

ORIGINAL ARTICLE

Clinical Trials and Investigations



Results of a 2-year lifestyle intervention for type 2 diabetes: the Reach Ahead for Lifestyle and Health-Diabetes randomized controlled trial

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Abstract

Objective: The Reach Ahead for Lifestyle and Health (REAL HEALTH)-Diabetes study assessed the comparative effectiveness of two Look AHEAD (Action for Health in Diabetes)-adapted lifestyle intervention (LI) arms targeting weight loss in type 2 diabetes compared with medical nutrition therapy (MNT) referral. At 1 year, LI had greater weight loss than MNT. This study reports outcomes at 24 (end of LI) and 36 months.

Methods: Participants ($N = 211$) with type 2 diabetes and BMI $> 25 \text{ kg/m}^2$ were randomly assigned to in-person LI, telephone conference call LI, or MNT. The primary outcome was percentage weight change. Secondary outcomes included 5% and 10% weight loss, glycated hemoglobin (HbA1c), and patient-reported outcomes.

Results: Participants were 61.7 (SD 10.2) years old; 55% were female; 77% were non-Hispanic White; and had mean (SD) weight of 98 (18.9) kg and mean (SD) HbA1c of 7.7% (1.2%). Mean (SD) weight change at 24 and 36 months was -4.4% (5.9%) and -4.4% (5.4%) in in-person LI, -4.0% (5.8%) and -5.3% (6.4%) in telephone LI, and -3.1% (5.2%) and -5.8% (7.1%) in MNT, with no statistically significant difference in weight or HbA1c at 24 and 36 months. Compared with MNT, LI arms had favorable changes in patient-reported outcomes related to learned dietary skills.

Conclusions: There were no differences in weight outcomes among LI participants compared with referral to MNT at the end of intervention or 1 year after its conclusion.

INTRODUCTION

Achieving and maintaining a 5% weight loss is a key treatment recommendation for patients with type 2 diabetes and overweight or obesity [1]. Behavioral lifestyle intervention (LI) that teaches the

strategies and skills necessary to achieve and maintain weight loss has been highly effective in clinical trials [2], but weight regain has been common after the end of intervention [3–6]. Many weight-loss interventions have been successfully adapted for delivery in primary care by nurses, health coaches, dietitians, and others and have been delivered in-person, in group settings, and via remote approaches [7–12]. The Look AHEAD (Action for Health in Diabetes) LI, designed to treat

obesity in type 2 diabetes and adapted from the highly successful Diabetes Prevention Program (DPP) LI, has demonstrated sustained weight loss, improved diabetes care parameters with less medication use, and improvements in other health outcomes that are not able to be treated with medications [13–17]. However, there has been variable effectiveness of Look AHEAD adaptations and delivery in other settings depending on the population studied and the approach used [18–21].

We adapted the intensive, multiyear Look AHEAD LI for delivery over 2 years, aiming to implement it in community health centers and primary care. Key features of the adapted program included decreased session frequency and delivery in a mostly group format. We randomly assigned participants to LI, delivered in-person or via telephone conference call (telephone), or referral to a dietitian for medical nutrition therapy (MNT), the current recommended standard of care. Interim analysis demonstrated mean weight loss of 4.7% in in-person and telephone LI arms compared with 2.0% in MNT ($p < 0.001$) at 12 months, when LI participants had completed a mean of 18 of 25 possible sessions [22]. Here, we report weight-loss results over the second year of LI, which offered monthly follow-up sessions, and at 36 months, 1 year after intervention conclusion, to assess comparative effectiveness of the in-person and telephone LI compared with MNT.

METHODS

Trial design

Details of the study design, intervention, participant characteristics, and 12-month outcomes have been previously reported [22, 23]. Briefly, Reach Ahead for Lifestyle and Health (REAL HEALTH)-Diabetes is a practice-based, three-arm, randomized comparative effectiveness trial with 1:1:1 allocation to in-person LI, telephone LI, or MNT. The trial is registered at [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02320253) (NCT02320253), and it was approved by the Massachusetts General Hospital Brigham Institutional Review Board. All participants provided written informed consent before any study procedures were performed.

Setting and participants

The trial was conducted at three community health centers and one diabetes specialty practice affiliated with Massachusetts General Hospital in Boston. Participants were recruited from community health centers, primary care, and local endocrinology practices [24]. Eligible participants were adults with type 2 diabetes, BMI $> 25 \text{ kg/m}^2$ (23 if Asian ancestry) but weight $\leq 159 \text{ kg}$, glycated hemoglobin (HbA1c) = 6.5% to $< 11.5\%$, blood pressure $< 160/100 \text{ mm Hg}$, and ability to communicate in English or Spanish. Potential participants were required to complete at least 5 days of a 7-day food diary as a behavioral task to demonstrate commitment to weight loss. Participants who were planning pregnancy, who were participating in

Study Importance

What is already known?

- Look AHEAD (Action for Health in Diabetes) and many other randomized controlled trials have demonstrated that intensive lifestyle change programs can lead to sustained weight loss and myriad health benefits in people with type 2 diabetes.

What does this study add?

- A less intensive, scalable adaptation of the Look AHEAD lifestyle intervention, based at community health centers and delivered either in-person or via telephone conference call group sessions, yielded clinically significant weight loss at 1 year. Weight loss at years 2 and 3 did not differ from an active comparator arm assigned to referral to a dietitian for medical nutrition therapy.

How might the results change the direction of research or the focus of clinical practice?

- Reach Ahead for Lifestyle and Health (REAL HEALTH)-Diabetes demonstrates that a lifestyle intervention delivered via in-person or telephone group formats can lead to effective weight loss in people with type 2 diabetes compared with referral to a dietitian for medical nutrition therapy at 1 year, with no difference at 2 and 3 years. These results can inform future research and clinical programs for patients with type 2 diabetes.

another weight-loss program or MNT, had weight change $> 3\%$ in the prior month, had previous or planned bariatric surgery, had use of medications likely to impact weight (e.g., glucocorticoids), or had medical or psychiatric conditions that would limit ability to participate were excluded.

Interventions

The adapted LI program included 37 sessions delivered over 2 years. Session content was adapted from the available English and Spanish Look AHEAD and DPP materials [25, 26]. The major adaptations from Look AHEAD were delivery of the majority of the content in group format with few individual sessions and further adaptation for telephone conference call delivery. The in-person and telephone LI arms had identical session content with the same interventionist delivering in-person and telephone interventions at each intervention site. Group sessions lasted 60 to 90 minutes, including 19 sessions in the first 6 months followed by 18 monthly sessions from month 7 to 24. LI participants were

offered three individual sessions in each year. In parallel to the MNT arm, lifestyle interventionists were dietitians. As in Look AHEAD, meal replacements were introduced in week 3. Participants were encouraged to purchase and use meal replacements to replace one to two meals per day. Participants were asked to monitor blood glucose levels, food intake, physical activity, and diabetes medication doses for medication adjustment, if needed, per protocol.

