Four-Year Change in Cardiorespiratory Fitness and Influence on Glycemic Control in Adults With Type 2 Diabetes in a Randomized Trial

The Look AHEAD Trial

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OBJECTIVE—To examine an intensive lifestyle intervention (ILI) compared with diabetes support and education (DSE) on 4-year change in fitness and physical activity (PA), and to examine the effect of change in fitness and PA, adjusting for potential confounders, on glycemic control in the Look AHEAD Trial.

RESEARCH DESIGN AND METHODS—Subjects were overweight/obese adults with type 2 diabetes mellitus (T2DM) with available fitness data at 4 years ($n = 3{,}942$). This clinical trial randomized subjects to DSE or ILI. DSE subjects received standard care plus information related to diet, PA, and social support three times per year. ILI subjects received weekly intervention contact for 6 months, which was reduced over the 4-year period, and were prescribed diet and PA. Measures included weight, fitness, PA, and HbA_{1c}.

RESULTS—The difference in percent fitness change between ILI and DSE at 4 years was significant after adjustment for baseline fitness and change in weight (3.70 vs. 0.94%; $P < 0.01$). At 4 years, PA increased by 348 (1,562) kcal/week in ILI vs. 105 (1,309) kcal/week in DSE ($P < 0.01$). Fitness change at 4 years was inversely related to change in HbA_{1c} after adjustment for clinical site, treatment, baseline HbA_{1c}, prescribed diabetes medication, baseline fitness, and weight change ($P < 0.01$). Change in PA was not related to change in HbA_{1c}.

CONCLUSIONS—A 4-year ILI increased fitness and PA in overweight/obese individuals with T2DM. Change in fitness was associated with improvements in glycemic control, which provides support for interventions to improve fitness in adults with T2DM.

Diabetes Care 36:1297–1303, 2013

Type 2 diabetes mellitus (T2DM) is an increasing health concern in the U.S., and it is projected that the prevalence of this disease could exceed 13% in adults >20 years of age by the year 2021 (1). This is of significant public health concern because of the known association between diabetes and cardiovascular disease (CVD) (2). The Look AHEAD Trial is a multicenter clinical trial that was undertaken to examine the effect of weight loss and fitness on CVD end points in individuals with T2DM. The year 4 outcomes of the Look AHEAD Trial, which were reported recently, demonstrated the effects of an intensive lifestyle intervention (ILI) compared with a diabetes support and education (DSE) intervention on weight loss and CVD risk factors, where weight loss was significantly greater in ILI compared with DSE (3).

An important component of the Look AHEAD Trial was the use of objective measures of fitness on all individuals randomized to participate in this study. We previously reported that fitness was significantly increased in ILI compared with DSE after 1 year of intervention (4), and that fitness remained significantly higher in ILI compared with DSE after 4 years of participation in this study (3). These are important findings because others (5) have reported a reduction in the risk of CVD mortality associated with higher levels of fitness.

The findings reported herein expand on those cited above in which we examine *1)* the 4-year change in fitness controlling for baseline fitness, weight loss, and various demographic characteristics, *2)* the 4-year change in physical activity (PA), *3)* the association between change in fitness, independent of change in body weight and other potential confounders, and glycemic control, and *4)* the association between change in PA, independent of change in body weight and other potential confounders, on glycemic control.

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Received 14 April 2012 and accepted 2 October 2012.
DOI: 10.2337/dc12-0712. Clinical trial reg. no. NCT00017953, clinicaltrials.gov.
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc12-0712/-/DC1.

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RESEARCH DESIGN AND METHODS

Trial design

The Look AHEAD Trial is a randomized clinical trial designed to examine the effects of an ILI compared with a DSE intervention on the incidence of major CVD events. Specifics of the Look AHEAD Trial design have been published previously (6). Data were collected across 16 clinical sites.

Subjects

A detailed description of the baseline characteristics and eligibility of subjects in the Look AHEAD Trial has previously been published (6). At baseline, all subjects were diagnosed as having T2DM. Data were available from 3,942 subjects who completed the assessment of fitness at baseline and year 4, which represents 76.6% of the subjects recruited and randomized into the Look AHEAD Trial. Descriptive data of subjects are presented in Table 1. Reasons for missing fitness data at year 4 are presented in Fig. 1.

