

Reduction in Weight and Cardiovascular Disease Risk Factors in Individuals With Type 2 Diabetes

One-year results of the Look AHEAD trial

THE LOOK AHEAD RESEARCH GROUP*

OBJECTIVE — The effectiveness of intentional weight loss in reducing cardiovascular disease (CVD) events in type 2 diabetes is unknown. This report describes 1-year changes in CVD risk factors in a trial designed to examine the long-term effects of an intensive lifestyle intervention on the incidence of major CVD events.

RESEARCH DESIGN AND METHODS — This study consisted of a multicentered, randomized, controlled trial of 5,145 individuals with type 2 diabetes, aged 45–74 years, with BMI >25 kg/m² (>27 kg/m² if taking insulin). An intensive lifestyle intervention (ILI) involving group and individual meetings to achieve and maintain weight loss through decreased caloric intake and increased physical activity was compared with a diabetes support and education (DSE) condition.

RESULTS — Participants assigned to ILI lost an average 8.6% of their initial weight vs. 0.7% in DSE group ($P < 0.001$). Mean fitness increased in ILI by 20.9 vs. 5.8% in DSE ($P < 0.001$). A greater proportion of ILI participants had reductions in diabetes, hypertension, and lipid-lowering medicines. Mean A1C dropped from 7.3 to 6.6% in ILI ($P < 0.001$) vs. from 7.3 to 7.2% in DSE. Systolic and diastolic pressure, triglycerides, HDL cholesterol, and urine albumin-to-creatinine ratio improved significantly more in ILI than DSE participants (all $P < 0.01$).

CONCLUSIONS — At 1 year, ILI resulted in clinically significant weight loss in people with type 2 diabetes. This was associated with improved diabetes control and CVD risk factors and reduced medicine use in ILI versus DSE. Continued intervention and follow-up will determine whether these changes are maintained and will reduce CVD risk.

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Look AHEAD (Action for Health in Diabetes) is an National Institutes of Health–funded clinical trial, conducted in 16 centers in the U.S., investigating the long-term health impact of an intensive lifestyle intervention (ILI) in 5,145 overweight or obese adults with type 2 diabetes. The design and methods of this trial have been reported elsewhere (1), as have the baseline characteristics of the randomized cohort (2). Its primary

objective is to determine whether cardiovascular morbidity and mortality in individuals with type 2 diabetes can be reduced by long-term weight reduction, achieved by an ILI that includes diet, physical activity, and behavior modification (3). The goal of this intervention is for individuals to achieve and maintain a loss of at least 7% of initial body weight. Results of the ILI group will be compared with a usual-care condition that includes

diabetes support and education (DSE). Follow-up of Look AHEAD participants is ongoing and is planned to extend for up to 11.5 years. For the study to continue for this period, two feasibility criteria were set by the Look AHEAD study group based on 1-year changes: 1) a difference between ILI and DSE participants of >5 percentage points in the average percent change in weight from baseline and 2) an average absolute percent weight loss from baseline among ILI participants (not using insulin at baseline) of >5%. This report documents the success of Look AHEAD in meeting these 1-year feasibility criteria and describes changes in the two groups at the end of the 1st year in fitness, cardiovascular disease risk factors, and use of medicines.

RESEARCH DESIGN AND METHODS

For inclusion in the study, participants were 45–74 years of age (which was changed to 55–74 years during the 2nd year of recruitment to increase the anticipated cardiovascular event rate), had a BMI >25 kg/m² (>27 kg/m² if currently taking insulin), A1C <11%, blood pressure <160 (systolic) and <100 (diastolic) mmHg, and triglycerides <600 mg/dl.

Participants completed maximal graded exercise tests to assess fitness before randomization. The test consisted of the participant walking on a motorized treadmill at a constant self-selected walking speed (1.5, 2.0, 2.5, 3.0, 3.5, or 4.0 mph). The elevation of the treadmill was initially set at 0% grade and increased by 1.0% every minute. Heart rate and rating of perceived exertion (RPE) using the Borg 15-category scale (4) were measured during the final 10 s of each exercise stage and at the point of test termination. To determine eligibility at baseline, a maximal exercise test was performed. For individuals not taking prescription medicine that would affect heart rate response during exercise (e.g., β -blocker), the baseline test was considered valid if the individual achieved at least 85% of age-predicted

Address correspondence and reprint requests to Mark Espeland, PhD, Division of Public Health Sciences, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157. E-mail: mespelan@wfubmc.edu.

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*Authors and members of the Look AHEAD trial are listed in the APPENDIX.

Abbreviations: ADA, American Diabetes Association; CVD, cardiovascular disease; DSE, diabetes support and education; ILI, intensive lifestyle intervention; AHEAD, Action for Health in Diabetes; METS, metabolic equivalents; RPE, rating of perceived exertion.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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maximal heart rate (age-predicted maximal heart rate = $220 - \text{age}$) and a minimum of 4 metabolic equivalents (METs). For individuals taking prescription medicine that would affect the heart rate response during exercise, the baseline test was considered valid if the individual achieved an RPE of at least 18 and a minimum of 4 METs. Individuals not achieving these criteria were not eligible for randomization into Look AHEAD. METs at each exercise stage and at test termination were estimated from a standardized formula that incorporates walking speed and grade (5).

The goal was to recruit approximately equal numbers of men and women, with >33% from racial and ethnic minority groups. Informed consent was obtained from all participants before screening and at enrollment, consistent with the Helsinki Declaration and the guidelines of each center's institutional review board. After all eligibility criteria were confirmed, participants were randomly assigned with equal probability to either the ILI or the DSE comparison condition. Randomization was stratified by clinical center.

Interventions

Before randomization, all study participants were required to complete a 2-week run-in period that included successful self-monitoring of diet and physical activity, and they were provided an initial session of diabetes education with particular emphasis on aspects of diabetes care related to the trial such as management of hypoglycemia and foot care. The session stressed the importance of eating a healthy diet and being physically active for both weight loss and improvement of glycemic control. All individuals who smoked were encouraged to quit and were provided self-help materials and/or referral to local programs as appropriate.