Referral to MNT was selected as the active comparator condition because MNT is the current standard of care in clinical practice. Although underused, it is the main nutritional intervention that is covered by health insurance. MNT, an American Diabetes Association-recommended component of diabetes self-management education, is defined as an evidence-based application of the nutrition care process provided by a registered dietitian and is the legal definition of nutrition counseling by a registered dietitian in the United States [27, 28]. MNT participants were referred to a dietitian at their health center or preferred location. The number of MNT visits and billing proceeded per usual care, in that individual MNT referrals did not contain any prespecified content or number of sessions. In general, MNT may include discussion of tailored treatment strategies for weight loss and diabetes control based on an individualized assessment; dietitians and MNT-arm participants agreed on the number and frequency of follow-up visits based on progress toward goals and willingness to return for follow-up [23].

Outcomes

The majority of data and outcome measurements were collected during in-person research visits conducted at baseline and at 6, 12, 24, and 36 months by blinded research assistants. Autonomous regulation was assessed at 6 and 24 months. Surveys could be completed on paper or via the REDCap electronic data capture system. In addition, participants gave consent to clinical data collection from the electronic health record; results within a 6-month window of the study visit target date (± 3 months) were allowed. Because of the onset of the COVID-19 pandemic, some of the 36-month outcome assessments scheduled after March 12, 2020, were conducted via telephone, with final weights obtained by emailing a photo of the weight with the participant standing on the home scale if the participant was unable to attend an in-person research or clinical visit ($n \leq 15$ at 36 months).

Patient characteristics, including socioeconomic variables, comorbidities, and medication data were reported by patients and confirmed by electronic health record review. Trained study staff measured weight (on clinically calibrated scales while the patient was wearing light clothing), height, and blood pressure. Medication adherence was captured with the Morisky Medication Adherence Scale (in which scores < 6 denote low adherence) [29]. The effectiveness of the interventions was also assessed using measures of fat-related diet behavior, with lower scores (1-5) indicating healthier dietary habits [30, 31]; dietary restraint (Dutch Eating Behavior Questionnaire), with higher scores (1-5) denoting greater self-regulation of dietary behaviors [32]; diet self-efficacy, with higher scores (1-5) denoting greater self-

confidence in managing diet [33]; and autonomous regulation, with higher scores (1-7) reflecting more autonomous or self-determined motivation for lifestyle change; autonomous regulation of eating is associated with healthy eating behavior, whereas controlled regulation of eating is associated with dysfunctional eating behavior [34]. Other patient-reported outcomes included the following: diabetes-related quality of life (DQOL; 4-20), with higher scores denoting greater dissatisfaction with diet and lifestyle related to diabetes [35]; diabetes distress, measured with the Problem Areas in Diabetes Scale (PAID; 0-100), with higher scores indicating greater emotional distress and a score ≥ 40 marking the threshold for severe emotional distress [36]; mood, measured with the Patient Health Questionnaire (PHQ)-8 (0-24), with score ≥ 10 indicating current depression [37], and overall self-rated health (excellent, good, fair, poor; 0-3). LI session attendance was tracked; participants were considered "completers" if they attended $\geq 70\%$ LI sessions (≥ 26 of 37 sessions over 2 years and ≥ 8 of 12 sessions in year 2). MNT visits were reported by participants and abstracted from the medical record.

The primary outcome was percentage weight change from baseline. Secondary outcomes included the proportion in each treatment arm achieving 5% and 10% weight loss, change in HbA1c, change in blood pressure, and change in lipid levels as well as changes in patient-reported quality of life, psychosocial measures, and diet behaviors. Correlation of weight loss with program completion was evaluated.

Sample size

The sample-size calculation was based on 80% power and a two-sided significance level of 0.0167 (0.5/3, accounting for three-arm multiple comparisons using the conservative Bonferroni adjustment). The study required 54 participants in each arm to detect a mean difference of 3.5% of body weight change between arms assuming an SD of 5.5% using a two-sample *t* test. To adjust for correlated outcomes within an intervention group, the sample size was increased to 62 per arm, assuming an intraclass correlation coefficient of 0.02 (inflation factor 1.15). The final target sample size was 210, or 70 in each arm, to account for a 10% lost to follow-up rate.

Randomization

A computer randomization algorithm stratified by sex and intervention site in randomly alternating blocks of 3 and 6 with 1:1:1 ratio assigned participants to treatment arms after informed consent was given.

Statistical methods

All analyses were intention-to-treat. We used three-level mixed effect models with two random effects (participant and intervention group) to account for the time-within-participant and participants-within-group data structure. We compared change in

outcomes over time between each of the three study arms with two-sided significance level of 0.0167. We performed sensitivity and exploratory analyses of mean weight change, censoring outcomes after March 12, 2020 (the onset of restrictions related to the COVID-19 pandemic), evaluating the interaction between glucagon-like peptide-1 (GLP-1) receptor agonist and sodium-glucose

cotransporter 2 (SGLT2) inhibitor use and weight loss, stratifying by community health center participants versus other, age < 60 years compared with 60 years or older, and excluding two patients who had bariatric surgery (one in the MNT arm and one in the telephone LI arm). Power calculations and analyses were conducted in SAS version 9.4 (SAS Institute, Inc.).

