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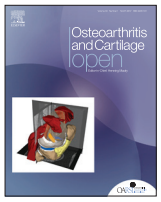

Effects of psychological distress on the general health to self-reported pain and function outcome relationship in knee arthroplasty: A causal mediation study

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ABSTRACT

Objectives: We examined two potential causal pathways that could be intervention targets to enhance knee arthroplasty outcomes. Data from a no-effect trial of persons with moderate to high pain catastrophizing were used to determined whether pain catastrophizing, depressive symptoms causally mediate the effect of preoperative general health on postoperative knee pain and functional difficulty.

Methods: We used natural-effects models to conduct causal mediation analyses using the preoperative dichotomized EQ-5D-5L general health measure as the exposure, 2-month postoperative pain catastrophizing, depressive symptoms, and localized knee pain as potential mediators, and 12-month dichotomized Western Ontario and McMaster's University Osteoarthritis Index (WOMAC) Pain and Function scores reflecting good versus poor outcome as the outcomes.

Results: Estimates of the indirect (mediating) effect suggested that pain catastrophizing mediated the effect of preoperative general health on 12-month WOMAC pain score by increasing odds of a good outcome by 8% (natural indirect effect odds ratio = 1.08, 95% CI: 0.88, 1.29). The direction of mediating effects and their magnitude were similar for depressive symptoms; Sensitivity analyses suggested similar magnitudes and mediating effects to those reported for the main analyses.

Conclusions: Our findings suggested that pain catastrophizing and depressive symptoms have a mediating role on the effect of baseline general health on self-reported pain and function outcomes. These findings support the continued treatment of pain catastrophizing and depressive symptoms as viable targets for interventions to potentially enhance pain and function outcomes for patients with moderate to high levels of psychological distress prior to surgery.

Pain catastrophizing and depressive symptoms have been reported in multiple systematic reviews to be prognostic indicators of poor outcome for patients undergoing knee arthroplasty (KA) [1–3]. A recent focus of several recently published clinical trials has been on the identification and treatment of persons undergoing KA who are at risk for poor outcome [4–6]. The trials showed no effects for the interventions of interest as compared to usual care [4–6]. One potential explanation for these no-effect trial findings may be that the prognostic indicators used to identify persons at risk may not have been causally related to the outcomes. Interventions are more likely to positively impact outcome if the intervention targets (i.e., the prognostic indicators) also are causally linked to or are on potential causal pathways to the outcome [7,8].

We undertook the current study to determine if two commonly-assessed prognostic indicators of poor outcome risk, pain catastrophizing and depressive symptoms also could have mediating roles with patient-relevant outcomes. Causal mediation methods have been developed to explain the mechanisms by which an exposure (or an intervention) exerts its effect on an outcome [9,10] and have recently been applied to persons with KA [11]. Causal mediation analyses are designed to identify and examine intermediate variables along a potential causal pathway from an exposure to an outcome. These approaches use the causal inference framework to quantify the extent that an exposure effect on an outcome of interest [9] could be mediated by candidate mediators. This is accomplished by decomposing a total effect of an exposure of

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interest (e.g., a person's general health before KA) on an outcome (e.g., a 12-month patient-reported outcome score) into an indirect (or mediated) effect, that is, those that are mediated by potential mediators (e.g., depressive symptom severity 2 months post-surgery) and the remaining direct (i.e., unmediated) effect not mediated by those specific mediators. Temporality is important in that the mediator is measured after the exposure but before the outcome to mitigate a reverse-causation bias. Fig. 1 presents a directed acyclic graph (DAG) for our causal mediation model.

No-effect trials of cognitive behavioral-based interventions for KA recovery [6,12] leave open questions of whether the lack of effect was due to an ineffective intervention or whether the target of the intervention (e.g., pain catastrophizing) was a causal risk factor for poor outcome. We posed three questions to attempt to disentangle this dilemma. First, to what extent do 2-month postoperative pain catastrophizing, depressive symptoms or localized knee pain causally mediate the effects of preoperative general health on 12-month knee pain with activity and functional difficulty? We hypothesized that all three mediators would causally mediate the relationship between preoperative general health and 12-month good or poor postoperative pain and function outcome. Second, do pain catastrophizing and depressive symptom mediators approximate the magnitude of mediation effect found for localized knee pain? We hypothesized, based on prior prognostic evidence, that 2-month postoperative pain catastrophizing and depressive symptom severity would approximate the mediating effects of 2-month postoperative localized knee pain severity, which is generally considered a primary target of KA surgery [13,14]. Third, are mediation findings consistent in sensitivity analyses focusing on continuously measured pain and function outcomes 6- and 12-months post-surgery?

