ORIGINAL INVESTIGATION

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

The Look AHEAD Research Group

Background: Lifestyle interventions produce short-term improvements in glycemia and cardiovascular disease (CVD) risk factors in individuals with type 2 diabetes mellitus, but no long-term data are available. We examined the effects of lifestyle intervention on changes in weight, fitness, and CVD risk factors during a 4-year study.

Methods: The Look AHEAD (Action for Health in Diabetes) trial is a multicenter randomized clinical trial comparing the effects of an intensive lifestyle intervention (ILI) and diabetes support and education (DSE; the control group) on the incidence of major CVD events in 5145 overweight or obese individuals (59.5% female; mean age, 58.7 years) with type 2 diabetes mellitus. More than 93% of participants provided outcomes data at each annual assessment.

Results: Averaged across 4 years, ILI participants had a greater percentage of weight loss than DSE participants (−6.15% vs −0.88%; $P<.001$) and greater improvements in treadmill fitness (12.74% vs 1.96%; $P<.001$), hemoglobin A_{1c} level (−0.36% vs −0.09%; $P<.001$), systolic (−5.33 vs −2.97 mm Hg; $P<.001$) and diastolic (−2.92 vs −2.48 mm Hg; $P=.01$) blood pressure, and levels of high-density lipoprotein cholesterol (3.67 vs 1.97 mg/dL; $P<.001$) and triglycerides (−25.56 vs −19.75 mg/dL; $P<.001$). Reductions in low-density lipoprotein cholesterol levels were greater in DSE than ILI participants (−11.27 vs −12.84 mg/dL; $P=.009$) owing to greater use of medications to lower lipid levels in the DSE group. At 4 years, ILI participants maintained greater improvements than DSE participants in weight, fitness, hemoglobin A_{1c} levels, systolic blood pressure, and high-density lipoprotein cholesterol levels.

Conclusions: Intensive lifestyle intervention can produce sustained weight loss and improvements in fitness, glycemic control, and CVD risk factors in individuals with type 2 diabetes. Whether these differences in risk factors translate to reduction in CVD events will ultimately be addressed by the Look AHEAD trial.

Trial Registration: clinicaltrials.gov Identifier: NCT00017953

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IMPROVING GLYCEMIC CONTROL AND cardiovascular disease (CVD) risk factors in patients with type 2 diabetes mellitus (DM) is critical for preventing long-term vascular complications of this disease and has led to increased emphasis on screening and pharmacologic management of these risk factors. Lifestyle-based weight loss interventions are also recommended to improve glycemic control and risk factors, but the

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evidence supporting the efficacy of lifestyle approaches is limited to short-term studies of typically less than 1 year.[1-4] With recent improvements in behavioral weight loss interventions[5,6] and increased recognition of the impact of lifestyle approaches for prevention of type 2 DM,[7,8] it is timely to examine the longer-term effects of these interventions on changes in glycemic control and CVD risk factors in individuals with type 2 DM.

See Invited Commentary at end of article

As perhaps the most extensive test of long-term multidisciplinary lifestyle intervention to date, the Look AHEAD (Action for Health in Diabetes) trial presents a unique opportunity to examine the long-term viability of lifestyle intervention as a clinical and public health strategy for obesity and type 2 DM. We have previously reported on the beneficial effects of the lifestyle intervention at 1 year.[1] This report examines the changes in weight, fitness, glycemic control, and CVD risk factors during a 4-year period for 5145 overweight or obese persons with type 2 DM randomized to an intensive lifestyle intervention

Group Information: A complete list of members of the Look AHEAD Research Group is listed on pages 1572 and 1573.

(ILI) or to diabetes support and education (DSE; usual care).