Intervention

ILI. ILI included a combination of group and individual sessions weekly for months 1–6. ILI participants attended two group meetings and one individual session per month, and one motivational campaign to promote adherence to the recommended weight loss behaviors, during months 7–12. During months 13–48, ILI participants were to have in-person monthly contact with their lifestyle counselor and monthly contact by telephone or e-mail and were offered two refresher campaigns each year that involved ancillary intervention classes. The focus of the ILI was to implement behavioral strategies that would facilitate adoption and maintenance of eating and PA behaviors that result in weight loss (7). Medical care and diabetes treatment for participants in ILI continued to be provided by their personal physicians. Temporary reductions in medicines that could lead to hypoglycemia were permitted during periods of intensive weight loss intervention using a standardized treatment protocol by the local study staff that included physicians, nurses, and certified diabetes educators.

Dietary intervention. Participants were instructed to reduce their energy intake to 1,200–1,800 kcal/day depending on body weight. Dietary fat intake was prescribed at <30% of total energy intake,

Table 1—***Baseline demographic characteristics for participants with valid baseline and 4-year fitness data***

	Overall	DSE			ILI			
Variable	Mean	Overall	Males	Females	Overall	Males	Females	*P* value*
Age at baseline graded exercise test	58.39 (6.74) (n = 3,942)	58.45 (6.80) (n = 1,926)	59.65 (6.81) (n = 782)	57.64 (6.67) (n = 1,144)	58.33 (6.69) (n = 2,016)	59.62 (6.57) (n = 821)	57.45 (6.64) (n = 1,195)	0.57
BMI (kg/m^2)	35.63 (5.72) (n = 3,941)	35.64 (5.61) (n = 1,926)	34.74 (5.20) (n = 782)	36.27 (5.79) (n = 1,144)	35.63 (5.84) (n = 2,015)	34.99 (5.60) (n = 821)	36.08 (5.96) (n = 1,194)	0.95
Baseline weight (kg)	95.09 (19.08) (n = 3,875)	99.31 (18.67) (n = 1,883)	107.43 (17.78) (n = 768)	93.72 (17.16) (n = 1,115)	91.10 (19.60) (n = 1,992)	98.11 (18.64) (n = 812)	86.29 (19.98) (n = 1,180)	<0.0001
Diabetes duration	6.57 (6.30) (n = 3,884)	6.55 (6.09) (n = 1,907)	6.85 (5.97) (n = 776)	6.34 (6.17) (n = 1,131)	6.59 (6.50) (n = 1,977)	6.93 (6.53) (n = 804)	6.36 (6.48) (n = 1,173)	0.81
HbA$_{1c}$	7.24 (1.15) (n = 3,942)	7.24 (1.16) (n = 1,926)	7.22 (1.14) (n = 782)	7.26 (1.17) (n = 1,144)	7.23 (1.15) (n = 2,016)	7.20 (1.15) (n = 821)	7.26 (1.15) (n = 1,195)	0.81
Waist circumference	113.25 (13.85) (n = 3,936)	113.13 (13.44) (n = 1,922)	117.63 (12.96) (n = 780)	110.06 (12.89) (n = 1,142)	113.36 (14.24) (n = 2,014)	118.15 (13.87) (n = 819)	110.08 (13.54) (n = 1,195)	0.61
Baseline maximum METs	7.35 (1.97) (n = 3,941)	7.38 (1.99) (n = 1,925)	8.16 (2.14) (n = 782)	6.84 (1.68) (n = 1,143)	7.32 (1.95) (n = 2,016)	8.08 (2.08) (n = 821)	6.80 (1.66) (n = 1,195)	0.37
Baseline submaximal METs**	5.25 (1.54) (n = 3,942)	5.26 (1.55) (n = 1,926)	5.83 (1.64) (n = 782)	4.87 (1.35) (n = 1,144)	5.25 (1.53) (n = 2,016)	8.85 (1.62) (n = 821)	4.84 (1.31) (n = 1,195)	0.88

Data are mean (SD) unless otherwise indicated. **P* value represents the difference between DSE and ILI for overall subject comparisons. **Using the criteria for determining the change in fitness from baseline to 4 years