1. Methods and participants

Our study was a retrospective analysis of prospectively collected randomized clinical trial data from a no-effect multicenter clinical trial [6].

1.1. Conceptual framework

Causal mediation analysis has largely been developed to focus on a single mediator under a hypothesized Directed Acyclic Graph (DAG) representing a specific causal pathway [15]. The DAG that informed our study design is presented in Fig. 1. The exposure of interest is the patient's general health. General health reflects the patient's overall health status prior to surgery and is conceptualized as being along a continuum from good to poor. A substantial evidence supports the association between preoperative general health and postoperative outcome in arthroplasty [16–18]. The outcome reflects patient-reported pain and function following surgical recovery. Improved pain and function are patients' most important reasons for undergoing KA [19,20]. A variety of factors potentially influencing this exposure to outcome association needs to be controlled for in the analyses. We selected a variety of potential confounders known to associate with the exposure, outcomes or mediators [21–24].

1.2. Participants

Our study was a secondary analysis of a Phase III multicenter randomized clinical trial (the KASTPain Study) of a pain coping skills intervention conducted in five university-based locations on persons with moderate to high pain catastrophizing. The full trial results [6] and protocol [25] have been published elsewhere and the trial was registered with ClinicalTrials.gov (NCT01620983). Briefly, participants were randomly assigned to one of three rehabilitation-based interventions (i.e., pain coping skills, arthritis education, and usual care) following KA for persons with moderate to high levels of pain catastrophizing [26] a psychological distress construct related to pain coping difficulty. The trial found no differences in primary and secondary outcomes and as a result, participants were combined to form an observational study design to address the hypotheses.

All participants provided written informed consent approved by Virginia Commonwealth University IRB and the study was carried out in accordance with relevant regulations of the US Health Insurance Portability and Accountability Act (HIPAA). Data collectors, trained in study methods and blinded to treatment group, obtained all follow-up data at 2-, 6-, and 12 months following KA. The focus of the current study was on data obtained prior to surgery and on 2-, 6- and 12-month follow-up from the entire sample.

1.3. Measurement of the exposure of interest

The exposure was defined as a preoperative measurement of the 5-level EQ-5D version (EQ-5D-5L) health related quality of life measure [27]. We chose this as the exposure of interest because this measure reflects the overall health of persons prior to KA and includes pain, mobility, physical activity and mental health concepts into a single score making it ideal for causal mediation versus multiple measures of this complex construct. This instrument has been used worldwide in various formats for two decades [28] and has been validated for US-based application [29]. Values range from −0.57 to 1.00, with 1 equating to perfect health and −0.57 equating to being unable to self-care, walk or do usual activities and having extreme pain and depression/anxiety [29]. Associations between preoperative EQ-5D-5L scores and Knee injury and

