TITLE: Mediators of weight change in underserved patients with obesity: Exploratory analyses from the PROPEL cluster-randomized trial.

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RUNNING HEAD: Weight change mediators in underserved individuals

ABBREVIATIONS: ANOVA, analysis of variance; BEVQ-15, Brief Questionnaire to Assess Habitual Beverage Intake; CI, confidence interval; EI, Eating Inventory; ES, effect size; ILI, intensive lifestyle intervention; IPAQ, international physical activity questionnaire; IWQOL, Impact of Weight on Quality of Life-Lite; MET, metabolic equivalent of task; NCI, National Cancer Institute; PROMIS-29, Patient-Reported Outcomes Measurement Information System-29; PROPEL, Promoting Successful Weight Loss in Primary Care in Louisiana; REDCap, Research Electronic Data Capture; SD, standard deviation; SE, standard error; UC, usual care.

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ABSTRACT

Background: Intensive lifestyle interventions (ILIs) stimulate weight loss in underserved patients with obesity, but the mediators of weight change are unknown.

Objective: Identify the mediators of weight change during an ILI versus usual care (UC) in underserved patients with obesity.

Design: The Promoting Successful Weight Loss in Primary Care in Louisiana (PROPEL) trial randomized 18 clinics (*n* = 803) to either an ILI or UC for 24 months. The ILI group received an intensive lifestyle program; the UC group had routine care. Body weight was measured; further, eating behaviors (restraint, disinhibition), dietary intake (percent fat intake, fruit and vegetable intake), physical activity, and weight- and health-related quality of life constructs were measured through questionnaires. Mediation analyses assessed whether questionnaire variables explained between-group variations in weight change during two periods: baseline to month 12 (*n* = 779) and month 12 to month 24 (*n* = 767).

Results: The ILI induced greater weight loss at month 12 versus UC (between-group difference: -7.19 kg; 95% CI: -8.43, -6.07). Improvements in disinhibition (-0.33 kg; 95% CI: -0.55, -0.10), percent fat intake (-0.25 kg; 95% CI: -0.50, -0.01), physical activity (-0.26 kg; 95% CI: -0.41 to -0.09), and subjective fatigue (-0.28 kg; 95% CI: -0.46, -0.10) at month 6 during the ILI partially explained this between-group difference. Greater weight loss occurred in the ILI at month 24, yet the ILI group gained 2.24 kg (95% CI: 1.32, 3.26) versus UC from month 12 to month 24. Change in fruit and vegetable intake (0.13 kg; 95% CI: 0.05, 0.21) partially explained this response, and no variables attenuated the weight regain of the ILI group.

Conclusions: In an underserved sample, weight change induced by an ILI compared to UC was mediated by several psychological and behavioral variables. These findings could help refine weight regimens in underserved patients with obesity.

Keywords: comprehensive lifestyle intervention; diet; eating attitudes; health disparities; minority groups; primary health care; weight loss; weight regain

INTRODUCTION

Obesity is a public health disease that increases the risk for type 2 diabetes, cardiovascular disease, cancer, and premature death (1,2). Overall, obesity affects approximately 40% of adults in the United States (3), and health disparities are present. Obesity is more prevalent in certain demographic groups with a low annual income (4). Moreover, compared to non-Hispanic White adults, Black and Hispanic populations exhibit higher rates of obesity (5). It is thus important to identify effective weight management methods for individuals with obesity in these populations to attain national health targets and decrease health disparities.

Usual care (UC) for weight loss and weight management within primary care typically involves behavioral counseling and therapy to improve dietary habits and physical activity, yet such regimens often yield substandard weight loss because of time constraints and a lack of training amongst practitioners (6). Intensive lifestyle interventions (ILIs) are recommended as alternative programs for weight loss in individuals with obesity in primary care (7). These aim to stimulate energy deficits and weight loss through reduced-calorie diets, increases in physical activity, and behavioral therapy in an on-site and intensive ($\geq$ 14 sessions in first 6 months) regimen delivered by trained interventionists (7,8).

In the Promoting Successful Weight Loss in Primary Care in Louisiana (PROPEL) trial, we demonstrated that underserved patients with obesity lose more weight and improve cardiometabolic risk markers during an ILI compared to UC over 24 months (9,10). However, it is unclear what factors drove the increased weight loss produced by the ILI relative to UC. It is additionally not known if the factors associated with midterm (6-12 month) weight loss during the ILI were effective at attenuating weight regain, which is common and can decrease the health benefits associated with lifestyle interventions (11). These factors could include those that have been associated with weight loss and were linked to behaviors and strategies covered in counseling sessions of the ILI, such as increased dietary restraint (i.e., the intent and ability to restrict food intake), reduced dietary disinhibition (i.e., the tendency to overeat) (12), increased intake of healthy foods with low fat (13), increased physical activity (14), and improved quality of life (15). Identifying the factors that mediate weight loss and weight loss maintenance during the PROPEL trial is important because related strategies and behaviors can be targeted and tested in future interventions, enhancing the efficacy of weight management programs that are delivered to underserved individuals with obesity in primary care.

The aim of this exploratory investigation was to use mediation analyses to identify the mediators of weight change during an ILI compared to UC in underserved patients with obesity. We hypothesized that improvements in eating behaviors (increased dietary restraint and reduced dietary disinhibition), dietary intake (reductions in dietary fat and increases in fruit and vegetable intake), physical activity, and quality of life shown in the ILI versus UC would mediate improved weight change.