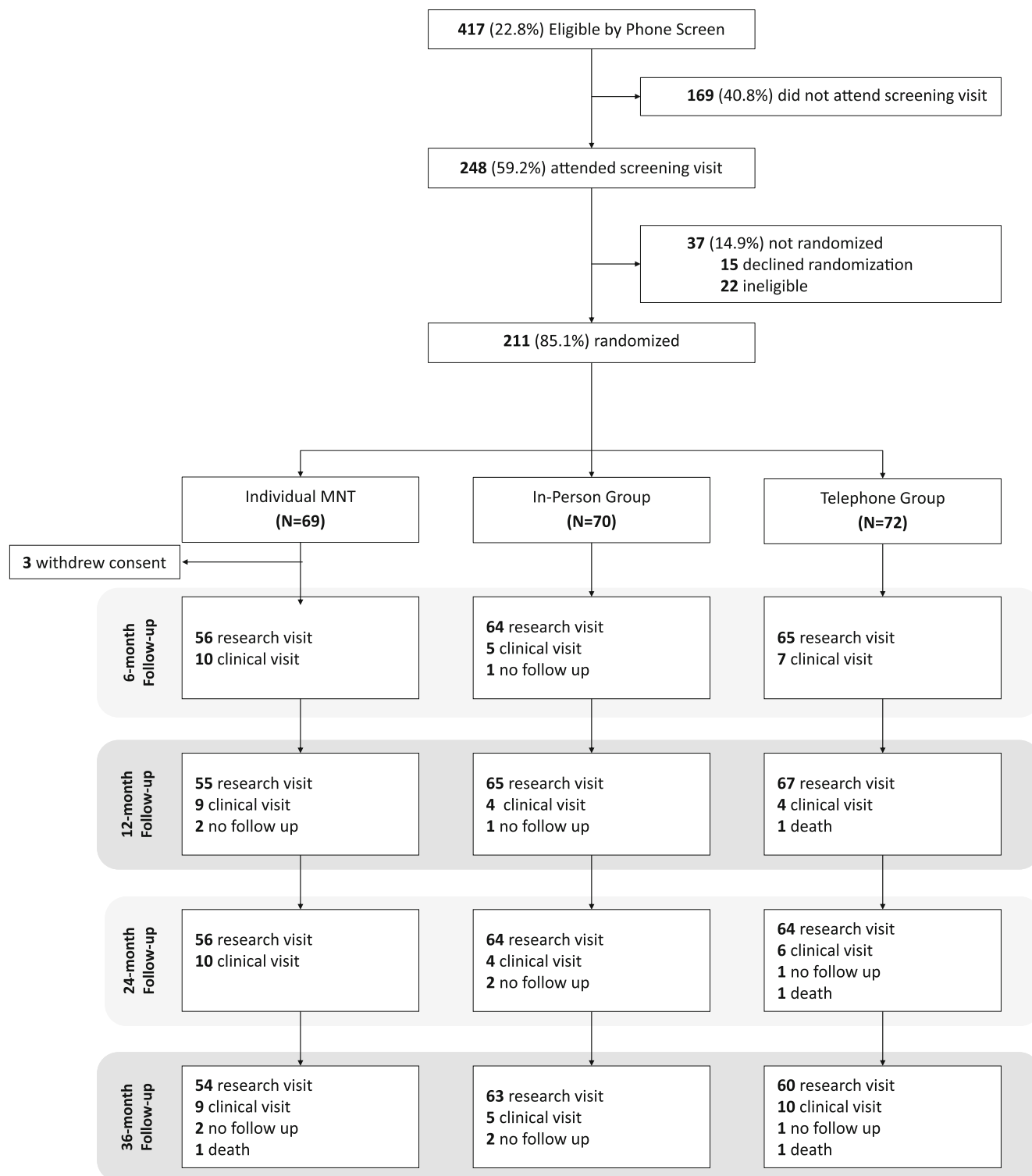


FIGURE 1 CONSORT diagram

TABLE 1 Baseline characteristics

	MNT (n = 66)	In-person LI (n = 70)	Telephone LI (n = 72)	Total (N = 208)
<i>Characteristics</i>				
Age, mean (SD)	61.4 (10.7)	61.3 (10.3)	62.4 (9.8)	61.7 (10.2)
Sex, n (%)				
Female	37 (56.1)	37 (52.9)	41 (56.9)	115 (55.3)
Male	29 (43.9)	33 (47.1)	31 (43.1)	93 (44.7)
Race or ethnic group, n (%)				
Non-Hispanic Asian	2 (3.0)	3 (4.3)	2 (2.8)	7 (3.4)
Non-Hispanic Black	5 (7.6)	2 (2.9)	2 (2.8)	9 (4.3)
Non-Hispanic White	47 (71.2)	55 (78.6)	58 (80.6)	160 (76.9)
More than one race or other	1 (1.5)	0 (0.0)	3 (4.2)	4 (1.9)
Hispanic or Latinx	11 (16.7)	10 (14.3)	7 (9.7)	28 (13.5)
Education, n (%)				
Less than 12th grade	8 (12.1)	5 (7.1)	4 (5.6)	17 (8.2)
12th grade (including GED)	12 (18.2)	13 (18.6)	18 (25.0)	43 (20.7)
1-3 years of college	18 (27.3)	20 (28.6)	22 (30.6)	60 (28.8)
4 or more years of college or graduate school	28 (42.4)	32 (45.7)	28 (38.9)	88 (42.3)
Income n (%)				
Less than \$30,000	17 (25.8)	17 (24.3)	14 (19.4)	48 (4.3)
\$30,000-\$49,999	3 (4.5)	9 (12.9)	9 (12.5)	21 (23.1)
\$50,000-\$99,999	17 (25.8)	23 (32.9)	28 (38.9)	68 (10.1)
\$100,000-\$150,000	14 (21.2)	11 (15.7)	10 (13.9)	35 (32.7)
More than \$150,000	12 (18.2)	6 (8.6)	9 (12.5)	27 (16.8)
Missing	3 (4.5)	4 (5.7)	2 (2.8)	9 (13.0)
Employment, n (%)				
Employed	35 (53.0)	39 (55.7)	36 (50.0)	110 (52.9)
Unemployed	5 (7.6)	3 (4.3)	3 (4.2)	11 (5.3)
Homemaker	2 (3.0)	2 (2.9)	3 (4.2)	7 (3.4)
Retired	22 (33.3)	23 (32.9)	28 (38.9)	73 (35.1)
Other	2 (3.0)	3 (4.3)	2 (2.8)	7 (3.4)
Primary care at community health center, n (%)	42 (63.6)	42 (60.0)	44 (61.1)	128 (61.5)
<i>Clinical characteristics^a</i>				
Diabetes duration, (y), mean (SD)	10.3 (8.0)	10.6 (7.4)	9.8 (8.7)	10.2 (8.0)
Hypertension, n (%)	51 (77.3)	59 (84.3)	54 (75.0)	164 (78.8)
Hyperlipidemia, n (%)	48 (75.0)	56 (80.0)	59 (81.9)	163 (79.1)
Coronary artery disease, n (%)	15 (22.7)	15 (21.4)	16 (22.2)	46 (22.1)
Congestive heart failure, n (%)	4 (6.1)	1 (1.4)	4 (5.6)	9 (4.3)
Retinopathy, n (%)	7 (10.6)	4 (5.7)	4 (5.6)	15 (7.2)
Neuropathy, n (%)	12 (18.2)	13 (19.4)	9 (12.5)	34 (16.6)
Weight, mean (SD)	99.7 (21.4)	98.8 (17.0)	96.1 (18.2)	98.1 (18.9)
BMI, mean (SD)	35.7 (6.2)	35.0 (4.9)	34.5 (5.0)	35.0 (5.4)
HbA1c (% NGSP), mean (SD)	7.8 (1.2)	7.8 (1.2)	7.6 (1.1)	7.7 (1.2)
HbA1c (mmol/mol, IFCC), mean (SD)	61.7 (13.2)	61.5 (12.8)	60.1 (12.5)	61.1 (12.8)
Systolic blood pressure (mm Hg), mean (SD)	125.1 (16.5)	126.0 (13.9)	123.6 (10.5)	124.9 (13.7)
Diastolic blood pressure, (mm Hg) mean (SD)	75.8 (10.2)	76.6 (7.2)	77.5 (7.5)	76.7 (8.3)
Total cholesterol (mg/dL), mean (SD)	162.6 (38.2)	164.7 (37.6)	162.8 (39.5)	163.4 (38.3)
Low-density lipoprotein (mg/dL), mean (SD)	87.5 (29.7)	90.4 (31.3)	88.3 (30.1)	88.8 (30.2)