METHODS

PARTICIPANTS

As reported previously,[9] participants for the Look AHEAD trial were recruited at 16 centers in the United States and were required to be 45 to 76 years of age (increased to 55-76 years in year 2 of randomization to increase the anticipated CVD event rate); to self-report having type 2 DM that was verified by use of diabetes medication, physician report, or testing of glucose levels; and to have a body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) of 25.0 or more (≥27.0 in patients receiving insulin therapy), hemoglobin A_{1c} (HbA_{1c}) level of less than 11% (to convert to a proportion of total hemoglobin, multiply by 0.01), systolic blood pressure (SBP) of less than 160 mm Hg, diastolic blood pressure (DBP) of less than 100 mm Hg, and triglycerides level of less than 600 mg/dL (to convert triglycerides levels to millimoles per liter, multiply by 0.0113). The goal was to recruit approximately equal numbers of men and women and more than 33% from racial and ethnic minority groups. Participants were required to successfully complete a maximal graded treadmill test and 2 weeks of self-monitoring and to attend a Look AHEAD diabetes education session. All participants signed a consent form approved by their local institutional review board.

INTERVENTIONS

Participants were randomly assigned within each center to the ILI or the DSE group. The ILI[10] included diet modification and physical activity and was designed to induce at least a 7% weight loss at year 1 and to maintain this weight loss in subsequent years. The ILI participants were assigned a calorie goal (1200-1800 kcal/d based on initial weight), with less than 30% of total calories from fat (<10% from saturated fat) and a minimum of 15% of total calories from protein. To increase dietary adherence, a portion-controlled diet was used, with liquid meal replacements provided free and recommendations to use other portion-controlled items. The exercise goal was at least 175 minutes of physical activity per week, using activities similar in intensity to brisk walking. Behavioral strategies, including self-monitoring, goal setting, and problem solving, were stressed.

The ILI participants were seen weekly for the first 6 months and 3 times per month for the next 6 months, with a combination of group and individual contacts. During years 2 through 4, participants were seen individually at least once a month, contacted another time each month by telephone or e-mail, and offered a variety of ancillary group classes. At each session, participants were weighed, self-monitoring records were reviewed, and a new lesson was presented, following a standardized treatment protocol.

The DSE participants were invited to 3 group sessions each year. These sessions used a standardized protocol and focused on diet, physical activity, or social support. Information on behavioral strategies was not presented, and participants were not weighed at these sessions.

The ILI and DSE programs were led by lifestyle counselors who were registered dieticians, behavioral counselors, or exercise specialists. The two groups attended sessions on different days and/or different times of day to reduce the possibility of interactions between groups.

For ILI and DSE participants, the participant's own physicians provided all medical care and made changes in medications, with the exception of temporary changes in diabetes medication made by Look AHEAD physicians during periods of intensive weight loss in the ILI group.

ASSESSMENTS

Assessments were completed annually, and a $100 honorarium was provided. All measures were obtained by certified staff masked to the participants' intervention assignment. Weight and height were measured in duplicate using a digital scale and stadiometer. Blood pressure was measured in duplicate using an automated device. All blood work was completed after at least a 12-hour fast and was analyzed by the Central Biochemistry Laboratory (Northwest Lipid Research Laboratories, University of Washington, Seattle) using standardized laboratory procedures. Low-density lipoprotein cholesterol levels were estimated using the Friedewald equation.[11] Participants brought all prescription medications to their assessments. A maximal graded exercise test was administered at baseline and a submaximal exercise test at years 1 and 4.[12] 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.

STATISTICAL ANALYSES

Means reported at baseline are unadjusted averages. All tests of group differences were based on the intent-to-treat principle using all available data. Missing data were rare, and there was no evidence that missing data depended on treatment assignment. The primary analyses focus on cumulative effects, averaged across the 4 years, to best reflect group differences in overall exposure to the effects of elevated risk factors. In the secondary analyses, we examined the group differences at each of the 4 years to illustrate the time course of the changes. Mixed-effects analysis of covariance models were used to obtain adjusted mean changes for each outcome at annual visits 1 through 4, except fitness, which was measured only at years 1 and 4. For binary outcomes, generalized estimating equation models were used. The intervention effect was estimated as the average difference between arms across all visits, with the baseline level of the outcome, clinical center, an indicator of visit for the repeated outcome measures, and intervention assignment included in the model. Adjustment for postrandomization medication therapy was performed with an indicator for use of medication at each follow-up visit. The mixed-effects maximum likelihood and generalized estimating equation analysis of repeated outcomes were performed in Proc Mixed software (SAS, version 9; SAS Institute Inc, Cary, North Carolina) using an α level of .05. An unstructured covariance matrix was used to account for correlation between repeated outcomes, except for triglycerides, which required a first-order autoregressive structure. Unless otherwise indicated, data are expressed as mean (SD).