METHODS

Patients

Primary inclusion criteria for PROPEL included an age of 20 to 75 y, a body mass index (BMI) of 30.0 to 50.0 kg/m^2, and being a patient at a participating primary care clinic. Patients were excluded if they used weight-loss medication, were presently partaking in a structured weight-loss program, previously had bariatric surgery or planned to have bariatric surgery within 2 years, or had lost > 10 lbs (4.5 kg) in the last 6 months. A full list of inclusion and exclusion criteria has been previously published (9,16), and all these criteria applied to these analyses.

Study Design

The PROPEL study was a cluster-randomized trial consisting of 18 primary care clinics from five health systems across Louisiana. Details of the trial's design, randomization and recruitment methods, and protocol have been published (9,16). The Pennington Biomedical Research Center Institutional Review Board approved the study. All procedures followed the ethical standards set by this Institutional Review Board, and all patients provided written informed consent (ClinicalTrials.gov number: NCT02561221). A self-report demographic questionnaire was used to obtain information about sex, race, and income.

Clinics were randomly assigned in a 1:1 allocation ratio to provide patients with an ILI or UC for 24 months. Randomization was stratified by health system, with the random allocation method generated by a study statistician. Patients were not blinded to their group assignment because randomization occurred at the clinic level and the interventions are distinct. Efforts were nonetheless made to blind staff involved in data collection to the clinic randomization, and intervention staff were blinded to the patient's official study measures. The PROPEL trial data were collected and managed via the use of Research Electronic Data Capture (REDCap) resources hosted by the Pennington Biomedical Research Center (9,17). The trial was conducted between April 2016 and September 2019, finishing when recruited patients who completed the trial had their month 24 assessments (9,16).

Patients in the ILI received a pragmatic, intensive lifestyle program, which was based on previous lifestyle regimens (18–20) and consistent with the 2013 recommendations for the management of overweight and obesity set out by the American Heart Association, American College of Cardiology, and The Obesity Society (8). The ILI regimen was administered by appropriately trained health coaches embedded within primary care clinics and comprised weekly sessions in the first 6 months (16 face-to-face and 6 delivered via telephone), followed by sessions that were held at least monthly. The objective for patients in the ILI was to lose 10% of their body weight through numerous strategies which aimed to change eating behaviors and physical activity. Strategies incorporated in the ILI included the provision of suitable pre-packaged foods and meal replacements, coaching on appropriate portion sizes, information on how to purchase, and prepare healthy foods. It also included encouragement to increase physical activity to 175 mins/wk in line with the physical activity goal of the Look AHEAD trial (21). In addition to these strategies, a weight loss calculator was used to formulate personalized energy intake targets and then display predicted weight loss to patients and health coaches (22).

Patients assigned to UC received the care routinely delivered by their clinic for the duration of the trial. They were also provided six newsletters that covered numerous topics such as sitting and health, goal setting, memory health, self-care, sleep hygiene, and smoking cessation. Primary care providers in the UC clinics received information at baseline and annually on the present Centers for Medicare and Medicaid Services approach to behavioral therapy for obesity (23).

Measures

Body weight

Body weight was measured using a digital scale (Seca Model 876) at assessment visits conducted at baseline and at months 6, 12, 18, and 24. Patients were instructed to wear light clothes and no shoes whilst measurements were conducted. Anthropometric measurements were made in duplicate, although a third measurement was taken if weight differed by 0.5 kg. The average of the two closest measurements was recorded.

Questionnaires

All questionnaires used in the present analysis were administered at baseline, month 6, month 12, and month 24.

The Eating Inventory (EI) is a 51-item that assesses dietary restraint, dietary disinhibition, and hunger (24). However, only restraint and disinhibition were assessed and thus a shortened 37-item Eating Inventory was provided to PROPEL patients, with items assessing hunger removed (9). Dietary restraint is defined as the intent and ability to restrict food intake; a higher score is generally positive for weight control when disinhibition is low (25). Dietary disinhibition is defined as the tendency to overeat, and a higher value is associated with eating disorder symptoms and poor weight control (26). Greater scores for restraint and disinhibition were indicative of higher levels of the eating behavior assessed.

A customized questionnaire was administered to measure aspects of dietary intake. The questionnaire utilized scales from several sources to measure three outcomes: a National Cancer Institute fat screener assessed percent fat intake (27); a 7-item screener devised by the National Cancer Institute (NCI) and National 5 A Day Program examined fruit and vegetable consumption (28,29); and three questions from the Brief Questionnaire to Assess Habitual Beverage Intake (BEVQ-15) assessed the frequency of alcohol intake (30).

Weight-related quality of life was measured through the 31-item Impact of Weight on Quality of Life-Lite (IWQOL) (31,32). This questionnaire measures obesity-related aspects of quality of life, with a total quality of life score and separate scores for physical function, self-esteem, sexual life, public distress, and work or daily activities yielded. Scores are transformed to a 0-100 scale; a score of 100 represents the highest quality of life. The questionnaire asks patients to reflect on quality of life constructs because of their weight (31). Hence, in line with other analyses (15), only the total IWQOL score was utilized in the current analysis to limit the inclusion of variables that may be causally affected by weight change.

The Patient-Reported Outcomes Measurement Information System-29 (PROMIS-29) questionnaire was also administered to measure health-related quality of life (33). This 29-

item questionnaire assesses health-related domains related to physical function, anxiety, fatigue, depression, sleep disturbance, ability to partake in social roles and activities, pain interference, and pain intensity. All constructs were used except for pain intensity due to its relationship with pain interference.

