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Mediating role of bone marrow lesion, synovitis, pain sensitization, and depressive symptoms on knee pain improvement following substantial weight loss

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Abstract

Objective.—Massive weight loss leads to marked knee pain reduction in persons with knee pain, but the reason for the reduction in pain is unknown. To quantify the contribution of MRI changes in pain sensitive structures, bone marrow lesions (BML), synovitis, and in pain sensitization, or depressive symptoms to knee pain improvement after substantial weight loss.

Methods.—Morbidly obese patients with knee pain on most days were evaluated before bariatric surgery or medical weight management and at 1-year follow-up for BML and synovitis seen on MRI, pressure pain threshold (PPT) at patella and right wrist, depressive symptoms (using CES-D), and WOMAC pain survey. Natural effects models quantified the extent that achieving minimal clinically important difference (MCID) of 18% on the WOMAC pain scale could be mediated by weight loss-induced changes in BML, synovitis, PPT, and depressive symptoms.

Results.—Of 75 participants, 53.3% lost 20% weight by 1-year; of these, 75% attained an MCID for pain improvement, compared with 34.3% in those who had <20% weight loss.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

Study conception and design. Jafarzadeh, Felson, Neogi, Stefanik.

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Mediation analyses suggested that, in those with at least 20% weight loss, the odds of pain improvement increased by 62%, 15%, and 22% through changes in patella PPT, wrist PPT, and CES-D, respectively, but pain improvement was not mediated by MRI changes in BMLs or synovitis.

Conclusion.—Weight loss-induced knee pain improvement is partially mediated by changes in pain sensitization and depressive symptoms, but is independent of MRI changes in BML and synovitis.

INTRODUCTION

Osteoarthritis (OA) is the most common cause of arthritis, which is estimated to affect 91.2 million adults in the United States (1), making OA a leading cause of disability. While pain is the most prominent cause of OA-related disability, the association between pain and structural features of joints affected by OA is incompletely understood. These structural features often include bone marrow lesions (BML) and synovitis visualized by magnetic resonance imaging (MRI). Some studies have suggested an association of pain with BML (2–8) and synovitis (4,7–10), while others have suggested no association (11–14). In addition to structural features, there are reports of other factors affecting knee pain. For example, pain sensitization is associated with pain severity in knee OA (15), and a recent study suggested an improvement in pain sensitization following bariatric surgery (16). Further, sustained depressive symptoms that often co-occur with OA (17) have been reported to be associated with pain severity (18).

Obesity is a major risk factor for OA (19), and is itself also associated with pain and depressive symptoms. Several studies have reported considerable improvement in knee pain following bariatric surgery (16,20,21), which causes substantial weight loss. However, no study to our knowledge has evaluated to what extent changes in BML, synovitis, pain sensitization, or depressive symptoms contribute to pain improvement in persons who experience substantial weight loss. A cause-specific assessment for the pain improvement would provide insights into causes of knee pain in obese persons and might provide clues to effective pain-relieving treatments.

Our study focuses on BML and synovitis assessed by longitudinal MRI evaluations, pain sensitization, and depressive symptoms, measured pre- and post-intervention, in morbidly obese persons who experienced substantial weight loss after bariatric surgery or medical weight management. Specifically, we quantified the extent to which changes in BML, synovitis, pain sensitization, or depressive symptoms that may occur with substantial weight loss could mediate the effect of weight loss on knee pain improvement.

METHODS

Setting.

Study participants were recruited from the Nutrition and Weight Management Center at Boston Medical Center in Boston, Massachusetts. The Institutional Review Board at the Boston University Medical Campus approved the study protocol. All study participants provided written informed consent.

The eligible participants included obese patients between 25–60 years of age and a body mass index (BMI) ≥ 35 kg/m² with a weight-related comorbidity or BMI of ≥ 40 kg/m². To be eligible for our study, subjects additionally had to have knee pain on most days of the past month and had to be able to undergo a knee MRI evaluation. If both knees were affected, the more painful knee was selected for the MRI. Patients with a history of knee surgery or inflammatory arthritis were not eligible.