The weight loss intervention prescribed in the 1st year has been described in detail (3). Briefly, it combines diet modification and increased physical activity and was designed to induce a minimum weight loss of 7% of initial body weight during the 1st year. Individual participants were encouraged to lose >10% of their initial body weight, with the expectation that aiming high would ensure that a greater number of participants would achieve the minimum 7% weight loss. The intervention was modeled on group behavioral programs developed for the treatment of obese patients with type 2 diabetes and included treat-

ment components from the Diabetes Prevention Program (6–8) and the National Heart, Lung, and Blood Institute's clinical guidelines (9). During months 1–6, participants were seen weekly with three group meetings and one individual session per month. During months 7–12, group sessions were provided every other week and the monthly individual session was continued. Sessions were led by intervention teams that included registered dietitians, behavioral psychologists, and exercise specialists.

Caloric restriction was the primary method of achieving weight loss. The macronutrient composition of the diet was structured to enhance glycemic control and to improve CVD risk factors. It included a maximum of 30% of total calories from fat (with a maximum of 10% of total calories from saturated fat) and a minimum of 15% of total calories from protein (10). Participants were prescribed portion-controlled diets, which included the use of liquid meal replacements (provided free of charge) and frozen food entrées, as well as structured meal plans (comprised of conventional foods) for those who declined the meal replacements. Monthly reviews took place at an individual session to reassess progress.

The physical activity program prescribed in the ILI relied heavily on home-based exercise with gradual progression toward a goal of 175 min of moderate-intensity physical activity per week. Although walking was encouraged, participants were allowed to choose other types of moderate-intensity physical activity, and programs were tailored based on the results of a baseline physical fitness test and safety concerns.

The ILI included a "toolbox" approach, as used in the Diabetes Prevention Program (6,7), to help participants achieve and maintain the study's weight loss and activity goals. Use of the toolbox was based on a preset algorithm and assessment of participant progress. After the first 6 months, the toolbox algorithm included use of a weight loss medicine (orlistat) and/or advanced behavioral strategies for individuals who had difficulty in meeting the trial's weight or activity goals. Specific protocols were used to determine when to initiate medication or other approaches, to monitor participants, and to determine when to stop a particular intervention.

Participants assigned to DSE attended the initial prerandomization diabetes education session (described above) and

were invited to three additional group sessions during the 1st year. A standard protocol was used for conducting these sessions, which provided information and opportunities for discussing topics related to diet, physical activity, and social support. However, the DSE group was not weighed at these sessions and received no counseling in behavioral strategies for changing diet and activity.

Ongoing clinical care

All participants in the ILI and DSE groups continued to receive care for their diabetes and all other medical conditions from their own physicians. Changes in all medicines were made by the participants' own physicians, except for temporary reductions in hyperglycemia medicines during periods of intensive weight loss intervention, which were made by the intervention sites following a standardized treatment protocol aimed at avoiding hypoglycemia.

Assessments

Anthropometry. All participants were scheduled to attend baseline and 1-year assessments, at which time measures were collected by staff members who were masked to participants' intervention assignments. Weight and height were assessed in duplicate using a digital scale and a standard stadiometer. Seated blood pressure was measured in duplicate, using an automated device after a 5-min rest. Participants brought all prescription medicines to the clinic to ensure recording accuracy. History of cardiovascular disease was based on self-report of myocardial infarction, stroke, transient ischemic event, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft.

Fitness. At 1 year, a submaximal exercise test was performed and terminated when the participant first achieved or exceeded 80% of age-predicted maximal heart rate (HR_{Max} in beats per min = $220 - \text{age}$). If the participant was taking a β -blocker at baseline or 1-year assessment, the submaximal test was terminated at the point when the participant first reported achieving or exceeding 16 on the 15-category RPE scale. For participants not taking a β -blocker, change in cardiorespiratory fitness was computed as the difference in estimated METs between points during the baseline and 1-year tests when >80% of age-predicted maximal heart rate was attained. For participants taking β -blockers at either base-