The International Physical Activity Questionnaire (IPAQ) short form was used to assess physical activity levels (34). The questionnaire, which asks questions related to physical activity over the previous 7 days, provides physical activity scores in median metabolic equivalent of task (MET)-mins/wk. Four constructs of physical activity were assessed in MET-mins/wk: vigorous, moderate, walking, and total. In the PROPEL trial, numerous patients had missing data for particular activity types (vigorous, moderate, and walking), meaning total MET-mins/wk scores could not be calculated for these patients per standardized scoring methods (35). Thus, in the present analysis, we only included vigorous, moderate, and walking MET-mins/wk variables.

Statistical analysis

The present manuscript is an exploratory analysis; accordingly, the sample size acquired in the trial was studied. As summary statistics, between-group differences in change scores for questionnaire variables were determined using unadjusted independent samples t-tests. Absolute Cohen's d effect size (ES) values were also assessed for change scores (36). The magnitude of ES values was considered trivial (< 0.20), small (0.20-0.49), medium (0.50-0.79), or large (≥ 0.80) (36).

Our objective was to identify the mediators of weight change in the ILI compared to UC; in other words, we aimed to test the extent to which a set of variables (mediators) explained weight differences between the ILI group and the UC group. Multilevel mediation analysis was used to measure the effects conveyed by intervening variables (mediators) to the observed relationship between an exposure and outcome variable (37,38). In this analysis, the mediator (change in questionnaire variables) and outcome (weight change) variables were continuous, while the exposure variable was binary (ILI or UC group). We build random intercept models to account for the correlation among subjects within the clinic. As part of the analysis, the total effect was estimated at the individual level; that is, the average difference in weight change (outcome variable) caused by the ILI versus UC (exposure variable). The analysis further separated the total effect of the ILI (vs. UC) on weight change into two components: the indirect effects from mediators and the direct effect. The indirect effect is the effect of the ILI (vs. UC) on weight change that is driven by each proposed mediator; the direct effect is the remaining effect of the ILI (vs. UC) on weight change that is not explained by the change in the proposed mediators.

In accord with the aims of the manuscript, two conceptual models were used to guide the statistical procedures in these analyses (**Figure 1**). The first model aimed to determine the mediators of weight change induced by the ILI relative to UC during the first 12 months of the trial. This was chosen to highlight mediators of midterm weight loss (6- ≤12 months) (39). The exposure variable was the trial group (ILI vs. UC), the proposed mediators were change in questionnaire variables from baseline to month 6, and the outcome variable was weight change from baseline to month 12. In the second model, the aim was to assess the mediators of weight change during the second 12 months of the trial. This was broadly chosen to identify mediators of weight change during periods of weight loss maintenance. This model had the same exposure variable as model 1, although change in questionnaire variables from baseline to month 12 were the proposed mediators and change in weight from month 12 to month 24 was the outcome variable. In both models, the proposed mediators preceded the outcome variable, with a time difference (6 months in model 1 and 12 months in model 2) between the final measurement of the proposed mediators and the outcome variable.

This was to ensure temporal ordering of our exposure variable, proposed mediators, and outcome variable, limiting the confounding influence of reverse causality. In addition, we removed patients with censored weights from the mediation models. Weight measurements were censored if a patient became pregnant, developed a medical condition, or died.

We conducted our analyses using the multilevel mediation analysis method of Yu and colleagues, which is implemented in the *mlma* package in the software R (38,40). Briefly, potential mediators from our proposed mediators were informally selected if two conditions were satisfied. First, the proposed mediator distributed differently with or without the study's intervention (ILI vs. UC). In this regard, we used the Analysis of Variance (ANOVA) method to test if the mean of the variable differed between the ILI and UC. Second, the variable was significantly related to the outcome (weight change) whilst adjusting for all other related factors. This condition was tested through mixed-effect generalized linear models, with linear regression models used for linear outcomes or mediators. If only the second condition was satisfied, the variable was included as a covariate; yet the variable was excluded if the second condition was not satisfied (41). Besides the tests of two conditions, the package allows related variables to be forced into the model as mediators or covariates and it can assess joint effects of groups of mediators. Since the PROMIS-29 is used to determine overall health-related quality of life and no total score is obtained in the measure, we forced all PROMIS-29 constructs into the model as potential mediators and their joint effect estimated. We likewise forced vigorous, moderate, and walking MET scores into the model as potential mediators and estimated the joint effect of these variables. Age, sex, race, baseline values for selected mediators, and weight (baseline weight for model 1; month 12 weight for model 2) were added as covariates. We estimated absolute total, direct, and indirect effects, as well as relative direct and indirect effects that provide the magnitude of these effects as a proportion of the total effect. For both the absolute and relative effect estimates, the standard error (SE) and asymmetric 95% confidence intervals (CI) around estimates were calculated, with inferences made using the bootstrap method. Unless noted otherwise, within the text, data are displayed as mean ± SD and 95% CI where inferences were made.

RESULTS

Patient characteristics

A total of 803 patients with obesity (BMI: 37.2 ± 4.7 kg/m^2) and a mean age of 49.4 (± 13.1) y were enrolled in the trial from 18 clinics; 452 patients from 9 clinics enrolled into the ILI and 351 patients from 9 clinics enrolled into UC (**Figure 2**). Details of the sample and the numbers who missed visits and withdrew are reported in the primary outcome paper (9). The majority of patients were female (n = 678; 84.4%), were black (n = 540; 67.2%), and had a total household income below $40,000 (n = 515; 64.1%; **Table 1**). Moreover, 247 patients (30.8%) were food insecure.

During the trial, 24 patients had month 12 weight censored, while a further 12 had weight censored at month 24 (Figure 2). Therefore, the first mediation analysis and related summary comparisons (change scores in mediators from baseline to month 6) included 779 (439 ILI; 340 UC) patients, whilst the second mediation analysis and related summary comparisons (change scores for mediators from baseline to month 12) included 767 patients (433 ILI; 334 UC). Baseline characteristics of these analytical samples are shown in **Supplementary Table 1** and **Supplementary Table 2**.