(Continues)

TABLE 1 (Continued)

	MNT (n = 66)	In-person LI (n = 70)	Telephone LI (n = 72)	Total (N = 208)
High-density lipoprotein (mg/dL), mean (SD)	45.3 (12.6)	42.7 (10.2)	43.7 (12.1)	43.9 (11.7)
Triglycerides (mg/dL), mean (SD)	146.4 (99.2)	196.5 (289.9)	152.2 (94.0)	165.3 (186.1)
<i>Medications, n (%)</i>				
Metformin	53 (80.3)	57 (81.4)	57 (79.2)	167 (80.3)
Sulfonylurea	19 (28.8)	27 (38.6)	19 (26.4)	65 (31.3)
Insulin	20 (30.3)	25 (35.7)	24 (33.3)	69 (33.2)
SGLT2 inhibitor	0 (0.0)	3 (4.3)	3 (4.2)	6 (2.9)
GLP-1 receptor agonist	5 (7.6)	5 (7.1)	4 (5.6)	14 (6.7)
Other glucose-lowering medication	3 (4.6)	5 (7.1)	5 (6.9)	13 (6.3)
No glucose-lowering medication	7 (10.8)	3 (4.3)	6 (8.3)	16 (7.7)
Blood pressure medication	53 (80.3)	59 (84.3)	62 (86.1)	174 (83.7)
Lipid-lowering medication	51 (78.5)	54 (77.1)	59 (81.9)	164 (79.2)
Statin	51 (77.3)	46 (65.7)	58 (80.6)	155 (74.5)
<i>Patient-reported outcomes^b</i>				
Medication adherence (MMAS), mean (SD)	6.5 (1.8)	6.6 (1.3)	6.7 (1.7)	6.6 (1.6)
PAID, mean (SD)	36.9 (23.1)	39.3 (19.5)	40.3 (23.3)	38.9 (22.0)
PHQ-8, mean (SD)	5.3 (5.4)	4.7 (4.4)	4.4 (3.8)	4.8 (4.6)
Diabetes quality of life score, mean (SD)	13.7 (2.9)	13.4 (3.6)	13.4 (3.4)	13.5 (3.3)
Self-rated health, mean (SD)	1.7 (0.8)	1.5 (0.8)	1.5 (0.7)	1.6 (0.7)
<i>Diet behavior^b</i>				
Fat-related diet behavior, mean (SD)	2.7 (0.6)	2.7 (0.5)	2.8 (0.6)	2.7 (0.6)
Dietary restraint (Dutch Eating Behavior Questionnaire), mean (SD)	2.8 (0.6)	2.9 (0.6)	2.8 (0.8)	2.8 (0.7)
Diet self-efficacy scale, mean (SD)	3.7 (0.6)	3.6 (0.7)	3.8 (0.7)	3.7 (0.7)
Autonomous regulation, mean (SD)	5.5 (1.0)	5.6 (1.1)	5.4 (1.0)	5.5 (1.0)

Abbreviations: DQOL, diabetes-related quality of life; GED, general equivalency diploma; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; LI, lifestyle intervention; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; MMAS, Morisky Medication Adherence Scale; MNT, medical nutrition therapy; NGSP, National Glycohemoglobin Standardization Program; PAID, Problem Areas in Diabetes Scale; PHQ-8, Patient Health Questionnaire-8; SGLT2, sodium-glucose cotransporter 2.

^aComorbidities were self-reported and confirmed by medical record review.

^bPatient-reported outcomes are defined and scaled as follows: MMAS (range 1-8), <6 denotes low adherence [29]. PAID (range 0-100), ≥40 indicates severe emotional distress [36]; PHQ-8 (range 0-24), ≥10 indicates current depression [37]. DQOL (range 4-20), with higher scores denoting greater dissatisfaction related to diabetes [35]; self-rated health (range 0-3 indicating excellent, good, fair, poor); fat-related diet behavior (range 1-5), with lower scores indicating lower fat dietary habits [30, 31]; dietary restraint (Dutch Eating Behavior Questionnaire), with higher scores (1-5) denoting greater self-regulation of dietary behaviors [32]; diet self-efficacy, with higher scores (1-5) denoting greater self-confidence in managing diet [33]; and autonomous regulation, with higher scores (1-7) reflecting more autonomous motivation for lifestyle change; autonomous regulation was collected only at 6 and 24 months [34].

RESULTS

Participants

Participant flow is depicted in the Consolidated Standards of Reporting Trials (CONSORT) diagram (Figure 1). Participants were recruited between January 2015 and July 2017, with recruitment previously described [23, 24]. At baseline, 69 participants were randomly assigned to MNT, 70 to in-person LI, and 72 to telephone LI. Three participants in the MNT arm withdrew consent and were not included in the analysis. Two participants in MNT, two in in-person LI, and one in telephone LI had no available follow-up data at 3 years, for 96% follow-up overall, with 86% of clinical outcomes

obtained through research assessments and the remainder through clinical records.