Following the baseline assessment, study participants received either medical weight management or bariatric surgery treatments. The medical management group received dietary recommendations with or without prescription medications that included phentermine with or without topiramate, lorcaserin, bupropion with or without naltrexone, or liraglutide. The dietary guidance consisted a 1200–1500 and 1500–1800 kilocalories/day high-protein low-fat diets with or without meal replacements for women and men, respectively. The bariatric surgery treatment was either laparoscopic Roux-en-Y gastric bypass or laparoscopic sleeve gastrectomy. Both treatment groups received the exercise recommendation of a minimum 30-minute walk per day in addition to resistance exercise twice weekly. The follow-up study visit occurred approximately one year after bariatric surgery or the baseline visit in the medical weight management group.

Measurements.

All study participants underwent 3T MRI by Philips Achieva and pulse sequences including a sagittal WATSc and 3D fat saturation SPAIR sequences. Semi-quantitative MRI assessments consisted of baseline and follow-up image paired readings by an experienced musculoskeletal radiologist using MRI Osteoarthritis Knee Score (MOAKS) for BML and synovitis. The reader was blinded to treatment received and weight loss experienced. For BML and synovitis in a knee, we tested both maximum (i.e., worst) and sum of scores for BML and synovitis, as described in previous work (22).

Pain sensitization was assessed by measuring pressure pain thresholds (PPT) with a hand-held algometer applied at a rate of 0.5kg/second as the point at which the pressure first changed to slight pain. PPT was obtained at the index patella and right wrist. Three consecutive PPT measurements were averaged. Low patella and wrist PPT are suggestive of greater pain sensitization. Depressive symptoms were assessed using the 20-item Center for Epidemiologic Studies Depression (CES-D) scale (23).

Knee-specific pain severity was assessed with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale (24). We defined the minimal clinically important difference (MCID) for WOMAC pain as a reduction of 18% or more in the WOMAC pain subscale score, as described in Angst et al (25).

Analytic approach.

Characteristics of the study sample were represented by frequencies for binary and categorical covariates and distribution summaries for continuous covariates. As in prior reports (22) and based on a cutoff that represented approximately the median distribution of weight loss, these descriptive statistics were stratified based on whether participant lost $\geq 20\%$ weight by the 1-year follow-up visit. Changes in mean PPT for the patella and wrist,

and mean CES-D changes between baseline and one-year follow-up were evaluated by linear mixed-effects models with random-effects specified for subjects to account for the correlation due to repeated measurements on the same knees across visits (26).

We performed causal mediation analysis to quantify the extent that specific causal pathways allow weight loss to exert its effects on pain improvement. These potential causal pathways included an *indirect* effect, that is the extent of pain improvement attributable to weight loss-induced changes in BML, synovitis, patella and wrist PPT, and CES-D score (Figure 1). The *direct* effect quantified any remaining effect not mediated by changes in BML, synovitis, patella and wrist PPT, and CES-D score (Figure 1).

To estimate indirect and direct effects, we fit a natural-effects model (27), which is a flexible and robust method to decompose the overall total effect into specific potential causal pathways, without reliance on a restrictive linear parametric statistical model (28). These indirect and direct effects are defined based on the counterfactual framework for causal inference, that is, the effect that would have been observed if the exposure or mediator were absent in contrast to the observed data (29).

Mediated interaction.

We assessed mediated interaction, that is, the effect modification of natural effects between the exposure, weight loss, and the mediators such that we assessed whether weight loss and BML, synovitis, patella or wrist PPT, or CES-D score interact in their effect on pain improvement. In this effect decomposition, both indirect and direct effects are decomposed into pure indirect and pure direct effects in addition to the interactive effect as described in VanderWeele (30).

Interpretation of natural effects.

Modern causal mediation analysis approaches rely on modeling techniques to estimate mediated/indirect effects under the counterfactual framework (for technical details see Shpitser and Tchetgen (31)). These sets of parametric models or non-parametric (i.e. model-free) approaches allow an estimate of effect by changing treatment assignment (e.g., exposure level of 20% and <20% weight loss) along specific pathways, but not along other pathways. A natural-effects model is one such approach that allows for model-free decomposition of exposure effect into indirect and direct effects. Identifying indirect and direct effects depends on three causal assumptions, exchangeability (e.g., those with 20% weight loss, had they lost <20% weight, would have experienced the same average outcome as those with <20% weight loss), consistency (e.g., the observed outcome for each subject with 20% weight loss equals the counterfactual outcome if the subject lost 20% weight, and same for those with <20% weight loss), and positivity (e.g., there is a non-zero positive probability that each subject could lose 20% or <20% weight). Consequently, this counterfactual framework under which causal mediating effects are estimated does not rely on other assumptions such as testing the statistical significance of the association between mediators and exposure (i.e., weight loss).