Change scores

The analysis in the primary outcome paper showed that weight loss in the ILI group was greater than the UC group at month 12 (ILI: -7.22 kg [95% CI: -8.25, -6.19]; UC: -0.99 kg [95% CI: -2.08, 0.09]) and month 24 (ILI: -5.43 kg [95% CI: -6.52, 4.34]; UC: -0.91 kg [95% CI: -2.07, 0.24]) (9).

Unadjusted independent sample t-tests suggested that the ILI group displayed a significant and large increase in restraint compared to the UC group at month 6 and month 12 ($P < 0.001$; ES ≥ 1.16), whereas a 0.9-point reduction in disinhibition was shown in the ILI relative to UC at month 6 ($P < 0.001$; ES = 0.33; **Table 2**). At month 6 and month 12, compared to the UC group, the ILI group showed a small reduction in percent fat intake and an increase in fruit and vegetable intake ($P \leq 0.010$; ES ≥ 0.20); yet both groups reported a similar change in alcohol intake at months 6 and 12 ($P \geq 0.662$; ES ≤ 0.03; Table 2). The ILI group reported an increase in all physical activity constructs at month 6 ($P \leq 0.035$; ES ≥ 0.17), though only change in vigorous physical activity was greater in the ILI group than the UC group at month 12 (Table 2).

There was an increase in weight-related quality of life in the ILI group relative to the UC group at months 6 and 12 ($P < 0.001$; ES ≥ 0.62; Table 2). Apart from sadness ($P = 0.177$; ES = 0.10), all health-related quality of life constructs of the PROMIS-29 were significantly improved in the ILI at month 6 compared to UC, with trivial-to-small effect sizes observed ($P \leq 0.008$; ES ≥ 0.20; Table 2). At month 12, however, statistically significant improvements were only observed for pain interference, physical function, social functioning, and fatigue in the ILI group relative to the UC group ($P \leq 0.041$; ES ≥ 0.16; Table 2).

Mediation analysis

Results from mediation analyses are summarized in **Table 3**. In model 1 (baseline to month 12 weight change), restraint, disinhibition, percent fat intake, and weight-related quality of life total score met the two criteria and were selected as potential mediators alongside the IPAQ and PROMIS-29 variables and their composite scores. Similar to the primary outcome paper (9), the total effect of the ILI (vs. UC) on weight change at month 12 was -7.19 kg (95% CI: -8.43, -6.07). The direct effect (i.e., effect of ILI [vs. UC] on 12-month weight change independent of change in mediators) was -5.36 kg (95% CI: -6.90, -3.94), with a relative effect estimate showing that 75% of the between-group weight change was not caused by mediators. Of the selected potential mediators, disinhibition, percent fat intake, moderate physical activity, walking, and fatigue change from baseline to month 6 were significant mediators of the improved weight loss displayed by the ILI group versus the UC group at month 12. Specifically, month 6 change in disinhibition, percent fat intake, moderate physical activity, walking, and fatigue explained -0.33 kg (95% CI: -0.55, -0.10), -0.25 kg (95% CI: -0.50, -0.01), -0.13 kg (95% CI: -0.23, -0.03), -0.11 kg (95% CI: -0.21, -0.02), and -0.28 kg (95% CI: -0.46, -0.10), respectively, of the 12-month weight change caused by the ILI (vs. UC). The joint indirect effect of physical activity (composite score for vigorous physical activity, moderate physical activity, and walking) was also significant and explained -0.26 kg (95% CI: -0.41, -0.09) the 12-month weight change caused by the ILI (vs. UC). The relative effect estimates indicated that disinhibition, percent fat intake, physical activity (joint effect), and fatigue explained 5%, 4%, 4%, and 4%, respectively, of the improved weight change seen in the ILI group compared to the UC group at month 12. Restraint was not a statistically significant mediator (-0.70 kg; 95% CI: -1.44, 0.03). Similarly, the individual and joint effects of other PROMIS-29 variables and the change in weight-related quality of life did not significantly mediate month 12 weight change induced by the ILI (vs. UC; Table 3).

In model 2 (month 12 to month 24 weight change), only fruit and vegetable intake met the two criteria and was selected as a potential mediator with the IPAQ and PROMIS variables. The ILI group displayed a significant 2.24 kg (95% CI: 1.32, 3.26) increase in weight from month 12 to month 24 compared to the UC group (Table 3). The direct effect in this model was 2.00 kg (95% CI: 1.09, 3.02), with relative effect estimates suggesting 89% of the increase in weight exhibited by the ILI group (vs. UC) was not explained by the selected mediators. The change in fruit and vegetable intake from baseline to month 12 was a significant mediator of the increase in weight shown by the ILI relative to UC from month 12 to month 24 (0.13 kg; 95% CI: 0.05, 0.21); relative effect estimates suggested that this explained 6% of the weight gain shown by the ILI (vs. UC). None of the other indirect effects of the selected mediators were significant (Table 3), suggesting 12-month change in these selected mediators from baseline did not explain or attenuate (i.e., inconsistent mediation) the increase in weight seen by the ILI group compared to the UC group from month 12 to month 24.