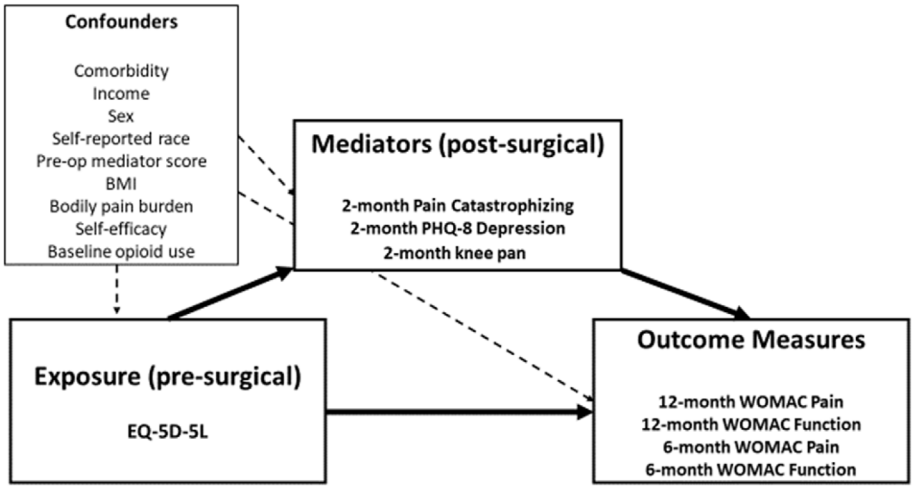

Fig. 1. Directed acyclic graph representing the natural indirect effect, mediated by 2-month postoperative pain catastrophizing, depressive symptoms and localized knee pain severity; and the natural direct non-mediated effect of general health on 12-month WOMAC Pain or Function (pathway not passing through the mediators). Potential confounders and their association with exposure, mediators and outcomes are included. A directed acyclic graph denotes hypothesized causal associations via solid directional arrows. The arrow from the exposure to the outcomes denotes a direct causal path and the arrow from the exposure to the mediator and a subsequent arrow from the mediator to the outcome indicates an indirect causal path in the figure. These solid arrows form a causal loop from exposure to outcome and from exposure to mediators to outcome.

Osteoarthritis Outcome Score (KOOS) knee scores (which were derived from WOMAC Pain and Function measures) [30] are robust, ranging from 0.58 to 0.68 [31] and preoperative KOOS scores are among the most powerful predictors of follow-up KOOS scores [30].

For all analyses, we dichotomized the EQ-5D-5L using its median value (median EQ-5D-5L score = 0.584). We were interested in assessing effects for persons with good health (scores ≥0.584) versus those with poor health (scores <0.584). Persons with poor health had a mean EQ-5D-5L score of 0.277 (sd = 0.292) while persons in good health had mean score of 0.720 (sd = 0.088). While dichotomization leads to some loss of information, it allows for the expression of effect sizes for mediating roles on an odds ratios scale with a more straightforward interpretation relative to beta coefficients from continuous data.

1.4. Measurement of the mediators of interest

We focused on three potential mediators, which were measured at a postoperative period of 2 months after KA to guarantee the improbability of reverse causation. At 2 months post-surgery, patients have generally recovered from the acute effects of surgery and still are likely to experience substantial pain-related and functional improvement [32]. This is a sound practice in mediation studies to ensure the temporal sequence of exposure measurements preceding mediators, and both preceding outcome measurements. The first two candidate mediators, pain catastrophizing and depressive symptoms are among the most commonly endorsed for identifying persons at-risk for poor outcome [1–3]. Our third candidate mediator was selected because localized knee pain severity is the most common target impairment for KA and the most frequently reported reason that patients seek the surgery [14,20].

We used the Pain Catastrophizing Scale, a 13-item validated scale with scores ranging from 0 (no pain catastrophizing to 52 (highest pain catastrophizing) [26,33]. The extent of depressive symptoms was quantified using the previously validated PHQ-8, which contains eight items with total scores ranging from 0 (no depressive symptoms) to 24 very severe depressive symptoms [34]. The composite pain rating applied to the surgical knee was used to quantify surgical knee pain severity. The scale consists of 4 items that ask the participant to rate the current knee pain and then average surgical knee pain, best and worst surgical knee pain over the past two weeks. The four items are averaged for the final score. Pain on each item is rated on a 0 to 10 scale with 0 equating to no surgical knee pain and 10 equating to the most intense pain imaginable. The composite knee pain scale has been shown to maximize reliability over individual item pain ratings [35].

1.5. Measurement of the outcomes of interest

The WOMAC Pain and WOMAC Function scales, obtained at 6- and 12-months were used to reflect the outcome of KA. For the main analyses, we dichotomized baseline to 12-month WOMAC scores based on a prior paper using KASTPain data that used latent class analysis methods and data collected over the entire 12-month period (preoperative, 2-, 6-, and 12-month postoperative) to confirm the presence of two subgroups - a good and a poor outcome subgroup [36]. These two latent classes clearly distinguished patients with good versus poor outcome. Approximately 17% were classified as having a poor WOMAC Pain or Function outcome and there was clear separation among good and poor outcome subgroups. For example, participants in the poor WOMAC Pain outcome group had an average score of 10.08 (sd = 2.17) while the good outcome group scored a 1.70 (sd = 1.86) at the 12-month post-surgical time point. For the current study, we used these dichotomized latent classes of good (coded as 1) versus poor (coded as 0) outcomes based on trajectory membership for our main analyses. In our latent class analysis study [36], participants demonstrated on average, 93% or higher probability of belonging to either the good or poor outcome subgroup. The dichotomized latent class approach from a prior paper does not rely on arbitrary cutpoints and is a more psychometrically rigorous method for subgrouping patients as compared to MCID or similar methods [36]. We have recently externally validated this approach using an all comers KA sample of 926 patients from England [37].