The natural direct effect was defined by Robins and Greenland (32) as the expected effect of an exposure on an outcome, while retaining the mediator constant at the level that would

have naturally occurred in the absence of the exposure. The natural indirect effect provides an estimate for the effect of an exposure on an outcome if all subjects were exposed by setting the mediator to a level that would have occurred in the absence of the exposure. Note that in estimating the natural indirect effect, the exposure status remains constant, whereas the mediator level is held constant in the natural direct effect estimate (28).

Computation.

We used the imputation-based approach developed by Vansteelandt et al (33) to estimate the parameters of the natural-effects model. In this approach, no model is specified for the distribution of mediator; thus, unlike a competing approach using weighting, it is not sensitive to the potential misspecification of the mediator model especially if the mediator is continuous (34). Nonetheless, in a sensitivity analysis, we calculated our effect measures using both imputation- and weighting-based approaches. Effects measures for our binary outcome were expressed as odds ratios (OR) and the corresponding confidence intervals (CI) that were calculated by bootstrap techniques. All analyses were implemented in R software version 3.4.0 (35) and the *medflex* library version 0.6–1 (36).

Sensitivity analyses.

We tested weight loss of $\geq 20\%$ vs. $<20\%$ in our primary analyses. We additionally carried out sensitivity analyses using a threshold of $\geq 10\%$ vs. $<10\%$ for weight loss and another analysis in which we limited the analyses to those with BML or synovitis at baseline as well as a sensitivity analysis where we compared mediating effects in bariatric surgery patients vs. those in medical weight management group regardless of percent weight loss.

RESULTS

Baseline data.

Baseline characteristics of the study participants are presented in Table 1, and consisted of 75 participants, 63% (47/75) from the bariatric surgery group and the remaining 37% (28/75) in the medical weight management group. Nearly half of the study participants (40/75; 53%) lost $\geq 20\%$ bodyweight by the 1-year follow-up visit, where 97.5% (39/40) of those were from the bariatric surgery group.

On baseline MRI assessment, 64% (48/75) and 56% (42/75) of the participants had BML and synovitis, respectively (Table 1) based on MOAKS scores of 1 or greater. Among patients who eventually experienced $\geq 20\%$ weight loss over the follow-up, 60.0% (24/40) had baseline BML as well as baseline synovitis, compared with 68.6% (24/35) and 51.4% (18/35) who had baseline BML and synovitis, respectively, among patients who did not achieve $\geq 20\%$ weight loss by the 1-year follow-up.

At baseline, neither patella PPT (mean difference = -84.2 , 95% confidence interval [CI]: -2.9 , 171.2) nor wrist PPT (mean difference = 5.4 , 95% CI: -75.4 , 64.6) were significantly different among participants who lost $\geq 20\%$ weight by the follow-up, compared with those with $<20\%$ weight loss (Table 1, Figure 3). At baseline, mean CES-D was lower (mean

difference = -4.9 , 95% CI: 0.0, 9.8) in those with 20% weight loss by 1-year, compared to those without (Table 1, Figure 3).

Change in Mediators: BML, synovitis, sensitization, and depressive symptoms.

Change in the worst score from baseline to follow-up for an individual patient for BML (coefficient for mean difference [coef.] = 0.1; 95% CI: -0.2 , 0.4) and synovitis (coef. = 0.1, 95% CI: -0.3 , 0.2), scores were not significantly different between the group of patients with 20% weight loss, compared with those who lost <20% weight (Figure 2). Similarly, when the sum of MRI scores was considered for each feature, changes in BML (coef. = 0.2, 95% CI: -0.7 , 1.2) and synovitis (coef. = 0.1, 95% CI: -0.5 , 0.2) were not significantly different among patients with 20% weight loss than those without (Figure 2).

