Weight Change During the Postintervention Follow-up of Look AHEAD

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OBJECTIVE

Patients with type 2 diabetes are encouraged to lose weight, but excessive weight loss in older adults may be a marker of poor health and subsequent mortality. We examined weight change during the postintervention period of Look AHEAD, a randomized trial comparing intensive lifestyle intervention (ILI) with diabetes support and education (DSE) (control) in overweight/obese individuals with type 2 diabetes and sought to identify predictors of excessive postintervention weight loss and its association with mortality.

RESEARCH DESIGN AND METHODS

These secondary analyses compared postintervention weight change (year 8 to final visit; median 16 years) in ILI and DSE in 3,999 Look AHEAD participants. Using empirically derived trajectory categories, we compared four subgroups: weight gainers ($n = 307$), weight stable ($n = 1,561$), steady losers ($n = 1,731$), and steep losers ($n = 380$), on postintervention mortality, demographic variables, and health status at randomization and year 8.

RESULTS

Postintervention weight change averaged −3.7 ± 9.5%, with greater weight loss in the DSE than the ILI group. The steep weight loss trajectory subgroup lost on average 17.7 ± 6.6%; 30% of steep losers died during postintervention follow-up versus 10–18% in other trajectories ($P < 0001$). The following variables distinguished steep losers from weight stable: baseline, older, longer diabetes duration, higher BMI, and greater multimorbidity; intervention, randomization to control group and less weight loss in years 1–8; and year 8, higher prevalence of frailty, multimorbidity, and depressive symptoms and lower use of weight control strategies.

CONCLUSIONS

Steep weight loss postintervention was associated with increased risk of mortality. Older individuals with longer duration of diabetes and multimorbidity should be monitored for excessive unintentional weight loss.

Patients with type 2 diabetes who are overweight or obese are typically encouraged by their health care providers to lose weight to improve glycemic control, cardiovascular risk factors, and overall health and well-being. The Look AHEAD trial, a randomized study comparing intensive lifestyle intervention (ILI) and control (diabetes support and education [DSE]) arms in 5,145 individuals age 45–76 years with

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type 2 diabetes who were overweight/obese, found no significant difference between the two groups for cardiovascular morbidity or mortality or all-cause mortality after a median of 9.6 years of intervention (1). Similarly, no difference between ILI and DSE groups was shown for cancer incidence (2) or cognition (3). However, the study has documented many benefits (4), including positive effects on diabetes control and remission (5), neuropathy (6), nephropathy (7), physical function (8,9), and depressive symptomatology (10), and only one adverse effect, a greater number of frailty fractures with ILI than with DSE (11). After 9.6 years of follow-up, all interventions were stopped, but Look AHEAD has continued to follow participants for ~8 years. In recent publications, Look AHEAD investigators reported that both ILI and DSE participants lost weight during follow-up (12,13), with greater weight loss in the DSE than in the ILI group. In addition, they reported no difference between ILI and DSE in risk of mortality over the full 16.7-year study, including both intervention and follow-up periods (14). However, given the many initial benefits of weight loss, the investigators continued to recommend weight loss for patients with diabetes who were overweight/obese.

Clinicians, however, have concerns that weight loss in older individuals is a marker of poor health and a risk factor for subsequent mortality, especially when the weight loss is excessive and/or unintentional. This concern is supported by a large number of observational studies that have shown an association between excessive weight loss and mortality in older individuals (15–18), especially unintentional weight loss. In contrast, some (19) but not all (20) randomized trials of intentional weight loss have shown positive effects of weight loss on mortality. These randomized trials have tended to include younger, healthier populations and have not examined subgroups of individuals who experience excessive weight loss. This study sought to extend prior research by studying older individuals with more health problems and identifying subgroups that would subsequently experience steep weight loss. To accomplish these aims, we compared weight change in ILI and DSE participants over the extended observational follow-up of Look AHEAD and examined whether it was possible to use baseline and end-of-intervention data to identify a subgroup of participants that might subsequently be at risk for steep weight loss and increased mortality.

RESEARCH DESIGN AND METHODS

Study Design

Look AHEAD was a randomized controlled trial comparing the effects of an ILI, focused on weight loss, with those of a control condition, DSE, in 5,145 adults with type 2 diabetes who were overweight/obese. The primary outcome and secondary outcomes of the original trial were based on different measures of cardiovascular morbidity and mortality (1). The trial was stopped for futility after a median of 9.6 years of follow-up when it was apparent that there were no meaningful differences in these outcomes by intervention arm. However, the study was continued as an observational study, and participants have now reached >16 years of postrandomization follow-up. The present analysis focuses on variables associated with weight change from year 8 to the participants' last postintervention follow-up visit. The mean ± SD (range) time between randomization and the last visit was 14.6 ± 2.7 years (median 16 years; range 9–18). We used the median value (16 years) in referring to this time point.

