



Association of Weight Loss Maintenance and Weight Regain on 4-Year Changes in CVD Risk Factors: the Action for Health in Diabetes (Look AHEAD) Clinical Trial

Diabetes Care 2016;39:1345–1355 | DOI: 10.2337/dc16-0509

The Action for Health in Diabetes (Look AHEAD) Study Group*

OBJECTIVE

Short-term weight loss improves cardiovascular disease (CVD) risk factors. We sought to determine the longer-term effects of maintaining weight loss or, conversely, regaining weight.

RESEARCH DESIGN AND METHODS

We used data from Action for Health in Diabetes (Look AHEAD), a randomized trial of intensive lifestyle intervention (ILI) compared to a control condition in overweight/obese individuals with type 2 diabetes. ILI participants were grouped according to weight change patterns, as follows: 1) no weight loss ($\pm 3\%$ at years 1 and 4); 2) moderate weight loss (3–8% at years 1 and 4); 3) large weight loss (8–20% at years 1 and 4); 4) moderate loss/full regain (3–8% at year 1/ $\pm 3\%$ at year 4); 5) large loss/full regain (8–20% at year 1/ $\pm 3\%$ year 4); and 6) large loss/partial regain (8–20% at year 1/3–8% at year 4) and changes in CVD risk factors were compared.

RESULTS

Adjusting for baseline differences and medication use, larger weight losses produced greater improvements in HbA_{1c}, systolic blood pressure, HDL cholesterol, and triglycerides at years 1 and 4 (all $P \leq 0.02$). Despite maintenance of weight loss, HbA_{1c} levels worsened between years 1 and 4, and remained below baseline only in those with large weight losses. We found no negative associations of losing and regaining weight relative to not having lost weight. Moreover, those who had large initial weight loss but full regain of weight had greater improvements in HbA_{1c} levels at year 4 than those with smaller or no initial weight loss.

CONCLUSIONS

Larger initial weight loss should be encouraged in individuals with type 2 diabetes, despite the possibility of regain.

Behavioral approaches are recommended for weight loss. These approaches typically involve face-to-face meetings, recommendations for changing both eating and physical activity, and strategies to achieve these behavior changes in the long term. However, despite the emphasis on long-term maintenance of weight loss, the greatest weight losses occur on average at approximately 6 months or 1 year, and are followed by gradual weight regain (1). Previous studies (2–4) show that ongoing

Corresponding author: Rena R. Wing, rwing@lifespan.org.

Received 8 March 2016 and accepted 5 May 2016.

Clinical trial reg. no. NCT00017953, clinicaltrials.gov.

This article contains Supplementary Data online at <http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc16-0509/-/DC1>.

*A complete list of the Action for Health in Diabetes (Look AHEAD) Study Group can be found in the Supplementary Data online. Members of the Action for Health in Diabetes (Look AHEAD) Writing Group are presented in the APPENDIX.

© 2016 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered.

treatment contact improves the maintenance of weight loss, but even with such contact, participants typically regain 30–50% of their initial weight loss over the next 2–3 years. Likewise, the greatest improvements in cardiovascular disease (CVD) risk factors are typically seen at 6 months or 1 year (5,6). Given that weight regain is common after behavioral treatment for obesity, it is important to know whether it is better to have lost and regained weight than to have never lost it at all.

The Action for Health in Diabetes (Look AHEAD) study provides an ideal opportunity to examine this question. Look AHEAD was a randomized clinical trial comparing the effects on an intensive lifestyle intervention (ILI) and a control group (referred to as Diabetes Support and Education) on cardiovascular outcomes in >5,000 overweight or obese individuals with type 2 diabetes (7). The present article focuses on the ILI because it was designed to produce intentional weight loss. We previously reported that participants who were assigned to ILI lost on average $8.6 \pm 0.2\%$ of initial weight (mean \pm SE) at year 1. The magnitude of weight loss was strongly associated with the degree of improvement in glycemic control, systolic blood pressure (SBP), triglycerides, and HDL cholesterol (HDL-C). Moreover, weight losses of 5–10% were associated with significant improvements in these CVD risk factors (8). After 4 years of ongoing intervention, the average weight loss in ILI had decreased to $4.7 \pm 0.2\%$ of initial weight. Of those who lost 10% initially, 42% still maintained a 10% weight loss at 4 years (4). Although ILI continued to have significantly greater improvements than Diabetes Support and Education in glycemia, SBP, and HDL-C at year 4, the improvements in risk factors in ILI were less at year 4 than at year 1 (6,9).

This article seeks to determine the associations between specific weight change patterns and changes in CVD risk factors over these 4 years. We examine the associations of both losing weight and maintaining it, and losing weight and regaining it with changes in CVD risk factors to address the following questions: 1) in individuals who lose weight and maintain their weight loss, is the improvement in cardiovascular risk factors seen at year 4 similar to what was seen at year 1?; and (2) are

the changes in CVD risk factors at year 4 greater or less in those who lost weight and regained it compared with those who did not initially lose weight? Although the Look AHEAD trial continued its intervention for almost 10 years, we focus on the first 4 years of the trial because weight loss during this period is more likely to reflect intentional weight loss. Weight loss and subsequent regain occurs most commonly during these years as well. Moreover, although the Look AHEAD trial found no significant effect of ILI on major cardiovascular event outcomes, it is important to understand the effect of weight change patterns on CVD risk factors. The changes in CVD risk factors have been related to microvascular complications in those with diabetes and may have a broad impact on health (10).

RESEARCH DESIGN AND METHODS

Participants

All enrollees in Look AHEAD trial were 45–76 years of age, were overweight or obese, and had type 2 diabetes. Baseline characteristics have been described in detail (11). Our current analyses focused on participants who were randomly assigned to receive the Look AHEAD ILI and fell into one of the six weight change categories described below ($N = 1,428$). The 1,428 participants included in these analyses were compared with those excluded (Supplementary Table 1). Excluded participants differed significantly from those included on several baseline characteristics, but the magnitude of the differences was small (e.g., excluded were younger [age 58.1 vs. 59 years] and heavier [BMI 36.5 vs. 35. kg/m²]).

Intervention

The ILI was designed to help participants lose weight by changing their eating and physical activity levels. Both group and individual sessions were provided throughout the intervention, with the frequency of sessions greatest during the first year of the program. The goal was to achieve a weight loss of at least 7% of body weight. To meet this goal, participants who weighed <250 pounds were prescribed an intake of 1,200–1,500 kcal/day, and those participants who weighed >250 pounds were prescribed 1,500–1,800 kcal/day. Physical activity was gradually increased over time until reaching a goal of 175 min/week

of moderate-intensity activity. Self-monitoring of weight, diet, and activity was stressed throughout the program, and standard behavioral strategies were emphasized. The program has been described in detail (12).

Assessments

Participants were seen annually for assessments by staff members who were masked to the intervention. Weight, height, blood pressure, and fasting blood work were assessed according to specified protocols (7). Demographic information and health history were defined by self-report. Biospecimens were analyzed at a central laboratory. Participants brought all prescription medications they were taking to be categorized at these sessions, but medication doses were not recorded. Hypertension was defined as blood pressure exceeding 140/90 mmHg or current treatment with antihypertensive medications. Both participants and their physicians received a letter each year with the results of these assessments. All medication changes were handled by each participant's physician. However, to reduce the risk of hypoglycemia, study staff managed diabetes medications according to preset algorithms during the initial intervention period.