The mean PPT increased significantly from baseline to follow-up for both the patella (coef. = 68.4, 95% CI: 10.8, 125.9) and the wrist (coef. = 88.5, 95% CI: 38.1, 138.0) for all subjects, suggesting less sensitization across visits. However, the change in mean PPT for patella (coef. = -11.3 , 95% CI: -84.6 , 62.6) and wrist (coef. = 18.0, 95% CI: -48.0 , 87.6) did not differ significantly between those with and without 20% weight loss (Figure 3). Mean CES-D score decreased from baseline to follow-up for all subjects (coef. = -0.8 , 95% CI: -3.1 , 1.67), and was significantly lower (coef. = -6.2 , 95% CI: -11.0 , -1.4) in those who lost 20% weight than those who did not (Figure 3).

Pain Improvement.

Among participants who lost 20% bodyweight, 75% (30/40) experienced the MCID improvement in WOMAC pain, compared with 35% (12/35) of those who experienced <20% weight loss.

Mediated effects.

Estimates for the natural indirect (i.e., mediating) effect suggested that the effect of weight loss on pain improvement was not mediated by BML score (for worst BML, odds ratio [OR] = 1.01; 95% CI: 0.78, 1.28) or synovitis (OR = 1.03; 95% CI: 0.73, 1.45). Results were similar for the sum of BML or synovitis score (Table 2). However, there was a 62% and 15% increased odds of attaining the MCID in pain improvement by changes in patella PPT (OR = 1.62-fold, 95% CI: 0.89-, 2.75-fold change) and wrist PPT (OR = 1.15-fold, 95% CI: 0.77-, 1.77-fold change), respectively, in participants who lost 20% body weight compared with those who did not (Table 2). Further, the estimate of the natural indirect effect for CES-D score suggested 22% increased odds (OR = 1.22-fold, 95% CI: 0.77-, 1.87-fold) of pain improvement in those with 20% weight loss than those without.

Unmediated effects.

Estimates for the natural direct effect, not mediated through changes in the worst scores for BML and synovitis, suggested 5.39-fold (95% CI: 1.43-, 16.99-fold) and 5.07-fold (95% CI: 1.38-, 15.33- fold) increase in the odds of pain improvement for patients with 20% weight loss compared with those without such weight loss, respectively (Table 2). Natural direct effect estimates not mediated through patella PPT and wrist PPT also suggested 2.47-fold (95% CI: 0.73-, 7.71-fold) and 3.82-fold (95% CI: 1.10-, 11.30-fold) increase in the odds of

pain improvement for subjects who lost 20% bodyweight compared with those who did not, respectively (Table 2). The estimate for the natural direct effect not mediated through changes in CES-D score suggested a 4.08-fold (95% CI: 1.08-, 13.17-fold) higher odds of pain improvement in those with 20% weight loss than for those without (Table 2).

Mediated interaction.

Estimates for the mediated interaction between weight loss and worst BML or synovitis scores suggested no evidence of effect modification between the effect of weight loss and BML (mediated interaction OR = 0.95-fold; 95% CI: 0.32-, 3.75-fold) or synovitis (mediated interaction OR = 0.88-fold, 95% CI: 0.50-, 1.40-fold) on pain improvement. Similar results were seen for the sum of BML or synovitis scores. Mediated interaction effect measures for patella PPT (mediated interaction OR = 0.81-fold, 95% CI: 0.44-, 1.35-fold), wrist PPT (mediated interaction OR = 0.89-fold, 95% CI: 0.51-, 1.86-fold), and CES-D score (mediated interaction OR = 1.05-fold, 95% CI: 0.59-, 1.95-fold) also suggested no effect modification between the effect of weight loss and patella or wrist PPT and CES-D score on pain improvement.

Sensitivity analyses.

The effect sizes for the natural effects were similar in sensitivity analyses when the analysis was restricted to those with BML and synovitis at baseline, or when a weight loss of 10%, rather than 20%, was considered. They were also similar when persons who had bariatric surgery were compared with those who underwent medical weight management regardless of weight loss percentage at follow-up visit, although all, except one of the patients who lost 20% bodyweight by the 1-year follow-up were in the bariatric surgery group (Supplementary Table 1).