Baseline characteristics

Baseline characteristics are shown in Table 1. The majority of participants (61.5%) participated through the community health center sites. Mean weight was 98.1 kg, mean BMI was 35, and mean HbA1c was 7.7%, with mean diabetes duration 10.2 years. Eighty percent of participants took metformin, with approximately one-third treated with sulfonylureas or insulin. Baseline use of other glucose-lowering medications was less than 10% for each

TABLE 2 Outcomes

	Mo	MNT	In-person LI	Telephone LI	p value ^a		
					MNT vs. in-person LI	MNT vs. telephone LI	In-person vs. telephone
Clinical characteristics, change from baseline							
Weight (% weight change), mean (SD)	6	−1.1 (3.7)	−5.6 (4.9)	−4.6 (5.8)	<0.0001	0.0003	0.34
	12	−2.0 (4.1)	−4.5 (6.1)	−4.8 (6.1)	0.008	0.003	0.74
	24	−3.1 (5.2)	−4.4 (5.9)	−4.0 (5.8)	0.2	0.37	0.68
	36	−5.8 (7.1)	−4.4 (5.4)	−5.3 (6.4)	0.13	0.6	0.31
5% Weight loss, n (%)	6	10 (15.2)	34 (49.3)	32 (44.4)	0.0002	0.0009	0.59
	12	14 (21.9)	33 (47.8)	31 (43.7)	0.005	0.017	0.63
	24	22 (33.3)	26 (38.2)	29 (41.4)	0.68	0.47	0.76
	36	33 (52.4)	28 (41.2)	39 (55.7)	0.19	0.77	0.11
10% Weight loss, n (%)	6	1 (1.5)	13 (18.8)	12 (16.7)	0.014	0.022	0.78
	12	2 (3.1)	12 (17.4)	12 (16.9)	0.031	0.034	0.97
	24	6 (9.1)	11 (16.2)	10 (14.3)	0.38	0.57	0.75
	36	12 (19.0)	13 (19.1)	15 (21.4)	0.79	0.95	0.74
Weight (kg), mean (SD)	6	−1.2 (3.7)	−5.6 (4.9)	−4.6 (6.0)	<0.0001	0.0009	0.36
	12	−2.1 (4.7)	−4.5 (5.5)	−4.6 (6.3)	0.021	0.012	0.84
	24	−3.0 (4.9)	−4.3 (5.5)	−3.9 (6.0)	0.2	0.38	0.68
	36	−6.2 (9.4)	−4.3 (5.4)	−5.2 (6.8)	0.048	0.29	0.35
HbA1c (% NGSP), mean (SD)	6	−0.3 (1.1)	−0.6 (0.8)	−0.5 (1.2)	0.24	0.49	0.64
	12	−0.4 (1.2)	−0.4 (0.8)	−0.2 (1.3)	1	0.44	0.46
	24	−0.2 (1.4)	−0.3 (1.3)	0.1 (1.4)	0.95	0.2	0.25
	36	−0.3 (1.6)	−0.0 (1.2)	0.3 (1.7)	0.32	0.021	0.21
HbA1c (mmol/mol, IFCC), mean (SD)	6	−3.0 (12.4)	−6.3 (9.1)	−5.1 (12.9)	0.24	0.49	0.64
	12	−4.1 (13.6)	−4.5 (9.1)	−2.5 (14.1)	1	0.44	0.46
	24	−2.5 (15.0)	−2.8 (14.4)	0.8 (14.8)	0.95	0.2	0.25
	36	−2.8 (17.1)	−0.3 (12.7)	3.2 (18.3)	0.32	0.021	0.21
Systolic blood pressure (mm Hg), mean (SD)	6	−0.0 (14.7)	−4.0 (15.0)	−2.3 (14.4)	0.13	0.42	0.51
	12	1.8 (15.8)	−1.8 (14.9)	−1.0 (14.7)	0.16	0.38	0.63
	24	−0.6 (16.3)	−3.5 (15.3)	−3.3 (14.7)	0.24	0.38	0.78
	36	−2.0 (16.9)	−2.4 (17.4)	−0.9 (13.8)	0.85	0.62	0.53
Diastolic blood pressure (mm Hg), mean (SD)	6	−0.9 (7.6)	−1.3 (8.1)	−2.0 (8.2)	0.8	0.47	0.67
	12	1.5 (8.0)	−0.3 (7.3)	−1.5 (7.6)	0.35	0.1	0.52
	24	0.9 (10.6)	−0.1 (7.5)	−1.9 (8.2)	0.54	0.083	0.3
	36	−1.0 (9.1)	−2.7 (8.2)	−2.4 (8.7)	0.54	0.57	0.97
Total cholesterol (mg/dL), mean (SD)	6	0.0 (25.1)	−6.2 (27.0)	−4.3 (27.9)	0.3	0.52	0.69
	12	−2.1 (29.7)	−7.3 (28.8)	1.7 (28.5)	0.24	0.65	0.091
	24	−6.4 (29.9)	−5.3 (36.1)	−5.1 (33.7)	0.8	0.65	0.83
	36	−13.7 (38.0)	−9.1 (43.4)	−3.6 (36.2)	0.29	0.047	0.34
Low-density lipoprotein (mg/dL), mean (SD)	6	−3.3 (22.4)	−3.0 (21.0)	−3.5(26.0)	0.88	0.98	0.9
	12	−3.5 (23.1)	−7.3 (23.9)	−0.1(24.5)	0.36	0.46	0.092
	24	−5.9 (20.7)	−7.1 (26.6)	−8.5(27.0)	0.94	0.78	0.83
	36	−13.4 (28.0)	−11.0 (32.8)	−6.6(25.6)	0.4	0.054	0.28
High-density lipoprotein (mg/dL), mean (SD)	6	1.0 (6.0)	1.7 (7.1)	2.9 (6.8)	0.76	0.26	0.4
	12	1.6 (5.8)	3.6 (6.3)	3.6 (6.5)	0.16	0.2	0.9
	24	3.3 (6.8)	3.7 (6.3)	3.6 (6.8)	0.71	0.85	0.84
	36	4.1 (7.4)	5.1 (13.4)	4.8 (8.0)	0.51	0.82	0.65

(Continues)

TABLE 2 (Continued)