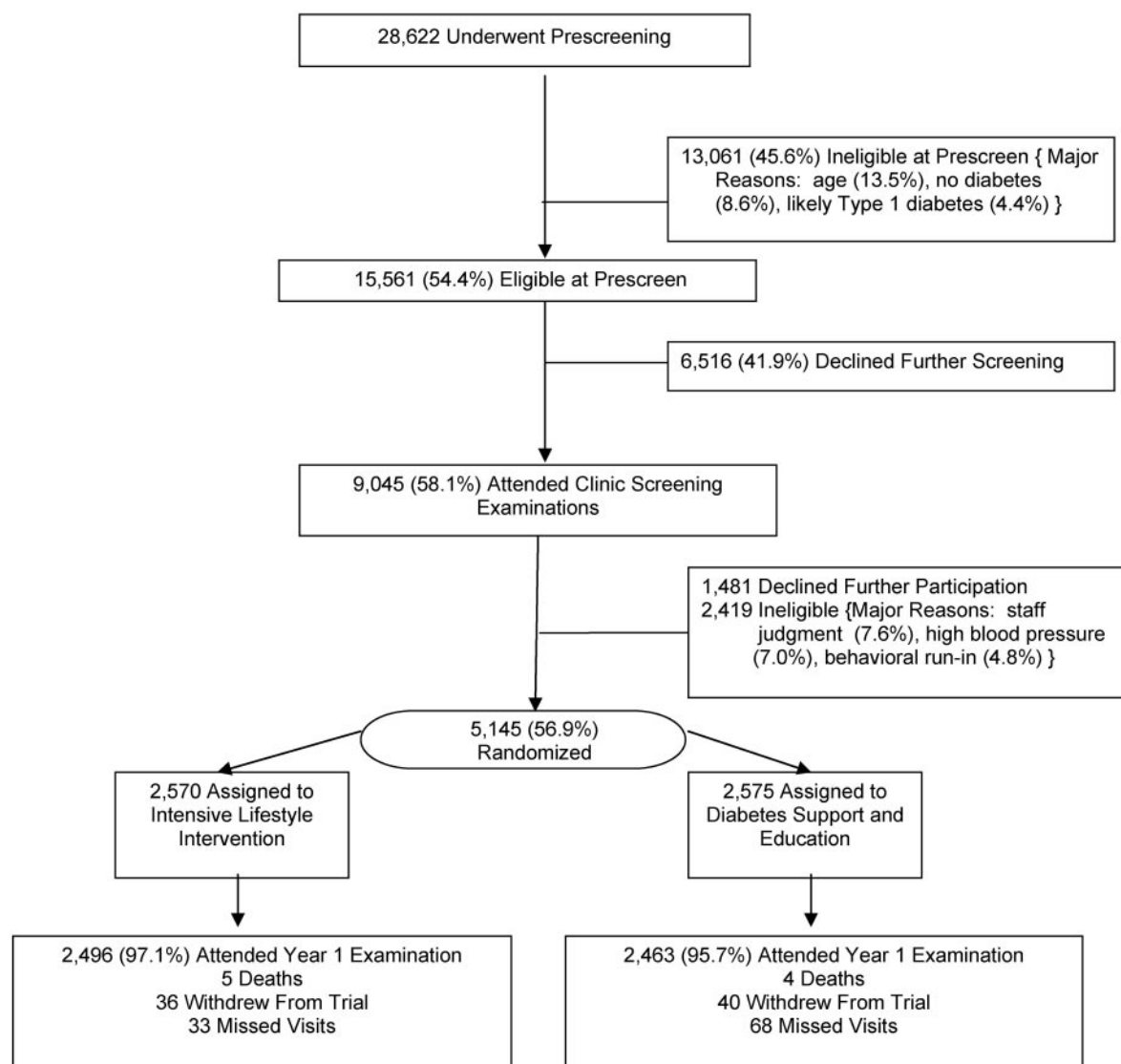


Figure 1—Enrollment of Look AHEAD participants.

line or 1 year, change in cardiorespiratory fitness was computed as the difference in estimated METS between points during the baseline and 1-year tests when RPE >16 was attained.

Serum measures. The Central Biochemistry Laboratory (Northwest Lipid Research Laboratories, University of Washington, Seattle, WA) conducted standardized analyses of shipped frozen specimens. A1C was measured by a dedicated ion exchange high-performance liquid chromatography instrument (Bio-rad Variant 11). Fasting serum glucose was measured enzymatically on a Hitachi 917 autoanalyzer using hexokinase and glucose-6-phosphate dehydrogenase. Total serum cholesterol and triglycerides were measured enzymatically using methods standardized to the Centers for

Disease Control and Prevention reference methods. LDL cholesterol was calculated by the Friedewald equation (11). HDL cholesterol was analyzed by the treatment of whole plasma with dextran sulfate minus Mg^{2+} to precipitate all of the apolipoprotein B-containing lipoproteins. Albumin and creatinine concentrations were measured from spot urine samples.

Participants were classified as having the metabolic syndrome using the criteria proposed by the National Cholesterol Education Program Adult Treatment Program III panel (12). They also were classified according to their success in meeting treatment goals published by the American Diabetes Association (ADA) (13). Glycemic control was defined as A1C <7.0%, blood pressure control as systolic blood pressure <130 and dia-

stolic blood pressure <80 mmHg, and lipid control as LDL cholesterol <100 mg/dl.

Statistical methods

Cross-sectional differences between participants assigned to the ILI and DSE conditions were assessed using ANCOVA and logistic regression, with adjustment for clinical center (the sole factor used to stratify randomization). Changes in outcome measures from baseline to 1 year were compared using ANCOVA and Mantel-Haenszel tests.

RESULTS

Participants' baseline characteristics

Figure 1 describes trial enrollment. Of 28,622 individuals who provided infor-

Table 1—Baseline characteristics of the ILI and DSE groups

Characteristic	Intervention assignment		P value
	ILI	DSE	
<i>n</i>	2,570	2,575	
Women	1,526 (59.3)	1,537 (59.6)	0.85*
Ethnicity			
African American	399 (15.5)	404 (15.7)	
American Indian/Alaskan Native	130 (5.1)	128 (5.0)	
Asian/Pacific Islander	29 (1.1)	21 (0.8)	0.28*
Hispanic/Latino	339 (13.2)	338 (13.2)	
Non-Hispanic white	1,618 (63.1)	1,628 (63.3)	
Other/multiple	48 (1.9)	50 (1.9)	
Age (years)	58.6 ± 6.8	58.9 ± 6.9	0.12†
History of cardiovascular disease‡	371 (14.4)	351 (13.6)	0.40*
Metabolic syndrome	2,406 (93.6)	2,431 (94.4)	0.32*
Use of insulin	381 (14.8)	408 (15.8)	0.31*
BMI (kg/m ²)			
Women	36.3 ± 6.2	36.6 ± 6.0	0.15†
Men	35.3 ± 5.7	35.1 ± 5.2	0.41†
Weight (kg)			
Women	94.8 ± 17.9	95.4 ± 17.3	0.34†
Men	108.9 ± 19.0	109.0 ± 18.0	0.94†
Waist circumference (cm)			
Women	110.5 ± 13.6	111.2 ± 13.2	0.14†
Men	118.7 ± 14.0	118.4 ± 12.9	0.62†
Fitness (METS)			
Women	6.7 ± 1.7	6.6 ± 1.7	0.38†
Men	7.9 ± 2.1	8.0 ± 2.2	0.89†

Data are means ± SD or frequency (%). * χ^2 test. †ANCOVA, adjusted for clinical center. ‡Self-report of prior myocardial infarction, stroke, transient ischemic attack, angioplasty/stent, coronary artery bypass graft, carotid endarterectomy, angioplasty of lower extremity, aortic aneurysm repair, or heart failure.

mation during prescreening, 15,561 (54.4%) were found to be eligible for clinic visits to confirm eligibility. The most common reasons for ineligibility at this stage were related to age (13.5%), lack of diabetes (8.6%), and the likelihood that the diabetes was type 1 (4.4%). Of 9,045 (58.1%) who attended clinic visits, 5,145 (56.9%) were ultimately randomized: 2,570 participants were assigned to ILI and 2,575 to DSE. At this stage, individuals were most commonly ineligible due to staff judgment (7.6%), elevated blood pressure (7.0%), or incomplete behavioral run ins (4.8%).

At baseline, the characteristics of participants assigned to the two intervention conditions were similar (Table 1). Overall, 14.0% reported a history of cardiovascular disease, 94.0% met the National Cholesterol Education Program Adult Treatment Panel III definition for the metabolic syndrome (12), 15.3% were taking insulin, 87.5% were using diabetes medicines (including insulin), 75.3% were using antihypertensive medicines, and 51.0% were using lipid-lowering medi-

cines. Baseline BMI, weight, waist circumference, and fitness are given by sex in Table 1. A BMI of ≥ 30.0 kg/m² was present in 85.1% of participants.