DISCUSSION

Over 24 months, an ILI induced weight loss relative to UC in a sample of underserved patients with obesity. These analyses showed that month 6 change in disinhibition, percent fat intake, physical activity, and subjective fatigue partially mediated the -7.19 kg weight change seen in the ILI group relative to the UC group at 12 months. The ILI group lost more weight than the UC group at month 24, but weight gain of 2.24 kg was observed in the ILI compared to UC from month 12 to month 24, with fruit and vegetable intake identified as a mediator. Analyses showed that the change in questionnaire constructs explained a small amount of the between-group weight change. More specifically, each mediator explained ≤10% of the between-group weight change, and relative direct effect values indicated that ≥75% of the between-group weight change was not explained by assessed constructs. Nonetheless, though other unmeasured factors drive between-group weight variations, these results could help improve weight regimens by highlighting critical constructs and behaviors.

Behavioral lifestyle interventions typically offer counseling sessions that aim to improve the eating behaviors of individuals with obesity via an increase in dietary restraint and a reduction in dietary disinhibition (8). In this analysis, we observed that a decrease in dietary disinhibition was a significant mediator of 12-month weight loss seen in the ILI group compared to the UC group. This is consonant with studies reporting a reduction in dietary disinhibition (12) is associated with weight loss in individuals with obesity during lifestyle interventions, and it suggests that regimens provided to underserved cohorts should place particular focus on behavioral strategies linked to disinhibition. Such strategies could consist of those utilized during the PROPEL ILI behavioral sessions, including controlled eating of foods, eating habits in response to stress and negative emotion, and healthy eating during special events. In contrast to the decrease in disinhibition, the increase in dietary restraint was not a significant mediator in our analyses. This supports research showing no association between restraint and weight loss (42), though in contrast to some work (12), we may have been underpowered to detect a positive influence of dietary restraint on weight loss.

A core strategy recommended for weight loss in individuals with obesity is the adoption of healthy dietary patterns. This includes limiting fat and alcohol intake and incorporating fruits, vegetables, and grains into a calorie deficit diet (8,39). Our results suggest that a decrease in percent fat intake was a mediator of the between-group difference in month 12 weight loss, supporting previous analyses (13,43) and suggesting that a reduction in fat intake is a key practice that assists the development of a calorie deficit and weight loss in underserved individuals with obesity. However, consistent with previous evidence (44), change in alcohol consumption did not mediate weight loss seen in the ILI versus UC. Additionally, though it did not influence weight loss in the first year of the trial, the increase in fruit and vegetable consumption seen in the ILI relative to UC did mediate the relative weight gain from month 12 to month 24. It is possible that fruit and vegetable consumption increased energy intake during a period of relapse in the ILI group, but it should be noted that research examining the influence of fruit and vegetable intake per se on long-term weight maintenance is mixed (14,45). Therefore, further research is needed to elucidate the role of fruit and vegetable intake during weight management interventions in underserved individuals with obesity.

Studies show that physical activity combined with dietary modifications stimulate greater weight loss over periods of at least 12 months compared to dietary modifications alone (46). We found, in line with these findings, that increased physical activity at month 6 mediated the greater 12-month weight loss in the ILI compared to UC, particularly the increase in moderate physical activity and walking. This suggests future weight loss regimens in similar patient populations should seek to increase physical activity to improve weight loss. It could also imply that interventions should set more ambitious activity goals that have been recommended for weight loss, such as ≥200 min/wk of walking or moderate physical activity (47). However, since physical activity did not influence between-group weight change from month 12 to month 24, future research should elucidate the long-term role of physical activity during ILI's in underserved populations, especially as others have suggested that physical activity may be crucial in preventing weight regain (48). These studies should identify methods to sustain elevations in physical activity, given there were no differences in moderate physical activity and walking between groups at month 12.

In addition to physical activity, model 1 revealed decreased fatigue as a mediator of improved 12-month weight change during the ILI. Speculatively, though concurrent changes in weight and fatigue may reciprocally affect each other (15), the behavioral strategies of the ILI may have decreased subjective fatigue and led to better adherence to the weight loss regimen compared to UC. Our analysis nonetheless indicated that other health- and weight-related quality of life constructs did not drive the greater weight loss seen in the ILI group during the first 12 months, and quality of life changes at month 12 did not influence between-group weight change during the trial from month 12 to month 24.

A strength of the analyses is that it comprises data from a cluster-randomized trial performed in a diverse sample of patients with obesity who are underserved and understudied within clinical studies. As a result, broadly, our findings have implications for socioeconomically disadvantaged individuals who are disproportionally affected by obesity and obesity-related conditions, and who face significant barriers for treatment. Another strength is that we collected mediator and weight measurements at multiple points during the 24-month trial, enabling us to investigate mediators of weight change during periods which, despite variations in definitions (49), can be generally considered midterm weight loss (39) and weight loss maintenance. This means our results can be utilized to develop enhanced ILIs which target constructs that are important for long-term weight management in similar at-risk populations. A final noteworthy strength is that trained health coaches of the trial were embedded within a care team in primary care. This may explain why our analyses revealed many findings that are similar to those derived from more controlled trials, and it could supply a model for weight management regimens in primary care (9).