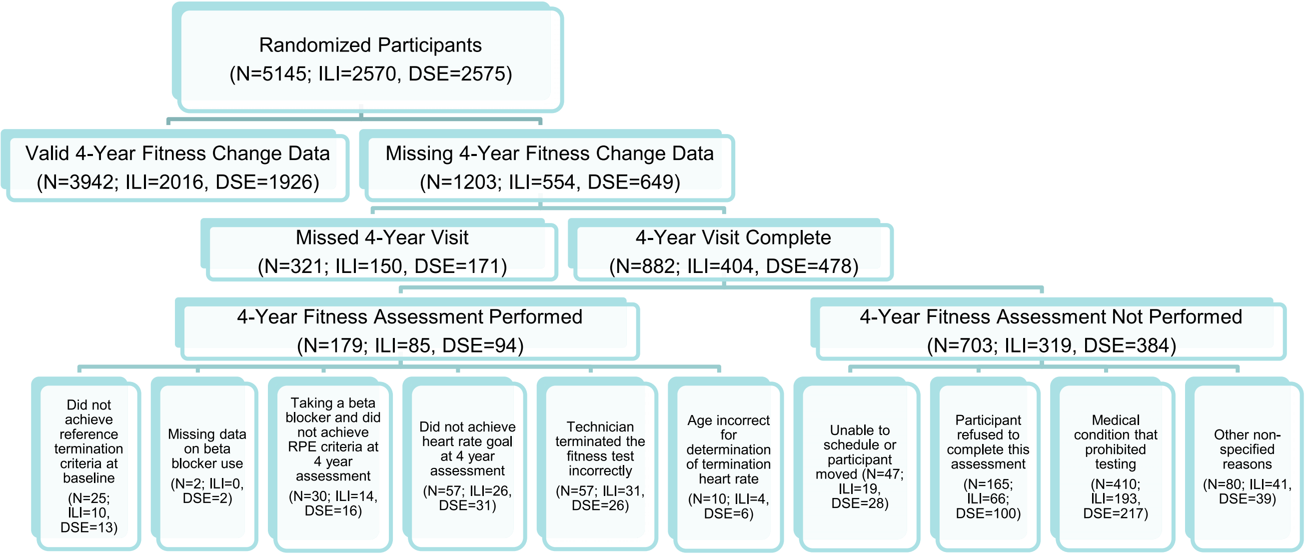

Figure 1—*Flowchart of participant randomization and completion of fitness testing.*

with <10% consumed as saturated fat. During weeks 3–20, prepackaged, commercially available liquid shakes and snack bars were provided to replace two meals per day at no cost to participants. After 16 weeks, the meal replacements provided to participants were reduced to one shake and one snack bar per day. Individuals who declined the use of the meal replacement options were provided detailed meal plans of conventional foods for their daily meals.

PA intervention. Participants were instructed initially to increase their PA to at least 50 min/week and progressively increase to at least 175 min/week by week 26 of the intervention. PA bouts of ≥10 min were counted toward the weekly activity goal, with intensity prescribed as moderate to vigorous (e.g., brisk walking). Resistance exercise was permitted to count up to 25% of the weekly activity goal. The PA intervention relied primarily on home-based forms of activity.

DSE

DSE participants were invited to attend three group sessions each year (years 1–4) that addressed topics related to diet, PA, and social support. However, DSE participants did not receive information on specific behavioral strategies regarding diet or PA that would result in weight loss or change in fitness. As in ILI, medical care and diabetes treatment for participants in DSE continued to be provided by their personal physician, with no medication adjustments made by study sites.

Assessments

Demographic characteristics. Baseline age, sex, ethnicity, duration of diabetes, and history of CVD were assessed via questionnaire.

Height, weight, BMI, and waist circumference. Height, weight, BMI, and waist girth were assessed using standardized procedures.

Cardiorespiratory fitness. A graded exercise treadmill test was scheduled to be performed on all randomized participants to assess cardiorespiratory fitness at baseline, 1 year, and 4 years. Fitness was also assessed in 25% of participants at 2 years to confirm that the intervention was successful at producing adequate changes in fitness as a component of the study stopping criteria. The protocol that was previously described for assessing change in fitness at year 1 was also implemented for the year 2 and 4 assessments of cardiorespiratory fitness (4). Fitness was defined as the estimated metabolic equivalent (MET) level based on the treadmill workload (i.e., speed and grade) achieved at the point of termination of the graded exercise test. The test was terminated when the participant reached 80% of age-predicted maximal heart rate (for those not taking a β-blocker) or attained a rating of 16 on the 15-category rating of perceived exertion (RPE) scale (8) (for those taking a β-blocker).