Weight loss

The 1-year examination was attended by 2,496 (97.1%) of the ILI and 2,463 (95.7%) of the DSE participants ($P = 0.004$). Among the factors listed in Table 1, only the distribution of baseline insulin use significantly varied between nonattendees (21.0%) versus attendees (15.1%) ($P = 0.04$). Over the 1st year of the trial, the ILI group lost an average of (means ± SD) $8.6 \pm 6.9\%$ of initial body weight compared with $0.7 \pm 4.8\%$ in the DSE group ($P < 0.001$). Figure 2A portrays the cumulative distribution of weight changes in the two groups. Within the ILI group, 37.8% of participants met the individual weight loss goal ($>10\%$ of initial weight) and 55.2% met the group average goal ($>7\%$) compared with 3.2 and 7.0% of DSE participants, respectively. These weight losses were accompanied by greater mean reductions in waist

circumference in the ILI than DSE group, with mean decreases of 6.2 ± 10.2 vs. 0.5 ± 8.5 cm ($P < 0.001$).

In the ILI group, the average weight loss among baseline insulin users was $7.6 \pm 7.0\%$ compared with $8.7 \pm 6.9\%$ in nonusers ($P = 0.002$). Insulin users, compared with noninsulin users, were less likely to achieve weight losses $>10\%$ (33.5 vs. 38.5%) or $>7\%$ (47.8 vs. 56.4%). In the DSE group, average weight loss was $0.3 \pm 5.1\%$ among insulin users versus $0.8 \pm 4.7\%$ among noninsulin users.

Changes in fitness

Figure 2B illustrates the cumulative distribution of measured 1-year fitness changes in 4,246 participants who had repeat testing. Fitness tended to increase in both groups; however, increases were more prevalent and tended to be larger among ILI participants; 70.1% of the ILI participants had increased fitness at 1 year compared with 46.3% of the DSE participants ($P < 0.001$). Fitness increases averaged $20.9 \pm 29.1\%$ among ILI participants compared with $5.8 \pm 22.0\%$ among DSE participants ($P < 0.001$). These changes could not be fully accounted for by changes in weight. After covariate adjustment for weight changes, the fitted mean difference in fitness increases between groups remained statistically significant (15.9% for ILI vs. 10.8% for DSE, $P < 0.001$).

Changes in medicines and cardiovascular risk factors

During the 1st year, use of glucose-lowering medicines among ILI participants decreased from 86.5 to 78.6%, whereas it increased from 86.5 to 88.7% among DSE participants ($P < 0.001$). As shown in Table 2, despite this difference, mean fasting glucose declined more among ILI participants compared with DSE participants ($P < 0.001$), as did mean A1C ($P < 0.001$).

As described in Table 2, the prevalence of antihypertensive medicine use remained unchanged among ILI participants but increased by 2.2% (0.6%) among DSE participants ($P = 0.02$). Mean systolic and diastolic blood pressure levels declined in both groups, but reductions were significantly greater in ILI than in DSE participants (both $P < 0.001$).

Use of lipid-lowering medicines increased in both groups; however, the increase was significantly smaller among ILI participants than in DSE participants

Table 2—Changes in measures of diabetes control, blood pressure control, measures of lipid/lipoproteins control, albumin-to-creatinine ratio, and prevalence of metabolic syndrome among participants seen at year 1

Measure	ILI	DSE	P value
<i>n</i>	2,496	2,463	
Use of diabetes medicines (%)			
Baseline	86.5 ± 0.7	86.5 ± 0.7	0.93*
Year 1	78.6 ± 0.8	88.7 ± 0.6	<0.001*
Change	−7.8 ± 0.6	2.2 ± 0.5	<0.001†
Fasting glucose (mg/dl)			
Baseline	151.9 ± 0.9	153.6 ± 0.9	0.21‡
Year 1	130.4 ± 0.8	146.4 ± 0.9	<0.001‡
Change	−21.5 ± 0.9	−7.2 ± 0.9	<0.001‡
A1C (%)			
Baseline	7.25 ± 0.02	7.29 ± 0.02	0.26‡
Year 1	6.61 ± 0.02	7.15 ± 0.02	<0.001‡
Difference	−0.64 ± 0.02	−0.14 ± 0.02	<0.001‡
Use of antihypertensive medicines (%)			
Baseline	75.3 ± 0.9	73.7 ± 0.9	0.23*
Year 1	75.2 ± 0.9	75.9 ± 0.9	0.54*
Change	−0.1 ± 0.6	2.2 ± 0.6	0.02†
Systolic blood pressure (mmHg)			
Baseline	128.2 ± 0.4	129.4 ± 0.3	0.01‡
Year 1	121.4 ± 0.4	126.6 ± 0.4	<0.001‡
Change	−6.8 ± 0.4	−2.8 ± 0.3	<0.001‡
Diastolic blood pressure (mmHg)			
Baseline	69.9 ± 0.2	70.4 ± 0.2	0.11‡
Year 1	67.0 ± 0.2	68.6 ± 0.2	<0.001‡
Change	−3.0 ± 0.2	−1.8 ± 0.2	<0.001‡
Use of lipid-lowering medicines (%)			
Baseline	49.4 ± 1.0	48.4 ± 1.0	0.52*
Year 1	53.0 ± 1.0	57.8 ± 1.0	<0.001*
Change	3.7 ± 0.8	9.4 ± 0.8	<0.001†
LDL cholesterol (mg/dl)			
Baseline	112.2 ± 0.4	112.4 ± 0.6	0.78‡
Year 1	107.0 ± 0.6	106.7 ± 0.7	0.74‡
Change	−5.2 ± 0.6	−5.7 ± 0.6	0.49‡
HDL cholesterol (mg/dl)			
Baseline	43.5 ± 0.2	43.6 ± 0.2	0.80‡
Year 1	46.9 ± 0.3	44.9 ± 0.2	<0.001‡
Change	3.4 ± 0.2	1.4 ± 0.1	<0.001‡
Triglycerides (mg/dl)			
Baseline	182.8 ± 2.3	180.0 ± 2.4	0.38‡
Year 1	152.5 ± 1.8	165.4 ± 1.9	<0.001‡
Change	−30.3 ± 2.0	−14.6 ± 1.8	<0.001‡
Albumin-to-creatinine ratio (>30.0 μg/mg) (%)			
Baseline	16.4 ± 0.7	16.9 ± 0.8	0.69‡
Year 1	12.5 ± 0.7	15.4 ± 0.7	0.005‡
Change	−3.9 ± 0.6	−1.5 ± 0.6	0.002‡
Metabolic syndrome (%)			
Baseline	93.6 ± 0.5	94.4 ± 0.5	0.23‡
Year 1	78.9 ± 0.8	87.3 ± 0.7	<0.001‡
Change	−14.7 ± 0.8	−7.1 ± 0.7	<0.001‡

Data are means ± SE or % ± SE. *Logistic regression with adjustment for clinical site. †Mantel-Haenszel test with adjustment for clinical site. ‡ANCOVA, with adjustment for clinical site.