Weight Change Patterns

We defined six patterns based on weight losses in ILI at year 1 and year 4. These patterns are referred to by number in the tables and figures, as follows:

1. No weight loss: year 1 and year 4 weight are both within $\pm 3.0\%$ of baseline weight ($N = 158$);
2. Moderate weight loss: year 1 and year 4 weights are both $\geq 3.0\%$ and $< 8.0\%$ below baseline ($N = 204$);
3. Large weight loss: year 1 and year 4 weights are both $\geq 8.0\%$ and $< 20\%$ below baseline and weight regain from year 1 to year 4 is $< 3\%$ (13) ($N = 251$);
4. Moderate weight loss/full regain: year 1 weight is $\geq 3.0\%$ and $< 8.0\%$ below baseline, and year 4 weight is within $\pm 3.0\%$ of baseline weight ($N = 289$);
5. Large weight loss/full regain: year 1 weight is $\geq 8.0\%$ and $< 20\%$ below baseline and year 4 weight is within $\pm 3.0\%$ of baseline weight ($N = 210$); and

Table 1—Mean (95% CI) percentage weight changes from mixed-effects models for the six weight patterns

Weight pattern	N	Mean (95% CI) percentage weight change		
		Year 1–baseline	Year 4–year 1	Year 4–baseline
1. No weight loss	158	−1.01 (−1.47, −0.55)	0.95 (0.33, 1.458)	−0.06 (−0.51, 0.40)
2. Moderate weight loss	204	−5.57 (−5.97, −5.17)	0.39 (−0.16, 0.94)	−5.18 (−5.58, −4.78)
3. Large weight loss	251	−11.93 (−12.30, −11.57)	−0.83 (−1.32, −0.33)	−12.76 (−13.13, −12.40)
4. Moderate weight loss/full regain	289	−5.50 (−5.83, −5.16)	5.21 (4.74, 5.67)	−0.29 (−0.63, 0.04)
5. Large weight loss/full regain	210	−11.34 (−11.74, −10.95)	10.82 (10.28, 11.36)	−0.52 (−0.92, −0.13)
6. Large weight loss/partial regain	316	−11.91 (−12.23, −11.59)	6.26 (5.82, 6.70)	−5.65 (−5.97, −5.33)

6. Large weight loss/partial regain: year 1 weight is $\geq 8.0\%$ and $< 20\%$ below baseline, and year 4 weight is $\geq 3.0\%$ and $< 8.0\%$ below baseline weight ($N = 316$).

These weight categories were defined based on the following literature: The no weight change category was defined as losing $< 3.0\%$ based on the criteria of Stevens et al. (13) that under 3% represents weight stability. The moderate

weight loss criterion of 3.0–8.0% was based on literature suggesting that standard behavioral weight loss programs typically produce weight losses of this magnitude; as noted above, ILI participants had a mean weight loss of 8.6% at 1 year (1,12,14). Weight losses of $\geq 8\%$ are considered large weight losses (14). We excluded those participants who lost and maintained $> 20\%$ ($N = 19$), who were not typical of the weight losses achieved in this category.

Statistical Methods

Participants were grouped according to the weight loss patterns described above, and baseline characteristics were compared using logistic regression and analyses of covariance, and with Tukey pairwise comparisons. Mixed-effects models were used to compare weight loss groups over time with respect to changes from baseline in CVD risk factors, with linear contrasts and Wald tests for group by time comparisons

Table 2—Baseline characteristics of the participants in the six groups based on weight change patterns

Characteristic	Pattern of weight change						P value for overall comparison of 6 patterns
	Pattern 1 (N = 158)	Pattern 2 (N = 204)	Pattern 3 (N = 251)	Pattern 4 (N = 289)	Pattern 5 (N = 210)	Pattern 6 (N = 316)	
Age, mean (SD), years	57.3 (7.0) ^{3,6}	59.4 (7.3)	60.6 (6.8) ^{1,4,5}	58.0 (6.2) ³	58.4 (6.4) ³	59.6 (7.2) ¹	<0.001
Sex, n (%)							0.09
Female	85 (53.8)	116 (56.9)	150 (59.8)	173 (59.9)	137 (65.3)	168 (53.2)	
Male	73 (46.2)	88 (43.1)	101 (40.2)	116 (40.1)	73 (34.8)	148 (46.8)	
Race/ethnicity, n (%)	^{5,6}	^{5,6}	^{4,5}	⁵	^{1,2,3,4}	^{1,2,3}	<0.001
African American	40 (25.3)	42 (20.6)	36 (14.3)	53 (18.3)	27 (12.9)	45 (14.2)	
American Indian	11 (17.2)	16 (7.8)	11 (4.4)	16 (5.5)	3 (1.4)	7 (2.2)	
Hispanic/Latino	19 (11.0)	23 (11.3)	43 (17.1)	32 (18.6)	21 (10.0)	34 (10.8)	
Non-Hispanic white	83 (52.5)	122 (59.8)	156 (62.2)	174 (60.2)	156 (74.3)	217 (68.7)	
Other/multiple	5 (3.2)	1 (0.5)	5 (2.0)	14 (4.8)	3 (1.4)	13 (4.1)	
BMI, mean (SD), kg/m ²	36.0 (5.7)	35.2 (5.9)	35.8 (6.0)	35.3 (5.9)	35.8 (5.7)	34.6 (5.4)	0.08
HbA _{1c} , mean (SD), %	7.49 (1.28) ^{3,5,6}	7.33 (1.07) ⁶	7.14 (1.13) ¹	7.26 (1.11)	7.09 (1.01) ¹	7.01 (1.06) ^{1,2}	<0.001
Insulin use, mean (SD) (missing = 51)	34 (22.7) ^{2,6}	21 (10.9) ¹	31 (12.7)	47 (16.9)	28 (13.9)	38 (12.2) ¹	0.02
Hypertension, n (%)	128 (81.0)	164 (80.4)	213 (84.9)	236 (81.7)	169 (80.5)	274 (86.7)	0.27
Blood pressure, mean (SD)							
SBP (mmHg)	129.0 (17.7)	128.9 (16.6)	128.0 (16.2)	127.0 (17.2)	128.3 (18.7)	128.1 (16.3)	0.83
DBP (mmHg)	71.1 (9.2)	71.4 (9.6)	68.9 (9.1)	69.9 (9.4)	69.2 (9.1)	70.5 (9.7)	0.03**
LDL-C, mean (SD), mg/dL (missing = 3)	112.0 (29.2)	113.9 (32.7)	109.1 (31.3)	113.6 (34.5)	112.1 (31.8)	107.9 (33.4)	0.20
HDL-C, mean (SD), mg/dL (missing = 2)	42.2 (10.8)	42.3 (10.9)	45.3 (12.9)	42.9 (11.1)	43.6 (11.5)	43.7 (11.6)	0.05**
Triglycerides (mean [SD], [mg/dL]) (missing = 2)	176.0 (114.6)	177.4 (99.4)	172.1 (105.9)	190.7 (140.1)	186.0 (114.2)	172.0 (106.3)	0.31
Receiving cholesterol medication, n (%) (missing = 34)	72 (47.4)	110 (54.5)	140 (56.7)	146 (51.8)	106 (52.0)	166 (54.1)	0.57

Superscript numbers indicate significant pairwise differences (Tukey test, $P < 0.05$) with pattern 1, no weight loss; pattern 2, moderate weight loss; pattern 3, large weight loss; pattern 4, moderate weight loss/full regain; pattern 5, large weight loss/full regain; pattern 6, large weight loss/partial regain. For example, the superscripts (3 and 6) for age for pattern 1 (no weight loss) indicate that this category differed from pattern 3 (large weight loss) and pattern 6 (large weight loss/partial regain). **No pairwise differences reached Tukey test–adjusted $P < 0.05$.

(15). In these models, age, BMI, gender, and baseline values of the risk factor being analyzed were used as fixed covariates, and changes in medications were used as time-varying covariates. To portray patterns over time, fitted means were generated, and *P* values from the marginal comparisons of mean changes over time were overlaid on figures.