Participants

This observational analysis used data from 3,999 Look AHEAD participants who consented to be followed in the observational phase of the trial. We excluded 970 with no weight data at year ≥8 and 270 participants who had bariatric surgery at some point during the study.

Measures

Participants were seen in clinic annually between baseline and year 11 and then once every 2 years and participated in telephone calls assessing outcome at 6-month intervals. All data were collected by assessors who were masked to participants' treatment assignment.

Baseline Demographics

Participants reported their age, their race/ethnicity, whether they had a history of cardiovascular disease, and when they were diagnosed with diabetes.

Weight Loss Percentage

Weight was measured in clinic by certified staff members at each clinic visit. Weight change during three phases of the study was examined: randomization to year 8 (intensive intervention), year 8 to the participant's last visit (follow-up), and randomization to the last visit (entire study).

Glycemic Control

At study entry and at each clinic visit, participants were asked to bring their medications with them. From this, we determined if they were using insulin to control their glucose levels (yes/no). HbA_{1c} was measured at each clinic visit and analyzed at the Northwest Lipid Laboratory.

Frailty

Frailty was assessed at baseline and year 8 using a deficit accumulation model, in which the numbers of symptoms, diseases, and abnormal laboratory values (of 38) seen in a particular individual were summed and compared with the total number of items (21). Scores >0.21 were used to define frailty.

Multimorbidity

Multimorbidity was defined by counting the number of chronic diseases an individual had of nine total diseases (cancer, cardiac arrythmia, chronic kidney disease, congestive heart failure, coronary artery disease, depression, dyslipidemia, hypertension, and stroke) (22). Multimorbidity was assessed by self-report or measurement at baseline and year 8 and divided into two categories fewer than two or two or more diseases).

Depression

Depressive symptoms were assessed at baseline and year 8 with the Beck Depression Inventory 1A (BDI) (23), with comparisons between those who scored <10 or ≥10 indicating mild or greater depression, respectively.

Weight Control Strategies

This self-report questionnaire was completed at year 8 (12). The questionnaire asked participants whether they had increased their physical activity during the past year (yes/no), reduced calorie or fat intake, or used meal replacement products and asked the frequency of self-weighing. The total number of

strategies was defined as the sum of the strategies used.

Mortality

Deaths were ascertained through death certificates, hospitalization records, informant interviews, and a National Death Index search. All deaths reported from September 2012 (year 8) through 30 June 2020 were included.

Intentionality

During telephone interviews in years 16–17, participants (n = 3,429) were asked if they had lost >10 pounds during the last year. If they answered yes, they were then asked if they were trying to lose weight. Because calls were conducted every 6 months but inquired about weight loss over the last year, data were combined from the participant's two most recent telephone interviews. Participant responses were used to define four groups: no weight loss >10 pounds (n = 1,925), intentional weight loss (n = 738), unintentional weight loss (n = 650), and a combination (n = 116). The no weight loss >10 pounds category reported no weight loss of this magnitude on either of these calls, the unintentional and intentional weight loss categories reported such an outcome on at least one of the two calls (with the possibility of no weight loss on the other call), and the combination category reported intentional weight loss on one of the two calls and unintentional on the other.

Statistical Analyses

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Initial analyses described the overall weight change in ILI and DSE (from randomization to final visit) (median 16 years) and during both intervention (randomization to 8 years) and postintervention follow-up (year 8 to final visit). Other baseline characteristics (age, race/ethnicity, and sex) were then considered as predictors of postintervention weight loss, using the Student t test or one-way ANOVA for unadjusted analyses or multivariate ANOVA for analyses that adjusted for initial weight loss.

The SAS PROC TRAJ algorithm was used to determine trajectories of weight change from year 8 to years 9, 10, 11, 12, 14, and 16. We sought to determine the best fit based on comparison of the Akaike and Bayesian information criteria between models with linear, quadratic, or cubic spline and number of trajectory groups ranging from three to six unique groups. Four trajectory groups with quadratic splines were selected using these criteria.

Subsequent analyses compared the association between the four trajectory groups and mortality over the follow-up period and their self-reported intentionality of weight loss. The four trajectory groups were also compared on baseline variables that might predict trajectory membership and then on similar predictors assessed at year 8. We selected frailty and multimorbidity as two composite indices to identify those with physical health problems and score on the BDI to identify those with psychological issues that might affect subsequent weight trajectories. Finally, nominal multinomial models were used to determine the odds of being a gainer, steady loser, or steep loser relative to remaining weight stable (reference group) based on baseline characteristics and baseline and year-8 health status measures and indices.

Analyses of the use of weight control strategies at year 8 were based on whether an individual reported using this strategy in the last year (yes/no). The odds of the use of the strategy were compared with the stable group as the reference in unadjusted logistic regressions.

