Self-Reported Gastrointestinal Symptoms in Type 2 Diabetes Improve With an Intensive Lifestyle Intervention: Results From the Action for Health in Diabetes (Look AHEAD) Clinical Trial

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IN BRIEF This article reports on an investigation of whether an intensive lifestyle intervention (ILI) would reduce gastrointestinal symptoms over 4 years of follow-up for participants in the Action for Health in Diabetes (Look AHEAD) trial compared to a diabetes support and education (DSE) group. Look AHEAD is a randomized, multicenter trial comparing overweight and obese adults with type 2 diabetes treated with ILI versus DSE. ILI, and weight loss in general, had beneficial effects on gastrointestinal (GI) symptoms, with some variability in the strength of the effect depending on the specific symptom and time course. Potential modifiers were analyzed, yet ILI retained an association with improvement in GI symptoms.

With approximately 29.1 million people in the United States with type 2 diabetes and another 86 million estimated to have prediabetes, the consequences of this disease will continue to escalate (1). Type 2 diabetes has been causally linked to a number of adverse physiological effects and comorbidities that are the result of the disordered response to glucose homeostasis that characterizes the disease (2–4). Of particular concern to this investigation are gastrointestinal (GI) symptoms, which are both prevalent in type 2 diabetes (5,6) and often difficult to treat.

Much of the literature relating GI symptoms to diabetes describes how hyperglycemia alters gastric motility (7–9). The process of trituration involves fundic propulsion, antral contraction, and antroduodenal coordination (9). If this process is disrupted, symptoms attributable to the metabolic effects of diabetes are likely to result. Other diabetes-related factors may also be involved, including diabetic neuropathy (10,11). Anxiety and depression, which are known to be more common in diabetes, are related to increased GI symptoms (3,12,13). Overweight and obesity are associated with abnormal GI function through pathology such as gastroesophageal reflux (14,15). Medications for diabetes (e.g., metformin) and obesity (e.g., orlistat) have well-known GI side effects.

The Action for Health in Diabetes (Look AHEAD) trial featured an intensive lifestyle intervention (ILI) that produced substantial weight loss, improved diabetes control, and decreased the use of diabetes-related medications (16,17). Here, we examine whether this intervention also reduced the prevalence of GI symptoms over 4 years, both in absolute prevalence and compared to a condition of diabetes support and education (DSE).

Research Design and Methods

Look AHEAD was a multicenter, randomized, controlled trial evaluating the effect of an intensive weight loss program in overweight or obese individuals with type 2 diabetes on major

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cardiovascular events. Volunteers were aged 45–76 years at enrollment with a BMI ≥25 kg/m^2 (27 kg/m^2 if using insulin), A1C <11% (<97 mmol/mol), systolic blood pressure <160 mmHg, diastolic blood pressure <100 mmHg, and triglycerides <600 mg/dL (18). These individuals underwent a maximal graded exercise test to ensure that exercise could be safely prescribed and completed 2 weeks of self-monitoring. All informed consent procedures were approved by local institutional review boards before use, and participants signed consent forms. The trial was registered at ClinicalTrials.gov (identifier: NCT00017953).

Interventions

The ILI was designed to achieve and sustain an average group weight loss of ≥7%, primarily through diet modification and increased physical activity. Caloric intake goals were 1,200–1,500 for individuals weighing <250 lb at baseline and 1,500–1,800 for individuals weighing >250 lb. Diets were developed to avoid large glycemic loads and maximize cardiovascular health. As such, they included a maximum of 30% of total calories from fat, a maximum of 10% of total calories from saturated fat, and a minimum of 15% of total calories from protein (19). The physical activity component of the ILI consisted mostly of home-based exercise, with a goal of 175 min/week of moderate-intensity physical activity.

The first 6 months of ILI included three group meetings and one personal session per month. For the remainder of the first year, individual sessions remained the same, but group meetings became biweekly. The leaders of each session were interventionists trained in nutrition and exercise counseling. In months 13–48, participants attended monthly individual meetings that were followed ~14 days later with phone calls or e-mails by the interventionists. Optional monthly group meetings were also offered during these months.

During the initial 6 months, lifestyle strategies were the main focus of ILI. Beginning in month 7, the "toolbox" algorithm began, which included the optional use of a weight loss medication (orlistat) and/or advanced behavioral strategies for participants who had not achieved the 10% individual weight loss goal (19).