The Look AHEAD trial was designed to have a greater than 80% power to detect an 18% difference in major CVD events between the 2 groups during a planned follow-up of 13.5 years. Comparisons of changes in weight, fitness, and risk factors in the ILI and DSE groups at year 4 were prespecified.

RESULTS

A total of 5145 participants were randomized, 2570 to ILI and 2575 to DSE. The baseline characteristics of participants assigned to ILI and DSE were similar and have been described in detail.[13] Overall, 59.5% of the participants were women, 36.9% were from racial or ethnic mi-

norities, and 14.0% reported a history of CVD. The average age was 58.7 (6.8) years, the average BMI was 36.0 (5.9), and the average duration of type 2 DM was 6.8 (6.5) years. More than 93% of participants completed the outcome assessments at each of the 4 years (**Figure 1**).

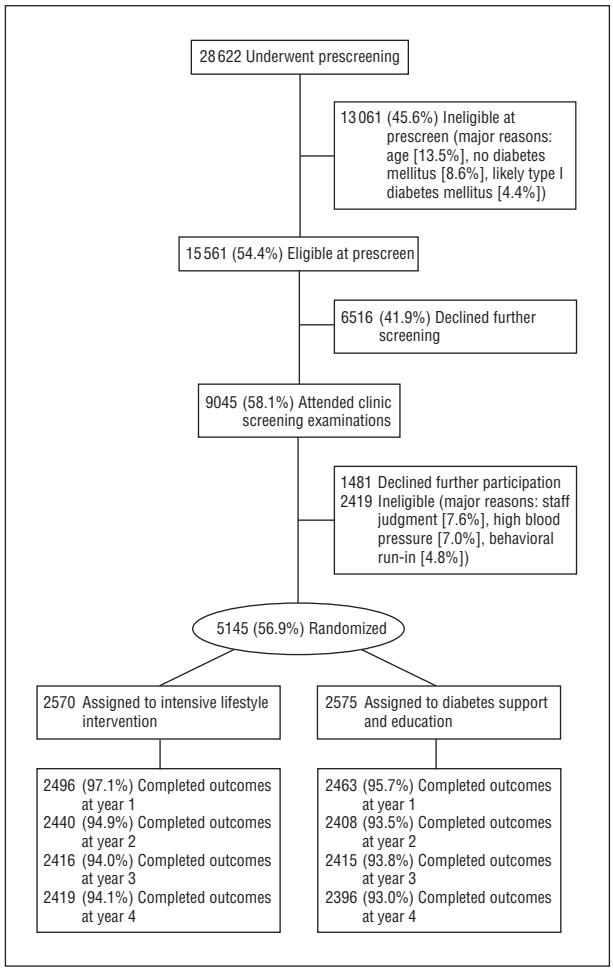

Figure 1. Flowchart for screening, randomization, and follow-up of participants in the Look AHEAD (Action for Health in Diabetes) trial. Remaining participants from the years 1 through 4 analyses were missing because of withdrawal from the study, death, or missed visits.

CUMULATIVE EFFECTS

Averaged across the 4 years, participants in the ILI group experienced greater improvements in weight, fitness, glycemic control, blood pressure, and levels of high-density lipoprotein cholesterol (HDL-C) and triglycerides than those in the DSE group (**Table 1**). The DSE group experienced greater overall reductions in low-density lipoprotein cholesterol (LDL-C) levels. Adjusting for medication use had no effect on changes in any risk factors except LDL-C level. After adjusting for use of lipid-lowering medications, changes in LDL-C levels did not differ between the ILI and DSE groups.

ANNUAL EFFECTS

Changes in weight and risk factors for DSE and ILI participants at each of the 4 years are shown in **Figure 2** (for greater detail, see the eTable; http://www.archinternmed.com). Weight losses in the ILI group were significantly greater than in the DSE group at each year. The mean maximal weight loss (8.6%) for the ILI group occurred at year 1, but participants in the ILI group maintained a mean weight loss of 4.7% at year 4 compared with 1.1% in the DSE group ($P<.001$).