Leisure-time PA (LTPA). LTPA was assessed at baseline, year 1, and year 4 on a subsample of subjects using a questionnaire (9) that was completed as part of a structured interview. The sample was based on selected clinical sites including this questionnaire as part of their assessments for this study. Data collected on the flights of stairs climbed, number of city blocks walked, and other fitness, sport, and recreational activities performed during the week prior to the assessment visit were used to compute kilocalories per week of LTPA.

Glycemic control. Analysis of blood chemistry was performed at the Central Biochemistry Laboratory (Northwest Lipid Research Laboratories, University of Washington, Seattle, WA) using standardized laboratory procedures for HbA_{1c}. Blood samples were obtained after a 12-h fast.

Statistical analysis

Analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC) with the type I error rate fixed at 0.05. Among participants who had fitness data measured at the year 4 visit, we compared the two treatment groups (ILI and DSE) on the distributions of selected baseline characteristics using the generalized linear model implemented in PROC GLM. Defining completers as those with year 4 fitness measures and incompleters as those with missing data, we examined the differences in baseline characteristics between completers and incompleters, both overall and within each treatment group. Bivariate associations between percent change in fitness at year 4 and baseline characteristics, including age, sex, race/ethnicity, insulin use, diabetes medication use, HbA_{1c}, smoking status, metabolic syndrome, BMI, and waist circumference, were evaluated using either two-sample Student *t* test, ANOVA, or Spearman rank correlation test based on the distributions of baseline variables. A mixed-effects model with three time points, baseline to years 1, 2, and 4, was fit to model percent change in fitness as the outcome variable. Independent variables included treatment group, time, and group-by-time interaction. Covariates adjusted were baseline characteristics that demonstrated significant bivariate associations. Weight change over time was included in the model as a time-varying covariate. Unstructured dependence structure was specified. Differences between least-squared means for ILI and DSE at years 1, 2, and 4 were obtained from the mixed-effects model. Because clinic site was the randomization stratification factor, it was adjusted in the mixed-effects model.

We fit separate linear regression models to examine the relationships between year 4 percent fitness change and changes in weight as well as glycemic control, both overall and stratified by treatment group. Year 4 percent fitness change was examined both as a continuous variable and as a categorical variable defined as >10% decline, 0–10% decline, >0–10% improvement, and >10% improvement. For the model with change in weight from baseline to year 4 as the outcome, we adjusted for baseline weight and fitness along with prescribed diabetes medication use. For the model with year 4 change in HbA_{1c} as the outcome, covariates included baseline HbA_{1c} and fitness, weight change from baseline to year 4, and prescribed diabetes medication use. Least-squared means for the various percent fitness change categories were obtained from these regression models and presented using bar plots. Because clinic site was the randomization stratification factor, it was adjusted in linear regression models.

Mediation analyses were conducted by fitting a series of three regression models according to the procedures introduced by Baron and Kenny (10). Model 1 regressed the outcome (change in HbA_{1c}) against treatment group to evaluate the total effect of treatment on the outcome. Model 2 regressed each potential mediator (changes in weight and fitness) against treatment group. Model 3 regressed the outcome against treatment and potential mediators. Significance of the indirect effects was assessed using bootstrap methods (11) with 10,000 replicates. If the 95% CI for the indirect effect excluded 0, then there was significant indirect effect. Contrast between two mediators was calculated along with its 95% CI to assess relative importance of the mediators.

RESULTS—There were 5,145 participants randomized (DSE = 2,575; ILI = 2,570) to participate in Look AHEAD. However, fitness data were available at 4 years on 3,942 of the randomized participants (76.6% of the randomized subjects). The baseline demographic characteristics of these 3,942 study participants are provided in Table 1. When compared with participants who did not provide fitness data at 4 years, at baseline, those who did provide fitness data were significantly younger, had a lower weight, BMI, and waist circumference, had lower HbA_{1c}, reported a shorter duration of diabetes, and had a higher level of fitness. Reasons for missing fitness data at year 4 are presented in Fig. 1, with 554 and 649 participants missing data in ILI and DSE, respectively. The number of participants in the DSE group missing fitness is significantly higher than in the ILI group (P = 0.002).