Participants assigned to DSE were invited to three group sessions annually throughout the 4-year study period (20). These sessions utilized a standardized protocol and focused on diet, physical activity, or social support. Information on behavioral strategies was not presented, and participants were not weighed at these sessions.

GI Symptoms

At baseline and annually thereafter, participants self-reported the presence and severity of the following GI symptoms within the past 4 weeks: abdominal pain above the navel, abdominal pain below the navel, constipation, diarrhea, feeling very full after eating little, heartburn, nausea, bloating or distention, regurgitation, and vomiting. Each symptom was rated on a scale ranging from 0 to 3, where 0 indicated that a symptom did not occur, and 1, 2, and 3 indicated mild, moderate, or severe symptoms, respectively. Participants who underwent gastric bypass surgery were excluded from analyses.

Participant Characteristics at Baseline

Information on demography, smoking, alcohol use, and cardiovascular disease (CVD) history was based on self-report. Weight and height were measured in duplicate using a digital scale and stadiometer. A maximal graded exercise test was administered as a measure of fitness (METS) (21). One MET is approximately resting metabolism; 4 METS approximates walking on flat ground at just under 4 miles per hour. Fasting A1C was analyzed by the Central Biochemistry Laboratory (Northwest Lipid Research Laboratories, University of Washington, Seattle, Wash.) using standardized laboratory procedures. Participants brought current prescription medications to assessments to update medication records. Hypertension was based on use of antihypertensive medications or measurement >140/90 mmHg. Depression was based on a Beck Depression Inventory (BDI) (22) score ≥11, indicating elevated depression symptoms. Staff collecting assessments were masked to intervention assignment.

Statistical Methods

χ^2 and t tests were used to assess the balance between intervention groups at baseline. The prevalence of GI symptoms across follow-up between groups was assessed using generalized estimation equations with baseline prevalence as reference. The odds of transitioning to more severe GI symptoms from baseline between intervention groups was assessed using multivariate multinomial mixed models with covariate adjustment for potential confounding baseline factors (23). The impact of including 1-year weight change as a covariate was assessed in the full model. We also examined whether symptoms varied among ILI participants grouped according to patterns of weight loss: those who maintained year-1 weight loss at year 4, lost at year 1 then gained at year 4, gained at year 1 then lost at year 4, and had no loss at either years 1 or 4 (24). Use of insulin and metformin were included as time-varying covariates in supporting analyses. The effect of orlistat use on GI symptom severity over time was evaluated by excluding orlistat users. All analyses were conducted using SAS version 9.3 (SAS Institute, Cary, N.C.).

Results

Our analyses included the 4,986 (96.9%) of 5,145 Look AHEAD participants who provided at least one follow-up assessment of GI symptoms during the first 4 years and had not had bariatric surgery at the time of their follow-up visit. Visits were excluded if they occurred after bariatric

TABLE 1. Baseline Characteristics of Look AHEAD Participants Included in Analysis by Intervention Assignment

Baseline Characteristic	DSE *n* = 2,483 (mean [SD] or *n* [%])	ILI *n* = 2,503 (mean [SD] or *n* [%])	*P*
Age (years)	58.8 (6.9)	58.6 (6.8)	0.19
Sex			
Female	1,485 (59.8)	1,485 (59.3)	0.73
Male	998 (40.2)	1,018 (40.7)	
Race/Ethnicity			
African American	386 (15.6)	390 (15.6)	0.89
Asian/Pacific Islander	20 (0.8)	29 (1.2)	
Hispanic	328 (13.2)	326 (13.0)	
Native American	127 (5.1)	130 (5.2)	
Non-Hispanic white	1,572 (63.3)	1,579 (63.1)	
Other/multiple	50 (2.0)	49 (2.0)	
BMI (kg/m^2)			
<30	349 (14.1)	395 (15.8)	0.11
30 to <35	865 (34.8)	889 (35.5)	
35 to <40	717 (28.9)	655 (26.2)	
≥40	552 (22.2)	564 (22.5)	
Fitness (METS)	7.18 (2.0)	7.2 (1.9)	0.63
A1C (% [mmol/mol])			
<7.0 (<31)	1,117 (45.0)	1,158 (46.3)	0.17
7.0–8.9 (31–74)	1,118 (45.0)	1,133 (45.3)	
9.0–11.0 (75–97)	248 (10.0)	212 (8.5)	
Insulin use			
No	2,094 (84.3)	2,134 (85.3)	0.36
Yes	389 (15.7)	369 (14.7)	
Metformin use			
No	994 (40.0)	972 (38.5)	0.39
Yes	1,489 (60.0)	1,531 (61.2)	
Acarbose use			
No	2,469 (99.4)	2,493 (99.6)	0.40
Yes	14 (0.6)	10 (0.4)	
Other diabetes medications*			
No	2,014 (81.1)	2,055 (82.1)	0.37
Yes	469 (18.9)	448 (17.9)	
Hypertension			
No	429 (17.3)	396 (15.8)	0.17
Yes	2,054 (82.7)	2,107 (84.2)	
Alcohol intake			
None	1,676 (67.5)	1,701 (68.0)	0.83
<1/day (<21 oz/week)	509 (20.5)	496 (19.8)	
≥1/day (≥21 oz/week)	298 (12.0)	306 (12.2)	