($P < 0.001$). Mean levels of LDL cholesterol declined by similar magnitudes in both groups ($P = 0.49$). Mean HDL cho-

lesterol levels increased more among ILI than DSE participants ($P < 0.001$), whereas mean triglyceride levels de-

creased more among ILI ($P < 0.001$). The prevalence of urine albumin-to-creatinine ratios ≥ 30.0 μg/mg decreased more among ILI participants than DSE participants ($P = 0.002$).

Classification of participants

The percentage meeting criteria for the metabolic syndrome decreased significantly more among ILI than DSE participants ($P < 0.001$). As shown in Table 2, the prevalence declined from 93.6 to 78.9% in the ILI group compared with a decline of 94.4 to 87.3% in the DSE group. The prevalence of meeting ADA goals for A1C, blood pressure, and LDL cholesterol increased among both ILI and DSE participants (Table 3). These increases were greater among ILI participants ($P < 0.001$) for A1C and blood pressure $26.4 \pm 1.0\%$ vs. $5.4 \pm 1.07\%$ and $15.1 \pm 1.1\%$ vs. $7.0 \pm 1.2\%$, respectively (both $P < 0.001$), but were of similar magnitudes for LDL cholesterol. The prevalence simultaneously meeting all three goals increased from 10.8 to 23.6% among ILI participants compared with an increase from 9.5 to 16.0% among DSE participants ($P < 0.001$).

CONCLUSIONS— The present results show that clinically significant weight loss is broadly achievable in subjects with type 2 diabetes and is associated with improved cardiovascular risk factors. At 1 year, participants in ILI achieved an average loss of 8.6% of initial body weight and a 21% improvement in cardiovascular fitness. Separate manuscripts are underway that will provide details on the relative contributions of individual strategies (e.g., meal replacement, orlistat) toward this successful outcome. Even participants on insulin lost an average of 7.6% of initial weight. The ILI was associated with an increase from 46 to 73% in the participants who met the ADA goal of A1C $< 7\%$ and a doubling in the percent of individuals who met all three of the ADA goals for glycemic control, hypertension, and dyslipidemia.

Look AHEAD is the first large clinical trial to compare an intensive weight loss intervention (i.e., ILI) with a support and education group (i.e., DSE) in individuals with type 2 diabetes. As expected, participants in the ILI group had significantly greater weight loss and improvement in fitness at 1 year than those in the DSE group. Moreover, they had a significantly greater decrease in the number of medicines used to treat their diabetes and

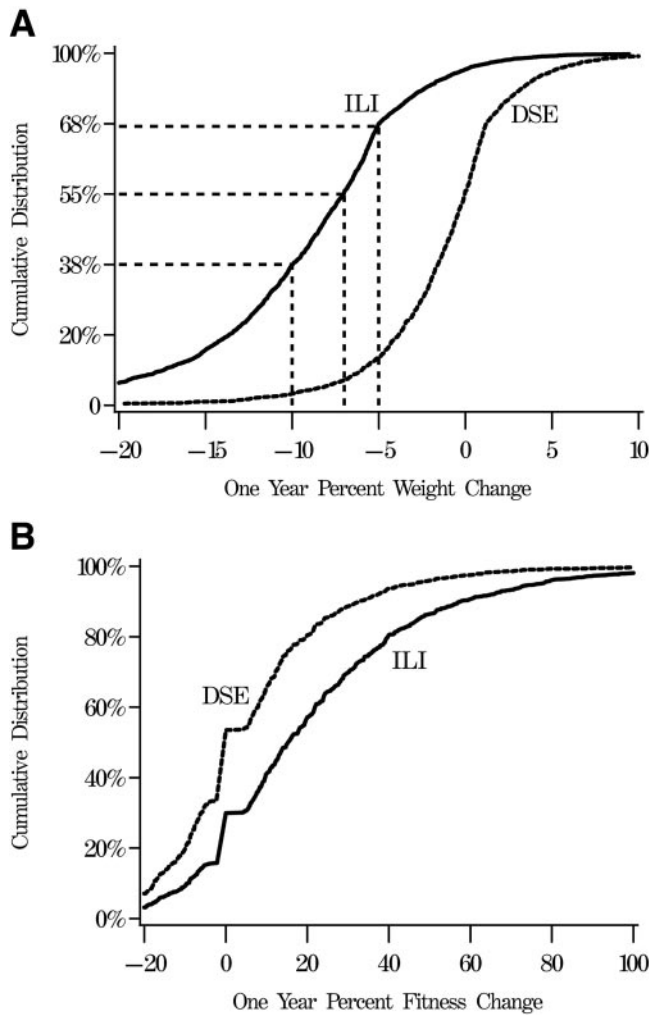


Figure 2—Distribution of 1-year changes in percent weight (A) and fitness (B) (METS) among individuals grouped by intervention assignment. Dashed lines are used to indicate the percentages of ILI participants with weight losses exceeding 10, 7, and 5%, respectively.

blood pressure. Despite the greater reductions in these medicines, the ILI group showed greater improvements in their glycemic control, albumin-to-creatinine ratio, systolic and diastolic blood pressure, triglycerides, and HDL cholesterol than the DSE group. Changes in LDL cholesterol were comparable in the two groups. Of particular note is that mean A1C fell from 7.2 to 6.6%. Few studies, even trials of newer diabetes medicines, have achieved levels of A1C of 6.6%. Although the DSE group had smaller benefits than ILI, it is important to recognize that these participants also experienced some improvement (not worsening), on average, in weight, fitness, and cardiovascular risk factors.