RESULTS

Participants

Participants included in these analyses (N = 3,999) were evenly divided between DSE (n = 1,983) and ILI (n = 2,016); almost 60% were women, and 38% were from underrepresented populations, with no significant difference between ILI and DSE. Their mean ± SD age at baseline was 58.7 ± 6.7 years; 31% were age 45–54, 53% were age 55–64, and 16% were age 65–76 years. The baseline characteristics of these individuals were similar to those reported for the original cohort in Look AHEAD (24).

Weight Change During Intervention (randomization to year 8), Postintervention Follow-up (year 8 to last visit), and Overall (randomization to last visit)

Weight at year 8 averaged 95.9 ± 19.6 kg for the 3,999 individuals included in these analyses (ILI and DSE combined). Their weight change (mean ± SD) averaged −3.40 ± 8.8% during the intervention, −3.7 ± 9.5% during postintervention follow-up, and −7.1 ± 11.3% overall. Results were similar using weight change in kilograms (Table 1).

As previously reported (1), participants randomized to ILI had greater weight loss during intervention than those in the DSE group; weight loss percentage from randomization to year 8 in the current cohort of 3,999 individuals averaged −4.9 ± 8.5% in ILI versus −1.9 ± 8.8% in DSE (P < 0.0001). However, during the postintervention follow-up period, DSE had a greater weight change percentage than ILI (−4.3 ± 9.3% vs. −3.0 ± 9.6%; P < 0.0001). Overall weight loss percentage was significantly greater in ILI than DSE (−7.9 ± 11.2% in ILI vs. −6.3 ± 11.3% in DSE; P < 0.0001). Table 1 and Supplementary Fig. 1 present the comparisons of weight change in ILI versus DSE through the last visit.

Weight change percentage during each of the three time periods differed significantly among the three age categories (45–54, 55–64, and 65–76 years), with greater weight loss in older participants (Table 1). Weight change percentage during postrandomization follow-up averaged −2.9 ± 9.5%, −3.9 ± 9.0%, and −4.5 ± 10.8% for the three age categories, respectively; overall weight change (randomization to last follow-up) averaged −5.5 ± 11.5%, −7.4 ± 10.9%, and −9.1 ± 11.6%, respectively.

Postintervention weight change percentage also differed by sex, baseline BMI, and race/ethnicity (Table 1). These differences tended to remain unchanged after adjustment for weight change from randomization to year 8 (P values not shown). The same factors also affected weight loss from randomization to the last visit. Postintervention weight loss did not differ by other baseline characteristics (history of cardiovascular disease, insulin use, or duration of diabetes).

Trajectories for Weight Change, Years 8–16

Collapsing across ILI and DSE, we identified four distinct quadratic trajectories characterizing weight change postintervention (year 8 to last available weight): gain (n = 307), weight stable (n = 1,581), steady loss (n = 1,731), and steep loss (n = 380).

Table 1—Weight change percentage during intervention, postintervention follow-up, and overall, by baseline demographic category

	Randomly assigned, *n*	Analyzed, *n*	Intervention (baseline to year 8)		Follow-up (year 8 to last visit*)		Overall (baseline to last visit*)	
			Weight change, %	*P*†	Weight change, %	*P*†	Weight change, %	*P*†
Overall cohort	5,145	3,999	−3.40 ± 8.8		−3.7 ± 9.5		−7.1 ± 11.3	
Randomization group				<0.0001		<0.0001		<0.0001
DSE	2,575	1,983	−1.9 ± 8.8		−4.3 ± 9.3		−6.3 ± 11.3	
ILI	2,570	2,016	−4.9 ± 8.5		−3.0 ± 9.6		−7.9 ± 11.2	
Baseline age group, years				<0.0001		0.0009		<0.0001
45–55	1,620	1,239	−2.5 ± 9.2		−2.9 ± 9.5		−5.5 ± 11.5	
56–65	2,651	2,110	−3.5 ± 8.7		−3.9 ± 9.0		−7.4 ± 10.9	
66–76	874	650	−4.7 ± 8.0		−4.5 ± 10.8		−9.1 ± 11.6	
Sex				0.1236		0.0012		0.0001
Male	2,082	1,632	−3.1 ± 8.3		−3.1 ± 8.9		−6.3 ± 10.7	
Female	3,063	2,367	−3.6 ± 9.1		−4.1 ± 9.9		−7.7 ± 11.6	
Race/ethnicity‡				0.7446		<0.0001		0.0026
Black	804	642	−3.3 ± 8.9		−4.8 ± 10.5		−8.1 ± 11.8	
Hispanic	680	519	−3.7 ± 9.3		−3.4 ± 9.5		−7.1 ± 11.2	
White	3,252	2,487	−3.4 ± 8.7		−3.2 ± 9.3		−6.6 ± 11.2	
Other	408	350	−3.0 ± 8.5		−5.5 ± 8.7		−8.5 ± 10.9	
Baseline CVD history				0.6754		0.7697		0.6234
No	4,433	3,476	−3.4 ± 8.8		−3.6 ± 9.6		−7.1 ± 11.3	
Yes	712	523	−3.6 ± 8.5		−3.8 ± 8.9		−7.3 ± 10.8	
Baseline weight status				0.0006		0.0429		<0.0001
Overweight	765	649	−2.4 ± 8.1		−3.1 ± 8.0		−5.4 ± 10.5	
Obese	4,380	3,350	−3.6 ± 8.9		−3.8 ± 9.7		−7.4 ± 11.4	
Baseline insulin use				0.0009		0.6065		0.0398
No	4,169	3,290	−3.6 ± 8.8		−3.7 ± 9.1		−7.3 ± 11.1	
Yes	795	565	−2.3 ± 8.9		−3.9 ± 9.7		−6.2 ± 11.7	
Diabetes duration, years				0.0660		0.1036		0.1737
<5	2,237	1,840	−3.8 ± 8.8		−3.6 ± 9.5		−7.3 ± 11.1	
5 to <10	1,410	1,107	−3.2 ± 8.6		−3.3 ± 9.1		−6.6 ± 10.9	
≥10	1,358	1,019	−3.1 ± 9.2		−4.2 ± 10.0		−7.3 ± 11.9	