Change in body weight

When data for only those subjects who completed the fitness test at year 4 were examined, there was a significant difference in weight change for ILI (−4.9% [95% CI −5.5 to −4.5%]) compared with DSE (–1.2% [−1.5 to −0.8%]). A similar pattern of weight change differences was also observed among subjects in the subsample assessed for LTPA (ILI = −4.8% [−5.3 to −4.4%]; DSE = −1.3% [−1.8 to −0.9%]).

Change in LTPA

Based on the subsample of subjects for whom LTPA data were available, the change in LTPA from baseline to year 1 was significantly greater in ILI (871.6 kcal/week [95% CI 775.6–967.6 kcal/week]; *n* = 1,120) compared with DSE (107.7 kcal/week [33.7–181.7]; *n* = 1,104) ($P < 0.0001$). However, there was a decrease in LTPA from year 1 to 4 in ILI to 348.3 (1,562.2) kcal/week (*n* = 1,078), whereas DSE remained relatively unchanged at 104.5 (1,308.7) kcal/week (*n* = 1,068). Despite this 535-kcal decrease in LTPA from year 1 to 4 in ILI, the difference in LTPA at year 4 compared with baseline remained significantly greater for ILI compared with DSE ($P <$ 0.0001).

Change in fitness

The difference in percent fitness change between ILI and DSE observed at year 4 was significant after adjustment for baseline fitness (5.40 vs. −0.83%; $P <$ 0.0001), change in weight (3.62 vs. 1.03%; P = 0.001), or both baseline fitness and change in weight (3.70 vs. 0.94%; $P < 0.001$). There was no effect of the test termination criterion (80% of age-predicted maximal heart rate vs. RPE = 16) on the pattern of these findings.

Bivariate analyses, adjusted for baseline fitness, were performed to determine the influence of baseline characteristics on change in fitness at the year 4 assessment. These analyses showed that the following baseline characteristics were associated with significantly greater improvements in fitness at year 4: lower BMI, younger age, male sex, race self-identified as white, not taking diabetes medication, not taking insulin, lower HbA_{1c}, not having metabolic syndrome, and no prior history of CVD. These parameters, along with important interaction effects, were examined using multivariate analysis to further determine factors that contributed to the change in fitness observed at years 1, 2, and 4 in this study. These multivariate analyses showed that percent change in fitness was greater in ILI versus DSE by 6.6% (95% CI 5.2–8.0%), 5.80% (3.2–8.4%), and 1.9% (0.5–3.3%) at years 1, 2, and 4, respectively ($P < 0.0001$).

Weight change and fitness change at year 4

Subjects were categorized by the magnitude of fitness change from baseline to year 4 (>10% decline [DSE, *n* = 735; ILI, *n* = 556], 0–10% decline [DSE, *n* = 514; ILI, *n* = 547], >0–10% improvement [DSE, *n* = 164; ILI, *n* = 200], and >10% improvement [DSE, *n* = 500; ILI, *n* = 702]) to examine if change in weight was associated with change in fitness from baseline to 4 years. After controlling for baseline weight, baseline fitness, clinical site, and treatment, there was an inverse relationship observed between change in weight and fitness ($P <$ 0.0001) (Fig. 2). These associations between change in weight and fitness remained statistically significant when data were analyzed separately for DSE