In sensitivity analyses, we kept the original continuous scale data for outcomes measured at both 6- and 12-months. The WOMAC Pain scale ranges from 0 to 20 with a score of 0 equating to no pain with the five activity items and 20 equating to extreme pain with all activities. The WOMAC Function scale contains 17 items with a score of 0 equating to no difficulty with all items and 68 equating to extreme difficulty with all items. The WOMAC scale has been repeatedly demonstrated to have strong measurement properties [38].

1.6. Measurement of potential confounders

We included nine potential confounders for each analysis. These were comorbidity, income, self-reported race, sex, extent of bodily pain, self-efficacy, baseline opioid use, body mass index and preoperative scores for each of the three potential mediators. These variables were chosen because of their likely association with the exposure, mediators or outcomes [22–24,39]. Comorbidity was measured with a validated Modified Charlson comorbidity questionnaire [40] with scores ranging from 0 to 45 with higher scores equating to greater comorbidity and greater self-reported impact on health. Annual income was measured using the following ordinal scale: Less than $10, 000, $10,000 to <$25,000, $25, 000 to <$50,000, $50,000 to <$100,000, $100,000 or greater, refused. Race was dichotomized as self-reporting either black/African American or other. Sex was coded as male or female. Chronic (i.e. > three months) bodily pain burden was measured using a scale that identified all bodily pain areas [41]. The scale ranges from 0 to 16 indicating pain in 16 body regions. Self-efficacy was measured with a previously validated arthritis self-efficacy scale [42], ranging from 8 indicating the participant is very uncertain about their self-efficacy for all 8 items to 80 indicating the participant is very certain about their self-efficacy for all items. Baseline opioid use was assessed by asking participants to bring medications with them to the initial preoperative visit. Body mass index was recorded from presurgical medical record data.

1.7. Statistical analysis

We used causal inference-based methods to perform mediation analyses. These included fitting natural-effects models, which are used to derive direct and indirect effects with regard to candidate mediators. To estimate the parameters of the natural-effects models, we used the imputation-based method developed by Vansteelandt et al. [43] which does not rely on specifying a model for the distribution of the mediators. Compared to an alternative approach of weighting that relies on the correct specification of a model for the mediator to calculate weights, the imputation-based approach provides robustness with regard to not relying on specifying a model for the mediator or providing numerical stability that may be of concern for a mediator that is measured on a continuous scale [44]. Effect measures and corresponding confidence intervals that were derived through bootstrapping technique were expressed per unit change in exposure (e.g., a unit increase in preoperative general health score) on outcomes (e.g., WOMAC score at 6- or 12-month). All analyses were conducted using the "medflex" library [44] with the software package R: A language and environment for statistical computing.

2. Results

Of the 402 participants who consented, 384 underwent KA and of these, 12-month follow-up data were collected on 346. The mean age of the surgical sample was 63.2 (sd = 8) years and the average body mass index was 32.3 (sd = 6.2) kg/m2. Sample characteristics are summarized on Table 1.

Table 1
Preoperative sample characteristics (n = 384).