Fitness increased by 20.4% in ILI participants and by 5.0% in DSE participants ($P<.001$) between baseline and year 1. At year 4, the fitness level of ILI participants was still 5.1% over baseline, whereas DSE participants were 1.1% below baseline ($P<.001$).

For several risk factors, the differences between ILI and DSE were most apparent at year 1 (Figure 2). However, ILI participants continued to have greater improvements in SBP and in HbA_{1c} and HDL-C levels than DSE participants at each of the 4 years. Initial differences between groups for DBP and triglycerides levels were not maintained at year 4. The ILI and the DSE groups had

Table 1. Mean Changes in Weight, Fitness, and CVD Risk Factors in ILI and DSE Groups and the Difference Between Groups Averaged Across 4 Years

Measure	Groups, Mean Change (95% CI)		Between-Group Mean Difference (95% CI)	*P* Value of Difference[a]
	DSE	ILI		
Weight, % initial weight	−0.88 (−1.12 to −0.64)	−6.15 (−6.39 to −5.91)	−5.27 (−5.61 to −4.93)	<.001
Fitness, % METS	1.96 (1.07 to 2.85)	12.74 (11.87 to 13.62)	10.78 (9.53 to 12.03)	<.001
HbA_{1c} level[b]	−0.09 (−0.13 to −0.06)	−0.36 (−0.40 to −0.33)	−0.27 (−0.32 to −0.22)	<.001
SBP, mm Hg[b]	−2.97 (−3.44 to −2.49)	−5.33 (−5.80 to −4.86)	−2.36 (−3.03 to −1.70)	<.001
DBP, mm Hg[b]	−2.48 (−2.73 to −2.24)	−2.92 (−3.16 to −2.68)	−0.43 (−0.77 to −0.10)	.01
HDL-C level, mg/dL[b]	1.97 (1.73 to 2.22)	3.67 (3.43 to 3.91)	1.70 (1.35 to 2.04)	<.001
Triglycerides level, mg/dL[b]	−19.75 (−22.11 to −17.39)	−25.56 (−27.91 to −23.21)	−5.81 (−9.14 to −2.48)	<.001
LDL-C level, mg/dL				
Without adjustment for medication use	−12.84 (−13.67 to −12.00)	−11.27 (−12.10 to −10.44)	1.57 (0.39 to 2.74)	.009
Adjusted for medication use	−9.22 (−10.04 to −8.39)	−8.75 (−9.56 to −7.94)	0.47 (−0.67 to 1.60)	.42

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; DSE, diabetes support and education; HbA_{1c}, hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; ILI, intensive lifestyle intervention; LDL-C, low-density lipoprotein cholesterol; METS, metabolic equivalents; SBP, systolic blood pressure.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; HbA_{1c} to a proportion of total hemoglobin, multiply by 0.01; and triglycerides to millimoles per liter, multiply by 0.0113.

[a] Adjusting for baseline use of medications or changes over time did not influence the average effect or the *P* value.

[b] Data presented are average effects unadjusted for medication use.