	Mo	MNT	In-person LI	Telephone LI	p value ^a		
					MNT vs. in-person LI	MNT vs. telephone LI	In-person vs. telephone
Triglycerides (mg/dL), mean (SD)	6	12.5 (79.7)	−56.0 (252.6)	−21.3 (80.7)	0.021	0.32	0.18
	12	7.9 (75.7)	−57.5 (259.4)	−1.1 (113.6)	0.016	0.68	0.044
	24	−8.6 (70.9)	−31.8 (228.0)	−4.1 (86.3)	0.18	0.87	0.13
	36	−15.4 (74.4)	−55.8 (276.5)	−9.0 (96.5)	0.21	0.69	0.097
<i>Patient-reported outcome measures, change from baseline</i>							
Medication adherence (MMAS), mean (SD)	6	−0.1 (1.4)	−0.1 (1.4)	−0.0 (1.5)	0.95	0.84	0.89
	12	0.0 (1.2)	0.1 (1.2)	−0.0 (1.1)	0.85	0.82	0.68
	24	−0.0 (1.6)	−0.0 (1.3)	−0.1 (1.4)	0.89	0.63	0.73
	36	0.0 (1.4)	0.2 (1.4)	−0.1 (1.4)	0.48	0.75	0.31
PAID, mean (SD)	6	−7.0 (17.6)	−12.4 (20.3)	−14.1 (19.4)	0.12	0.028	0.52
	12	−5.8 (18.0)	−14.4 (15.0)	−15.1 (21.9)	0.008	0.005	0.9
	24	−9.2 (22.8)	−13.0 (15.3)	−16.3 (20.0)	0.16	0.011	0.25
	36	−13.4 (22.9)	−14.1 (17.8)	−14.3 (18.6)	0.56	0.36	0.75
PHQ-8, mean (SD)	6	−0.6 (4.5)	−1.0 (3.3)	−0.7 (3.1)	0.63	0.73	0.89
	12	−0.9 (4.1)	−1.2 (2.8)	−0.4 (3.7)	0.56	0.57	0.23
	24	−1.0 (4.3)	−0.8 (3.2)	−0.1 (3.1)	0.93	0.37	0.39
	36	−0.9 (5.2)	−0.7 (3.7)	0.2 (4.3)	0.65	0.14	0.29
Diabetes quality of life, mean (SD)	6	−2.4 (3.9)	−4.2 (4.9)	−3.9 (4.4)	0.023	0.082	0.58
	12	−2.6 (4.2)	−4.0 (3.4)	−2.9 (4.4)	0.11	0.92	0.13
	24	−3.3 (3.4)	−4.0 (3.9)	−4.4 (3.3)	0.31	0.15	0.68
	36	−3.5 (4.1)	−3.1 (4.2)	−3.6 (4.8)	0.58	0.94	0.52
Self-rated health, mean (SD)	6	−0.2 (0.6)	−0.2 (0.6)	−0.3 (0.6)	0.99	0.66	0.67
	24	−0.3 (0.7)	−0.3 (0.7)	−0.3 (0.7)	0.61	0.66	0.94
	36	−0.4 (0.7)	−0.3 (0.8)	−0.3 (0.7)	0.52	0.47	0.94
Fat-related diet behavior, mean (SD)	6	−0.1 (0.4)	−0.4 (0.5)	−0.3 (0.5)	0.016	0.025	0.85
	12	−0.2 (0.4)	−0.4 (0.5)	−0.3 (0.5)	0.06	0.18	0.56
	24	−0.2 (0.4)	−0.4 (0.4)	−0.4 (0.5)	0.016	0.017	0.99
	36	−0.3 (0.5)	−0.3 (0.4)	−0.3 (0.4)	0.64	0.5	0.83
Dietary restraint, mean (SD)	6	0.4 (0.7)	0.6 (0.6)	0.6 (0.7)	0.073	0.16	0.68
	12	0.5 (0.7)	0.5 (0.6)	0.5 (0.7)	0.71	0.98	0.72
	24	0.3 (0.7)	0.7 (0.7)	0.6 (0.6)	0.028	0.13	0.48
	36	0.4 (0.6)	0.3 (0.7)	0.4 (0.8)	0.79	0.61	0.42
Diet self-efficacy, mean (SD)	6	−0.2 (0.7)	0.3 (0.7)	0.1 (0.6)	0.0004	0.041	0.12
	12	−0.3 (0.8)	0.2 (0.8)	−0.1 (0.8)	0.004	0.44	0.027
	24	−0.2 (0.8)	0.3 (0.7)	−0.1 (0.8)	0.007	0.77	0.002
	36	−0.1 (0.9)	−0.1 (0.9)	−0.4 (0.8)	0.79	0.006	0.009
Autonomous regulation, mean (SD)	6	0.1 (1.6)	0.5 (1.2)	0.3 (1.3)	0.079	0.48	0.29
	24	−0.3 (1.6)	0.5 (1.3)	0.4 (1.3)	0.003	0.017	0.53
<i>Medication use at each time point</i>							
Metformin, n (%)	6	51 (78.5)	59 (85)	58 (80.6)	0.76	0.48	0.32
	12	52 (81.3)	56 (81.2)	54 (77.1)	0.41	0.58	0.79
	24	50 (76.9)	56 (82.4)	56 (80.0)	0.57	0.84	0.45
	36	50 (80.6)	56 (82.4)	56 (80.0)	0.94	0.76	0.83

(Continues)

TABLE 2 (Continued)

	Mo	MNT	In-person LI	Telephone LI	p value ^a		
					MNT vs. in-person LI	MNT vs. telephone LI	In-person vs. telephone
Sulfonylurea, n (%)	6	18 (27.7)	20 (29.0)	14 (19.4)	0.25	0.29	0.93
	12	16 (25.0)	21 (30.4)	11 (15.7)	0.2	0.06	0.54
	24	12 (18.5)	19 (27.9)	15 (21.4)	0.36	0.79	0.25
	36	14 (22.6)	18 (26.5)	16 (22.9)	0.77	0.97	0.8
Insulin, n (%)	6	18 (27.7)	23 (33.3)	24 (33.3)	0.53	0.98	0.51
	12	20 (31.3)	24 (34.8)	24 (34.3)	0.99	0.77	0.79
	24	20 (30.8)	24 (35.3)	26 (37.1)	0.56	0.77	0.77
	36	19 (30.6)	23 (33.8)	25 (35.7)	0.4	0.58	0.75
SGLT2 inhibitor, n (%)	6	4 (6.2)	5 (7.2)	4 (5.6)	0.88	0.68	0.8
	12	5 (7.8)	4 (5.8)	4 (5.7)	0.63	0.98	0.65
	24	7 (10.8)	7 (10.3)	6 (8.6)	0.67	0.73	0.93
	36	9 (14.5)	11 (16.2)	7 (10.0)	0.43	0.29	0.79
GLP-1 receptor agonist, n (%)	6	8 (12.3)	3 (4.3)	7 (9.7)	0.83	0.25	0.17
	12	8 (12.5)	3 (4.3)	7 (10.0)	0.84	0.24	0.17
	24	13 (20.0)	10 (14.7)	11 (15.7)	0.7	0.83	0.55
	36	18 (29.0)	15 (22.1)	12 (17.1)	0.18	0.56	0.46

Note: NGSP is the organization previously known as the National Glycohemoglobin Standardization Program; NGSP reports HbA1c in percentage glycohemoglobin. IFCC denotes the International Federation of Clinical Chemistry, which reports HbA1c in mmol HbA1c/mol Hb. PHQ-8 is the Patient Health Questionnaire. See Table 1 footnote for definitions and scales of all measures.

Abbreviations: GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; LI, lifestyle intervention; MMAS, Morisky Medication Adherence Score; MNT, medical nutrition therapy; PAID, Problem Areas in Diabetes Scale; SGLT2, sodium-glucose cotransporter 2.

^ap values < 0.017 are denoted in bold font.

other medication class, including GLP-1 receptor agonists (6.7%) and SGLT2 inhibitors (2.9%).