Variable	Value
Potential Confounders	
Modified Charlson comorbidity [a]	8.64 ± 4.08
Current Income, N (%)	
< $10,000	9% (35)
$10,000 to $24,999	20% (78)
$25,000 to $49,999	23% (88)
$50,000 to $99,999	24% (93)
$100,000 or >	14% (53)
Declined	10% (37)
Black/African American race	35.2% (135)
Female	67% (257)
Chronic bodily pain score[b]	11.04 ± 9.18
Arthritis Self-efficacy Scale, mean (SD)[c]	49.31 ± 17.74
Opioid use at baseline, N, (%)	31% (120)
Exposure	
EQ-5D-5L	0.50 ± .28
Mediators	
Patient Health Questionnaire[d]	8.40 ± 5.05
Pain Catastrophizing Scale[e]	29.95 ± 9.27
Composite knee pain scale	6.10 ± 1.88
Outcomes	
WOMAC Pain Scale[f]	11.40 ± 3.36
WOMAC Function Scale[g]	37.07 ± 11.49

Continuous variables are presented as mean ± SD; discrete variables are presented as the percentage (number); Abbreviations: WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

[a] Modified Charlson Comorbidity score range is 0–45. Higher scores equate to greater comorbidity burden.

[b] Chronic bodily pain scores range from 0 to 64 with higher scores equating to greater number of very severe bodily pain sites.

[c] Arthritis Self Efficacy Scale score range is 0–80. Higher scores equate to more self-efficacy.

[d] PHQ-8 score range is 0–24. Higher scores equate to more depressive symptoms.

[e] Pain Catastrophizing Scale range is 0–52. Higher scores equate to more pain catastrophizing.

[f] WOMAC Pain Scale score range is 0–20. Higher scores equate to more function limiting pain.

[g] WOMAC Function scale range is 0–68. Higher scores equate to more difficulty with functional activities.

2.1. Causal mediation analyses for pain catastrophizing, depressive symptoms and knee pain

Table 2 summarizes estimates for natural indirect (i.e., mediated), natural direct (i.e., unmediated), and total effects of preoperative general health on knee pain and function outcomes. Effect sizes for the natural indirect effects suggested mediating roles for pain catastrophizing, depression symptoms, and knee pain scale on the effect of preoperative general health on good versus poor knee pain outcome at 12-months. The bootstrap confidence intervals for these effect measures slightly overlapped with null; however, estimated effect sizes suggested that an improvement in preoperative general health (i.e., poor health to good health) improved the likelihood of a good 12-month WOMAC Pain outcome that was mediated by aforementioned factors. Specifically, the odds of a good WOMAC Pain outcome increased by 8%, and 12%, in those with preoperative good health, compared to those with poor health, that was mediated by pain catastrophizing (natural indirect effect odds ratio = 1.08, 95% CI = 0.88, 1.29), and depressive symptoms (natural indirect effect odds ratio = 1.12, 95% CI = 0.91, 1.37) respectively. Estimates of natural direct effects, not mediated by the considered mediators, also contributed to the odds of an improved WOMAC Pain 12-month outcome. Estimates for the total effects indicated that the odds of a good WOMAC Pain outcome increased by approximately 50%, on average, when considering both direct and indirect effects.

With regard to WOMAC Function, the magnitude and direction of mediation effects were similar to those found for WOMAC Pain. The odds of a good WOMAC Function outcome increased by 10%, and 13% that was mediated by pain catastrophizing (natural indirect effect odds ratio = 1.10, 95% CI = 0.87, 1.36), and depressive symptoms (natural indirect effect odds ratio = 1.13, 95% CI = 0.89, 1.41), respectively. Estimates for direct and total effects for WOMAC Function models were as almost double those reported for WOMAC Pain models.

2.2. Effect size comparisons of pain catastrophizing and depressive symptoms with knee pain

For the effects of general health on WOMAC Pain outcome, the magnitude of the mediating effects of pain catastrophizing and depressive symptoms were approximately a third as large as mediating effects attributable to localized knee pain at two months. Similar relationships across mediators were found for the general health effect on WOMAC Function outcomes (Table 2).

2.3. Sensitivity analyses using 6- and 12-month continuously scaled WOMAC scores

In sensitivity analyses, we examined mediation models using continuous scaled WOMAC outcomes obtained at both 6- and 12-months post-surgery. Sensitivity analyses were considered to indicate stable findings to the extent that the directions of direct, indirect and total effects were consistent with the main analyses. While the beta coefficients in the sensitivity analyses cannot be directly compared to the odds ratios in the main analyses, we found the direction of effects were consistent with those found for the main analyses. For example, point estimates consistently indicated that good as compared to poor health on the EQ-5D-5L was associated with lower (i.e., improved) 6- and 12-month WOMAC Pain and Function scores and that pain catastrophizing, depressive symptoms and localized knee pain mediated effects of general health on 6-and 12-month WOMAC Pain and Function (Table 2). Estimates were typically not statistically significant, much like those for the primary analysis.