The current manuscript has limitations. First, the trial consisted mostly of females, restricting our ability to generalize our results to underserved males with obesity. Second, as there were no sessions offered in the UC group, we could not incorporate number of sessions attended into our analyses. It is possible that session attendance was a significant driver of weight change, since it predicts weight loss (8). Third, these analyses are exploratory, so though our analyses comprised a relatively large number of participants from an understudied population, we included several variables and may be underpowered to detect some effects. Fourth, unmeasured mediator variables and mediator-outcome confounders may be more causally linked to between-group weight differences, limiting our ability to make causal inferences. Finally, measurement errors likely explain, at least in part, why our mediators explained a small proportion of between-group weight differences (50). Indeed, we used self-report assessments of diet and physical activity, which in contrast to objective measures (e.g., waist devices for physical activity), are prone to systematic and random errors, primarily because they rely on recall and can be influenced by demand characteristics (51). The

PROPEL trial was a pragmatic trial performed in a low-literate population in primary care; hence, a large battery of sophisticated assessments was unfeasible, and we decreased the burden of some questionnaires (e.g., not administering EI hunger subscale). Yet additional research is needed during lifestyle interventions in underserved populations to elucidate the causal drivers of weight change. Such studies could examine further potential mediators of weight change like calorie intake, consistency of eating (52), hunger, energy density (53), and sugar-sweetened beverage consumption (54). Further, where possible, they should utilize reliable and objective assessment methods, particularly for diet (e.g., emerging technologies like food photography) and physical activity (e.g., pedometers or accelerometers) (51).

In conclusion, among underserved patients with obesity, our analyses indicated that 12-month weight loss during an ILI versus UC was explained by improvements in disinhibition, percent fat intake, physical activity, and subjective fatigue. These variables did not, however, attenuate the weight gain shown during the ILI compared to UC in the final 12 months of the trial, and fruit and vegetable intake may partially explain this response. Although additional work is needed using precise assessment methods to illuminate causal drivers of weight change during ILIs, these findings highlight psychological and behavioral constructs that could be targeted to refine interventions and facilitate weight management in underserved patients with obesity.

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Table 1. Baseline characteristics and measures of the PROPEL trial cohort.

		All (n = 803)	ILI (n = 452)	UC (n = 351)
Age (y)		49.4 ± 13.1	48.8 ± 12.7	50.1 ± 13.6
Sex				
	Male	125 (15.6)	54 (11.9)	71 (20.2)
	Female	678 (84.4)	398 (88.1)	280 (79.8)
Race				
	White	208 (25.9)	95 (21.0)	113 (32.2)
	Black	540 (67.2)	332 (73.5)	208 (59.3)
	Other	55 (6.8)	25 (5.5)	30 (8.5)
Total annual household income				
	<$10,000	156 (19.4)	86 (19.0)	70 (19.9)
	$10,000-$19,999	168 (20.9)	95 (21.0)	73 (20.8)
	$20,000-$39,999	191 (23.8)	112 (24.8)	79 (22.5)
	$40,000-$59,999	117 (14.6)	69 (15.3)	48 (13.7)
	>$60,000	154 (19.2)	83 (18.4)	71 (20.2)
	Missing	17 (2.1)	7 (1.5)	10 (2.8)
Household food security status				
	Food insecure	247 (30.8)	129 (28.5)	118 (33.6)
	Food secure	556 (69.2)	323 (71.5)	233 (66.4)
Weight (kg)		102.1 ± 16.7	101.6 ± 16.4	102.7 ± 17.0
Body mass index (kg/m^2)		37.2 ± 4.7	37.3 ± 4.6	37.2 ± 4.8
Eating Inventory				
	EI, Restraint	9.6 ± 4.5	9.6 ± 4.5	9.5 ± 4.5
	EI, Disinhibition	6.9 ± 3.7	7.0 ± 3.6	6.7 ± 3.7
Dietary intake questionnaire				
	NCI, Percent fat intake	35.3 ± 6.4	35.9 ± 6.7	34.6 ± 5.9
	NCI, Fruit and vegetable intake	2.2 ± 1.7	2.2 ± 1.6	2.3 ± 1.8
	BEVQ-15, Alcohol intake	0.2 ± 0.4	0.2 ± 0.4	0.2 ± 0.4
Physical activity				
	IPAQ, Vigorous (MET-mins/wk)	561.4 ± 956.1	504.7 ± 891.1	634.3 ± 1030.3
	IPAQ, Moderate (MET-mins/wk)	475.2 ± 839.4	435.9 ± 803.3	525.2 ± 881.9
	IPAQ, Walking (MET-mins/wk)	808.9 ± 1011.2	780.8 ± 1027.3	844.0 ± 991.2
Weight-related quality of life				
	IWQOL, Total score	73.9 ± 19.0	72.8 ± 19.5	75.3 ± 18.3
Health-related quality of life				
	PROMIS-29, Sadness	47.5 ± 8.6	47.0 ± 8.5	48.1 ± 8.7

PROMIS-29, Pain interference	51.9 ± 9.6	51.5 ± 9.7	52.5 ± 9.4
PROMIS-29, Physical function	48.6 ± 8.0	48.9 ± 7.9	48.1 ± 8.1
PROMIS-29, Social functioning	54.8 ± 9.0	55.2 ± 8.9	54.3 ± 9.1
PROMIS-29, Fatigue	50.1 ± 10.1	49.4 ± 9.8	50.9 ± 10.4
PROMIS-29, Anxiety	51.9 ± 9.9	51.7 ± 9.7	52.2 ± 10.1
PROMIS-29, Sleep disturbance	50.7 ± 9.4	50.2 ± 9.2	51.5 ± 9.5

Continuous data are mean ± SD; categorical variables are number (%).

Abbreviations: BEVQ-15, Brief Questionnaire to Assess Habitual Beverage Intake; EI, Eating Inventory; ILI, intensive lifestyle intervention; IPAQ, International Physical Activity Questionnaire; IWQOL, Impact of Weight on Quality of Life-Lite; MET, metabolic equivalent of task; NCI, National Cancer Institute; PROMIS-29, Patient-Reported Outcomes Measurement Information System-29; PROPEL, Promoting Successful Weight Loss in Primary Care in Louisiana; UC, usual care.