The Look AHEAD participants are of similar ethnic distribution to that observed in the National Health and Nutrition Examination Survey 1999–2000

(14), but their average baseline BMI was higher. Overall, they are healthier than diabetic individuals in the National Health and Nutrition Examination Survey with regard to glucose, A1C, and lipid levels and are less likely to smoke. A large percentage was taking medicines for risk factors at study enrollment, and many had a significant history of cardiovascular disease. Despite the level of health of the sample, fewer than half met the ADA goal for A1C and only 10% met all three ADA goals (13). The ILI was extremely effective in increasing the percent of participants who met these goals. At 1 year, 72.7% met the goal for A1C and 23.6% met all three goals, compared with only 50.8 and 16.0%, respectively, for the DSE group. The ILI also was associated with significantly greater remission of the metabolic syndrome than was the DSE intervention.

Several large clinical trials of individuals with impaired glucose tolerance (6,15) or hypertension (16,17) have achieved average weight losses of 4–7% at 1 year using intensive lifestyle interventions that emphasized behavior change. These weight losses were associated with marked improvement in health status. Although a number of smaller studies (18,19) have shown that it is possible, using strong behavioral programs, to produce significant weight loss in patients with type 2 diabetes, most studies of weight loss in such individuals have had only modest success. It appears that individuals with diabetes (especially those on insulin) may have more difficulty losing

Table 3—Changes in percentage of participants meeting ADA goals for risk factors

Measure	ILI	DSE	P value
A1C (<7%)			
Baseline	46.3 ± 1.0	45.4 ± 1.0	0.50*
Year 1	72.7 ± 0.9	50.8 ± 1.0	<0.001*
Difference	26.4 ± 1.0	5.4 ± 1.0	<0.001†
Blood pressure (<130/80 mmHg) (%)			
Baseline	53.5 ± 1.0	49.9 ± 1.0	0.01*
Year 1	68.6 ± 0.9	57.0 ± 1.0	<0.001*
Change	15.1 ± 1.1	7.0 ± 1.2	<0.001†
LDL cholesterol (<100 mg/dl) (%)			
Baseline	37.1 ± 1.0	36.9 ± 1.0	0.87*
Year 1	43.8 ± 1.0	44.9 ± 1.0	0.45*
Change	6.7 ± 1.0	8.0 ± 1.0	0.34†
All three goals			
Baseline	10.8 ± 0.6	9.5 ± 0.6	0.13*
Year 1	23.6 ± 0.8	16.0 ± 0.7	<0.001*
Change	12.8 ± 0.9	6.5 ± 0.8	<0.001†

Data are % ± SD. *Logistic regression with adjustment for clinical site. †Mantel-Haenszel test with adjustment for clinical site.

weight and then keeping it off than those without diabetes (20). For example, among adult Pima Indians receiving standard clinical care for type 2 diabetes, those treated with insulin lost less weight than those treated without drugs or with oral agents (21). The larger weight losses in Look AHEAD than in prior clinical trials may be attributable to the combination of group and individual contact, the higher physical activity goal that was prescribed, and/or the more intense dietary intervention, which included not only calorie and fat restrictions but also structured meal plans, each of which has previously been associated with successful weight loss and maintenance (22–25). Although Look AHEAD participants using insulin achieved less average weight loss than those not on insulin (7.6 vs. 8.7%), the weight loss of the participants on insulin demonstrates that use of insulin does not prevent successful weight loss. A recent meta-analysis (26) found that the use of meal replacements increased both short- and long-term average weight loss by ~2.5 kg, compared with prescription of a conventional reducing diet with the same calorie goals. Our findings that participants in the ILI had significant improvements in cardiovascular risk factors confirms prior studies showing that initial weight loss in type 2 diabetes is associated with improved glycemic control and cardiovascular risk factors at 1 year (27,28). However, the long-term impact of such weight losses remains unclear.

Estimated fitness improved in both groups over the year, but it improved significantly more in the ILI group. It is unknown how much of the improvement in either treatment group was due to measurement variability and greater familiarity with the testing procedure at the 1-year visit and how much represented physiologic change. The difference in improvement between the ILI and DSE groups, however, can be taken as a measure of the ILI treatment effect. This treatment effect persisted even after adjustment for the 1-year weight change. The changes in fitness compared favorably with those observed in prior studies with both diabetic (29,30) and nondiabetic (29,31,32) participants. Thus, the modest increase in physical activity, primarily walking, had a very beneficial effect. This may translate into a lower rate of cardiovascular events, including mortality, as suggested in some observational studies (33,34).

The primary outcome of the Look

AHEAD trial is the effect of weight loss on the development of cardiovascular disease. Although the difference between the ILI and DSE groups in the change in risk factors at 1-year points to the potential cardiovascular benefits of the ILI, we will need several additional years to determine whether the initial weight loss can be maintained, whether weight loss has a long-term effect on the risk factors, and whether the favorable risk factor changes translate into reduced cardiovascular events. This is critical information for establishing evidence-based recommendations with regard to weight loss for the prevention of cardiovascular disease in individuals with diabetes.

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APPENDIX

Authors

Xavier Pi-Sunyer, MD; George Blackburn, MD, PhD; Frederick L. Brancati, MD, MHS; George A. Bray, MD; Renee Bright, MS; Jeanne M. Clark, MD, MPH; Jeffrey M. Curtis, MD, MPH; Mark A. Espeland, PhD; John P. Foreyt, PhD; Kathryn Graves, MPH, RD, CDE; Steven M. Haffner, MD; Barbara Harrison, MS; James O. Hill, PhD; Edward S. Horton, MD; John Jakicic, PhD; Robert W. Jeffery, PhD; Karen C. Johnson, MD, MPH; Steven Kahn, MB, ChB; David E. Kelley, MD; Abbas E. Kitabchi, MD, PhD; William C. Knowler, MD, DrPH; Cora E. Lewis, MD, MSPH; Barbara J. Maschak-Carey, MSN, CDE; Brenda Montgomery, RN, MS, CDE; David M. Nathan, MD; Jennifer Patricio, MS; Anne Peters, MD; J. Bruce Redmon, MD; Rebecca S. Reeves, DrPH, RD; Donna H. Ryan, MD; Monika Safford, MD; Brent Van Dorsten, PhD; Thomas A. Wadden, PhD; Lynne Wagenknecht, DrPH; Jacqueline Wesche-Thobaben, RN, BSN, CDE; Rena R. Wing, PhD; Susan Z. Yanovski, MD.