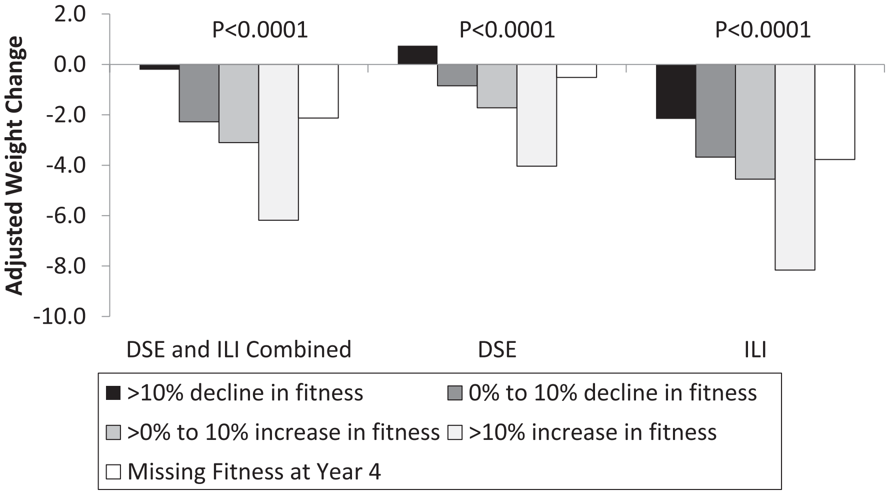

Figure 2—*Change in weight by percent change in fitness adjusted for baseline weight, baseline fitness, clinical site, and treatment assignment.*

and ILI ($P < 0.001$). Data were also analyzed with both weight and fitness change considered as continuous variables. Results of these analyses showed that a greater increase in fitness was associated with a greater weight loss with DSE and ILI combined ($\beta = -0.10035$, SE = 0.00492, $P < 0.0001$) and when examined separately for DSE ($\beta = -0.09563$, SE = 0.00785, $P < 0.0001$) and ILI ($\beta = -0.10389$, SE = 0.00624, $P < 0.0001$).

Glycemic control and fitness change at year 4

Data were analyzed to examine if change in glycemic control, measured by HbA_{1c}, was influenced by fitness improvement, with fitness change categorized as described above. When adjusted for clinical site, treatment, baseline HbA_{1c}, diabetes medication use, baseline fitness, and weight change, the inverse relationship between change in HbA_{1c} and fitness was significant both overall ($P < 0.0001$) and for both DSE ($P < 0.0001$) and ILI ($P < 0.001$) (Fig. 3). Post hoc analysis showed that there was a significant difference for change in HbA_{1c} between subjects grouped as having a >10% increase in fitness and both subject groups as having a >10% decline in fitness ($P < 0.0001$) and a 0–10% decline in fitness ($P < 0.0001$) at 4 years, with these comparisons remaining significant when data were analyzed separately for DSE and ILI. Post hoc analysis also showed that there was a significant difference for change in HbA_{1c} between subjects grouped as having a >0–10% improvement in fitness and subjects grouped as having a >10% decline in fitness ($P = 0.007$), with this comparison not significant when analyzed separately for DSE and ILI. When change in fitness was treated as a continuous variable and with adjustment for selected covariates, there was a significant inverse association between HbA_{1c} and change in fitness at 4 years ($\beta = -0.00431$, SE = 0.00048, $P < 0.0001$), and this was consistent when analyzed separately for DSE ($\beta = -0.0286$, SE = 0.00130, $P = 0.03$) and ILI ($\beta = -0.00295$, SE = 0.00106, $P < 0.0001$).

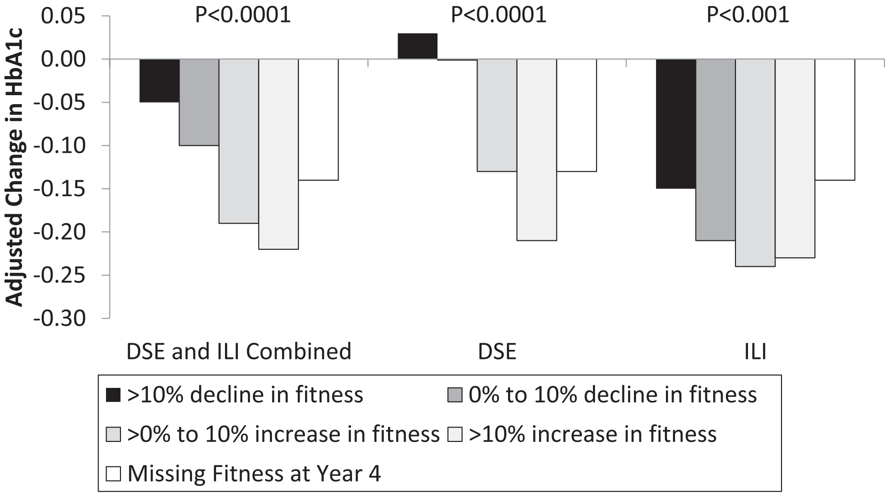

Figure 3—*Change in HbA_{1c} by percent change in fitness adjusted for clinical site, treatment, baseline HbA_{1c}, prescribed diabetes medication use, baseline fitness, and weight change.*