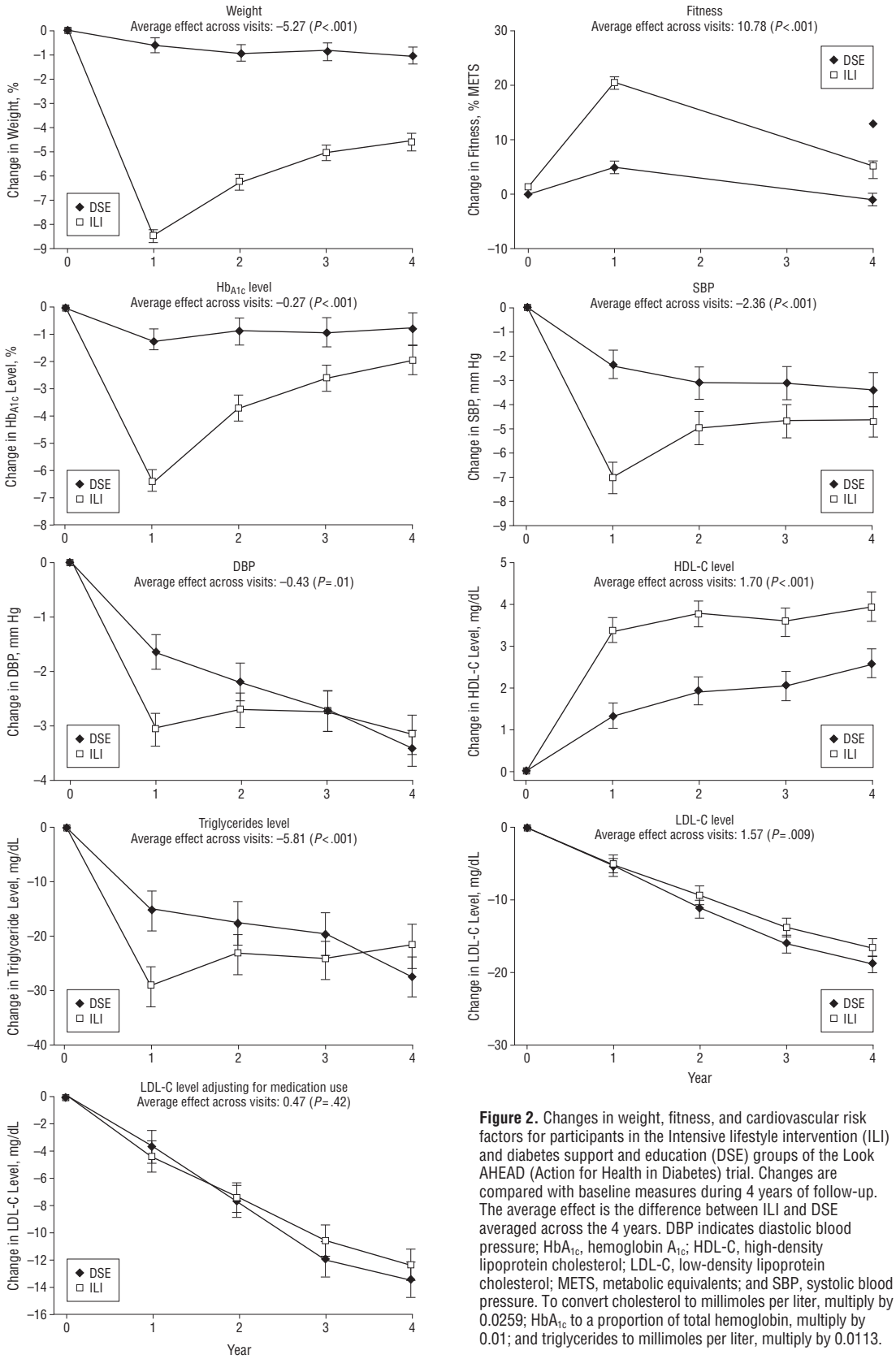

Figure 2. Changes in weight, fitness, and cardiovascular risk factors for participants in the Intensive lifestyle intervention (ILI) and diabetes support and education (DSE) groups of the Look AHEAD (Action for Health in Diabetes) trial. Changes are compared with baseline measures during 4 years of follow-up. The average effect is the difference between ILI and DSE averaged across the 4 years. DBP indicates diastolic blood pressure; HbA_{1c}, hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; METS, metabolic equivalents; and SBP, systolic blood pressure. To convert cholesterol to millimoles per liter, multiply by 0.0259; HbA_{1c} to a proportion of total hemoglobin, multiply by 0.01; and triglycerides to millimoles per liter, multiply by 0.0113.