CVD, cardiovascular disease. *Last visit was mean ± SD 14.7 ± 2.6 years or median (minimum, maximum) 16 (9, 18) years from randomization. †*P* value is from Student *t* test for two-category variables and unadjusted ANOVA for three or more category variables. ‡Participants self-reported race from the following options: African American/Black, American Indian/Alaska Native, Asian, Native Hawaiian/Pacific Islander, White, and other; participants self-reported ethnicity from the following options: Latino, Hispanic, or Spanish origin or not. We provide data on the three largest racial/ethnic categories (African American/Black, Hispanic, and White) and a fourth category (other) that combines the smaller groups and those who selected multiple race categories.

Table 2—Baseline and year-8 characteristics for the four trajectory groups

	Gain	Stable	Steady loss	Steep loss	*P*
Total	307 (7.7)	1,581 (39.5)	1,731 (43)	380 (9.5)	
Baseline					
Randomization group					<0.0001
DSE	133 (6.7)	709 (35.8)	931 (47.0)	210 (10.6)	
ILI	174 (8.6)	872 (43.3)	800 (39.7)	170 (8.4)	
Age, years					<0.0001
45–54	118 (9.5)	525 (42.4)	508 (41.0)	88 (7.1)	
55–64	165 (7.8)	824 (39.1)	915 (43.4)	206 (9.8)	
65–76	24 (3.7)	232 (35.7)	308 (47.4)	86 (13.2)	
Sex					0.0017
Female	190 (8.0)	878 (37.1)	1,058 (44.7)	241 (10.2)	
Male	117 (7.2)	703 (43.1)	673 (41.2)	139 (8.5)	
Race/ethnicity					0.0028
Black	46 (7.2)	221 (34.4)	306 (47.7)	69 (10.8)	
Hispanic	46 (8.9)	200 (38.5)	233 (44.9)	40 (7.7)	
White	202 (8.1%)	1,024 (41.2)	1,029 (41.4)	232 (9.3)	
Other	13 (3.7)	135 (38.6)	163 (46.6)	39 (11.1)	
Obesity					0.0072
No	44 (6.8)	277 (42.7)	288 (44.4)	40 (6.2)	
Yes	263 (7.9)	1,304 (38.9)	1,443 (43.1)	340 (10.2)	
Diabetes duration, years	6.52 ± 6.09	6.34 ± 5.98	6.68 ± 6.64	8.01 ± 7.19	0.0001
HbA_{1c}, %	7.25 ± 1.22	7.23 ± 1.16	7.23 ± 1.16	7.27 ± 1.07	0.8934
Insulin use					0.0253
No	249 (7.6)	1311 (39.9)	1434 (43.6)	296 (9.0)	
Yes	46 (8.1)	208 (36.8)	238 (42.1)	73 (12.9)	
Multimorbidity index					<0.0001
0–1	55 (6.3)	391 (44.9)	371 (42.6)	54 (6.2)	
≥2	252 (8.1)	1,190 (38.0)	1,360 (43.5)	326 (10.4)	
Frailty index					0.3754
<0.021	208 (7.6)	1,109 (40.3)	1,188 (43.1)	250 (9.1)	
≥0.21	99 (8.0)	472 (37.9)	543 (43.7)	130 (10.5)	
BDI depressive symptoms					0.4613
<10	254 (7.6)	1,333 (40.0)	1,434 (43.0)	311 (9.3)	
≥10	53 (8.1)	242 (36.9)	292 (44.5)	69 (10.5)	
Year 8					
Insulin use					0.0302
No	178 (7.5)	946 (39.9)	1,040 (43.9)	205 (8.7)	
Yes	102 (8.5)	490 (40.7)	480 (39.8)	133 (11.0)	
Multimorbidity index					0.0002
0–1	11 (7.2)	80 (52.3)	61 (39.9)	1 (0.7)	
≥2	296 (7.7)	1,501 (39.0)	1,670 (43.4)	379 (9.9)	
Frailty index					<0.0001
<0.21	163 (7.8)	897 (42.7)	889 (42.3)	152 (7.2)	
≥0.21	144 (7.6)	684 (36.0)	842 (44.3)	228 (12.0)	
BDI depressive symptoms					0.0003
<10	238 (7.1)	1,365 (40.7)	1,442 (43.0)	308 (9.2)	
≥10	64 (10.8)	197 (33.3)	265 (44.8)	66 (11.2)	

