Impact of Intensive Lifestyle Intervention on Depression and Health-Related Quality of Life in Type 2 Diabetes: The Look AHEAD Trial

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OBJECTIVE
We examined the effects of an intensive lifestyle intervention (ILI), compared with a diabetes support and education (DSE) control intervention, on long-term changes in depression symptoms, antidepressant medication (ADM) use, and health-related quality of life (HRQoL) in overweight/obese individuals with type 2 diabetes.

RESEARCH DESIGN AND METHODS
Look AHEAD was a multisite randomized controlled trial of 5,145 overweight/obese participants assigned to ILI (designed to produce weight loss) or DSE and followed for a median of 9.6 years. The Beck Depression Inventory (BDI) was administered at baseline, annually at years 1–4, and again at year 8. Mean BDI scores and incidence of BDI scores $\geq 10$, indicative of likely mild or greater depression, were examined. Annually through year 10, participants reported their ADM use and completed the Medical Outcomes Study Short Form 36 (SF-36) questionnaire, which yields physical component summary (PCS) and mental component summary (MCS) scores.

RESULTS
ILI significantly reduced the incidence of mild or greater depression symptoms (BDI scores $\geq 10$) compared with DSE (hazard ratio [HR] = 0.85; 95% CI 0.75–0.97; $P = 0.0145$). Although SF-36 PCS scores worsened over time in both groups, ILI participants reported better physical function than DSE throughout the first 8 years (all $P$ values $<0.01$). There were no significant differences between treatment arms in the proportion of participants who used ADMs or in SF-36 MCS scores.

CONCLUSIONS
ILI for overweight/obese patients with type 2 diabetes may reduce the risk of developing clinically significant symptoms of depression and preserve physical HRQoL. These findings should be considered when evaluating the potential benefits of ILIs.
Individuals with type 2 diabetes are at high risk of depression (1) and have poor health-related quality of life (HRQoL), particularly concerning perceived general health and limitations in physical functioning (2,3). Depression in individuals with type 2 diabetes is associated with less active diabetes self-management (4), persistent hyperglycemia (5), higher rates of diabetes-related complications and mortality (3,5), and a 4.5-fold increase in health care expenditures (6).

Obesity is also associated with increased morbidity and mortality (7,8) and with higher levels of depression (9,10) and poorer HRQoL (11,12). Reducing the incidence of depression and improving HRQoL in obese persons with diabetes is an important clinical objective.

Behavioral weight loss interventions consistently induce reductions of 5% or more of initial weight in overweight/obese persons with type 2 diabetes (13), losses that are associated with initial improvements in the control of blood glucose, blood pressure, and lipid levels (14). Several studies also suggest that behavioral weight loss interventions facilitate short-term reductions in depression symptoms, as assessed by the Beck Depression Inventory (BDI) (15–18), as well as improvements in the physical health component of quality of life (19–22). However, only a few studies of weight loss and mood were conducted in persons with type 2 diabetes, and none followed participants for more than 4 years. Whether the effects observed in the short-term studies are sustained remains unknown. This question is of particular relevance because of lingering concerns about the possible adverse psychological effects of weight loss interventions, as reported in early weight reduction programs (23). The Look AHEAD (Action for Health in Diabetes) trial provides a unique opportunity to assess the effects of long-term intensive lifestyle intervention (ILI) designed to achieve weight loss, on depression symptoms and HRQoL.

RESEARCH DESIGN AND METHODS

Participants

Look AHEAD was a randomized clinical trial that investigated the long-term health impact of an ILI in 5,145 overweight or obese adults with type 2 diabetes. The design and methods of this trial have been reported elsewhere (24), as have the baseline characteristics of the randomized cohort (25). The trial’s primary objective was to determine whether cardiovascular disease (CVD) morbidity and mortality would be reduced with an ILI designed to achieve weight reduction. As reported previously (26), the trial was stopped early on the basis of a futility analysis (when the median duration of follow-up was 9.6 years). No significant differences were observed between treatment arms on the primary outcome, a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina. The trial currently is continuing as an observational cohort study.