DISCUSSION

We found that the clinically meaningful improvement in knee pain that occurred in morbidly obese patients following 20% weight loss over a one-year follow-up period was not explained by changes in BML and synovitis. However, changes in pain sensitization assessed as patella and wrist PPT, and depressive symptoms quantified by CES-D partially explained the effects of weight loss on pain reduction. No effect modification was found between these mediated effects and weight loss levels on knee pain improvement.

As expected, persons with knee pain undergoing bariatric surgery experienced a marked reduction in pain. To our knowledge, there have been no studies examining factors potentially mediating the effect of weight loss on pain. The inclusion of persons undergoing substantial weight loss and knee pain reduction offered us a unique opportunity to explore potential mechanisms of pain reduction. While our goal was to report the effect sizes for natural direct and indirect effects, the uncertainty around our reported effect sizes, expressed by bootstrap confidence intervals, slightly overlapped the null, partially attributable to the study sample size (37,38). Our inference focused on effect sizes more than the results of hypothesis testing and corresponding p-values. While we hoped that we could achieve a narrower confidence interval around our calculated estimates, power analysis for the main

study outcome (i.e., pain improvement) assumed satisfactory sample size. However, power analysis for a mediation analysis is more complex and much less developed in statistical literature, and no statistical development exists for imputation-based (and non-parametric) natural-effects model to the best of our knowledge. However, the width of confidence bounds that we calculated by bootstrap resampling (for increased accuracy) appear reasonable. As we noted earlier in the interpretation of natural direct and indirect effects and assessing mediating roles, the status of BML or synovitis have to stay at a level that naturally occurs for a given level of weight loss. This means that the natural levels of BML and synovitis scores could be the same across exposure levels (i.e., 20% and <20% weight loss levels), regardless of the significance of their mediating role.

Beyond our initial study aims, we also tested a mediation hypothesis to examine how much pain improvement could be due to bariatric surgery potentially mediated by weight loss. The results of this new mediation hypothesis suggested that compared to persons undergoing medical weight management, the direct (unmediated) effect of bariatric surgery on pain improvement was 39% greater, (odds ratio for natural direct effect = 1.39; 95% CI: 0.14, 12.13). Further, there was a 2.75-fold increase in the odds of pain improvement by bariatric surgery that was mediated by weight loss (odds ratio for natural indirect effect = 2.75; 95% CI: 0.42, 16.98). These effect sizes suggest that bariatric surgery effect on pain improvement are mostly mediated by weight loss; however, the sample size for this secondary mediation hypothesis was small.

In an earlier work, we assessed cartilage both semi-quantitatively and quantitatively in this study sample (22) and reported no effect of weight loss on this measure over a year, although morphologic change in cartilage would be unusual in this time frame. BMLs and synovitis have both been shown to change within a few weeks (2,5,39). Our longitudinal MRI assessments revealed statistically insignificant changes in BML and synovitis scores within one year despite massive weight loss. Similarly, Gudbergsen, *et al.* (14) reported lack of improvement in BML in response to rapidly decreasing bodyweight following a weight loss intervention, and also concluded that there was a lack of association between changes in BML and clinical symptoms including pain; however, no formal assessment of a potential mediating role (i.e., an estimate for indirect effect) was presented (14). Further, results of the CAROT trial on the influence of weight loss therapy on cartilage in obese knee OA subjects have similarly suggested insignificant changes in synovitis at 1-year follow-up after the intervention, but reported increased BML only in those who lost weight by exercise compared with those who experienced weight loss by diet or a no-attention group (40). Moreover, in the Intensive Diet and Exercise for Arthritis (IDEA) trial in which 10% weight loss by the 18-month follow-up through diet and exercise, solely by diet, and solely through exercise were studied, no significant changes in structural features such as BML and synovitis were found, despite improvement in knee pain (41).

While previous studies have both supported (2,4–8,10) and not supported (11–14) the association between BML and synovitis with pain in OA, few studies have explored the underlying causal mechanisms by which these structural features could be related to pain. Exceptions were studies (15,42) that attributed chronic pain in OA to changes in central sensitization during OA development and progression. A strength of our study was the

assessment of these mediating effects in a population losing a lot of weight (i.e., 20%) in contrast to previous studies that assessed lesser degrees of weight loss (14,40,41). Another strength was the use of modern approaches to causal mediation that allow assessment of intermediate variables on a causal pathway to quantify knee pain reduction mediated by these factors as part of the effect of weight loss.