Mediation analysis was also conducted to examine the effect that change in weight and change in fitness had on change in HbA_{1c}. Results showed that both change in weight (indirect effect = −0.0779 [95% CI −0.1026 to −0.0554]) and change in fitness (−0.0264 [−0.0401 to −0.0156]) were significant mediators of the change in HbA_{1c}. However, the effect of the change in HbA_{1c} mediated by change in weight was significantly greater than the effect mediated by fitness (difference between indirect effects = 0.0515 [95% CI 0.0230–0.0813]).

LTPA and change in weight and glycemic control

With LTPA treated as a continuous variable, there was a significant association ($P = 0.02$) between change in LTPA and change in weight after adjustment for baseline LTPA, clinic, treatment, clinic*treatment, and baseline weight. This association remained significant when data were analyzed separately for ILI ($P = 0.02$) but not for DSE. With change in LTPA treated as a continuous variable and with adjustment for selected covariates, there was no significant association observed between HbA_{1c} and LTPA.

CONCLUSIONS

—As previously reported, ILI was effective at increasing fitness in overweight/obese individuals with T2DM after a 4-year intervention (3). Additional data presented here show that ILI was more effective than DSE at increasing fitness even after adjustment for baseline fitness and change in weight. We also report that change in fitness was associated with improvements in glycemic control, after controlling for both change in weight and the use of diabetes medications. An interesting finding is that this association was present for both ILI and DSE interventions, with the reduction in $\mathrm{HbA_{1c}}$ observed with an increase in fitness of $>10\%$ being significantly greater than the change in $\mathrm{HbA_{1c}}$ observed with a decline in fitness (see Fig. 3). Moreover, fitness was a significant mediator of the change in glycemic control in this population of individuals with T2DM. These findings have significant clinical implications and provide support for interventions to improve fitness in adults with T2DM. This may support the need for healthcare providers to encourage behavior changes that result in improved fitness in overweight and obese individuals with T2DM regardless of whether they are able to lose or sustain significant weight loss.

The ILI in the Look AHEAD Trial focused on both improving fitness and reducing weight, and the results of the analyses presented suggest that interventions for individuals with T2DM should focus on both of these outcomes. For example, the results of our mediation analysis showed that both weight loss and fitness change mediated the effect on change in $\mathrm{HbA_{1c}}$. However, it is important to recognize that the effect of weight loss on change in $\mathrm{HbA_{1c}}$ was significantly greater than the effect of change in fitness, but this does not minimize the important contribution of fitness in improving glycemic control. Rather these results suggest that fitness can have an important effect on glycemic control, and fitness appears to enhance the effect that weight loss has on improving glycemic control.

Whether the improvements in fitness, and the association with glycemic control, will ultimately reduce the incidence of CVD-related events, the primary outcome of the Look AHEAD Trial, remains unknown. Higher levels of fitness have been shown to be associated with delayed onset of CVD events in patients with T2DM (5), and fitness has been shown to have an independent effect of CVD morbidity and mortality (5,12–14). Within the Look AHEAD Trial for participants providing fitness data at year 4, 35.0% (n = 702) of participants in ILI achieved a 10% or greater increase in fitness at year 4, compared with 26.1% (n = 500) of participants in DSE. Moreover, 44.9% (n = 902) and 34.7% (n = 664) improved their fitness at year 4 compared with baseline in ILI and DSE, respectively. The contribution of fitness to improving glycemic control, and the finding that ILI resulted in greater improvements in fitness compared with DSE, may be of particular importance in the Look AHEAD Trial, where the primary research question is to compare CVD outcomes in response to ILI compared with DSE.