Look AHEAD participants were recruited at 16 clinical centers in the U.S. (25). Eligibility requirements included age 45 to 76 years of age; self-reported type 2 diabetes mellitus verified by physician report, use of diabetes medication, or tested blood glucose levels; BMI $\geq 25$ kg/m$^2$ (or $\geq 27$ kg/m$^2$ in those taking insulin); hemoglobin A$_1c$ (HbA$_{1c}$) levels $\leq 11\%$ ($\leq 97$ mmol/mol); systolic blood pressure $\leq 160$ mmHg; diastolic blood pressure $\leq 110$ mmHg; and triglyceride levels $\leq 600$ mg/dL. Individuals with a current diagnosis of psychosis or bipolar disorder, or who had been hospitalized for depression in the past 6 months, were excluded.

Prior to randomization, participants completed 2 weeks of diet and exercise self-monitoring and successfully completed a maximal graded treadmill test to assess ability to exercise safely. All participants signed a consent form approved by their local institutional review board.

Interventions

Study participants were randomly assigned within each center to the ILI or to diabetes support and education (DSE), the comparison condition for this trial. As reported previously (14), the ILI was designed to induce $\approx 7\%$ weight loss in the first year of the trial and to maintain the weight loss in subsequent years. ILI participants were prescribed a calorie goal of 1,200–1,800 kcal/day (based on initial weight), with $<30\%$ of total calories from fat ($<10\%$ from saturated fat) and $\approx 15\%$ of total calories from protein. ILI participants were encouraged to engage in $\approx 175$ min per week of moderate intensity exercise (e.g., brisk walking). The ILI incorporated behavioral strategies, including regular self-recording, to facilitate achievement of the above goals (13).

ILI participants were seen in a combination of individual and group sessions, weekly for the first 6 months and three times per month for the next 6 months. Sessions addressed behavioral adherence and ways to improve it. In all subsequent years, ILI participants were offered monthly in-person sessions. In addition, two to three times per year, they were invited to participate in a once-weekly 6–8 week group program designed to achieve a specific weight loss (e.g., 3–5 lbs.) or activity goal.

DSE participants were invited to three group sessions per year for the first 4 years. These sessions addressed general issues of diet, exercise, and social support using a standardized protocol. One group session per year was provided thereafter.

Outcome Measures

At baseline and study years 1, 2, 3, 4, and 8, participants completed the BDI-1A, a self-report depression symptom scale with well-documented psychometric properties (i.e., validity, reliability, and sensitivity to change) across a wide spectrum of clinical and nonclinical populations (15). The BDI-1A lists 21 symptoms, with responses scored from 0 to 3 for each item in ascending symptom severity, yielding a total score ranging from 0 to 63. Higher scores indicate more depression symptom burden. For this study, presence of elevated depression symptoms, indicating likely mild or greater depression, was defined as a BDI score $\geq 10$ (15). (This study used the BDI-1A, rather than the BDI-II, which has different cut points for mild or greater depression [27].) The BDI-1A also may be scored, as it was in the current study, by separating the 14 items that assess principally cognitive and affective components of depression (e.g., negative mood and guilt) from the seven items that evaluate predominantly somatic components (e.g., appetite and sleep). Participants’ history of depression was assessed at baseline by questionnaire in response to the item: “Has a doctor or other health care provider ever said that you have depression?”
Twice annually for the first 4 years and then annually through year 10, participants completed the Medical Outcomes Study Short Form 36 (SF-36), a self-report HRQoL measure with well-documented psychometric properties across a wide range of clinical and non-clinical populations (28). The SF-36 provides eight subscale scores: general health perceptions; physical functioning; role limitations due to physical problems; bodily pain; mental health; role limitations due to emotional problems; vitality; and social functioning. Two summary norm-based T-scores (U.S. mean = 50, SD = 10) can also be derived from the SF-36: the physical component summary (PCS) score and mental component summary (MCS) score, with higher scores indicating more favorable HRQoL. The PCS score is derived from the first four subscales listed above, and the MCS from the last four subscales. Only the two summary scores were used in the present analyses, and only values from the annual assessments (at years 1–10) were examined.

Participants brought all prescription medications to their annual assessment visits, at which study staff recorded medications used (but not dosages). Antidepressant medications (ADMs) were identified using the Food and Drug Administration’s classification system.