Data are presented as n (%) or mean ± SD. Percentages are *n* for trajectory group divided by total *N* for the row.

Weight change from year 8 to the last available weight averaged +11.8 ± 9.1%, +1.2 ± 5.8%, −7.8 ± 5.4%, and −17.7 ± 6.6% for the four trajectories, respectively. The baseline characteristics of participants in the weight trajectories are shown in Table 2.

The trajectory groups differed not only in their postintervention weight change but also in their weight change during intervention (years 1–8). Initial weight loss was greatest (−8.5%) in those who were categorized postintervention as gainers and smallest (0.7%) in those categorized as steep losers ($P < 0.0001$). All pairwise comparisons were significant. Figure 1 shows both the early weight change and the follow-up weight change of the four trajectory groups. The relationship between early and later weight change was similar in ILI and DSE participants separately (Supplementary Fig. 2).

Association Between Weight Loss Trajectory and Proportion Who Died During Follow-up and Intentionality

The four weight trajectories that characterized postintervention weight change also differed in proportion of participants who died during follow-up ($P < 0.0001$). Between year 8 and the last visit, deaths occurred as follows: gain, 31 (10%) of 307; stable, 223 (14%) of 1,581; steady loss, 303 (18%) of 1,731; and steep loss,

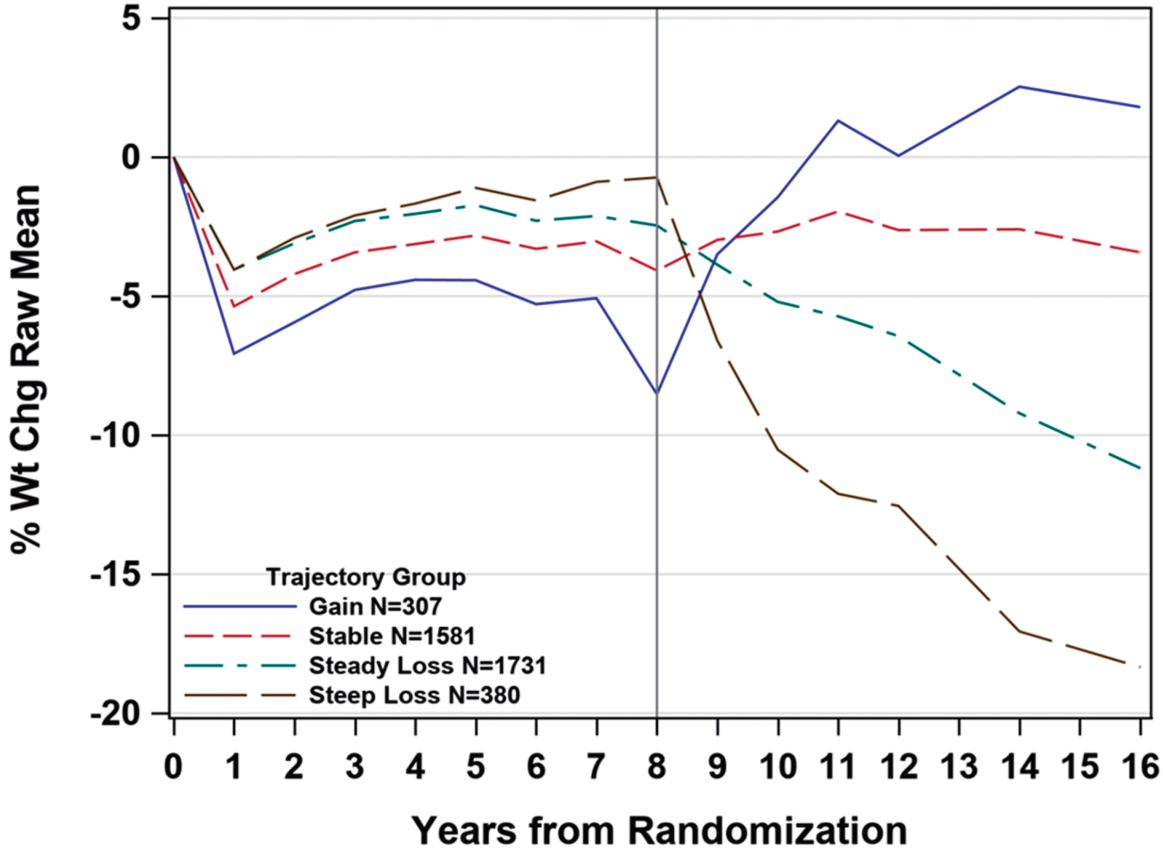

Figure 1—Unadjusted weight changes from randomization to year 8 (intervention) and from year 8 to final visit (follow-up) by trajectory group. Trajectory groups were defined using weight change from year 8 to final visit.