TABLE CONTINUED ON P. 184 →

TABLE 1. Baseline Characteristics of Look AHEAD Participants Included in Analysis by Intervention Assignment, *continued from p. 183*

Baseline Characteristic	DSE *n* = 2,483 (mean [SD] or *n* [%])	ILI *n* = 2,503 (mean [SD] or *n* [%])	*P*
Current smoking			
No	2,377 (95.7)	2,391 (95.5)	0.72
Yes	106 (4.3)	112 (4.5)	
Prior CVD			
No	2,151 (86.6)	2,149 (85.9)	0.43
Yes	332 (13.4)	354 (14.1)	
Depression (BDI score ≥11)			
No	2,175 (87.6)	2,135 (85.3)	0.02
Yes	308 (12.4)	368 (14.7)	

**Other diabetes medications defined as not metformin, not insulin, or not acarbose diabetes drugs. Thus, the "no" category in this item includes insulin, metformin, and acarbose users.*

TABLE 2. Distribution of Self-Reported GI Symptoms in the Look AHEAD Cohort Over Time by Treatment Group

GI Condition		Percentage With Condition at:					Treatment Group *P**	Time *P**	Treatment Group by Time *P**
		Baseline	Year 1	Year 2	Year 3	Year 4			
Abdominal pain above navel	DSE	10.5	12.5	12.8	13.6	14.0	0.44	0.0002	0.22
	ILI	11.4	11.0	12.2	13.1	12.4			
Abdominal pain below navel	DSE	14.7	17.4	17.1	17.9	18.6	0.28	0.0008	0.08
	ILI	15.7	15.2	16.1	17.5	16.4			
Constipation	DSE	28.2	31.9	33.2	35.5	35.6	0.03	<0.0001	0.003
	ILI	29.0	37.8	35.6	37.4	36.4			
Diarrhea	DSE	33.1	35.2	35.5	35.8	35.6	0.0005	0.51	0.27
	ILI	31.9	32.0	31.0	32.2	31.5			
Feeling very full after eating little	DSE	16.6	19.3	20.9	23.2	21.8	0.05	<0.0001	0.0005
	ILI	17.9	15.9	18.2	19.1	21.4			
Heartburn	DSE	35.1	36.6	36.4	36.2	36.2	0.0002	<0.0001	<0.0001
	ILI	35.3	26.9	29.8	34.4	35.4			
Nausea	DSE	16.6	21.5	22.3	22.8	21.9	0.16	<0.0001	0.0007
	ILI	18.8	18.6	18.8	21.2	21.8			
Bloating or distention	DSE	38.8	41.4	38.9	37.8	38.1	0.49	0.03	<0.0001
	ILI	41.4	36.8	37.8	38.8	36.4			
Regurgitation	DSE	18.2	20.7	21.3	20.8	23.2	0.0001	<0.0001	<0.0001
	ILI	19.7	14.5	16.2	18.7	20.1			
Vomiting	DSE	4.3	6.6	6.7	7.4	7.9	0.009	<0.0001	0.26
	ILI	4.3	5.1	4.7	6.7	6.5			

**Models of change in prevalence from baseline are adjusted for repeated measures.*

surgery, resulting in exclusion of 11 visits at year 1, 32 visits at year 2, 51 visits at year 3, and 71 visits at year 4. Baseline characteristics were similar between the intervention groups (Table 1), except for BDI score, for which slightly more participants in ILI had elevated depressive symptoms (14.7% in ILI vs. 12.4% for DSE, $P = 0.02$).