Table 2. Change scores in questionnaire variables at month 6 and month 12 during the PROPEL trial.[1]

		Baseline to Month 6				Baseline to Month 12			
		ILI (n = 439)	UC (n = 340)	*P*	Cohen's d	ILI (n = 433)	UC (n = 334)	*P*	Cohen's d
Eating Inventory									
	EI, Restraint	6.3 ± 4.5	0.7 ± 3.6	<0.001	1.37	5.6 ± 4.4	0.8 ± 3.9	<0.001	1.16
	EI, Disinhibition	-1.8 ± 3.1	-0.9 ± 2.5	<0.001	0.33	-1.3 ± 3.1	-1.0 ± 2.7	0.109	0.12
Dietary intake questionnaire									
	NCI, Percent fat intake	-3.7 ± 6.0	-1.2 ± 5.5	<0.001	0.43	-2.9 ± 6.0	-1.0 ± 5.1	<0.001	0.34
	NCI, Fruit and vegetable intake	0.2 ± 1.6	-0.2 ± 1.7	0.003	0.23	0.2 ± 1.7	-0.1 ± 1.9	0.010	0.20
	BEVQ-15, Alcohol intake	0.0 ± 0.3	0.0 ± 0.3	0.662	0.03	0.0 ± 0.3	0.0 ± 0.3	0.881	0.01
Physical activity									
	IPAQ, Vigorous (MET-mins/wk)	300.5 ± 1038.2	43.4 ± 1172.5	0.003	0.23	272.8 ± 1124.7	74.0 ± 1173.4	0.030	0.17
	IPAQ, Moderate (MET-mins/wk)	189.0 ± 1049.8	17.3 ± 989.6	0.035	0.17	238.0 ± 1047.3	138.8 ± 964.0	0.228	0.10
	IPAQ, Walking (MET-mins/wk)	211.1 ± 1203.9	9.5 ± 1047.3	0.034	0.18	125.4 ± 1283.0	-4.4 ± 1117.0	0.215	0.11
Weight-related quality of life									
	IWQOL, Total score	10.9 ± 14.0	3.2 ± 10.8	<0.001	0.62	12.1 ± 14.4	3.4 ± 11.5	<0.001	0.67
Health-related quality of life									
	PROMIS-29, Sadness	-0.1 ± 7.1	0.7 ± 7.9	0.177	0.10	0.2 ± 7.7	0.8 ± 7.4	0.281	0.08
	PROMIS-29, Pain interference	-1.3 ± 8.1	0.3 ± 8.3	0.008	0.20	-0.9 ± 9.2	0.9 ± 8.3	0.009	0.20

PROMIS-29, Physical function	2.3 ± 6.4	0.1 ± 6.7	<0.001	0.34	1.8 ± 6.9	-0.1 ± 6.6	<0.001	0.28
PROMIS-29, Social functioning	2.0 ± 7.5	0.1 ± 7.4	<0.001	0.26	2.0 ± 8.2	0.4 ± 7.8	0.007	0.21
PROMIS-29, Fatigue	-3.0 ± 9.2	-0.6 ± 8.2	<0.001	0.28	-2.2 ± 9.2	-0.8 ± 8.9	0.041	0.16
PROMIS-29, Anxiety	-1.4 ± 9.2	0.6 ± 8.9	0.003	0.22	-1.0 ± 8.9	0.0 ± 8.5	0.153	0.11
PROMIS-29, Sleep disturbance	-1.8 ± 8.0	0.3 ± 7.7	<0.001	0.28	-0.8 ± 8.7	0.1 ± 8.5	0.174	0.10

Data are mean ± SD.

[1]Independent sample t-tests compared change scores between groups at month 6 and month 12. Absolute Cohen's d effect size (ES) values were used to compare changes scores between groups at month 6 and month 12.

Abbreviations: BEVQ-15, Brief Questionnaire to Assess Habitual Beverage Intake; EI, Eating Inventory; ILI, intensive lifestyle intervention; IPAQ, International Physical Activity Questionnaire; IWQOL, Impact of Weight on Quality of Life-Lite; MET, metabolic equivalent of task; NCI, National Cancer Institute; PROMIS-29, Patient-Reported Outcomes Measurement Information System-29; PROPEL, Promoting Successful Weight Loss in Primary Care in Louisiana; UC, usual care.

Table 3. Total, direct, and indirect effects of the PROPEL ILI (versus UC) on weight change, with questionnaire variables as mediators.[1]

		Absolute effect		Relative effect	
		Estimate	95% CI	Estimate	95% CI
Model 1 (Baseline to month 12 weight change)[2]					
Eating Inventory					
	EI, Restraint	-0.70 ± 0.40	-1.44, 0.03	0.10 ± 0.05	-0.01, 0.20
	EI, Disinhibition	-0.33 ± 0.11	-0.55, -0.10	0.05 ± 0.02	0.02, 0.07
Dietary intake questionnaire					
	NCI, Percent fat intake	-0.25 ± 0.12	-0.50, -0.01	0.04 ± 0.02	0.00, 0.07
Physical activity					
	IPAQ, Joint effect of constructs[4]	-0.26 ± 0.08	-0.41, -0.09	0.04 ± 0.01	0.01, 0.06
	IPAQ, Vigorous (MET-mins/wk)	0.02 ± 0.06	-0.14, 0.11	0.00 ± 0.01	-0.02, 0.02
	IPAQ, Moderate (MET-mins/wk)	-0.13 ± 0.05	-0.23, -0.03	0.02 ± 0.01	0.00, 0.03
	IPAQ, Walking (MET-mins/wk)	-0.11 ± 0.05	-0.21, -0.02	0.02 ± 0.01	0.00, 0.03
Weight-related quality of life					
	IWQOL, Total score	-0.35 ± 0.21	-0.76, 0.04	0.05 ± 0.03	-0.01, 0.11
Health-related quality of life					
	PROMIS-29, Joint effect of constructs[5]	0.06 ± 0.13	-0.19, 0.33	-0.01 ± 0.02	-0.05, 0.03
	PROMIS-29, Sadness	0.01 ± 0.03	-0.05, 0.06	-0.00 ± 0.00	-0.01, 0.01
	PROMIS-29, Pain interference	-0.02 ± 0.06	-0.13, 0.09	0.00 ± 0.01	-0.01, 0.02
	PROMIS-29, Physical function	0.14 ± 0.09	-0.03, 0.31	-0.02 ± 0.01	-0.04, 0.01