113 (30%) of 380. After adjusting for age, the odds ratio (OR) for mortality was 2.28 (95% CI 1.73, 3.01; $P < 0.0001$) in steep loss versus stable (reference). In addition, we found an association between weight loss trajectory and self-reported unintentional weight loss in years 16–17. Looking at only those participants who reported that they had lost >10 pounds in the last year ($n = 1{,}420$), we found that more than a third of participants in all trajectory categories reported that their weight loss was unintentional. Moreover, there was a significant difference ($P = 0.0079$) among the trajectory categories; weight loss was reported as unintentional by 36% (43 of 118) of the gainers, 40% (214 of 531) of the stable, 45% (284 of 631) of the steady losers, and 54% (75 of 140) of the steep losers.

Baseline Predictors of Trajectory Category

Given this evidence supporting the concerns regarding excessive weight loss in older individuals, we next sought to identify variables that would allow clinicians to predict who might be at risk for steep weight loss. Table 2 indicates the number and percentage of participants in each trajectory group with the baseline characteristic. Table 3 (top two sections) shows the odds of being in the gainer, steep loss, or steady loss trajectory relative to the stable group (reference group) using baseline demographic and health predictors. A significant difference was seen for treatment group; the odds of being in in the steady loss or steep loss group were 30% lower for ILI participants compared with the DSE group (steady loser ILI vs DSE: OR 0.70; 95% CI 0.61, 0.80; steep loser ILI vs DSE: OR 0.66; 95% CI 0.53, 0.82). Those with older age, higher BMI, longer duration of diabetes, and insulin use had significantly greater odds of being in the steep loss trajectory compared with the stable group. HbA_{1c} did not differ among trajectory groups. After adjusting for these baseline demographic variables, presence of multimorbidity was the only health variable related to subsequent odds of being in one of the trajectory groups. Having at least two multimorbidities at baseline increased a participant's odds of being in the steep loss trajectory relative to maintaining a stable weight. Multimorbidity at baseline also increased the odds of being in the gainer group. BDI score and frailty index at baseline were not predictive of trajectory group.

Year-8 Predictors of Trajectory Category

Finally, we sought to determine whether year-8 mental or physical health (Table 2 and Table 3 bottom two sections) or self-reported use of weight control strategies (Supplementary Table 1) were related to weight loss trajectory. Poorer mental and physical health at year 8 (BDI ≥10, multimorbidity ≥2, and frailty ≥0.21) significantly increased the odds of being in the steep loss and the steady loss trajectories relative to the stable group. At year 8, only one of the 380 steep losers had fewer than two multimorbidities. Greater depressive symptoms at year 8 were also related to increased odds of being in the gain trajectory (OR 1.86; 95% CI 1.33,

Table 3—Nominal multinomial model estimates of odds of trajectory group membership by baseline demographic characteristics, baseline health status, or year-8 health status