The ILI participants included in this report lost an average of 8.6% (SD 6.8%) of their BMI at year 1, compared to 0.7% (SD 4.6%) for DSE participants. At year 4, mean losses were 4.5% (SD 7.6%) for ILI participants and 0.7% (SD 7.2%) for DSE participants. Differences in weight losses between groups were highly significant ($P < 0.0001$) throughout all 4 years of follow-up.

At baseline, bloating was the most common GI symptom, being reported by 40% of participants, with >12% rating it as either moderate or severe. The next most commonly reported symptom was heartburn, experienced by 35.3% of participants, with 8.4% considering it either moderate or severe. More than 32% of participants reported having diarrhea, with almost 8% considering it moderate or severe. Constipation was reported by 29% of participants, with 7.1% rating it moderate or severe. The remaining symptoms were reported by <20% of the cohort. The symptom that occurred least often among participants at baseline was vomiting, reported by 4.3% of participants, with only 1.3% reporting it as moderate or severe.

At years 1–4, 96.5, 94.0, 93.4, and 91.9% of the participants provided data on symptoms, respectively; follow-up was balanced between intervention groups. Table 2 presents the prevalence of symptoms at annual assessments by group. In general, the prevalence of symptoms tended to increase with time, with significant ($P < 0.05$) time trends for all except diarrhea. The average post-randomization prevalence across follow-up was significantly lower among ILI

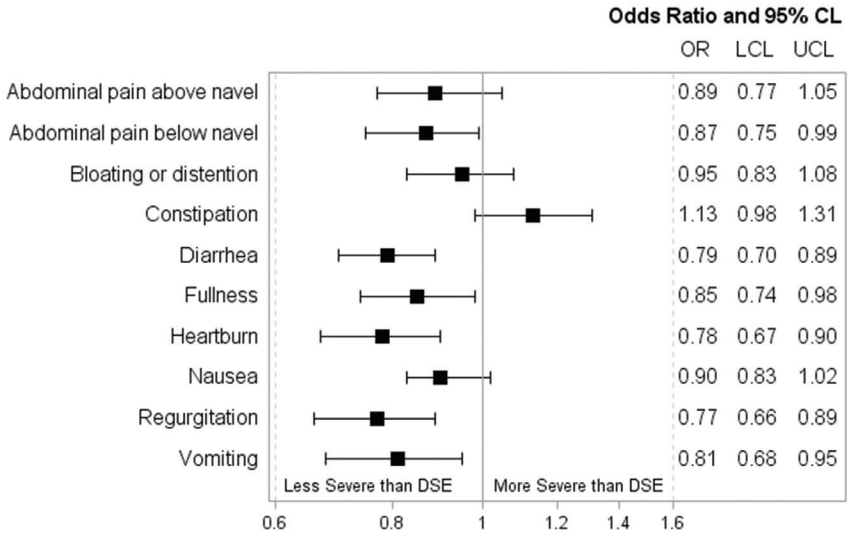

FIGURE 1. Overall ORs of increasing severity of GI symptoms: ILI compared to DSE from model adjusted for BMI category, CVD history, BDI score ≥11, sex, race, current smoking status, A1C level, hypertension, alcohol intake, age, maximum METS, and repeated measures. CL, confidence limits; LCL, lower CL; UCL, upper CL.

than among DSE participants for diarrhea, feeling full after eating little, heartburn, and regurgitation, but significantly higher for constipation. The time course for the prevalence of symptoms also varied for several symptoms. For feeling full after eating little, heartburn, nausea, bloating or distention, and regurgitation, there was a pattern for relative decreases in the prevalence of symptoms among ILI participants at year 1 that waned or disappeared over time. For diarrhea, the relative increase in prevalence among ILI participants that was evident at year 1 also disappeared by year 4.

Figure 1 summarizes the relative intervention effects on the odds of progressing to more severe GI symptoms (e.g., from none to mild, from mild to moderate, and so on) across 4 years, with adjustment for baseline levels of all factors in Table 1. As can be seen, 95% confidence intervals (CIs) favoring overall relative benefit for ILI participants across the 4 years excluded 1.00 for abdominal pain below the navel, diarrhea, fullness, heartburn, regurgitation, and vomiting. The associated odds ratios (ORs) for these symptoms ranged from 0.74 (heartburn) to 0.87 (abdominal pain below the navel), translating to overall 13–26% reductions in the odds of increasing severity. For only one symptom (constipation) was there a (nonsignificant) trend toward relative worsening in symptom severity among ILI participants.