At baseline, participants reported that their self-rated health was good to fair (mean 1.6 [0.7]) and reported moderately high levels of emotional distress related to diabetes (with MNT participants reporting higher levels of distress compared with the telephone LI group). Fifteen percent of participants met thresholds consistent with depression (≥ 10) on the PHQ-8 [37], and 46% met criteria for significant emotional distress (> 40) on the PAID [38]. DQOL scores showed that participants were not satisfied with their knowledge about diet and lifestyle, their eating and activity habits, or their ability to manage diet and lifestyle. They also did not consistently practice healthy diet behaviors or flexible dietary restraint and reported moderate levels of diet self-efficacy and autonomous motivation for lifestyle change.

Intervention participation

Mean session attendance was 24.8 (9.4) of 37 sessions in in-person LI and 26.6 (9.8) in telephone LI, with 61% of in-person LI participants and 69% of telephone LI participants considered completers (attended $\geq 70\%$ of sessions). Mean number of visits in MNT was 4.3 (4.3) over 2 years. However, most MNT visits took place in the first year after randomization, with a mean of 3.6 (3.3) in year 1, 0.7 (1.3) in year 2, and 0.8 (1.9) visits in year 3, after the LI had concluded. LI session attendance was not

affected by the COVID-19 pandemic because the intervention, but not the 36-month assessment, concluded prior to March 2020.

Outcomes

Both LI arms achieved comparable mean weight loss during the 2-year intervention and at the 36-month assessment, 12 months after intervention end. In intention-to-treat analyses, in-person LI had a mean 4.5% weight loss at 12 months, 4.4% at 24 months, and 4.4% at 36 months. Telephone LI had mean weight loss of 4.8% at 12 months, 4.0% at 24 months, and 5.3% at 36 months. MNT had a mean weight loss of 2% at 12 months, 3.1% at 24 months, and 5.8% at 36 months (Table 2). Over time, combined weight loss in LI groups showed that, at 24 months, 40% of LI participants had 5% weight loss, with 49% reaching this benchmark at 36 months, compared with 33% and 52% of MNT participants at 24 and 36 months, respectively. Fifteen percent of LI participants had weight loss of 10% or higher at 24 months compared with 9% of MNT participants. By 36 months, 20% of LI participants and 19% of MNT participants met this threshold. Overall weight loss was statistically significantly greater in LI arms than in the MNT arm at 12 months, but not at 24 or 36 months (Figure 2). Weight loss was proportional to session attendance in the LI arms, with significantly more weight loss at 36 months in completers compared with non-completers (in-person: -5.1 vs. -3.2 [diff = 1.9, 95% CI: -0.8 to

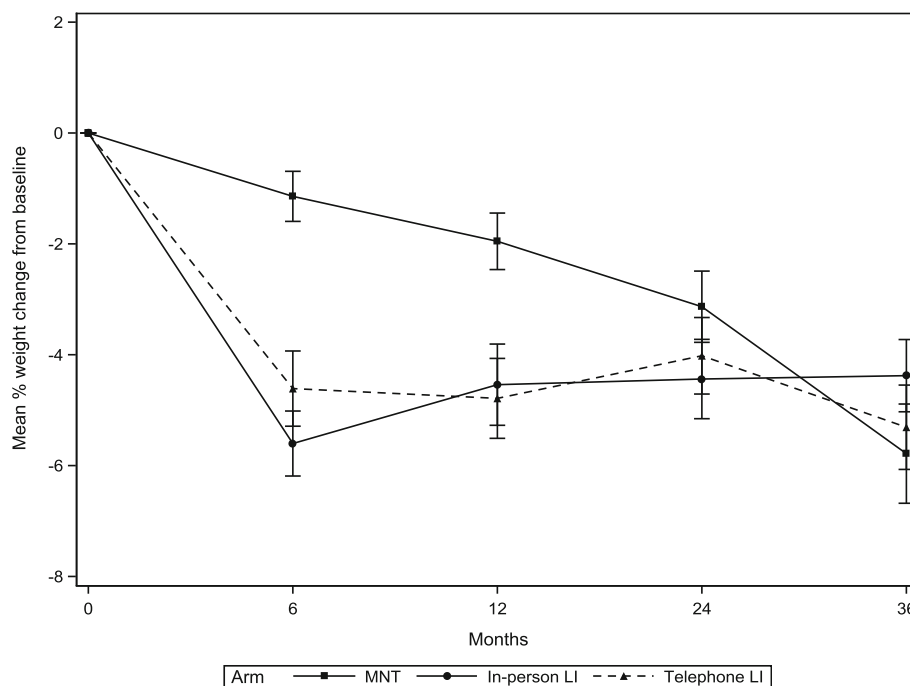


FIGURE 2 Weight trajectory over time

4.6]; telephone: -6.5 vs. -2.6 [diff = 3.9, 95% CI: 0.7 to 7.1]. Weight-loss outcomes did not differ when stratified by community health center enrollment or by age < 60 years or 60 years or older at baseline (data not shown). Sensitivity analyses excluding participants who had bariatric surgery or excluding outcomes obtained after the pandemic onset did not affect the results (data not shown). There were no differences in glycemic, blood pressure, or lipid levels among the three arms over the course of follow-up (Table 2).

There were significant changes in glucose-lowering medication use over time. We observed increasing use of GLP-1 receptor agonists and SGLT2 inhibitors and decreasing use of sulfonylureas in all three arms, with no significant differences among treatment arms. There was no interaction between GLP-1 receptor agonist or SGLT2 inhibitor use and weight outcomes (data not shown).

Patient-reported outcomes (Table 2) showed improvements in diabetes emotional functioning measured by PAID in all participants, with more improvements in telephone LI compared with MNT at 24 months, but not at 36 months. Self-rated health and DQOL improved in all participants over the course of the study, with no differences at 24 or 36 months. Fat-related dietary intake and autonomous regulation of diet showed greater improvement in both LI arms compared with MNT at 24 months. Dietary restraint increased in all participants, with no significant differences among groups. Diet self-efficacy was significantly higher in in-person LI compared with MNT throughout the intervention period and compared with telephone LI at the conclusion of the intervention at 24 months and 1 year after intervention end, at 36 months.

Satisfaction with care was high in all groups, with 83% of in-person, 76% of telephone, and 50% of MNT participants reporting that sessions were mostly or very helpful in learning to manage diet, and

84% of in-person, 73% of telephone, and 48% of MNT participants reporting that sessions were mostly or very helpful in learning to deal with challenges that make weight loss hard.