Statistical Analyses
Analyses included all randomized participants according to intervention assignment (i.e., by intention to treat) and were performed using SAS version 9.3 (SAS Institute, Cary, NC). All data were censored at 14 September 2012, the day the intervention was stopped by the National Institutes of Health on the recommendation of the Data and Safety Monitoring Board. At this time in the trial, all study participants had reached the 10-year assessment of HRQoL when the study was halted, resulting primarily from the larger reduction in BMI of 36.0 (5.9) kg/m², and duration of diabetes of 6.8 (6.5) years (see Table 1). At baseline, 18.2% of participants had a BMI ≥10, and 17.1% were taking ADMs, most frequently selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, and tricyclic antidepressants (in that order). At baseline, significantly (P < 0.0088) more ILI than DSE participants reported a history of depression (22.1 vs. 19.2%).

At year 1, ILI and DSE participants lost a mean of 8.6 and 0.7% of initial weight, respectively. Losses at end of study were 6.0 and 3.5%, respectively (both P values <0.0001).

Symptoms of Depression
The ILI significantly reduced the incidence of mild or greater depression compared with DSE (HR = 0.85; 95% CI 0.75–0.97; P = 0.0145) (Fig. 2A). In the 81.8% of participants with baseline BDI scores in the nondepressed range (BDI scores <10), ILI participants were on average 15% less likely than those in DSE to progress to symptoms of likely mild or greater depression (BDI scores ≥10). (Adjusting for baseline history of depression, the HR was 0.82, 95% CI 0.732–0.935, and P = 0.0029.)

In participants who at baseline reported symptoms of mild depression (BDI score = 10–18; 403 in ILI, 410 in DSE), there were no significant differences between treatment arms in the proportion of individuals who progressed to moderate or greater symptoms of depression (BDI score ≥19; 79 participants [19.3%] in ILI, 71 [17.6%] in DSE; P value = 0.5441). In these same participants, a total of 337 (83.6%) in ILI and 342 (83.4%) in DSE had remission to a BDI score <10 (i.e., no/minimal depression symptoms) at some point during the follow-up, with no significant difference between treatment arms in time to first BDI <10 (HR = 1.11; 95% CI 0.96–1.30; P = 0.1718).

For the sample as a whole (n = 5,145), BDI scores averaged across the 8 years were significantly (P < 0.001) lower (i.e., better) in the ILI than the DSE group over the 8 years (Fig. 2B), resulting primarily from the larger reduction at year 1 in ILI than DSE participants (P < 0.001) (Fig. 2B). Subset analyses examined mean scores of participants who at baseline had no/minimal symptoms of depression (BDI score <10) and those with mild or greater symptoms (BDI score ≥10). In the nondepressed group (n = 4,197), Fig. 2C shows that there were significant differences between the ILI and DSE participants during each of the first 4 years, owing, in part, to small increases in mean BDI scores in the DSE group.

In participants who began the trial with mild or greater symptoms of depression...
(n = 932, which included a total of 119 participants with moderate or greater symptoms), mean BDI scores fell substantially in both groups the first year, though significantly (P = 0.0045) more in ILI than DSE (Fig. 2D). Thereafter, mean scores for both treatment arms varied by 1 to 1.5 points but generally remained in the nondepressed range (BDI score <10), with no significant differences between ILI and DSE participants in this subgroup.
Lifestyle Intervention and Incident Depression follow-up. By contrast, 773 (15.9%) took ADMs at baseline or at any time during of 3,130 (64.3%) participants did not use of the improvement likely was attributable to spontaneous remission of depression typically observed in 3 to 12 months (23). The ILI’s benefit was not attributable to differential use of ADMs in the two treatment arms during the course of the trial. In addition to its protective effects in nondepressed individuals, the ILI did not appear to harm individuals who had depression symptoms at the trial’s outset. Subgroup analyses showed that in participants who at baseline had mild depression symptoms (BDI score of 10–18), the lifestyle intervention did not increase the risk of progressing to moderate or greater depression symptoms (BDI score ≥19). Instead, at the end of the first year, ILI participants who began the trial with mild or greater depression symptoms (BDI score >10) experienced substantial improvements in mood, with reductions in mean BDI scores from 14.1 to 8.8. Part of the improvement likely was attributable to the spontaneous remission of depression, typically observed in 3 to 12 months (29). A similar (though more modest) pattern of improvement was observed the first year in comparable DSE.