There are some limitations to our study as well. Our study participants were almost entirely women despite our efforts to recruit men. Our sample size was relatively small, resulting in limited precision manifested by relatively wide confidence intervals. While MRI is an ideal instrument for quantifying the changes in structural features of OA compared with plain radiography, the semi-quantitative nature of MOAKS scoring method does not allow a volumetric measurement for quantifying the size of these structural features. Future studies should assess other potential causal pathways through which substantial weight loss could exert its effect on knee pain improvement, such as changes in biomechanical or inflammatory factors.

In conclusion, pain is a complex phenomenon in knee OA. Our findings suggest that changes in pain sensitization and in depressive symptoms mediate in part the knee pain improvement experienced by those undergoing substantial weight loss, especially following bariatric surgery. This suggests that pain sensitization and depressive symptoms could be a promising target for future intervention studies in those with chronic knee pain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

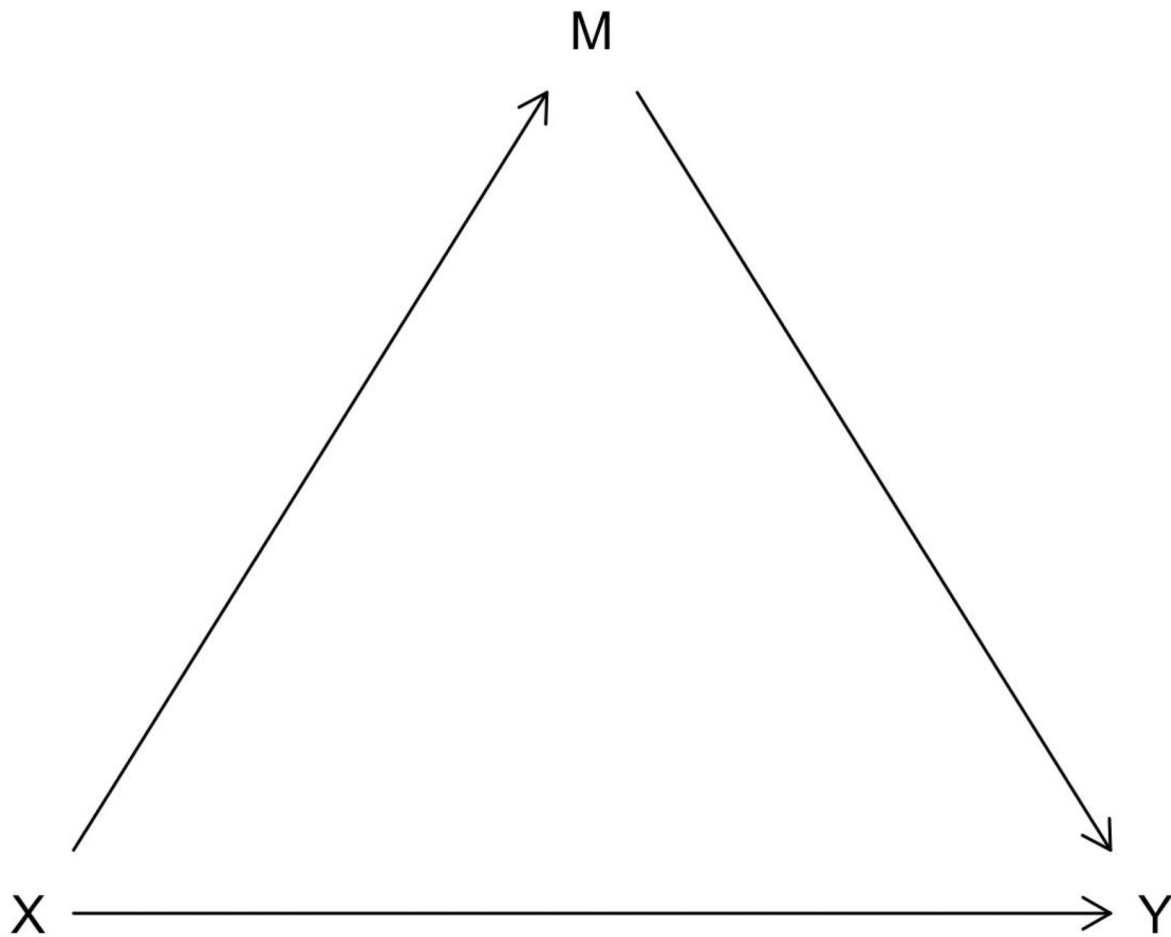
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Exposure (X): $\geq 20\%$ Weight Loss

Mediator (M): Change in BML, Synovitis, PPT, CES-D

Outcome (Y): $\geq 18\%$ Reduction in WOMAC Pain Score

Figure 1.