RESULTS

Table 1 presents the mean percentages of weight loss over time for participants in these six groups. As shown, the two groups with moderate initial weight loss (groups 2 and 4) and the three groups with large initial weight loss (groups 3, 5, and 6) had similar initial percentages of weight loss, but very different weight losses at year 4. The two moderate weight loss groups lost ~5% of their body weight initially, whereas the three large weight loss groups averaged an 11% weight loss (the median for the

initial weight loss in the three large weight loss groups was ~11%, 25% of participants in the large weight loss category lost <10%, and 75% of participants lost <14% of their baseline weight).

Table 2 compares these six groups on baseline characteristics. The groups differed significantly with respect to mean age, HbA_{1c}, the racial/ethnic distribution, diastolic blood pressure (DBP), and the prevalence of insulin use (all *P* < 0.05), but not sex, BMI, or the presence of hypertension or dyslipidemia.

Association Between Maintenance of Weight Loss and Changes in Risk Factors

To determine whether the maintenance of weight loss was associated with the maintenance of CVD risk factor changes, we first compared those who remained in the same category of percentage weight loss at both year 1 and year 4 (no weight loss; moderate weight

loss; large weight loss [categories 1–3, as defined above]). Table 3 and Fig. 1 describe changes in weight and selected CVD risk factors for these three groups. Changes in DBP and LDL cholesterol (LDL-C) did not differ systematically for no, moderate, and large weight losses at year 1 or year 4. In contrast, for the other CVD risk factors (HbA_{1c}, SBP, HDL-C, and triglycerides) the greatest improvements in CVD risk factors at both year 1 and year 4 were in the large weight loss pattern (see Fig. 1).

We next examined whether these three groups that had maintained their weight losses between years 1 and 4 also maintained their improvements in risk factors. Table 3 (middle column) shows that HbA_{1c} levels worsened significantly over time in all three categories; there was a trend (*P* = 0.06) for the increases in HbA_{1c} to be smallest in the large weight loss pattern. Moreover, only the HbA_{1c} levels in the large weight

Table 3—Mean changes in risk factors for the three groups that remained in the same percentage weight change category from year 1 to year 4

Risk factor	Weight pattern	Mean (95% CI) changes		
		Year 1–baseline	Year 4–year 1	Year 4–baseline
HbA _{1c} (%)	1. No weight loss	−0.29 (−0.44, −0.14) ³	0.38 (0.19, 0.57)	0.08 (−0.07, 0.24) ³
	2. Moderate weight loss	−0.52 (−0.65, −0.39) ³	0.44 (0.27, 0.61)	−0.08 (−0.22, 0.05) ³
	3. Large weight loss	−0.75 (−0.87, −0.63) ^{1,2}	0.18 (0.03, 0.33)	−0.57 (−0.69, −0.45) ^{1,2}
	<i>P</i> value	<0.001	0.06	<0.001
SBP (mmHg)	1. No weight loss	−4.35 (−6.73, −1.96) ³	3.63 (0.41, 6.86)	−0.71 (−3.12, 1.70) ^{2,3}
	2. Moderate weight loss	−4.69 (−6.78, −2.60)	−0.32 (−3.17, 2.52)	−5.01 (−7.12, −2.90) ¹
	3. Large weight loss	−8.07 (−9.96, −6.19) ¹	0.35 (−2.20, 2.90)	−7.73 (−9.62, −5.83) ¹
	<i>P</i> value	0.02	0.59	<0.001
DBP (mmHg)	1. No weight loss	−2.51 (−3.72, −1.31)	0.56 (−1.04, 2.16)	−1.96 (−3.18, −0.74)
	2. Moderate weight loss	−2.22 (−3.28, −1.16)	−0.53 (−1.95, 0.88)	−2.75 (−3.82, −1.69)
	3. Large weight loss	−3.48 (−4.43, −2.52)	0.11 (−1.16, 1.37)	−3.37 (−4.32, −2.41)
	<i>P</i> value	0.19	0.84	0.20
LDL-C (mg/dL)	1. No weight loss	−10.08 (−14.00, −6.18)	−1.33 (−6.61, 3.95)	−11.42 (−15.33, −7.50)
	2. Moderate weight loss	−7.51 (−10.86, 4.15)	−9.14 (−13.71, −4.57)	−16.65 (−20.04, −13.25) ³
	3. Large weight loss	−5.38 (−8.39, −2.37)	−5.69 (−9.77, −1.61)	−11.07 (−14.10, −8.04) ²
	<i>P</i> value	0.17	0.09	0.04
HDL-C (mg/dL)	1. No weight loss	1.81 (0.63, 3.00) ³	−0.03 (−1.50, 1.44)	1.78 (0.59, 2.97) ³
	2. Moderate weight loss	2.48 (1.47, 3.50) ³	0.53 (−0.75, 1.80)	3.01 (1.98, 4.04) ³
	3. Large weight loss	4.36 (3.45, 5.28) ^{1,2}	1.65 (0.52, 2.78)	6.01 (5.09, 6.93) ^{1,2}
	<i>P</i> value	0.001	0.17	<0.001
Triglycerides (mg/dL)	1. No weight loss	−11.0 (−28.2, 6.2) ³	9.7 (−11.3, 30.6)	−1.4 (−18.6, 15.9) ³
	2. Moderate weight loss	−16.4 (−31.2, −1.6) ³	11.4 (−6.7, 29.5)	−5.0 (−20.0, 9.9) ³
	3. Large weight loss	−42.8 (−56.1, −29.6) ^{1,2}	4.1 (−12.1, 20.4)	−38.7 (−52.1, −25.3) ^{1,2}
	<i>P</i> value	0.005	0.83	<0.001

Pattern 1, no weight loss (year 1 and year 4 weight within ±3.0% of baseline; *N* = 158); pattern 2, moderate weight loss (year 1 and year 4 weights ≥3.0% and <8.0%; *N* = 204); and pattern 3, large weight loss (year 1 and year 4 weights ≥8.0% and <20%; *N* = 251). *P* values indicate significant differences among the three patterns, with covariate adjustment for baseline level of the risk factor, age, race/ethnicity, BMI, sex, and change in the use of medications for that risk factor during the 4-year period. Superscripts indicate significant pairwise differences (Tukey test, *P* < 0.05).