	Gain vs. stable	Steady loss vs. stable	Steep loss vs. stable	*P*
Baseline demographic characteristics				
Randomization group, ILI vs. DSE	1.06 (0.83, 1.36)	**0.70 (0.61, 0.80)**	**0.66 (0.53, 0.82)**	<0.0001
Age, 5-year increase	**0.86 (0.78, 0.94)**	**1.09 (1.03, 1.14)**	**1.21 (1.11, 1.31)**	<0.0001
BMI, 5 kg/m^2 unit	1.10 (0.99, 1.23)	**1.06 (1.00, 1.13)**	**1.36 (1.24, 1.49)**	<0.0001
Diabetes duration, 5 years	1.02 (0.93, 1.13)	1.04 (0.99, 1.10)	**1.20 (1.11, 1.29)**	0.0001
Baseline health status adjusted for baseline demographic characteristics				
Insulin, yes vs. no	1.06 (0.72, 1.57)	0.96 (0.77, 1.20)	1.16 (0.83, 1.62)	0.7278
Frailty index, ≥0.21 vs. <0.21	1.08 (0.83, 1.42)	1.03 (0.88, 1.19)	0.98 (0.77, 1.26)	0.9313
Multimorbidity index, ≥2 vs. 0–1	**1.61 (1.17, 2.21)**	1.14 (0.96, 1.34)	**1.62 (1.17, 2.23)**	0.0018
Depressive symptoms, ≥10 vs. <10	1.08 (0.78, 1.50)	1.13 (0.93, 1.36)	1.17 (0.86, 1.58)	0.5789
Year-8 health status				
Insulin, yes vs. no	1.11 (0.85, 1.44)	0.89 (0.76, 1.04)	1.25 (0.98, 1.60)	0.0307
Frailty index, ≥0.21 vs. <0.21	1.15 (0.91, 1.48)	**1.24 (1.08, 1.42)**	**1.97 (1.57, 2.47)**	<0.0001
Multimorbidity index, ≥2 vs. 0–1	1.43 (0.75, 2.73)	**1.46 (1.04, 2.05)**	**20.2 (2.8, 145.72)**	0.0046
Depressive symptoms, ≥10 vs. <10	**1.86 (1.36, 2.55)**	**1.27 (1.36, 2.55)**	**1.48 (1.09, 2.01)**	0.0004
Year-8 health status adjusted for baseline demographic and health characteristics				
Insulin, yes vs. no	0.94 (0.69, 1.29)	**0.80 (0.66, 0.95)**	1.01 (0.75, 1.35)	0.0752
Frailty index, ≥0.21 vs. <0.21	1.18 (0.89, 1.55)	**1.18 (1.01, 1.37)**	**1.70 (1.31, 2.19)**	0.0007
Multimorbidity index, ≥2 vs. 0–1	1.10 (0.55, 2.20)	1.22 (0.84, 1.76)	**11.00 (1.5, 80.62)**	0.0982
Depressive symptoms, ≥10 vs. <10	**1.84 (1.32, 2.58)**	**1.26 (1.02, 1.56)**	**1.44 (1.03, 2.00)**	0.0019

Data are presented as OR (95% CI). Baseline demographic characteristics were age and randomization arm, and baseline health characteristics were BMI, diabetes duration, insulin use, frailty, multimorbidity, and depressive symptoms (BDI). Bold font indicates that the comparison is statistically significant.

2.60) relative to the stable reference group. After adjusting for baseline demographic and health characteristics, frailty index, multimorbidity, and depression continued to increase the risk of being in the steep loss category.

The four trajectory groups also differed in their use of key strategies for weight loss at year 8 (Supplementary Table 1). Participants who would subsequently be in the steep loss trajectory were less likely to report reduced calorie intake, reduced fat intake, and both daily and weekly self-weighing compared with those who would remain weight stable. Conversely, those in the gain trajectory group were more likely than those in the stable group to report use of these strategies. The groups did not differ in their reported increases in exercise at year 8. For example, reducing calorie intake was reported at year 8 by 48.5% of those who would subsequently be steep losers, 53% of steady losers, 58% of stable, and 65.5% of gainers, with a significant difference in the odds of reporting reducing calories in each of the three groups relative to stable ($P = 0.0002$). Daily self-weighing was reported by 21% of those who would subsequently be steep losers, 21% of steady losers, 28% of stable, and 34.5% of gainers. Again, the odds of reporting this behavior were significantly lower in steep losers and steady losers and higher in gainers relative to stable ($P < 0.001$).

CONCLUSIONS

We compared weight loss during the postintervention follow-up (year 8 to a median of 16 years) for ILI and DSE participants in Look AHEAD and sought to determine the characteristics of participants in Look AHEAD who had excessive weight loss during these later years. On average, participants lost 3.7% of their weight during this follow-up interval, with greater weight loss in DSE than in ILI. Post hoc trajectory analyses with the cohort objectively assigned to four groups based on their postintervention weight change suggest that individuals with steep weight loss represent a subgroup of potential clinical concern. This subgroup lost on average of 17% of their weight during ∼8 years of follow-up and had the highest mortality during this interval. Participants in the steep weight loss group were older, were more likely to be obese, had longer duration of diabetes, and had higher prevalence of multimorbidity at baseline relative to those who would remain weight stable. At year 8 (end of the intervention), they reported using fewer intentional weight loss strategies and had higher levels of frailty and depression, findings that suggest their steep weight loss may have been associated with poor health.

As reported previously, participants randomly assigned to ILI lost a greater percentage of their body weight during the initial years of the intervention (years 1–8) but had a smaller weight loss percentage than those assigned to DSE during the 2 years immediately following the intervention (12). We now show that greater weight loss with DSE relative to ILI persisted throughout the follow-up. This pattern of greater initial weight loss, followed by weight regain (or less weight loss) in ILI versus DSE in later years would be expected based on the prior literature on weight loss outcomes following lifestyle intervention (25,26), but it was not expected in the control group.