The importance of PA in long-term weight loss within the context of a comprehensive lifestyle behavior intervention has previously been demonstrated (15–19). The results from this current investigation support the association between LTPA and weight loss after a period of 4 years. However, we were unable to show an association between self-reported LTPA and improved glycemic control. This is in contrast to what other studies have previously reported. For example, the Italian Diabetes and Exercise Study showed a significant reduction in $\mathrm{HbA_{1c}}$ (-0.30 [95% CI -0.49 to -0.10) in response to 12 months of exercise, compared with control (20), with the exercise intervention including twice-a-week supervised sessions. In contrast, the Look AHEAD Trial included primarily PA that was home based, and PA was self-reported in a subsample of subjects using a questionnaire. Moreover, despite an ongoing ILI intervention across 4 years, there was a considerable decline in LTPA in ILI from year 1 to 4. These factors may have contributed to the lack of a significant association between LTPA and $\mathrm{HbA_{1c}}$ after 4 years in the Look AHEAD Trial.

The Look AHEAD Trial is one of the longest prospective randomized clinical trials to implement a lifestyle intervention targeting weight loss and improvement in fitness in overweight and obese adults with T2DM. However, this study is not without limitations that may have impacted the results presented. Fitness measures were obtained from 76.6% of the randomized sample, and there are differences in baseline demographic characteristics between subjects providing and not providing fitness data. Moreover, the number of participants in DSE missing fitness measures is significantly higher than in ILI (P = 0.002). This pattern of findings may affect the generalizability of the results observed. Moreover, although fitness was measured objectively, we did implement a submaximal graded exercise test that was terminated at a predetermined heart rate or RPE rather than a maximal exercise test. This may have influenced the precise assessment of fitness in this study. LTPA was also assessed on a subsample of subjects using a questionnaire, which may have influenced the accuracy of this measurement.

In summary, during the first 4 years of Look AHEAD, the ILI intervention produced greater weight loss, higher levels of PA, and improved fitness when compared with the DSE group. This has added importance for patients with T2DM. These results demonstrated an association between change in fitness and improvements in glycemic control, expressed as $\mathrm{HbA_{1c}}$, even after controlling for weight loss in both ILI and DSE. These findings highlight the importance of promoting interventions that will result in improved fitness, and the potential blunting of age-related declines in fitness in people with T2DM. This may be of particular importance within the primary care setting, which is similar to the intervention of the DSE group in this study. Despite minimal change in body weight in response to the DSE intervention, improved fitness was significantly related to improved glycemic control. This finding supports the need for primary care interventions to promote PA that results in significant improvements in fitness in patients with T2DM. The influence of these findings on long-term clinical outcomes awaits further examination within the Look AHEAD Trial.

Acknowledgments—J.M.J. is supported by grants from BodyMedia, Inc.; has been paid by Nestle Nutrition Institute for lectures and manuscript preparation; and is a member of the Scientific Advisory Board for Alere Wellbeing. A.N.F. is employed by and has stock options with Nutrisystem, Inc. This study is supported by the Department of Health and Human Services through the following cooperative agreements from the National Institutes of Health: DK57136, DK57149, DK56990, DK57177, DK57171, DK57151, DK57182, DK57131, DK57002, DK57078, DK57154, DK57178, DK57219, DK57008, DK57135, and DK56992. The following federal agencies have contributed support: National Institute of Diabetes and Digestive and Kidney Diseases; National Heart, Lung, and Blood Institute; National Institute of Nursing Research; National Center on Minority Health and Health Disparities; Office of Research on Women's Health; the Centers for Disease Control and Prevention; and the Department of Veterans Affairs. 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 (IHS) provided personnel, medical oversight, and use of facilities.

Additional support was received from The Johns Hopkins 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 a National Institutes of Health grant (DK 046204); 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. No other potential conflicts of interest relevant to this article were reported.

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.

J.M.J., S.A.G., and W.L. wrote, reviewed, and edited the manuscript, contributed to discussion, and researched data. C.M.E., A.N.F., S.P.G., L.A.H., and P.M.R. contributed to discussion and reviewed and edited the manuscript. W.C.K. and D.H.R. reviewed and edited the manuscript, contributed to discussion, and researched data. J.G.R. wrote, reviewed, and edited the manuscript and contributed to discussion. J.M.J., W.L., and S.A.G. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Parts of this study were presented in abstract form at the 71st Scientific Sessions of the American Diabetes Association, San Diego, California, 24–28 June 2011.

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