Clinical sites

The Johns Hopkins Medical Institutions: Frederick L. Brancati, MD, MHS; Jeff Honnas, MS; Lawrence Cheskin, MD; Jeanne M. Clark, MD, MPH; Kerry Stewart, EdD; Richard Rubin, PhD; Jeanne Charleston, RN; Kathy Horak, RD.

Pennington Biomedical Research Center: George A. Bray, MD; Kristi Rau; Allison Strate, RN; Brandi Armand, LPN; Frank L. Greenway, MD; Donna H. Ryan, MD; Donald Williamson, PhD; Amy Bachand; Michelle Begnaud; Betsy Berhard; Elizabeth Caderette; Barbara Cerniauskas; David Creel; Diane Crow; Helen Guay; Nancy Kora; Kelly LaFleur; Kim Landry; Missy Lingle; Jennifer Perault; Mandy Shipp, RD; Marisa Smith; Elizabeth Tucker.

The University of Alabama at Birmingham: Cora E. Lewis, MD, MSPH; Sheikilya Thomas, MPH; Monika Safford, MD; Vicki DiLillo, PhD; Charlotte Bragg,

MS, RD, LD; Amy Dobelstein; Stacey Gilbert, MPH; Stephen Glasser, MD; Sara Hannum, MA; Anne Hubbell, MS; Jennifer Jones, MA; DeLavallade Lee; Ruth Luketic, MA, MBA, MPH; Karen Marshall; L. Christie Oden; Janet Raines, MS; Cathy Roche, RN, BSN; Janet Truman; Nita Webb, MA; Audrey Wrenn, MAEd.

Harvard center: Massachusetts General Hospital: David M. Nathan, MD; Heather Turgeon, RN, BS, CDE; Kristina Schumann, BA; Enrico Cagliero, MD; Linda Delahanty, MS, RD; Kathryn Hayward, MD; Ellen Anderson, MS, RD; Laurie Bissett, MS, RD; Richard Ginsburg, PhD; Valerie Goldman, MS, RD; Virginia Harlan, MSW; Charles McKittrick, RN, BSN, CDE; Alan McNamara, BS; Theresa Michel, DPT, DSc, CCS; Alexi Poulos, BA; Barbara Steiner, EdM; Joclyn Tosch, BA. Joslin Diabetes Center: Edward S. Horton, MD; Sharon D. Jackson, MS, RD, CDE; Osama Hamdy, MD, PhD; A. Enrique Caballero, MD; Sarah Bain, BS; Elizabeth Bovaird, BSN, RN; Ann Goebel-Fabbri, PhD; Lori Lambert, MS, RD; Sarah Ledbury, MEd, RD; Maureen Malloy, BS; Kerry Ovalle, MS, RCEP, CDE. Beth Israel Deaconess Medical Center: George Blackburn, MD, PhD; Christos Mantzoros, MD, DSc; Kristina Day, RD; Ann McNamara, RN.

University of Colorado Health Sciences Center: James O. Hill, PhD; Marsha Miller, MS, RD; JoAnn Phillip, MS; Robert Schwartz, MD; Brent Van Dorsten, PhD; Judith Regensteiner, PhD; Salma Benchekroun, MS; Ligia Coelho, BS; Paulette Cohrs, RN, BSN; Elizabeth Daen-inck, MS, RD; Amy Fields, MPH; Susan Green; April Hamilton, BS, CCRP; Jere Hamilton, BA; Eugene Leshchinskiy; Michael McDermott, MD; Lindsey Munkwitz, BS; Loretta Rome, TRS; Kristin Wallace, MPH; Terra Worley, BA.

Baylor College of Medicine: John P. Foreyt, PhD; Rebecca S. Reeves, DrPH, RD; Henry Pownall, PhD; Ashok Balasubramanyam, MBBS; Peter Jones, MD; Michele Burrington, RD; Chu-Huang Chen, MD, PhD; Allyson Clark, RD; Molly Gee, MEd, RD; Sharon Griggs; Michelle Hamilton; Veronica Holley; Jayne Joseph, RD; Patricia Pace, RD; Julieta Palencia, RN; Olga Satterwhite, RD; Jennifer Schmidt; Devin Volding, LMSW; Carolyn White.

University of California at Los Angeles School of Medicine: Mohammed F. Saad, MD; Siran Ghazarian Sengardi, MD; Ken C. Chiu, MD; Medhat Botrous; Mich-

elle Chan, BS; Kati Konersman, MA, RD, CDE; Magpuri Perpetua, RD.

The University of Tennessee Health Science Center: Karen C. Johnson, MD, MPH; Helen Lambeth, RN, BSN; Carolyn M. Gresham, RN; Abbas E. Kitabchi, MD, PhD; Stephanie A. Connelly, MD, MPH; Lynne Lichtermann, RN, BSN.

University of Minnesota: Robert W. Jeffery, PhD; Carolyn Thorson, CCRP; John P. Bantle, MD; J. Bruce Redmon, MD; Richard S. Crow, MD; Scott Crow, MD; Susan K. Raatz, PhD, RD; Kerrin Brelje, MPH, RD; Carolyne Campbell; Jeanne Carls, MEd; Tara Carmean-Mihm, BA; Emily Finch, MA; Anna Fox, MA; Elizabeth Hoelscher, MPH, RD, CHES; La Donna James; Vicki A. Maddy, BS, RD; Therese Ockenden, RN; Birgitta I. Rice, MS, RPH CHES, BS; Ann D. Tucker, BA; Mary Susan Voeller, BA; Cara Walcheck, BS, RD.

St. Luke's Roosevelt Hospital Center: Xavier Pi-Sunyer, MD; Jennifer Patricio, MS; Stanley Heshka, PhD; Carmen Pal, MD; Lynn Allen, MD; Diane Hirsch, RNC, MS, CDE; Mary Anne Holowaty, MS, CN.

University of Pennsylvania: Thomas A. Wadden, PhD; Barbara J. Maschak-Carey, MSN, CDE; Stanley Schwartz, MD; Gary D. Foster, PhD; Robert I. Berkowitz, MD; Henry Glick, PhD; Shiriki K. Kumanyika, PhD, RD, MPH; Johanna Brock; Helen Chomentowski; Vicki Clark; Canice Crerand, PhD; Renee Davenport; Andrea Diamond, MS, RD; Anthony Fabricatore, PhD; Louise Hesson, MSN; Stephanie Krauthamer-Ewing, MPH; Robert Kuehnel, PhD; Patricia Lipschutz, MSN; Monica Mullen, MS, RD; Leslie Womble, PhD, MS; Nayyar Iqbal, MD.