Likewise, the finding that greater weight gain during intervention was

followed by greater weight loss during follow-up was unexpected. Prior studies (27) have shown that early weight loss is related positively to long-term weight loss, but these studies focused on very early weight loss (1–2 months) rather than the 8 years of the intervention. Although it is surprising that participants who did not lose weight initially lost weight during the follow-up, the data presented here suggest that their later weight loss may have been related to health problems and depression at year 8 and not to their engagement with the behavioral weight loss strategies. Even at baseline, those who would subsequently be in the gainers group had an increased likelihood of having two or more multimorbidities.

Trajectory analyses showed that most participants were in the stable (n = 1,581) or steady loss (n = 1,731) groups, whereas smaller numbers gained weight (n = 307) or were steep losers (n = 380). Although they represent only 10% of the Look AHEAD participants, the steep losers are a subgroup of concern because of their higher risk of mortality. As shown in Fig. 1, the steep losers lost weight rapidly during the follow-up; their average weight loss of 17% exceeds that seen during the intensive lifestyle intervention, when participants were actively engaged in efforts to lose weight. The steep weight losers were characterized by several demographic variables at baseline, including older age and longer duration of diabetes, as shown in prior studies (28–30). Among the oldest participants in the trial (age 65–76 years at baseline), the percentage of participants with steep weight loss was almost double that of the youngest age group (45–64 years). Health parameters, particularly at year 8, also helped differentiate the trajectories. At baseline, only multimorbidity was associated with subsequent weight change and was higher in both gainers and steep losers relative to the stable group. However, by year 8, all three health parameters, multimorbidity, frailty, and depression, were related to being in the steep loss trajectory. The finding that steep losers reported lower use of weight control strategies at year 8 suggests that these individuals were losing weight unintentionally, perhaps because of poor health, not as a result of intentional weight loss efforts.

Multimorbidity was common in the Look AHEAD sample. Excluding diabetes, which was common to all Look AHEAD participants, participants averaged 2.2 diseases at baseline, with hypertension and dyslipidemia affecting 79% and 87%, respectively (22). Between baseline and year 8, the multimorbidity index increased on average by 0.98 diseases, with the greatest increases in depression and chronic kidney disease. In the current sample, 86% of those who would be steep losers had two or more diseases at baseline (vs. 75% of the weight stable); at year 8, 99.7% of steep losers had two or more diseases compared with 95% in the weight stable group.

A key question is how clinicians should use these results in counseling older patients with diabetes who are overweight/obese regarding weight loss. The many positive benefits of initial weight loss (4) and the fact that <10% of patients were in the severe weight loss trajectory group suggest that it is prudent to continue to recommend weight loss. This recommendation is also supported by a recent finding from Look AHEAD that there was no difference in mortality between participants randomly assigned to ILI or DSE (14). As suggested in many guidelines for treating these patients, the goal should be to lose and maintain a 5–10% reduction in body weight through healthy eating and increase in physical activity (31,32). Clinicians should monitor weight loss in older individuals with multimorbidity; excessive weight loss and weight loss that is unintentional should be warning signs for clinicians. Further research is needed to develop a model to predict who is at risk for severe weight loss. More frequent monitoring of weight and/or identification of more proximal causes of such weight loss might permit earlier interventions to minimize excessive weight loss.

A strength of this study is that the weights used to determine the change between year 8 and the last study visit and the trajectories of weight change were actually measured over this follow-up interval, whereas in other studies, participants have self-reported their weights from many years prior (33). The large sample size and the prospective assessment of multimorbidity, frailty, and depression are additional strengths. There are also limitations, however, including the fact that the weight change and mortality data were occurring over the same time period and that intentionality of weight loss was self-reported, covered the period of years 16–17, and was assessed after the weight loss had already occurred. Participants were enrolled in a clinical trial; results may therefore not be generalizable. Other causes of weight loss (e.g., changes in appetite, loss of spouse, or financial difficulty) were not assessed. Use of a screening tool such as the Nutrition Screening Initiative Checklist (DETERMINE) (34) could help to identify causes of unintentional weight loss.

In conclusion, we found that on average, participants lost 3.7% of their body weight between year 8 and the end of the follow-up, with greater weight loss in participants who were randomly assigned to DSE, in older individuals, and in those who had previously gained weight. Although most participants were weight stable or had modest weight loss over the follow-up, 9.5% of participants were categorized as having a steep weight loss trajectory. These participants lost on average almost 20% of their body weight (mean 17.7%) over the follow-up and had twice the risk of mortality as those who were weight stable. Although other studies have shown an association between involuntary weight loss and mortality, our findings extend the prior research by identifying variables that may help clinicians determine prospectively those in whom weight loss may be a sign of impending health problems, including greater multimorbidity, frailty, and depressive symptomatology and self-report that their weight loss was not intentional. Given the many positive effects of weight loss, we feel it is appropriate for clinicians to continue to encourage moderate weight reduction for patients with diabetes who are overweight/obese but recommend that they become concerned if older individuals with multimorbidity experience rapid, unintentional weight loss.

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