3. Discussion

Our finding of a causal mediating role for pain catastrophizing and depressive symptoms extend findings of earlier studies endorsing the prognostic role of these psychological distress constructs [3]. The key difference is that our findings suggested a causal role in determining outcome and not strictly a prognostic role. A variable can be prognostic of an outcome but not a causal determinant of the outcome [45]. Despite findings in no-effect trials designed to reduce pain catastrophizing [6,12], our data suggest that pain catastrophizing and depressive symptoms are important causal mediators of effects on outcome. In our view, it is likely that these trials were unsuccessful at hitting the target – that is, reducing pain catastrophizing relative to the control groups. The challenge is to find effective treatments for pain catastrophizing and depressive symptoms that can be incorporated into routine practice. We were unsuccessful in testing a pain coping skills intervention for patients in our parent trial study [6]. An integrated approach combining both pain coping skills and physical therapy may be more effective. In KASTPain, pain coping training and physical therapy were delivered independently of one another. Depressive symptoms also may be more amenable to treatment than pain catastrophizing for patients with KA [46].

Preoperative general health, a relatively novel measure in the KA literature, was measured with the EQ-5D-5L, and was dichotomized using the median score. This scale is used worldwide to reflect the construct of overall general health but clinicians are likely unfamiliar with the scale. Persons scoring below the median in our sample had a mean score of 0.277 (sd = 0.292). Persons using a single item rating for general health to rate general health as “poor” scored 0.338 (0.380) on the EQ-5D-5L [47]. Persons above the median in our sample had a mean score of 0.720 (sd = 0.088) and this score is associated with a single item

Table 2
Estimates of the natural direct (unmediated), natural indirect (mediated), and total effect of general health score on knee pain and function at 6- and 12-month postoperative periods.[a]

	Exposure	Mediator	Outcome	Direct (95% CI)	Indirect (95% CI)	Total (95% CI)
Main Analyses				Odds Ratio	Odds Ratio	Odds ratio
	EQ-5D-5L[b]	2mo PCS	12mo WOM Pain[c]	1.20 (0.48, 2.75)	1.08 (0.88, 1.29)	1.29 (0.51, 3.00)
	EQ-5D-5L	2mo PHQ-8	12mo WOM Pain	1.52 (0.62, 3.33)	1.12 (0.91, 1.37)	1.70 (0.69, 3.72)
	EQ-5D-5L	2mo knee pain	12mo WOM Pain	1.05 (0.47, 2.18)	1.35 0.89, 2.05	1.41 (0.57, 3.23)
	EQ-5D-5L	2mo PCS	12mo WOM Fun[c]	2.06 (0.80, 4.42)	1.10 (0.87, 1.36)	2.26 (0.85, 4.91)
	EQ-5D-5L	2mo PHQ-8	12mo WOM Fun	2.40 (0.96, 5.04)	1.13 (0.89, 1.41)	2.73 (1.08, 5.62)
	EQ-5D-5L	2mo knee pain	12mo WOM Fun	1.61 (0.70, 3.23)	1.33 (0.88, 1.94)	2.13 (0.85, 4.56)
Sensitivity Analyses (12-month)[d]				Coefficient[e]	Coefficient	Coefficient
	EQ-5D-5L	2mo PCS	12mo WOM Pain	−0.563 (−1.29, 0.21)	−0.136 (−0.33, 0.07)	−0.699 (−1.44, 0.08)
	EQ-5D-5L	2mo PHQ-8	12mo WOM Pain	−0.743 (−1.48, 0.03)	−0.141 (−0.33, 0.05)	−0.884 (−1.63, −0.11)
	EQ-5D-5L	2mo knee pain	12mo WOM Pain	−0.357 (−1.07, 0.38)	−0.217 (−0.55, 0.11)	−0.574 (−1.33, 0.21)
	EQ-5D-5L	2mo PCS	12mo WOM Fun	−1.261 (−3.87, 1.49)	−0.569 (−1.36, 0.24)	−1.830 (−4.45, 0.94)
	EQ-5D-5L	2mo PHQ-8	12mo WOM Fun	−1.966 (−4.54, 0.70)	−0.630 (−1.42, 0.17)	−2.596 (−5.18, 0.10)
	EQ-5D-5L	2mo knee pain	12mo WOM Fun	−0.610 (−3.03, 1.96)	−0.735 (−1.86, 0.40)	−1.345 (−3.96, 1.43)
Sensitivity Analyses (6-month)[d]				Coefficient[e]	Coefficient	Coefficient
	EQ-5D-5L	2mo PCS	6mo WOM Pain	−0.407 (−1.23, 0.45)	−0.155 (−0.37, 0.06)	−0.562 (−1.40, 0.32)
	EQ-5D-5L	2mo PHQ-8	6mo WOM Pain	−0.574 (−1.41, 0.28)	−0.143 (−0.33, 0.05)	−0.716 (−1.55, 0.14)
	EQ-5D-5L	2mo knee pain	6mo WOM Pain	−.0147 (−0.75, 0.76)	−0.275 (−0.69, 0.15)	−0.289 (−1.11, 0.58)
	EQ-5D-5L	2mo PCS	6mo WOM Fun	−2.786 (−5,27, - 0.18)	−0.634 (−1.48, 0.22)	−3.420 (−6.03, −0.69)
	EQ-5D-5L	2mo PHQ-8	6mo WOM Fun	−3.440 (−6.05, −0.74)	−0.649 (−1.44, 0.15)	−4.088 (−6.75, −1.34)
	EQ-5D-5L	2mo knee pain	6mo WOM Fun	−2.179 (−4.52, 0.28)	−0.823 (−2.07, 0.46)	−3.001 (−5.61, −0.24)