Differences between intervention groups on symptom severity tended to be largest at year 1 and to diminish over time, with significant ($P < 0.05$) attenuation based on tests of interaction for bloating or distention, constipation, fullness, heartburn, nausea, and regurgitation. Figure 2 portrays the characteristic longitudinal pattern, as seen for heartburn. Including year-1 weight change in the models of symptom severity attenuated the effects of treatment group such that there were no longer significant differences for the main effect of treatment. Weight-change patterns over time were related to increase in bloating or distention, as well as feeling full after eating little for participants who did not lose weight at either year 1 or year 4 (bloating OR 2.00 [95% CI 1.27–3.13]; fullness OR 1.84 [1.17–2.90]) and in diarrhea for participants who lost at year 1 and

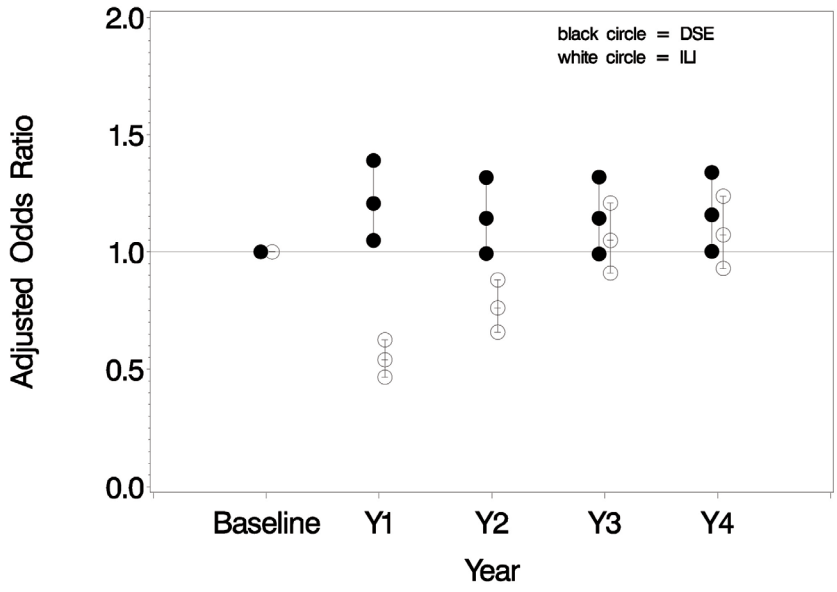

FIGURE 2. Adjusted ORs of increasing severity of heartburn at follow-up in reference to baseline from model adjusted for BMI category, CVD history, BDI score >11, sex, race, current smoking status, A1C level, hypertension, alcohol intake, age, maximum METS, and repeated measures.

then gained at year 4 (OR 1.29 [1.04–1.60]) compared to participants who maintained their weight loss at years 1 and 4.

Use of metformin increased over time among DSE participants (P <0.001); the OR (95% CI) of current compared to baseline use rose from OR 1.16 (1.09–1.24) at year 1 to OR 1.49 (1.36–1.64) at year 4. Use of metformin initially decreased among ILI participants (OR 0.90 [0.85–0.96]) at year 1, but was unchanged at year 4 (OR 1.09 [0.99–1.18]). Overall, metformin use was associated with a greater prevalence of diarrhea (OR 1.88 [1.67–2.11]), feeling full after eating little (OR 1.18 [1.03–1.36]), heartburn (OR 1.28 [1.13–1.45]), nausea (OR 1.25 [1.10–1.42]), and regurgitation (OR 1.19 [1.03–1.37]). Inclusion of metformin use as a time-varying covariate comparing the prevalence of symptoms between intervention groups, however, did not materially affect results.

Use of insulin was associated with an increased prevalence of bloating or distention (OR 1.20 [1.05–1.39]), feeling full after eating little (OR 1.33 [1.14–1.57]), nausea (OR 1.29 [1.12–1.50]), and vomiting (OR 1.37 [1.12–1.69]). Similar to metformin, including insulin use as a time-varying covariate did not materially alter the results from comparisons of the prevalence of symptoms between intervention groups. Low prevalence of use of exenatide and acarbose prohibited analysis of their effects on GI symptom expression.