	PROMIS-29, Social functioning	0.03 ± 0.08	-0.12, 0.20	-0.00 ± 0.01	-0.03, 0.02
	PROMIS-29, Fatigue	-0.28 ± 0.09	-0.46, -0.10	0.04 ± 0.01	0.01, 0.06
	PROMIS-29, Anxiety	0.12 ± 0.08	-0.03, 0.27	-0.02 ± 0.01	-0.04, 0.00
	PROMIS-29, Sleep disturbance	0.06 ± 0.09	-0.12, 0.25	-0.01 ± 0.01	-0.03, 0.02
Direct effect		-5.36 ± 0.76	-6.90, -3.94	0.75 ± 0.06	0.62, 0.87
Total effect		-7.19 ± 0.60	-8.43, -6.07	-	-
Model 2 (Month 12 to month 24 weight change)[3]					
Dietary intake questionnaire[4]					
	NCI, Fruit and vegetable intake	0.13 ± 0.04	0.05, 0.21	0.06 ± 0.02	0.01, 0.11
Physical activity					
	IPAQ, Joint effect of constructs[4]	0.03 ± 0.04	-0.06, 0.10	0.01 ± 0.02	-0.03, 0.05
	IPAQ, Vigorous (MET-mins/wk)	0.02 ± 0.04	-0.06, 0.09	0.01 ± 0.02	-0.03, 0.04
	IPAQ, Moderate (MET-mins/wk)	0.01 ± 0.02	-0.03, 0.05	0.00 ± 0.01	-0.02, 0.02
	IPAQ, Walking (MET-mins/wk)	0.00 ± 0.03	-0.05, 0.06	0.00 ± 0.01	-0.02, 0.03
Health-related quality of life					
	PROMIS-29, Joint effect of constructs[5]	0.09 ± 0.07	-0.06, 0.23	0.04 ± 0.03	-0.03, 0.10
	PROMIS-29, Sadness	0.02 ± 0.02	-0.02, 0.06	0.01 ± 0.01	-0.01, 0.03
	PROMIS-29, Pain interference	0.06 ± 0.06	-0.06, 0.17	0.02 ± 0.03	-0.03, 0.08
	PROMIS-29, Physical function	0.09 ± 0.07	-0.05, 0.23	0.04 ± 0.03	-0.03, 0.11

	PROMIS-29, Social functioning	-0.03 ± 0.05	-0.13, 0.07	-0.02 ± 0.03	-0.07, 0.03
	PROMIS-29, Fatigue	-0.01 ± 0.04	-0.08, 0.06	0.00 ± 0.02	-0.04, 0.03
	PROMIS-29, Anxiety	-0.05 ± 0.03	-0.10, 0.01	-0.02 ± 0.01	-0.05, 0.01
	PROMIS-29, Sleep disturbance	0.01 ± 0.02	-0.04, 0.05	0.00 ± 0.01	-0.02, 0.03
Direct effect		2.00 ± 0.49	1.09, 3.02	0.89 ± 0.04	0.81, 0.98
Total effect		2.24 ± 0.49	1.32, 3.26	-	-

[1]Values and 95% confidence intervals are calculated with the *mlma* package of Yu and colleagues (38,40). Absolute effects are estimated means (± SE), while relative direct and indirect effects which are the corresponding direct or indirect effect divided by the total effect (±SE).

[2]Exposure variable was group (ILI vs. UC), the proposed mediators were change in questionnaire variables from baseline to month 6, and the outcome variable was weight change from baseline to month 12. Adjusted for age, sex, race, baseline questionnaire variables for selected mediators, and baseline weight; n = 779 (439 ILI; 340 UC).

[3]Exposure variable was group (ILI vs. UC), the proposed mediators were change in questionnaire variables from baseline to month 12, and the outcome variable was weight change from month 12 to month 24. Adjusted for age, sex, race, baseline questionnaire variables for selected mediators, and month 12 weight; n = 767 (433 ILI; 334 UC).

[4]Indirect effect is composite score of the joint effect of all constructs: vigorous MET-mins/wk, moderate MET-mins/wk, and walking MET-mins/wk.

[5]Indirect effect is composite score of the joint effect of all constructs: sadness, pain interference, physical function, social functioning, fatigue, anxiety, and sleep disturbance.

Abbreviations: EI, Eating Inventory; ILI, intensive lifestyle intervention; IPAQ, International Physical Activity Questionnaire; IWQOL, Impact of Weight on Quality of Life-Lite; MET, metabolic equivalent of task; NCI, National Cancer Institute; PROMIS-29, Patient-Reported Outcomes Measurement Information System-29; PROPEL, Promoting Successful Weight Loss in Primary Care in Louisiana; UC, usual care.

FIGURE LEGENDS

Figure 1. Hypothetical mediation models.

Figure 2. Participant flow chart for the analyses.