**ADMs at baseline and continued to do so during follow-up. (Supplementary Fig. 1A presents these data by treatment arm.) A total of 897 participants (18.5%) initiated ADM use at some point after their baseline assessment (Supplementary Fig. 1B). There was no difference between the ILI and DSE groups in incident ADM use (HR = 1.08; 95% CI 0.95–1.23; P = 0.2316). Fifty-eight (1.2%) individuals who used ADMs at baseline permanently discontinued them within the first 4 years (32 ILI, 26 DSE participants) of randomization. There also were no significant differences at any time between the ILI and DSE groups in the mean number of ADMs used (P = 0.1472) (Supplementary Fig. 1C).

**Quality of Life**

PCS scores declined (i.e., worsened) in both treatment arms over the 10-year follow-up. However, PCS scores remained significantly higher (i.e., better) in the ILI than the DSE arm over the decade (mean difference between groups = 0.93; SE = 0.2; P < 0.001) (Fig. 3A).

**CONCLUSIONS**

This study found that a lifestyle intervention, designed to induce weight loss, reduced the risk of progressing to mild or greater symptoms of depression by an average of 15% over 8 years of follow-up, relative to DSE. The present findings confirm the results of previous studies of shorter duration (16–18,20) and provide the strongest evidence to date that ILI protects overweight/obese individuals from depression rather than precipitating it (23). The ILI’s benefit was not attributable to differential use of ADMs in the two treatment arms during the course of the trial.
participants, in whom mean BDI scores fell from 13.2 to 9.6.

The ILI’s prevention of mild or greater depression symptoms has important public health implications, particularly for people with type 2 diabetes. According to the World Health Organization, unipolar depression was the third most important cause of disease burden worldwide in 2004 and the most important in middle- and high-income countries (30). Depression is more prevalent among people with diabetes than it is in the general population. A study that included national samples reported...
that 6.1% of individuals without diabetes, and 9.3% of those with the condition, were currently depressed (5). The combination of depression and diabetes leads to negative effects on self-care behaviors (31) and glycemic control (4) and ultimately increases morbidity (5), mortality (5), and health care costs (6). Reducing the risk of developing depression over 8 years in individuals with diabetes could thus have an important health impact.

A second principal finding of this study is that participating in ILI may mitigate the effects of aging on physical HRQoL. Epidemiological studies have consistently reported a decline in SF-36 PCS scores with age (32–34). None of these studies involved follow-up of >5 years, and none was restricted to overweight/obese individuals or to those with type 2 diabetes. The current study, which followed participants for a median of 9.6 years, also found that PCS scores declined (i.e., worsened) in both treatment arms. However, participants in the ILI arm experienced significantly less decline than those in DSE over the course of the study and at every year of follow-up through year 8. This ILI advantage is consistent with the findings of other lifestyle interventions of shorter duration in overweight/obese adults (20–22). The lifestyle intervention, for example, in the Diabetes Prevention Program resulted in a mean 1.3 point increase in the PCS score at 1 year, as compared with a 0.04 decline in the placebo group.

Some investigators have suggested that people perceive a 3% difference in HRQoL scores (e.g., 1 to 1.5 T-score points on PCS) as beneficial or deleterious (35). By this criterion, the ILI, compared with DSE, produced a perceptible improvement in physical HRQoL over the first 8 years of follow-up. Other health professionals (36–38), however, have proposed that a 3 to 5 T-score point change on the PCS is required to be considered clinically meaningful, a magnitude which the ILI group only approached at year 1.

Slowing age-related decline in physical HRQoL has important public health implications, especially for individuals with diabetes. HRQoL is increasingly recognized as an essential measure of health status, especially in chronic diseases. An analysis of 118 studies found that SF-36 PCS scores were lower in
individuals with type 2 diabetes compared with U.S. population norms (39), suggesting that interventions that mitigate age-related decline in physical functioning may have substantial benefits for those with type 2 diabetes.