Directed acyclic graph (DAG) representing the natural indirect effect (that is mediated by changes in bone marrow lesion, synovitis, patella and wrist sensitization, or depressive symptoms; X to Y pathway through M) and the natural direct effect (that is not mediated; X to Y pathway not passing through M) of weight loss on knee pain improvement.

BML, bone marrow lesion; PPT, pressure pain threshold; CES-D, Center for Epidemiologic Studies Depression scale



Figure 2. Longitudinal changes in bone marrow lesion (BML) and synovitis worst scores, measured semi-quantitatively by magnetic resonance imaging, stratified by weight loss at 1-year follow-up.

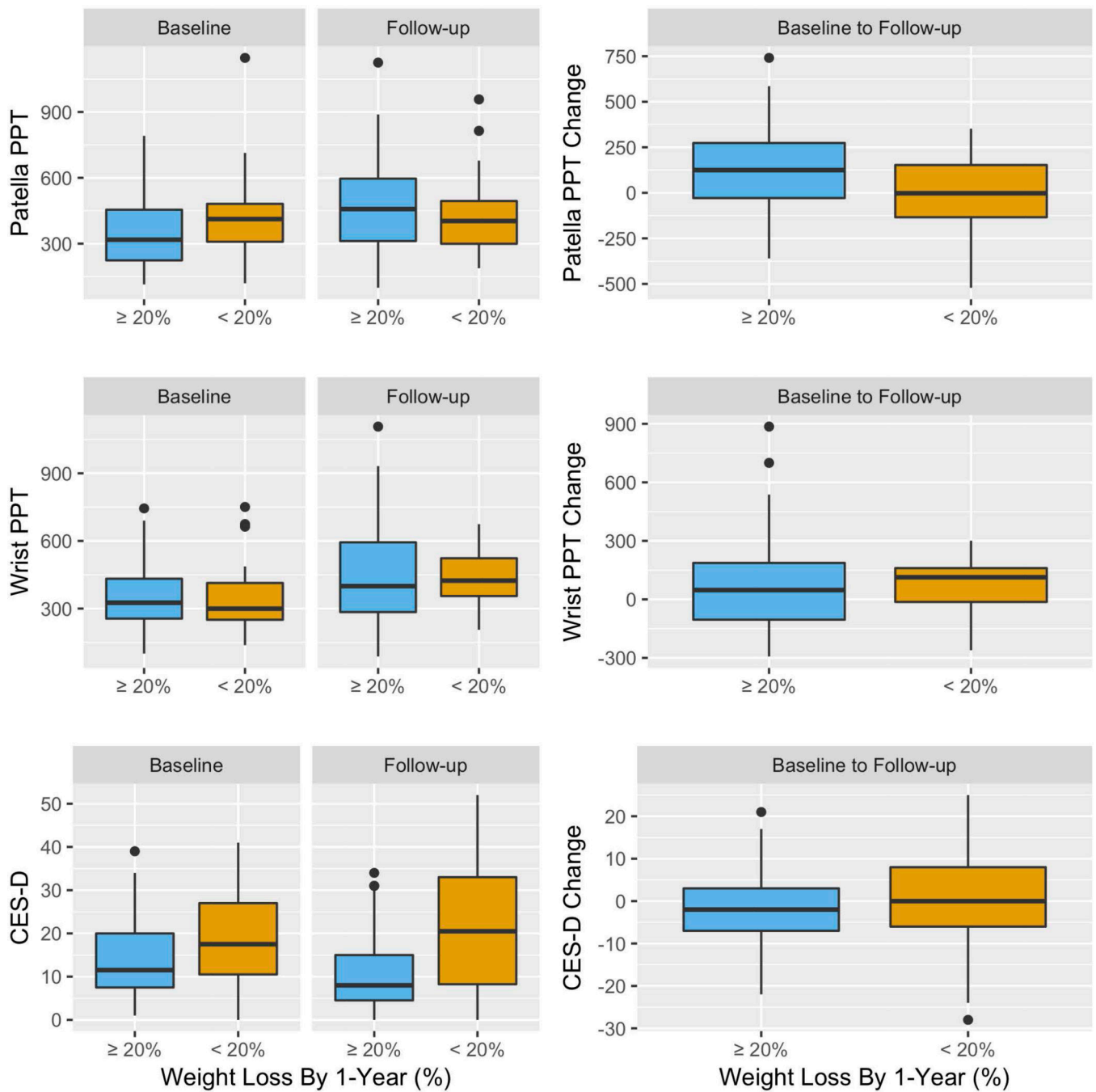


Figure 3.

Boxplots of baseline and follow-up measures of the pressure pain threshold (PPT) for index patella and right wrist, and Center for Epidemiologic Studies Depression (CES-D) scale stratified by weight loss at 1-year.

The middle bold horizontal lines are the median (i.e. 50th percentile). The lower and upper hinges are the first (i.e. 25th percentile) and third (i.e. 75th percentile) quartiles. Dots along the whiskers are beyond the 1.5 times of the interquartile range.

TABLE 1.

Baseline characteristics of the study population stratified by weight-loss at 1-year follow-up visit.

Characteristic at Baseline N = 75	< 20% Weight Loss at 1-Year N = 35	20% Weight Loss at 1-Year N = 40
Age [mean (SD), median]	47.3 (8.3), 49.0	42.5 (9.6), 49.0
Female (%)	30 (85.7)	39 (97.5)
African-American (%)	27 (77.1)	19 (47.5)
Bariatric surgery (%)	8 (22.9)	39 (97.5)
BMI [mean (SD), median]	40.9 (4.5), 40.0	42.3 (4.5), 41.6