Abbreviations: WOM, Western Ontario and McMaster Universities Osteoarthritis Index. 2mo, 2 month. PCS, Pain Catastrophizing Scale. PHQ-8, Patient Health Questionnaire 8. EQ5D5L, 5-level EQ-5D version dichotomized using the median score. Knee pain, Composite knee pain scale.

[a] All analyses adjusted for baseline comorbidity, income, self-reported race, sex, bodily pain burden, self-efficacy, baseline opioid use and baseline score for the mediator of interest.

[b] The EQ-5D-5L was dichotomized using the median score for all analyses. Scores at or below the median (i.e., poorer general health) were coded as 0 and scores above the median (i.e., better general health) were coded as 1.

[c] 12-month WOMAC Pain and WOMAC Function scores in the main analysis were dichotomized based on a prior study that reported a good and a poor outcome latent class trajectory. Scores for the poor outcome latent class were coded as 0 and scores for the good outcome latent class were coded as 1.

[d] In the sensitivity analyses, 12-month and 6-month WOMAC Pain and Function scores were kept on their original continuous scales.

[e] The coefficients for the direct, indirect and total effects in the sensitivity analyses were derived from linear models.

self-rated health score approximating a "good" rating [47]. Ackerman and colleagues recently reported EQ-5D-5L data collected on patients with KA from Australia. Mean preoperative scores obtained from 6619 patients were 0.45 (sd = 0.31) and 6-month postoperative mean scores were 0.76 (sd = 0.20). While formulas for calculating EQ-5D-5L utility scores in Australia are slightly different than for US-based persons, these data provide additional perspective on interpretation of our preoperative EQ-5D-5L dichotomized scores and support our argument that a median split for the EQ-5D-5L provides an exposure variable with meaningful differences in overall health between the two subgroups.

With the important caveat that our findings were statistically non-significant for the most part, these findings have important clinical implications. Successfully intervening to improve a patient's perioperative psychological distress in patients with moderate to high pain catastrophizing or depressive symptoms may shift a patient's likely outcome from poor (e.g., average 12-month WOMAC Pain of 10) to good (i.e., average WOMAC Pain of 2).

In a posteriori analyses, we examined for the presence of multiple mediation by both pain catastrophizing and depressive symptoms [48]. Using the same exposure and outcome as the primary analyses, we found that the indirect (mediating) effect of these combined mediators was odds ratio = 1.15 (95% CI = 0.89, 1.46) for WOMAC Pain and 1.17 (95% CI = 0.89, 1.51) for WOMAC Function. These data suggest that the mediators contributed approximately equally relative to individual mediation analyses and supports our suggestion that both catastrophizing and depressive symptoms play a mediating role in KA recovery.