University of Pittsburgh: David E. Kelley, MD; Jacqueline Wesche-Thobaben, RN, BSN, CDE; Lewis Kuller, MD, DrPH; Andrea Kriska, PhD; Janet Bonk, RN, MPH; Rebecca Danchenko, BS; Daniel Edmundowicz, MD; Mary L. Klem, PhD, MLIS; Monica E. Yamamoto, DrPH, RD, FADA; Barb Elnyczky, MA; George A. Grove, MS; Pat Harper, MS, RD, LDN; Janet Krulia, RN, BSN, CDE; Juliet Mancino, MS, RD, CDE, LDN; Anne Mathews, MS, RD, LDN; Tracey Y. Murray, BS; Joan R. Ritchea; Jennifer Rush, MPH; Karen Vujevich, RN-BC, MSN, CRNP; Donna Wolf, MS.

The Miriam Hospital/Brown Medical School: Rena R. Wing, PhD; Renee Bright, MS; Vincent Pera, MD; John Jakicic, PhD; Deborah Tate, PhD; Amy Gorin, PhD; Kara Gallagher, PhD; Amy Bach, PhD;

Barbara Bancroft, RN, MS; Anna Bertorelli, MBA, RD; Richard Carey, BS; Tatum Charron, BS; Heather Chenot, MS; Kimberley Chula-Maguire, MS; Pamela Coward, MS, RD; Lisa Cronkite, BS; Julie Currin, MD; Maureen Daly, RN; Caitlin Egan, MS; Erica Ferguson, BS, RD; Linda Foss, MPH; Jennifer Gauvin, BS; Don Kieffer, PhD; Lauren Lessard, BS; Deborah Maier, MS; J.P. Massaro, BS; Tammy Monk, MS; Rob Nicholson, PhD; Erin Patterson, BS; Suzanne Phelan, PhD; Hollie Raynor, PhD, RD; Douglas Raynor, PhD; Natalie Robinson, MS, RD; Deborah Robles; Jane Tavares, BS.

The University of Texas Health Science Center at San Antonio: Steven M. Haffner, MD; Maria G. Montez, RN, MSHP, CDE; Carlos Lorenzo, MD.

University of Washington/VA Puget Sound Health Care System: Steven Kahn MB, ChB; Brenda Montgomery, RN, MS, CDE; Robert Knopp, MD; Edward Lipkin, MD; Matthew L. Maciejewski, PhD; Dace Trencze, MD; Terry Barrett, BS; Joli Bartell, BA; Diane Greenberg, PhD; Anne Murillo, BS; Betty Ann Richmond, MEd; April Thomas, MPH, RD.

Southwestern American Indian Center, Phoenix, Arizona, and Shiprock, New Mexico: William C. Knowler, MD, DrPH; Paula Bolin, RN, MC; Tina Killeen, BS; Jonathan Krakoff, MD; Jeffrey M. Curtis, MD, MPH; Justin Glass, MD; Sara Michaels, MD; Peter H. Bennett, MB, FRCP; Tina Morgan; Shandiin Begay, MPH; Bernadita Fallis, RN, RHIT, CCS; Jeanette Hermes, MS, RD; Diane F. Hollowbreast; Ruby Johnson; Cathy Manus, LPN; Maria Meacham, BSN, RN, CDE; Julie Nelson, RD; Carol Percy, RN; Patricia Poorthunder; Sandra Sangster; Nancy Scurlock, MSN, ANP-C, CDE; Leigh A. Shovestull, RD, CDE; Janelia Smiley; Katie Toledo, MS, LPC; Christina Tomchee, BA; Darryl Tonemah, PhD.

University of Southern California: Anne Peters, MD; Valerie Ruelas, MSW, LCSW; Siran Ghazarian Sengardi, MD; Kathryn Graves, MPH, RD, CDE; Kati Konersman, MA, RD, CDE; Sara Serafin-Dokhan.

Coordinating center

Wake Forest University: Mark A. Espeland, PhD; Judy L. Bahnson, BA; Lynne Wagenknecht, DrPH; David Reboussin, PhD; W. Jack Rejeski, PhD; Alain Bertoni, MD, MPH; Wei Lang, PhD; Gary Miller, PhD; David Lefkowitz, MD; Patrick S. Reynolds, MD; Paul Ribisl, PhD; Mara Vitols, DrPH; Michael Booth, MBA; Kathy

M. Dotson, BA; Amelia Hodges, BS; Carrie C. Williams, BS; Jerry M. Barnes, MA; Patricia A. Feeney, MS; Jason Griffin, BS; Lea Harvin, BS; William Herman, MD, MPH; Patricia Hogan, MS; Sarah Jaramillo, MS; Mark King, BS; Kathy Lane, BS; Rebecca Neiberg, MS; Andrea Ruggiero, MS; Christian Speas, BS; Michael P. Walkup, MS; Karen Wall, AAS; Michelle Ward; Debra S. West, PhD; Terri Windham.

Central resources centers

Dual-Energy X-Ray Absorptiometry Reading Center, University of California at San Francisco: Michael Nevitt, PhD; Susan Ewing, MS; Cynthia Hayashi; Jason Maeda, MPH; Lisa Palermo, MS, MA; Michaela Rahorst; Ann Schwartz, PhD; John Shepherd, PhD.

Central Laboratory, Northwest Lipid Research Laboratories: Santica M. Marcovina, PhD, ScD; Greg Strlewick, MS.

Electrocardiogram Reading Center, EPICARE, Wake Forest University School of Medicine: Ronald J. Prineas, MD, PhD; Teresa Alexander; Lisa Billings; Charles Campbell, AAS, BS; Sharon Hall; Susan Hensley; Yabing Li, MD; Zhu-Ming Zhang, MD.

Diet Assessment Center, University of South Carolina, Arnold School of Public Health, Center for Research in Nutrition and Health Disparities: Elizabeth J Mayer-Davis, PhD; Robert Moran, PhD.

Hall-Foushee Communications: Richard Foushee, PhD; Nancy J. Hall, MA.

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