Table 2. Proportion of DSE and ILI Participants Who Initiated or Maintained Use of Medication for Diabetes, Hypertension, or Lowering Lipid Levels

	Use of Medication at Follow-up by Group					
	No Use at Baseline			Continued Use From Baseline		
	DSE	ILI	*P* Value	DSE	ILI	*P* Value
Diabetes medication						
No. at baseline[a]	348	354		2208	2202	
Follow-up year, %						
1	33.1	10.4	<.001	97.5	89.4	<.001
2	46.3	17.4	<.001	96.3	88.2	<.001
3	58.6	27.3	<.001	95.4	89.2	<.001
4	66.8	41.8	<.001	96.0	90.6	<.001
Insulin						
No. at baseline[a]	2167	2190		408	380	
Follow-up year, %						
1	3.7	1.7	<.001	91.6	80.6	<.001
2	6.7	3.1	<.001	86.4	76.1	<.001
3	8.9	4.3	<.001	86.3	77.7	.004
4	11.5	6.9	<.001	88.0	77.4	<.001
Hypertension medication						
No. at baseline[a]	684	661		1872	1895	
Follow-up year, %						
1	21.9	16.4	.01	89.9	81.3	<.001
2	31.9	24.7	.005	90.4	81.0	<.001
3	40.3	33.3	.01	91.2	82.9	<.001
4	47.2	43.0	.15	92.7	85.0	<.001
Lipid-lowering medication						
No. at baseline[a]	1313	1310		1243	1246	
Follow-up year, %						
1	25.3	17.6	<.001	92.3	89.6	.03
2	39.8	29.0	<.001	90.7	89.1	.22
3	47.4	38.5	<.001	88.6	90.0	.26
4	53.2	47.2	.004	90.9	90.4	.72

Abbreviations: DSE, diabetes support and education; ILI, intensive lifestyle intervention.

[a] Indicates the number of participants in DSE and ILI who were not using or who were using this class of medications at baseline.

reductions in LDL-C levels at years 1 and 2, with no differences between the 2 groups. However, by years 3 and 4, DSE participants experienced greater decreases in LDL-C levels than ILI participants, resulting from their greater use of lipid-lowering medications.

Table 2 presents the changes in medication use in ILI and DSE participants. Among those who were using medications to control their blood glucose levels or blood pressure at baseline, a greater proportion of ILI than DSE participants discontinued use of these medications. Likewise, among those not using these medications at baseline, fewer ILI participants initiated these treatments. The percentage of participants using lipid-lowering medications almost doubled during the 4 years, with greater initiation of lipid medication therapy in the DSE than in the ILI group.

The proportions of participants achieving the American Diabetes Association (ADA) goals for HbA_{1c} level, blood pressure, and LDL-C level in each year of the trial are presented in **Table 3**. A significantly greater proportion of ILI participants met the ADA goal for HbA_{1c} level at each year and for blood pressure at years 1, 2, and 3. The percentage of participants achieving the ADA goals for LDL-C level did not differ until year 4, when

Table 3. Proportion of Participants in DSE and ILI Who Achieved the ADA Treatment Goals at Baseline and Years 1 Through 4

Treatment Goal[a]	% of Group		
	DSE	ILI	*P* Value
HbA_{1c} level			
Baseline	45.1	46.5	
Year 1	50.1	72.5	<.001
Year 2	50.9	62.7	<.001
Year 3	51.4	60.1	<.001
Year 4	51.1	57.4	<.001
Blood pressure			
Baseline	49.6	53.6	
Year 1	57.2	68.9	<.001
Year 2	60.0	64.2	.003
Year 3	60.1	62.9	.049
Year 4	60.5	62.9	.09
LDL-C level			
Baseline	37.4	36.9	
Year 1	45.3	44.0	.36
Year 2	52.7	51.3	.37
Year 3	60.3	57.6	.07
Year 4	64.5	61.0	.01

Abbreviations: ADA, American Diabetes Association; DSE, diabetes support and education; HbA_{1c}, hemoglobin A_{1c}; ILI, intensive lifestyle intervention; LDL-C, low-density lipoprotein cholesterol.

[a] The ADA treatment goals are as follows: HbA_{1c} level, less than 7% (to convert to a proportion of total hemoglobin, multiply by 0.01); blood pressure, less than 130/80 mm/Hg; and LDL-C level, less than 100 mg/dL (to convert triglycerides levels to millimoles per liter, multiply by 0.0113).

64.5% of DSE participants compared with 61.0% of ILI participants (P=.01) met this goal.