College/graduate education	15 (42.9)	14 (35.0)
Employment (%)	9 (25.7)	9 (22.5)
KL grade (%)		
0	6 (17.1)	8 (20.0)
1	11 (31.4)	11 (27.5)
2	8 (22.9)	14 (35.0)
3	9 (25.7)	7 (17.5)
4	1 (0.0)	0 (0.0)
WOMAC pain (0–24 scale) [mean (SD), median]	12.5 (4.9), 13.0	11.8 (4.2), 12.0
BML worst score > 0 (%)	24 (68.6)	24 (60.0)
Synovitis worst score > 0 (%)	18 (51.4)	24 (60.0)
Patella PPT [mean (SD), median]	429.6 (198.1), 412.2	345.4 (158.0), 318.1
Wrist PPT [mean (SD), median]	346.4 (150.0), 299.5	351.7 (144.9), 326.0
CES-D scale	19.3 (11.6), 17.5	14.4 (9.2); 11.5

Continuous variables are summarized by mean (standard deviation) and median. Categorical variables are summarized by frequency and percentages.

BMI, body mass index; BML, bone marrow lesion; KL, Kellgren-Lawrence; PPT, pressure pain threshold; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

TABLE 2.

Estimates of the natural indirect and direct effects of massive (20%) weight loss on knee pain improvement.

Feature	Odds Ratio (95% Bootstrap CI)	
	Natural Indirect Effect (Mediated)	Natural Direct Effect (Not Mediated)
BML		
Worst score	1.01 (0.78, 1.28)	5.39 (1.43, 16.99)
Sum of scores	1.01 (0.72, 1.30)	4.70 (1.35, 15.22)
Synovitis		
Worst score	1.03 (0.73, 1.45)	5.07 (1.38, 15.33)
Sum of scores	0.98 (0.73, 1.33)	4.87 (1.44, 13.82)
PPT		
Patella	1.62 (0.89, 2.75)	2.47 (0.73, 7.71)
Wrist	1.15 (0.77, 1.77)	3.82 (1.10, 11.30)
CES-D	1.22 (0.77, 1.87)	4.08 (1.08, 13.17)

BML, bone marrow lesion; CI, confidence interval; PPT, pressure pain threshold; CES-D, Center for Epidemiologic Studies Depression scale