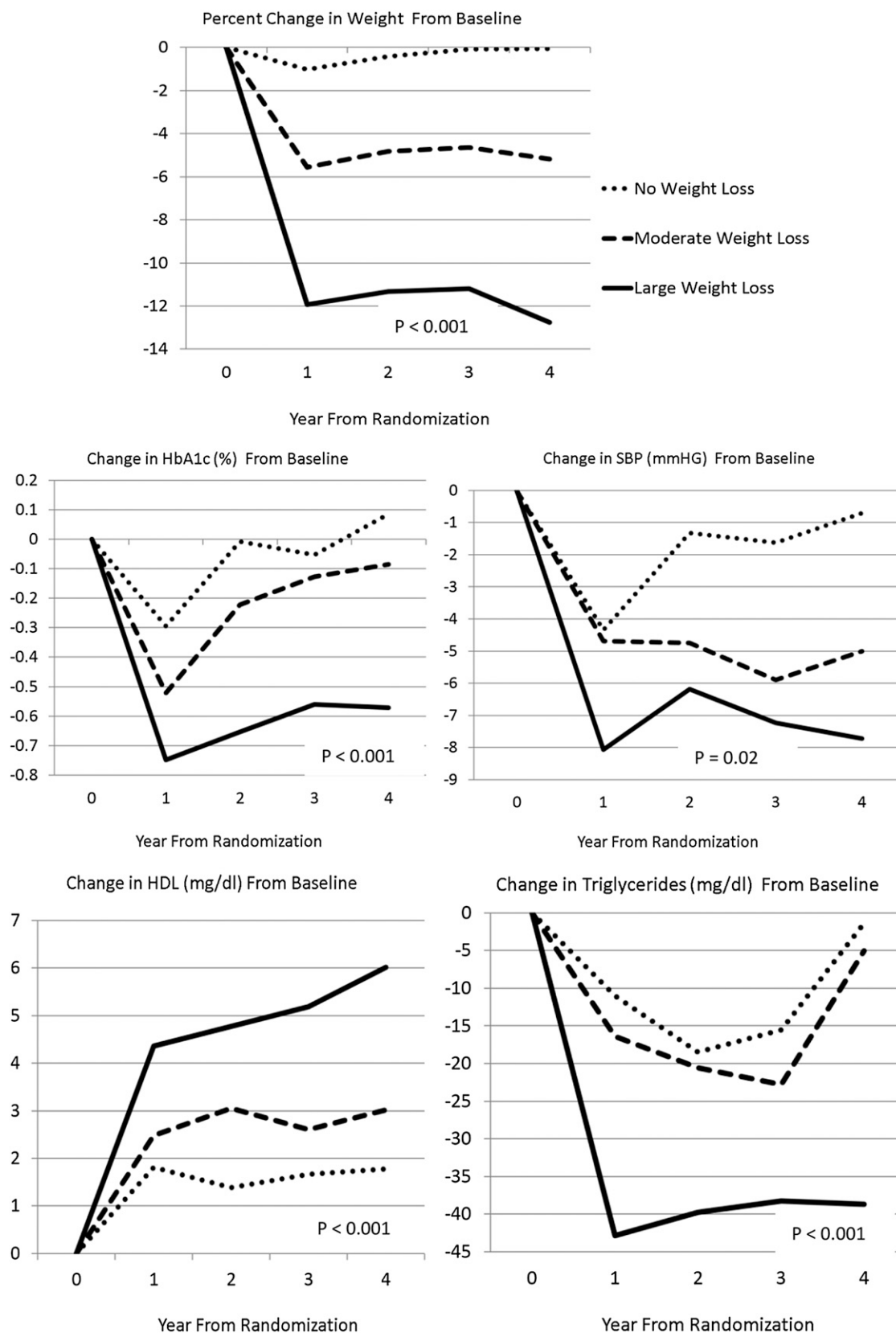


Figure 1—Mean change in weight and CVD risk factors from baseline for ILI participants who lost weight and maintained it from year 1 to year 4. The following three patterns are compared: no weight loss (year 1 and year 4 weight are both within $\pm 3.0\%$ of baseline weight; $N = 158$); moderate weight loss (year 1 and year 4 weights are both $\geq 3.0\%$ and $< 8.0\%$ below baseline; $N = 204$); and large weight loss (year 1 and year 4 weights are both $\geq 8.0\%$ and $< 20\%$ below baseline, and weight regain from year 1 to year 4 is $< 3\%$; $N = 251$). With covariate adjustment for sex, race/ethnicity, baseline age, BMI, baseline level of the risk factor, and changes in medication for that risk factor over time. P values are from mixed-effects models that assess the overall differences in the average changes from baseline.

loss category were still below baseline at year 4. Changes in other risk factors between year 1 and year 4 did not differ between the weight loss categories, but LDL-C levels improved significantly from year 1 to year 4 in the moderate and large weight loss categories, and HDL-C levels improved significantly in the large weight loss category.

Association Between Weight Regain and Changes in CVD Risk Factors

To address the question of whether losing and regaining weight had adverse associations with changes in risk factors, we compared participants who had similar weight losses at year 4, but had different trajectories to this common end point. First, we compared those who never lost any weight with those who had lost either large or moderate amounts of weight at Year 1 and then regained it all by year 4 (comparison of groups 1, 4, and 5). Table 4 and Fig. 2 show the CVD risk factor changes for these three groups. Of greatest interest

is the comparison of their risk factors at year 4 when the three groups were all close to their baseline weights (-0.06% , -0.29% , and -0.52% weight losses for groups 1, 4, and 5 respectively). CVD risk factors did not differ significantly among the three groups at year 4, with the exception of HbA_{1c} level. For HbA_{1c} those who lost a large amount of weight initially and then regained it all had better long-term outcomes than those who lost moderate amounts of weight initially and regained the weight in full.

A second way to examine whether there were adverse relationships between weight regain and changes in CVD risk factors was to compare participants with large initial weight losses who at 4 years maintained only moderate weight losses with participants who achieved and maintained moderate weight losses at both years 1 and year 4 (group 2 vs. group 6). At year 4, the large weight loss/partial regain group had better mean risk factor changes

compared with the moderate weight loss for HbA_{1c} levels ($P = 0.005$), and moderately better HDL-C ($P = 0.06$) and triglyceride ($P = 0.07$) levels (Table 5 and Fig. 3).

CONCLUSIONS

Our analyses led to several important conclusions. First, these analyses confirm our findings for changes in weight and risk factors during the first year of the Look AHEAD trial for ILI participants and extend them to 4 years. We found that the magnitude of the improvement in HbA_{1c}, SBP, HDL-C, and triglyceride levels from baseline to 4 years differed for those who had no weight loss versus 3–8% weight loss or 8–20% weight loss. In contrast, there was no evidence that greater magnitude of weight loss was associated with greater changes in LDL-C or DBP levels at year 1 or year 4. Second, our data suggest that in individuals with diabetes there is a gradual worsening in HbA_{1c} levels even among

Table 4—Mean changes in risk factors for the three weight patterns that are all within 3.0% of baseline at year 4

Risk factor	Weight pattern	Mean (95% CI) changes		
		Year 1–baseline	Year 4–year 1	Year 4–baseline
HbA _{1c} (%)	1. No weight loss	−0.29 (−0.44, −0.14) ^{4,5}	0.38 (0.19, 0.57)	0.08 (−0.07, 0.24)
	4. Moderate weight loss/full regain	−0.54 (−0.65, −0.43) ¹	0.63 (0.49, 0.77)	0.09 (−0.02, 0.20) ⁵
	5. Large weight loss/full regain	−0.81 (−0.94, −0.68) ¹	0.67 (0.50, 0.84)	−0.14 (−0.27, −0.01) ⁴
	P value	<0.001	0.06	0.02
SBP (mmHg)	1. No weight loss	−4.35 (−6.73, −1.96)	3.63 (0.41, 6.86)	−0.71 (−3.12, 1.70)
	4. Moderate weight loss/full regain	−5.80 (−7.57, −4.04)	4.75 (2.36, 7.14)	−1.05 (−2.81, 0.71)
	5. Large weight loss/full regain	−7.24 (−9.33, −5.15)	6.21 (3.39, 9.03)	−1.04 (−3.11, 1.04)
	P value	0.20	0.49	0.97
DBP (mmHg)	1. No weight loss	−2.51 (−3.72, −1.31)	0.56 (−1.04, 2.16)	−1.96 (−3.18, −0.74)
	4. Moderate weight loss/full regain	−2.80 (−3.69, −1.91)	0.54 (−0.64, 1.73)	−2.26 (−3.15, −1.37)
	5. Large weight loss/full regain	−3.37 (−4.63, −2.51)	0.96 (−0.44, 2.35)	−2.61 (−3.67, −1.56)
	P value	0.38	0.89	0.72
LDL-C (mg/dL)	1. No weight loss	−10.09 (−14.00, −6.18)	−1.33 (−6.61, 3.95) ⁵	−11.42 (−15.33, −7.50)
	4. Moderate weight loss/full regain	−7.84 (−10.67, −5.00)	−8.73 (−12.59, −4.86)	−16.56 (−19.41, −13.72)
	5. Large weight loss/full regain	−5.92 (−9.26, −2.57)	−9.90 (−14.43, −5.37) ¹	−15.81 (−19.16, −12.47)
	P value	0.28	0.03	0.10
HDL-C (mg/dL)	1. No weight loss	1.81 (0.63, 3.00) ⁵	−0.03 (−1.50, 1.44)	1.78 (0.59, 2.97)
	4. Moderate weight loss/full regain	2.12 (1.26, 2.98) ⁵	0.35 (−0.73, 1.43) ⁵	2.48 (1.61, 3.34)
	5. Large weight loss/full regain	5.11 (4.10, 6.13) ^{1,4}	−1.88 (−3.14, −0.62) ⁴	3.23 (2.22, 4.45)
	P value	<0.001	0.02	0.18
Triglycerides (mg/dL)	1. No Weight Loss	−11.0 (−27.2, 6.2) ⁵	9.7 (−11.3, 30.6) ⁵	−1.4 (−18.6, 15.9)
	4. Moderate weight loss/full regain	−16.4 (−31.2, −1.6)	14.0 (−1.4, 29.3) ⁵	−5.0 (−20.0, 9.9)
	5. Large weight loss/full regain	−42.8 (−56.1, −29.6) ¹	45.3 (27.4, 63.3) ^{1,4}	−38.7 (−52.1, −25.3)
	P value	0.005	0.01	0.45