The implications of pain catastrophizing and depressive symptoms being causally related to pain and function outcome are substantial. Causal mediation analyses provide the most rigorous and state-of-the-art approach from observational study designs to support the incorporation of causal mediators as potential intervention targets for a disorder [49]. In the case of depressive symptoms and pain catastrophizing, our study provides useful information to estimate the magnitude of impact an effective treatment might have on outcome. For example, when considering the general health to 12-month WOMAC Pain good or poor outcome relationship, our study suggests that pain catastrophizing and depressive symptoms mediate effects of general health on the likelihood of a good versus poor outcome. Pain catastrophizing and depressive symptoms each mediate this relationship to the extent that their impact is approximately a third of that attributable to localized knee pain, the primary reason that patients seek out KA. In our view, these data support a targeting of depressive symptoms and pain catastrophizing, particularly for patients judged to be at risk for poor outcome. Our data suggests a similar argument holds for potentially improving functional status outcomes.

3.1. Effect size comparisons of pain catastrophizing and depressive symptoms with knee pain

Localized knee pain is typically a key intervention target for surgery and a key patient motivator for seeking out KA [13,14]. While our effect sizes for pain catastrophizing and depressive symptoms were only a third as large as mediation effects for localized knee pain, we are still of the opinion that mediation effects attributable to pain catastrophizing and depressive symptoms are clinically important. For example, point estimates form our analysis indicate that pain catastrophizing increased odds of a good WOMAC Function outcome by 10% which we believe to be clinically important.

3.2. Sensitivity analyses using 6- and 12-month postoperative WOMAC scales

Our sensitivity analyses supported the consistency of our findings with regard to mediating roles of both pain catastrophizing and depressive symptoms across outcomes measured on a continuous scale and measured at 6- and 12-months postoperatively. Sensitivity analyses are a common component of causal mediation studies and provide a stronger argument for study meaningfulness [49].

3.3. Limitations

While we applied contemporary causal mediation methods, our study was observational in nature and while we adjusted for several confounding variables in the analyses, residual confounding by unmeasured factor(s) may have influenced our findings. Despite consistency on the magnitude of effect sizes and the direction of effects, our study did not have enough precision, partly due to our study sample size, to exclude the null from the confidence intervals for most of the mediated and unmediated effects. We followed the guidance from the American Statistical Association [50] on reporting research findings and the recommendations [51] from methodology experts in highlighting effect sizes rather than a binary interpretation of positive or negative study findings based on an arbitrary cutoff for p-values or whether confidence bounds overlapped with a null value. To this end, effect size is a much more frequently endorsed method for judging the meaningfulness of potential associations in studies like ours. Much has been written about the importance of consideration of effect sizes, particularly with studies of limited sample size combined with effect sizes approximating those in our study [51,52]. Assuming similar effect sizes, future work will require larger samples. Finally, our findings may not generalize to a heterogeneous sample of patients with KA who were not pre-screened for the presence of psychological distress, as they were in our KASTPain trial.

5. Conclusions

Pain catastrophizing and depressive symptoms, two common forms of elevated psychological distress in patients undergoing KA, could causally mediate effects of preoperative general health on 12-month pain and function outcomes. These effects are smaller than mediating effects seen with localized knee pain but are still viewed as large enough to be potentially clinically important. Despite no-effect trials designed to reduce pain catastrophizing [6,12], our data suggests pain catastrophizing and depressive symptoms are causally related to outcome. Our study suggests that surgeons should consider perioperative interventions to address pain catastrophizing and depressive symptoms in patients with these elevated forms of psychological distress.

Data statement

Deidentified data from this study is available pending approval of a study proposal by the investigative team of the KASTPain trial.

Author contributions

Daniel L. Riddle and S. Reza Jafarzadeh both contributed the following: (1) the conception and design of the study, or analysis and interpretation of data (2) drafting the article or revising it critically for important intellectual content, and (3) final approval of the version to be submitted. Daniel L. Riddle was responsible for acquiring the data.

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Author disclosure

Daniel L. Riddle and S. Reza Jafarzadeh report no personal or financial conflict of interest that could potentially and inappropriately influence (bias) this work and conclusions.

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