At some point during the 4 years of follow-up, 693 participants reported orlistat use (ILI: baseline n = 1, year 1 n = 409, year 2 n = 324, year 3 n = 148, year 4 n = 64; DSE: baseline n = 0, year 1 n = 10, year 2 n = 3, year 3 n = 2, year 4 n = 1). Excluding these individuals from analyses did not alter findings.

Conclusions

We examined a cluster of GI symptoms that are prevalent in the general population, but more so in individuals with diabetes (6). We found that the Look AHEAD ILI yielded a modest, statistically significant overall reduction in the prevalence and severity of GI symptoms across 4 years. The reductions were largest for bloating, heartburn, and regurgitation. Benefits tended to be greatest during the first year of the intervention, when weight losses were greatest, and to wane over time. Inclusion of 1-year weight losses in models accounted for intervention effects, suggesting that these effects could be at least partially attributable to weight loss. The GI benefits of the intervention were evident after covariate adjustment for metformin and insulin use. Excluding orlistat users from analyses did not materially alter findings.

Participants in the DSE group had significantly higher odds of reporting a more severe symptom at follow-up than they had reported at baseline for several GI symptoms. In contrast, those in the ILI group reported symptoms that were significantly less severe symptoms than at baseline for these same symptoms or no difference in likelihood of a more severe symptom than at baseline. The observed improvements in GI symptoms for the ILI group are consistent with our hypothesis.

It is interesting to note that weight regain at years 1 and 4 appeared to attenuate the beneficial effects to some extent, suggesting that weight maintenance is an important factor in sustaining the apparent benefit of weight loss on GI symptoms. At year 1, those in the ILI group had a loss of 8.6% of initial weight versus 0.7% in DSE, which was significant (P <0.001) (25). This effect of magnitude of weight loss is also likely reflected in the finding that intervention effects tended to be greatest at the point of maximal weight loss at the end of year 1, with attenuation found in subsequent years of follow-up as some weight regain occurred.

The findings of this study mirror the results found in a previous investigation, in which a combination of a healthy diet and higher levels of physical activity, both of which were core features of the ILI in Look AHEAD, resulted in a reduction in GI symptoms in a weight loss inter-

vention (26). Our analyses covered a longer follow-up (48 vs. 24 months) and involved a more controlled intervention. Other studies have also reported a direct relationship between GI symptoms and either BMI or obesity but did not examine the effect of changes in weight on symptoms in a population of people with type 2 diabetes (14,27,28).

Although this study was not designed to identify the mechanism(s) responsible for the beneficial effects on GI symptoms of ILI compared to DSE, it is well known that weight loss interventions have favorable effects on various facets of both physical and psychological functioning in people with diabetes (29–31). More specifically, previous studies have shown that mood disorders can have a significant impact on GI symptoms (3,12,13). Of note, previous research with the Look AHEAD cohort found that ILI reduces depression after 1 year (31).

There are several strengths and some limitations of this study. Its strengths include its large size, the fact that participants were randomized, and that there was significant weight loss in the ILI group. Individuals who volunteer for clinical trials may not represent clinical populations; this may limit the generalizability of our findings. In addition, although this study examined GI symptoms, it is unclear whether the reported reductions in symptoms are clinically meaningful.

In summary, ILI yielded beneficial effects on GI symptoms, with some variability in the strength of these effects depending on the specific symptom and a general increase in the magnitude of the beneficial effect with greater weight loss. Potential modifiers to the effect were analyzed for several variables, but, despite this, ILI retained an association with improvement in GI symptoms. The intervention may have affected other aspects of the study participants' lives that may, in turn, affect GI symptomology, such as medication use and depression, but we view these as potential mediators of change rather than confounding factors to the interpretation of our findings. Our findings suggest that weight loss through an intensive lifestyle change intervention may be beneficial to many obese individuals with type 2 diabetes who suffer from most common GI symptoms.

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Author Contributions

RHN performed the analyses and wrote the manuscript. JJR participated in the development, coauthored several sections, and provided feedback on drafts. WBA participated in the development and writing and provided critical feedback. JMC, WCK, GAB, and LJC reviewed the work and provided critical feedback. MAE participated in the development of the manuscript, coauthored several sections, reviewed the work, and provided critical feedback. RHN is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. A complete listing if the Look AHEAD clinical sites and staff members can be found online in Supplementary Table 1.

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Duality of Interest

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

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