Pattern 1: No weight loss, (year 1 and year 4 weight are both within $\pm 3.0\%$ of baseline; $N = 158$); pattern 4: moderate weight loss/full regain (year 1 weight loss $\geq 3.0\%$ and $< 8.0\%$, but year 4 weight is within $\pm 3.0\%$ of baseline; $N = 289$); and pattern 5: large weight loss/full regain (year 1 weight is $\geq 8.0\%$ and $< 20\%$, and year 4 weight is within $\pm 3.0\%$ of baseline; $N = 210$). P values indicate significant differences among the three patterns, with covariate adjustment for baseline level of the risk factor, age, BMI, sex, and change in the use of medications for that risk factor during the 4-year period. Superscript numbers show the difference between groups in the presence of significant pairwise differences (Tukey test, $P < 0.05$).

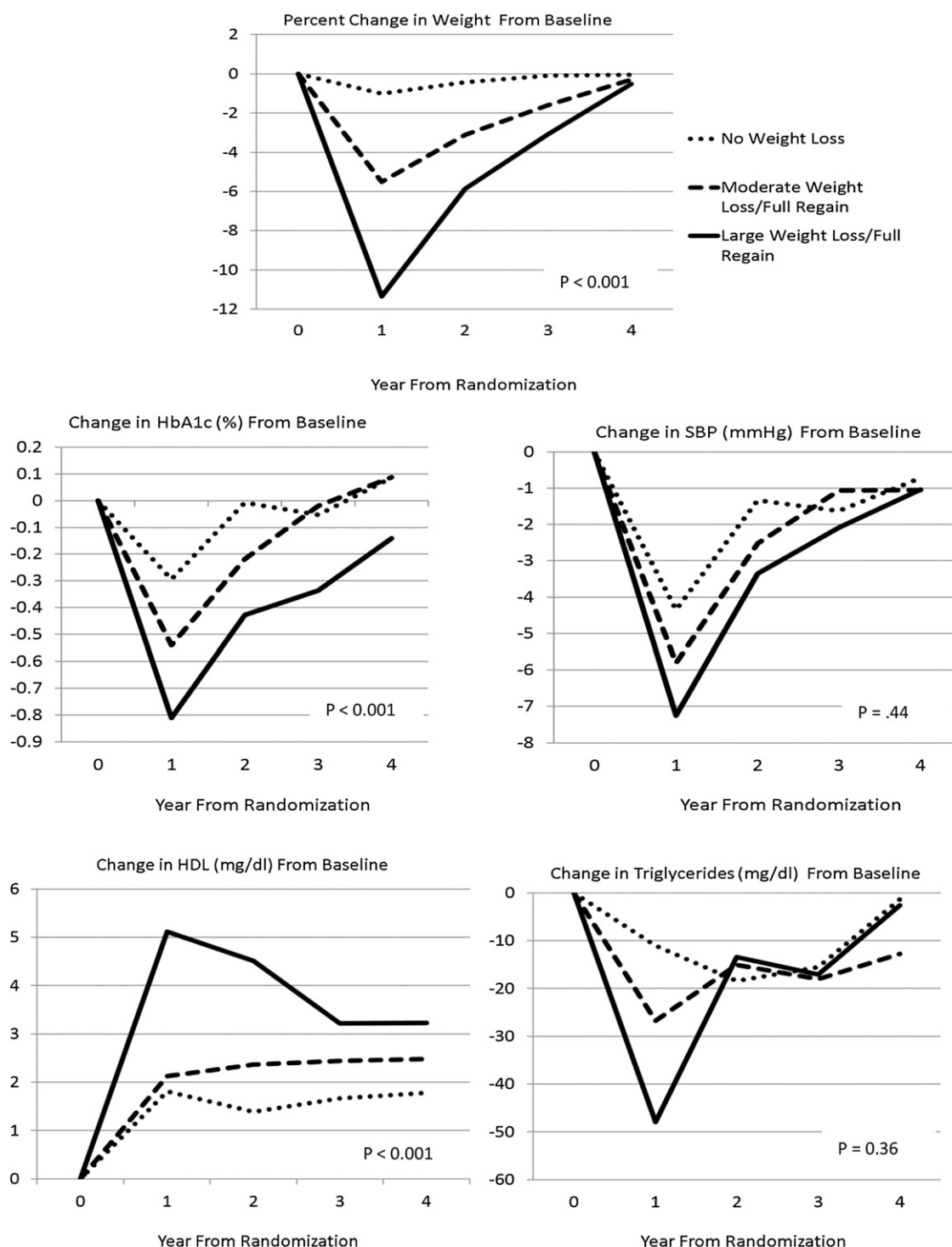


Figure 2—Mean change in weight and CVD risk factors from baseline for ILI participants who all had no weight loss at year 4 but differed in weight loss at year 1. The following three patterns are compared: no weight loss (year 1 and year 4 weight are both within $\pm 3.0\%$ of baseline weight; $N = 158$); moderate weight loss/full regain (year 1 weight is $\geq 3.0\%$ and $< 8.0\%$ below baseline, and year 4 weight is within $\pm 3.0\%$ of baseline weight; $N = 289$); and large weight loss/full regain (year 1 weight is $\geq 8.0\%$ and $< 20\%$ below baseline, and year 4 weight is within $\pm 3.0\%$ of baseline weight; $N = 210$), with covariate adjustment for sex, race/ethnicity, baseline age, BMI, baseline level of the risk factor, and changes in medication for that risk factor over time. P values are from mixed-effects models that assess the overall differences in the average changes from baseline.

those who maintain their weight losses; however, this worsening is mitigated in the large weight loss group relative to those who lost and maintained less weight. In addition, the large weight

loss group is the only group whose HbA_{1c} levels remained significantly below baseline at year 4. In contrast, HDL-C levels improved from year 1 to year 4 in those who maintained large

weight losses over this interval, and LDL-C levels improved in those who maintained large or moderate weight losses. Finally, our data reveal no negative effects of losing weight and regaining

Table 5—Mean changes in risk factors for the two weight patterns that are within $\geq 3.0\%$ to $< 8.0\%$ of baseline at year 4