DISCUSSION

This comparative effectiveness trial of a Look AHEAD-adapted LI program targeting weight loss in type 2 diabetes and delivered in-person or via telephone conference call demonstrated that both LI delivery modalities achieved early, clinically significant weight loss at 6 and 12 months compared with referral to a dietitian for MNT. We observed similar weight-loss outcomes across study arms at 24 and 36 months, when there was decreased intervention intensity in the second year of the intervention and no intervention or study contact between months 24 and 36. Glucose-lowering medications were adjusted based on clinical considerations in all three arms, resulting in no difference in glycemic outcomes. In addition, there were changes in the pattern of diabetes medication use over time, with no difference across treatment arms.

The goal of this project was to determine whether the Look AHEAD LI, which demonstrated sustained weight loss and multiple additional benefits over time compared with standard diabetes education [15], could be adapted for delivery with fewer sessions and in a group format, either in-person in community health centers to increase local community accessibility or via telephone conference call to increase scalability, while maintaining overall efficacy. In the current era of telemedicine, questions about the efficacy of in-person versus telephone group intervention have become even more salient. We observed no statistically significant difference in attendance and

weight loss, both initially and over time, regardless of LI modality. However, satisfaction with care was similarly high in both intervention modalities, with slightly higher numerical satisfaction in the in-person arm, perhaps related to relational factors such as connection with the interventionist or group cohesion. This provides reassurance that group LI content may be delivered equally well in-person or via telephone conference call, which is even simpler and more accessible than videoconference.

Some decrement in efficacy compared with the clinical trial setting was expected with this adaptation, given the decrease in intensity (fewer individual sessions and without provision of free meal replacements), less restrictive inclusion criteria, and primary-care-based recruitment and setting. Compared with Look AHEAD, REAL HEALTH-Diabetes participants were slightly older (mean age 62 vs. 59 years), with a higher proportion of men (45% vs. 40%) and self-reported White race (76% vs. 63%) but with a similar proportion of Hispanic ethnicity (13% in both trials). At baseline, mean weight was slightly lower in REAL HEALTH-Diabetes than in Look AHEAD (98 vs. 101 kg), with higher prevalence of cardiovascular disease (22% vs. 14%), higher HbA1c (7.7% vs 7.3%), and more use of insulin (30% vs. 15%) [39, 40]. REAL HEALTH-Diabetes 2-year weight-loss outcomes were less than those in Look AHEAD (in-person LI −4.4% [5.9%], telephone LI −4.0% [5.8%] vs. −6.5% [0.2%] in Look AHEAD) [40, 41]. Forty percent of REAL HEALTH-Diabetes LI participants achieved a mean weight loss of ≥5% at 3 years compared with 46% in Look AHEAD, whereas more than 15% of REAL HEALTH-Diabetes LI participants achieved ≥10% weight loss compared with 23% of Look AHEAD participants [6]. Overall, the project demonstrated a small decrement in efficacy coupled with generalizability to a population with longer diabetes duration and higher prevalence of cardiovascular disease compared with Look AHEAD.

Patient-reported outcome measures showed increased autonomous motivation for regulation of diet and fat intake, as well as improved diet self-efficacy in LI compared with MNT arms, factors that have been shown to be predictive of better long-term weight-loss outcomes [42]. All treatment groups reported improvements in dietary restraint, depressive symptoms, and self-reported health and DQOL, with no significant difference among groups. In addition, at the end of the 24-month intervention period, satisfaction with care in terms of learning skills to manage diet and challenges related to weight loss was high in all groups but was somewhat higher in the LI groups than MNT.

A strength of this project was the inclusion of an active comparator, making this a true comparative effectiveness evaluation. REAL HEALTH-Diabetes was designed to enhance the likelihood that the findings would be generalizable to clinical practice. That the degree of weight loss in the MNT arm was equivalent to the LI arms is a surprising finding. Although we aimed to recruit usual care populations, participants who enrolled in this program were highly motivated: in order to participate, they had to be willing to commit to an intensive behavioral lifestyle program and had to demonstrate motivational readiness to engage in the intervention by completing 5 of 7 days of a food diary. Use of diabetes medications that promote weight loss did not differ across treatment arms. Look AHEAD

also observed earlier weight loss in the LI arm, with convergence of weight loss in comparison to the diabetes support and education arm over time as participants aged, albeit over a longer time course [6]. There may have been unintentional weight loss in the MNT arm in REAL HEALTH at years 2 and 3; this may also have occurred in the LI arms. We conclude that there are many factors contributing to weight loss in motivated patients over time.

These findings should be considered in the context of several limitations. Although the intervention was conducted at four separate sites, all were within a single health care system. Weight-loss interventions pursued in the MNT arm were incompletely captured. Finally, in this comparative effectiveness trial, there was no “placebo” control; all three arms included active treatments and participants actively seeking weight loss, which prevented estimation of the effectiveness of any of the interventions compared with usual care as is commonly practiced.

In conclusion, the adapted REAL HEALTH-Diabetes LI, delivered in-person or via telephone groups, demonstrated comparable efficacy to the original Look AHEAD intervention in practice-based settings. Among people with type 2 diabetes and obesity committed to weight loss, weight change was greater with LI compared with referral to a dietitian for MNT at 12 months but it did not differ with less-intensive follow-up in year 2 and no intervention in year 3.○

AUTHOR CONTRIBUTIONS

Deborah J. Wexler and Linda M. Delahanty contributed to the conception and design of research for this manuscript. Deborah J. Wexler, Jeanna McCarthy, Anthony Rodriguez Romero, Valerie Goldman, Paul M. Copeland, Jeanne Steppel-Reznik, and Linda M. Delahanty contributed to the acquisition of data for the manuscript. Deborah J. Wexler, Yuchiao Chang, Douglas E. Levy, Bianca Porneala, and Linda M. Delahanty contributed to the statistical analysis for the manuscript. Deborah J. Wexler and Linda M. Delahanty contributed to the supervision and management of research. Deborah J. Wexler and Linda M. Delahanty contributed to the drafting of the manuscript. Deborah J. Wexler, Yuchiao Chang, Douglas E. Levy, Paul M. Copeland, Jeanne Steppel-Reznik, and Linda M. Delahanty contributed to the critical review of the manuscript.

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CONFLICT OF INTEREST

Deborah J. Wexler reports serving on data monitoring committees for Novo Nordisk A/S. Linda M. Delahanty serves on the Advisory Boards

of Omada Health, JanaCare, and WW, Inc., and has stock options in Omada Health and JanaCare. All other authors declared no conflict of interest.

CLINICAL TRIAL REGISTRATION

ClinicalTrials.gov identifier NCT02320253.

DATA AVAILABILITY STATEMENT

Deidentified individual participant data that underlie the results reported in this paper will be available following article publication to investigators with IRB approval to conduct meta-analyses. Proposals and requests should be directed to the first and/or last author.

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