**Small Gain (0.5 to 1.0)**	**Medium Gain (1.0 to 2.0)**	**Large Gain (>2.0)**	**HR per SD fitness change**	**P value**
Primary Outcome							
Events / person years	303 / 19025	148 / 8025	53 / 3081	64 / 4743	59 / 4190		
Crude rate/100 person years	1.59	1.84	1.72	1.35	1.41		
Unadjusted HR (95% C.I.)	1.0	1.18 (0.97 – 1.43)	1.06 (0.79 – 1.42)	0.84 (0.64 – 1.10)	0.87 (0.66 – 1.15)	0.90(0.80 –1.01)	0.08
Adjusted HR ǂ (95% C.I.)	1.0	1.19 (0.97 – 1.46)	1.06 (0.78 – 1.43)	0.85 (0.64 – 1.13)	0.90 (0.68 – 1.21)	0.91(0.80 – 1.03)	0.15
Secondary Outcome							
Events / person years	433 / 18657	211 / 7844	78 / 3041	92 / 4663	86 / 4111		
Crude rate/100 person years	2.32	2.69	2.57	1.97	2.09		
Unadjusted HR (95% C.I.)	1.0	1.18 (1.00 – 1.39)*	1.09 (0.86 – 1.39)	0.85(0.68 – 1.06)	0.90 (0.71 – ;1.13)	0.91 (0.83 – 1.01)	0.07

Adjusted HR ≠ (95% C.I.)	1.0	1.17 (0.99 – 1.39)	1.08 (0.84 – 1.38)	0.83 (0.66 – 1.05)	0.93 (0.73 – 1.18)	0.92 (0.83 – 1.02)	0.12

≠adjusted for sex, age, baseline weight (weight change models), baseline fitness (fitness change models), CVD history, insulin use, diabetes duration, smoking status, LDL, SBP, DBP. Primary Outcome: (non-fatal MI, stroke, hospitalized angina, CVD death); Secondary Outcome: (non-fatal MI, stroke, hospitalized angina, CABG/PTCA, hospitalized CHF, carotid endarterectomy, PVD, total mortality).