Risk factor	Weight pattern	Mean (95% CI) changes		
		Year 1–baseline	Year 4–year 1	Year 4–baseline
HbA _{1c} (%)	2. Moderate weight loss	−0.52 (−0.65, −0.39)	0.44 (0.27, 0.61)	−0.08 (−0.22, 0.05)
	6. Large weight loss/partial regain	−0.83 (−0.93, −0.72)	0.50 (0.37, 0.64)	−0.32 (−0.43, −0.22)
	P value	<0.001	0.55	0.005
SBP (mmHg)	2. Moderate weight loss	−4.69 (−6.78, −1.96)	−0.32 (−3.17, 2.52)	−5.01 (−7.12, −2.90)
	6. Large weight loss/partial regain	−9.45 (−11.16, −7.78)	3.88 (1.60, 6.16)	−5.59 (−7.27, −3.91)
	P value	<0.001	0.02	0.67
DBP (mmHg)	2. Moderate weight loss	−2.22 (−3.28, −1.16)	−0.53 (−1.95, 0.88)	−2.75 (−3.82, −1.69)
	6. Large weight loss/partial regain	−3.90 (−4.75, −3.04)	0.48 (−0.65, 1.62)	−3.41 (−4.26, −2.56)
	P value	0.02	0.27	0.34
LDL-C (mg/dL)	2. Moderate weight loss	−7.51 (−10.86, −4.15)	−9.14 (−13.71, −4.57)	−16.65 (−20.04, −13.25)
	6. Large weight loss/partial regain	−7.36 (−10.09, −5.00)	−6.22 (−9.90, −2.53)	−13.58 (−16.29, −10.88)
	P value	0.95	0.33	0.17
HDL-C (mg/dL)	2. Moderate weight loss	2.48 (1.47, 3.50)	0.53 (−0.75, 1.80)	3.01 (1.98, 4.04)
	6. Large weight loss/partial regain	5.01 (4.18, 5.83)	−0.72 (−1.75, 0.31)	4.28 (3.46, 5.10)
	P value	<0.001	0.13	0.06
Triglycerides (mg/dL)	2. Moderate weight loss	−16.4 (−31.2, −1.6)	11.4 (−4.8, 27.7)	−5.0 (−20.0, 9.9)
	6. Large weight loss/partial regain	−41.2 (−53.2, −29.2)	15.3 (2.4, 28.2)	−22.6 (−34.5, −10.7)
	P value	0.01	0.54	0.07

Pattern 2, moderate weight loss ($\geq 3.0\%$ and $< 8.0\%$ at both year 1 and year 4; $N = 204$); and pattern 6, large weight loss/partial regain ($\geq 8.0\%$ and $< 20\%$ at year 1, and $\geq 3.0\%$ and $< 8.0\%$ at year 4; $N = 316$). *P* values indicate significant differences between the two groups with covariate adjustment for baseline level of the risk factor, age, BMI, sex, and change in the use of medications for the risk factor during the 4-year period.

it on these CVD risk factors at year 4. In contrast, we found positive legacy effects of having lost large amounts of weight initially, even if that weight loss was not maintained in full. The positive legacy effect was most apparent for HbA_{1c}, for which large weight losses, followed by partial or even full regain, were associated with greater improvements in glycemic control relative to those who had smaller weight losses initially. It is possible that the initial weight losses delayed progression of their diabetes.

The Guidelines for Managing Overweight and Obesity in Adults (14) described the magnitude of weight loss needed to improve a variety of different risk factors. Our analyses add to this evidence base. Our results suggest that patients with diabetes will need to maintain large weight losses (which we defined as $\geq 8\%$ to $< 20\%$ in this study) to maintain long-term (4-year) improvements in triglyceride, HDL-C, and HbA_{1c} levels. Weight losses of $\geq 3\%$ to $< 8\%$, if maintained, do not seem sufficient to produce long-term improvements in these risk parameters. In contrast, smaller weight losses appear sufficient to produce significant long-term improvements in SBP from baseline.

The Guidelines for Managing Overweight and Obesity (14) concluded that weight loss has positive effects on

lipid and blood pressure levels. In our previously reported 1-year results (8), we noted that weight loss did not affect LDL-C or DBP levels; the current year 4 data continue to show no systematic effects of weight loss on these outcomes. Although we adjusted for the use of lipid-lowering and blood pressure-lowering medications, the fact that a large proportion of participants were treated with these medications and their prescribed use, especially the use of statins, increased over the 4 years may have made it difficult to detect an effect. The fact that even the group with no weight loss had significant improvements in LDL-C and DBP levels from baseline to year 4 suggests that the changes were most likely affected by medication use.

In contrast to LDL-C, we found very strong associations between weight loss and HDL-C. Those participants who had 8–20% weight loss and maintained it at 4 years had initial increases of 4.36 mg/dL in HDL-C levels and even larger increases at 4 years (6.01 mg/dL). This is the only risk factor that showed significantly greater improvements at year 4 compared with year 1 with maintenance of weight loss over this interval, perhaps reflecting long-term beneficial effects of physical activity on HDL-C levels (16).

Behavioral weight loss programs are becoming increasingly successful at

helping individuals achieve initial weight loss, but maintenance remains problematic (17). This issue, along with concerns about weight cycling, have led some to question whether weight loss should be a treatment goal if it is likely to be followed by weight regain. In our categorical analyses, we found that it was more common for participants who had lost 8–20% at 1 year to maintain their weight loss at 4 years than it was to regain weight back to baseline. Moreover, we found no evidence that weight loss followed by weight regain led to worsening in risk factors. In fact, for HbA_{1c} levels, participants with large initial weight losses who regained all the way back to baseline levels had better levels at year 4 than those who never lost weight initially. For all other measures, those who regained weight in full did not differ significantly from those who had never lost any weight. A more common occurrence among those with large initial weight losses was to regain a part (but not all) of the initial weight loss. There were trends for these individuals to have better levels of HbA_{1c}, triglycerides, and HDL-C at year 4 relative to those who initially lost these more modest amounts of weight (3–8%) and maintained it. These results suggest a positive legacy effect of having achieved a larger initial weight loss, even if it is partially regained.