The current study found no significant difference between the treatment and comparison arms in changes in mean MCS scores over the course of the study, a finding consistent with that from several similar trials (20,22,38). We examined the mental health subscale of the MCS to see if there were statistically significant treatment effects for this subscale (i.e., results more similar to those for BDI score; we found no such effects). The SF-36 mental health subscale is more general than the BDI, assessing mental health issues other than depression (e.g., anxiety) (30). This view is supported by the moderate correlation ($r = 0.49$) between the MCS and BDI observed in the current study and suggests that the mental health benefits of the ILI intervention were specific to protection from developing significant symptoms of depression.

We similarly observed that the baseline PCS score correlated only moderately with both the full BDI ($r = 0.34$) and the BDI somatic subscale ($r = 0.39$). While the PCS and BDI somatic subscale assess some similar domains (e.g., worry about health), the PCS includes numerous items on specific physical abilities (e.g., walking stairs) and bodily pain, which the BDI does not include. Conversely, the BDI somatic subscale evaluates complaints about sleep, appetite, appearance, and sexual function—hallmarks of depression—which are not assessed by the PCS. While the ILI participants reported significantly greater improvements on both the PCS and the BDI somatic subscale at all assessments during the first 8 years, we believe that the two measures captured different aspects of participants’ psychosocial and physical function (as also suggested by the scales’ shared variance of only 15.2%). ILI as compared with DSE participants reported greater reductions on the BDI cognitive subscale only at year 1, the time when the ILI group experienced its greatest improvement on the full BDI score (see Fig. 28).

Several aspects of the lifestyle intervention may have contributed to the reduced risk of depression and improved HRQoL observed in this study. These include the greater initial weight losses and improvements in cardiorespiratory fitness achieved by ILI versus DSE participants (25). ILI participants also received extensive group and individual support that could have protected them from depression, as could their improvements in diabetes control and cardiovascular risk factors, which were generally greater in ILI than DSE participants during most of the trial (14,26). A separate paper will examine the factors that potentially mediated the reported improvements in depression and physical quality of life, as well as explore the relationships between initial depression level, changes in depression over time, and subsequent weight change. As reported previously, among ILI participants who began the study free of symptoms of depression (BDI score <10), those who experienced incident depression at 1 year lost significantly less weight at this time than their ILI counterparts who remained free of a mood disorder (mean losses of 4.6 vs. 9.0% of initial weight, respectively). By contrast, ILI participants who began the study with mild or greater symptoms of depression (BDI score >10) lost only marginally (though significantly) less weight at 1 year than ILI participants who were free of baseline depression (mean losses of 7.8 vs. 8.7%, respectively) (17).

Strengths of the current study include its large racially/ethnically diverse population, long duration of intervention, excellent participant retention, and use of well-validated questionnaires. Study limitations include that all participants had type 2 diabetes, potentially limiting the generalizability of our findings to populations without diabetes (although our results are similar to those observed in earlier trials of nondiabetic individuals) (18). Participants also generally had average to good mental health, as indicated by their BDI and MCS scores, thus raising questions about the generalizability of the findings to populations with a greater mental health burden. Our study would have been improved by the use of a structured clinical interview to evaluate depression (which also was conducted at all annual assessment visits). Alternatively, we could have administered the Patient Health Questionnaire-9 (40), which, unlike the BDI-1A, evaluates multiple domains needed to diagnosis major depressive disorder according to recognized criteria (29). Other study limitations included our not determining the dose of ADMs used and not identifying reasons other than depression that participants may have taken ADMs (e.g., anxiety, neuropathy). In addition, quality of life was assessed in fewer than 40% of participants at year 10, the approximate percentage of persons who, based on their date of enrollment in the trial, had been eligible to complete this assessment when the intervention was stopped in September 2012.

In summary, participation in an ILI, designed to produce weight loss, protected overweight/obese individuals with type 2 diabetes from developing mild or greater symptoms of depression, as well as reductions in HRQoL. Clinicians may want to take these findings into account when evaluating the potential benefits of behavioral weight loss treatment.

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