COMMENT

The Look AHEAD trial is, to our knowledge, the first study to examine the effects of an intensive lifestyle intervention through 4 years of follow-up in a large cohort of overweight and obese individuals with type 2 DM. This study shows that lifestyle interventions can produce long-term weight loss and improvement in fitness and sustained beneficial effects on CVD risk factors. Across the 4 years, the ILI group experienced significantly greater average improvements in all risk factors except LDL-C levels. Although the differences between the 2 groups were greatest initially and decreased over time for several measures, the differences between the groups averaged across the 4 years were substantial (Table 1) and indicate that the ILI group spent a considerable time at lower CVD risk.

Averaged across the 4 years, ILI produced greater weight losses, increases in fitness, and greater improvements in all CVD risk factors, except LDL-C level, compared with the control group. Thus, during this period, ILI participants had lower exposure to a number of potentially negative effects of elevated CVD risk factors than did DSE participants. Although medications typically affect only 1 risk factor, the lifestyle intervention produced positive changes in glycemic control, blood pressure, and lipid levels simultaneously.

The average weight losses achieved in the ILI group at 1 year were greater than those seen in other multicenter lifestyle trials.[5,14,15] Although few studies have reported

weight loss data for 2 or more years of follow-up, the ILI results (weight losses of 6.4%, 5.1% and 4.7% of initial body weight at years 2, 3, and 4 respectively) appear comparable to or better than those reported previously,[5,16-18] and the rate of weight regain appears to be slowing over time. The weight losses in the Look AHEAD trial are impressive in light of the perception that individuals with type 2 DM have more difficulty losing weight than do their nondiabetic counterparts[19] and may reflect the careful selection of participants for this trial, the ongoing intensive contact,[20] the combination of group and individual contact, the use of meal replacement products,[21] and the larger goals prescribed for weight loss.[22] Both the diet and physical activity components of the ILI program likely contributed to the weight losses and risk factor benefits.[23,24]

Because no intervention studies have reported fitness changes beyond 1 year for participants with type 2 DM,[25] the Look AHEAD trial provides unique data on long-term changes in fitness. The improvements in fitness seen in the ILI group at year 4 exceed those reported previously for patients with type 2 DM in response to a 52-week diet plus exercise intervention.[26] The sustained improvements in fitness are important in light of the large number of studies showing that fitness levels are associated with CVD and all-cause mortality.[27-30]

Figure 2 shows that the positive impact of the intervention on several of the risk factors was greatest at year 1, followed by recidivism toward baseline levels. Because assessments were conducted only annually, the time point of the maximum difference between ILI and DSE cannot be determined and may have occurred even before year 1. Previous studies suggest that improvements in glycemic control occur quickly with the onset of caloric restriction, before weight loss.[31,32] Similarly, increases in caloric intake, regain of weight, and decreases in fitness may each contribute to the changes from years 1 to 4. The observed pattern of changes may also reflect the stronger effect of weight loss on CVD risk factors immediately after weight loss than at longer time intervals, even in those who maintain their weight loss in full.[33,34] In the Swedish Obese Subjects Study, much larger weight losses achieved through gastric surgery led to short-term improvements in CVD risk factors, which were not necessarily sustained long-term[35]; despite this, there were marked benefits of weight loss on cardiovascular mortality.[36] Finally, the decrease in the beneficial effects of lifestyle, relative to DSE, during the 4 years for some measures, such as DBP, was also due to the improvements that occurred in the DSE group. These improvements in the control group may reflect secular trends in the treatment of CVD risk factors or the effects of type 2 DM on body weight,[37] the benefit of joining a clinical trial, and/or the beneficial effects of the educational classes.