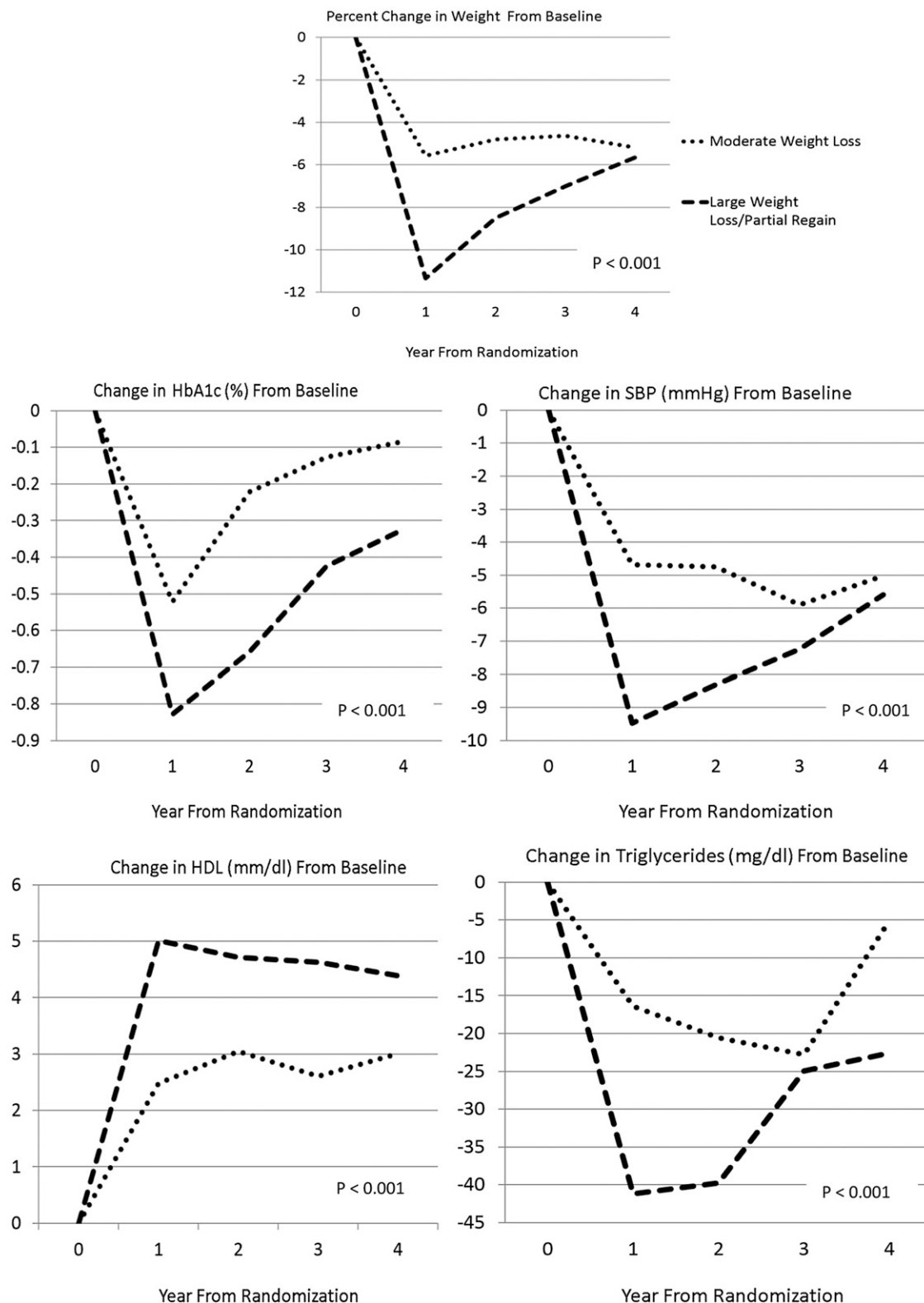


Figure 3—Mean change in weight and CVD risk factors from baseline for ILI participants who had moderate weight loss at year 4 but differed in weight loss at year 1. The following two patterns are compared: moderate weight loss (year 1 and year 4 weights are both $\geq 3.0\%$ and $< 8.0\%$ below baseline; $N = 204$); and large weight loss/partial regain (year 1 weight is $\geq 8.0\%$ and $< 20\%$ below baseline, and year 4 weight is $\geq 3.0\%$ and $< 8.0\%$ below baseline weight; $N = 316$), with covariate adjustment for sex, race/ethnicity, baseline age, BMI, baseline level of the risk factor, and changes in medication for that risk factor over time. P values are from mixed-effects models that assess the overall differences in the average changes from baseline.

Although clearly controversial, a number of epidemiological studies (18–22) have suggested that weight cycling increases the risk for cardiovascular and all-cause mortality. However, one study (23) found that weight fluctuations were associated with higher mortality only in those who did not have diabetes. Mechanisms suggested to underlie the adverse effects of weight cycling include increased blood pressure and risk for insulin resistance, type 2 diabetes, and dyslipidemia (24,25). Our data do not support these mechanisms. Other mechanisms, such as increases in visceral fat (25), have also been discussed, and recent studies (24,26) have suggested that it may not be the cycling per se, but rather weight regain over the initial level (weight overshooting) that causes these negative effects. However, of the 900 ILI participants (23%) who lost at least 10% of their body weight at year 1, only 10% exceeded their baseline weight at year 4; 20% were maintaining a weight loss of 0–5%, 28% were maintaining a weight loss of 5–9.9%, and 42% were still maintaining a weight loss of >10%. Thus, in this analysis we have focused on the patterns of weight regain and the type of weight cycling that is most typically seen in a lifestyle intervention.

Several limitations must be kept in mind when considering our results. Most important is the fact that we developed post hoc categorizations of participants based on their year 1 and year 4 weight changes, and only a subgroup of the ILI participants fell into one of these categories. We adjusted statistically for some of the differences that existed among the various weight change groups in demographic characteristics and changes in medications over the trial, but other confounders may still exist. The adjustments in medication may not fully account for the effects of changes in dose and types of medication used for diabetes, hypertension, or cholesterol. Although we focused on the magnitude of the weight change, these groups also may have differed in other ways, for example, changes in physical activity. They may also have experienced additional cycles of weight loss and regain between years 1 and 4. We selected the cut points for weight change categories based on prior publications (13,14), but, clearly, slightly different cut points could have been chosen. There is no standard, validated criterion for weight stability. After

careful consideration of the issues (normal weight fluctuations; biological relevance), Stevens et al. (13) recommended the 3% criterion, which we adopted and which has been used in other studies (27). The goal in this study was to compare different patterns of weight change rather than to identify a specific threshold for the percentage weight change that was associated with beneficial effects. In addition, although Look AHEAD trial has continued to observe participants for >10 years, we have focused on the initial 4 years. This allowed us to compare a discrete number of weight change categories and to focus on intentional weight loss. In later years of the Look AHEAD trial, participants in both the lifestyle intervention and control group began to lose weight, which was due to loss of lean body mass (28) and likely reflected unintentional, rather than intentional, weight loss.

There are also important strengths to this analysis, including the large sample size and the objective assessments of weight, cardiovascular risk factors, and medications annually over the 4 years. In addition, these individuals were all participating in a lifestyle intervention, and, thus, their weight changes reflect intentional weight loss. The participants all had type 2 diabetes, which is a large and growing population. In 1993, Wadden (29) suggested that practitioners needed information about whether larger weight loss followed by weight regain was detrimental to health in order to make informed decisions regarding very low-calorie diets compared with moderate caloric restriction. The current data provide information for making decisions about the benefits of larger versus smaller initial weight losses. They also provide important insights for clinicians and patients who wonder about the broader question of whether weight loss should be attempted because these weight losses are often not maintained.

In conclusion, on average, participants who had an 8–20% weight loss at 1 year and maintained their weight loss at year 4 (i.e., regained <3% between years 1 and 4) achieved sustained improvements in levels of HbA_{1c}, SBP, triglycerides, and HDL-C. Even those who regained part of this weight loss over the next several years still had significant improvements in several of these parameters at 4 years relative to

their baseline. Finally, we found that participants who lost 8–20% at 1 year and regained some or all of their weight loss had better long-term changes in HbA_{1c} levels than those with more modest initial weight loss. Thus, achieving larger initial weight losses, even if followed by some regain, should be strongly encouraged in overweight/obese patients with type 2 diabetes.

Appendix

Members of the Action for Health in Diabetes (Look AHEAD) Writing Group: Rena R. Wing (Miriam Hospital, Providence, RI), Mark A. Espeland (Wake Forest School of Medicine, Winston-Salem, NC), Jeanne M. Clark (Johns Hopkins University, Baltimore, MD), Helen P. Hazuda (University of Texas Health Science Center, San Antonio, TX), William C. Knowler (National Institute of Diabetes and Digestive and Kidney Diseases, Phoenix, AZ), Henry J. Pownall (The Methodist Hospital Research Institute, Houston, TX), Jessica Unick (Miriam Hospital, Providence, RI), Thomas Wadden (University of Pennsylvania, Philadelphia, PA), and Lynne Wagenknecht (Wake Forest School of Medicine, Winston-Salem, NC).

Funding. This study is supported by the Department of Health and Human Services through the following cooperative agreements with the National Institutes of Health: DK-57136, DK-57149, DK-56990, DK-57177, DK-57171, DK-57151, DK-57182, DK-57131, DK-57002, DK-57078, DK-57154, DK-57178, DK-57219, DK-57008, DK-57135, and DK-56992. 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 provided personnel, medical oversight, and use of facilities. Additional support was received from The Johns Hopkins Medical Institutions Bayview General Clinical Research Center (grant M01-RR-02719), the Massachusetts General Hospital Mallinckrodt General Clinical Research Center and the Massachusetts Institute of Technology General Clinical Research Center (grant M01-RR-01066), the University of Colorado Health Sciences Center General Clinical Research Center (grant M01-RR-00051) and Clinical Nutrition Research Unit (P30-DK-48520), the University of Tennessee at Memphis General Clinical Research Center (M01-RR-0021140), the University of

Pittsburgh General Clinical Research Center (M01-RR-000056), the Clinical Translational Research Center funded by a Clinical and Translational Science Award (UL1 RR 024153), a National Institutes of Health grant (DK-046204), and a Frederic C. Bartter General Clinical Research Center grant (M01-RR-01346). The following organizations have committed to make major contributions to the Look AHEAD Study: FedEx Corporation; Health Management Resources; LifeScan, Inc., a Johnson & Johnson Company; OPTIFAST of Nestle HealthCare Nutrition, Inc.; Hoffmann-La Roche Inc.; Abbott Nutrition; and Slim-Fast Brand of Unilever North America.

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

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Neither the Indian Health Service nor any other funding sources played a role in the conduct of the study, collection of data, management of the study, analysis of data, interpretation of data, or preparation of the manuscript.

Author Contributions. R.R.W. researched data and wrote the manuscript. M.A.E. conducted all data analyses, and contributed to the writing and editing of the manuscript. J.M.C., H.P.H., W.C.K., and T.W. collected data and reviewed the manuscript. H.J.P. reviewed the manuscript and contributed to discussion. J.U. and L.W. reviewed and edited the manuscript. M.A.E. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

- Wing RR. Behavioral approaches to the treatment of obesity. In *Handbook of Obesity: Clinical Applications*. 3rd ed. Bray G, Bouchard C, Eds. New York, Informa Health Care USA, Inc., 2008, p. 227–248
- Svetkey LP, Stevens VJ, Brantley PJ, et al. Comparison of strategies for sustaining weight loss: the weight loss maintenance randomized controlled trial. *JAMA* 2008;299:1139–1148
- Wing RR, Hamman RF, Bray GA, et al. Achieving weight and activity goals among diabetes prevention program lifestyle participants. *Obes Res* 2004;12:1426–1434
- Wadden TA, Neiberg RH, Wing RR, et al. Four-year weight losses in the Look AHEAD study: factors associated with long-term success. *Obesity (Silver Spring)* 2011;19:1987–1998
- Wing RR, Jeffery RW. Effect of modest weight loss on changes in cardiovascular risk factors: are there differences between men and women or between weight loss and maintenance? *Int J Obes* 1995;19:67–73
- Wing RR, Bolin P, Brancati FL, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013;369:145–154
- Look AHEAD Research Group. Look AHEAD: Action for Health in Diabetes: Design and methods for a clinical trial of weight loss for the prevention of cardiovascular disease in type 2 diabetes. *Control Clin Trials* 2003;24:610–628
- Wing RR, Lang W, Wadden TA, et al. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care* 2011;34:1481–1486
- Wing RR. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. *Arch Intern Med* 2010;170:1566–1575
- Knowler WC, Bahnson JL, Bantle JP, et al. Effect of a long-term behavioural weight loss intervention on nephropathy in overweight or obese adults with type 2 diabetes: a secondary analysis of the Look AHEAD randomised clinical trial. *Lancet Diabetes Endocrinol* 2014;2:801–809
- Bray G, Gregg E, Haffner S, Pi-Sunyer XF, Wagenknecht LE, Walkup M, et al.; Look Ahead Research Group. Baseline characteristics of the randomised cohort from the Look AHEAD (Action for Health in Diabetes) study. *Diab Vasc Dis Res* 2006;3:202–215
- Look AHEAD Research Group. The Look AHEAD study: a description of the lifestyle intervention and the evidence supporting it. *Obesity (Silver Spring)* 2006;14:737–752
- Stevens J, Truesdale KP, McClain JE, Cai J. The definition of weight maintenance. *Int J Obes* 2006;30:391–399
- National Heart, Lung, and Blood Institute. Guidelines (2013) for managing overweight and obesity in adults: preface to the Expert Panel Report (comprehensive version which includes systematic evidence review, evidence statements, and recommendations). *Obesity (Silver Spring)* 2014;22(Suppl. 2):S40
- Littell RC, Milliken GA, Stroup WW, Wolfinger RD. *SAS System for Mixed Models*. Cary, NC, SAS Institute Inc., 1996
- Kodama S, Tanaka S, Saito K, et al. Effect of aerobic exercise training on serum levels of high-density lipoprotein cholesterol: a meta-analysis. *Arch Intern Med* 2007;167:999–1008
- MacLean PS, Wing RR, Davidson T, et al. NIH working group report: innovative research to improve maintenance of weight loss. *Obesity (Silver Spring)* 2015;23:7–15
- Blair SN, Shaten J, Brownell K, Collins G, Lissner L. Body weight change, all-cause and cause-specific mortality in the Multiple Risk Factor Intervention Trial. *Ann Intern Med* 1993;119:749–757
- Hamm PB, Shekelle RB, Stamler J. Large fluctuations in body weight during young adulthood and 25-year risk of coronary death in men. *Am J Epidemiol* 1989;129:312–318
- Lissner L, Odell PM, D'Agostino RB, et al. Variability of body weight and health outcomes in the Framingham population. *N Engl J Med* 1991;324:1839–1844
- Peters ET, Seidell JC, Menotti A, et al. Changes in body weight in relation to mortality in 6441 European middle-aged men: the Seven Countries Study. *Int J Obes Relat Metab Disord* 1995;19:862–868
- Diaz VA, Mainous AG 3rd, Everett CJ. The association between weight fluctuation and mortality: results from a population-based cohort study. *J Community Health* 2005;30:153–165
- Hanson RL, Jacobsson LT, McCance DR, et al. Weight fluctuation, mortality and vascular disease in Pima Indians. *Int J Obes Relat Metab Disord* 1996;20:463–471
- Montani JP, Viecelli AK, Prevot A, Dulloo AG. Weight cycling during growth and beyond as a risk factor for later cardiovascular diseases: the 'repeated overshoot' theory. *Int J Obes* 2006;30(Suppl. 4):S58–S66
- Montani JP, Schutz Y, Dulloo AG. Dieting and weight cycling as risk factors for cardiometabolic diseases: who is really at risk? *Obes Rev* 2015;16(Suppl. 1):7–18
- Field AE, Manson JE, Laird N, Williamson DF, Willett WC, Colditz GA. Weight cycling and the risk of developing type 2 diabetes among adult women in the United States. *Obes Res* 2004;12:267–274
- Truesdale KP, Stevens J, Cai J. Nine-year changes in cardiovascular disease risk factors with weight maintenance in the atherosclerosis risk in communities cohort. *Am J Epidemiol* 2007;165:890–900
- Pownall HJ, Bray GA, Wagenknecht LE, et al. Changes in body composition over 8 years in a randomized trial of a lifestyle intervention: the Look AHEAD study. *Obesity (Silver Spring)* 2015;23:565–572
- Wadden TA. Treatment of obesity by moderate and severe caloric restriction. Results of clinical research trials. *Ann Intern Med* 1993;119:688–693