Despite some lessening in effects over time, there were sustained positive effects of ILI relative to DSE across all 4 years for SBP and HbA_{1c} and HDL-C levels; the beneficial effects of the intervention on DBP and triglycerides levels were maintained for 2 and 3 years, respectively. We found no previous intervention studies in which individuals with type 2 DM were followed up for as long as 4 years. Based on studies with nondiabetic subjects, the long-term effects of the lifestyle intervention in the Look AHEAD trial are consistent with or greater than those reported previously in other randomized trials with 2- to 3-year follow-up periods or in meta-analyses for blood pressure[15,38,39] and triglycerides[16,17,39] and HDL-C levels.[16,17,40]

Of particular note is the sustained effect of lifestyle intervention on HDL-C level. In contrast to several other risk factors, the effect on HDL-C level of the ILI relative to the control group was as great at year 4 as it had been at year 1. Early randomized controlled trials[41,42] showed that the combination of weight loss and increased physical activity had the greatest effect on HDL-C levels and parallel the type of approach used in the Look AHEAD trial. Given the evidence from the Helsinki Heart Study of a strong association between increases in HDL-C levels and reduced heart disease,[43] the sustained effects of lifestyle intervention on HDL-C level may provide important long-term cardiovascular benefit.

The finding from the Look AHEAD trial of greater benefits of lifestyle intervention for HDL-C than for LDL-C levels is consistent with those of previous studies.[2] Levels of LDL-C decreased consistently during the 4 years of follow-up in both groups in the Look AHEAD trial, likely owing to the large number of participants in both groups who started lipid-lowering medication therapy, typically statins, and reflecting the increasing emphasis given to treating LDL-C levels in individuals with diabetes.[44] The DSE group had lower LDL-C levels than the ILI group, which appeared to result from their greater use of these medications.

Further evidence of beneficial effects of the lifestyle intervention is seen in the larger proportion of ILI than DSE participants who achieved the blood pressure and HbA_{1c} goals and the smaller proportion of ILI participants who needed medication to achieve these goals. Participants in both groups, however, experienced substantial improvements in the proportion achieving the ADA goals during the 4 years, particularly for LDL-C levels. In recent (1999-2002) population-based surveys of individuals with diabetes,[45] 42% had an HbA_{1c} level of less than 7%, 48% had an SBP of less than 130 mm Hg, and 64% had an LDL-C level of less than 130 mg/dL (to convert cholesterol levels to millimoles per liter, multiply by 0.0259). A greater proportion of Look AHEAD participants in both groups thus met the blood pressure and HbA_{1c} goals than reported nationally and a comparable proportion met the LDL-C goal, suggesting that Look AHEAD participants may be healthier or receive better care than the general population of individuals with type 2 DM.

CONCLUSIONS

The ILI was successful in producing sustained weight losses and improvements in cardiovascular fitness through 4 years of follow-up. The ILI group also experienced significantly greater improvements than the usual-care (DSE) group in all CVD risk factors averaged across this period, with the exception of LDL-C levels; for LDL-C levels, after adjusting for medication use, improvements were similar in both groups. The ILI group in the Look AHEAD trial is being offered ongoing intervention activities in an effort to sustain the

The Look AHEAD Research Group at Year 4

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improvements in risk factors. Cost-effectiveness analyses are being conducted. The critical question is whether the differences between groups in risk factors will translate into differences in the development of CVD. These results will not be available for several additional years. However, effects of the magnitude that we observed for fitness, HDL-C and HbA_{1c} levels, and blood pressure have been associated with decreased cardiovascular events and mortality in previous medication trials and observational studies.[28,29,46-48] Moreover, there may be long-term beneficial effects from the 4-year period in which ILI participants have been exposed to lower CVD risk factors, as seen in other clinical trials.[49,50] Longer follow-up will allow us to determine whether the differences between groups in CVD risk factors can be maintained and whether the ILI has positive effects on cardiovascular morbidity and mortality.

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INVITED COMMENTARY

Risk of Diabetes and Cardiovascular Disease

Best to Return Back to the Basics

The prevalence of type 2 DM is rapidly increasing throughout the world. Recent data from the Centers for Disease Control and Prevention indicate that by 2050 nearly 50 million Americans will have type 2 DM. Because the risk of macrovascular disease leading to myocardial infarction or stroke begins on average 6 to 8 years before the onset of clinical diabetes, there has been an ongoing search for novel markers for identification of individuals at high risk of developing type 2 DM.

The article by Chao et al[1] in this issue of the *Archives* evaluates the role of circulating biomarkers of inflammation and endothelial dysfunction in predicting the risk of

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type 2 DM during a 6-year follow-up period among postmenopausal women who were free of type 2 DM and CVD at the time of enrollment in the Women's Health Initia-