A commentary by Robert J. Barth, PhD, is linked to the online version of this article at jbjs.org.

Moderators and Mediators of Activity Intolerance Related to Pain

Teun Cremers, BSc, Michael Zoulfi Khatiri, BSc, Koen van Maren, BSc, David Ring, MD, PhD, Teun Teunis, MD, PhD, and Amirreza Fatehi, MD

Investigation performed at the Department of Orthopedic Surgery, Dell Medical School, The University of Texas at Austin, Austin, Texas

Background: There is wide variation in activity intolerance for a given musculoskeletal pathophysiology. In other words, people often experience illness beyond what one would expect given their level of pathophysiology. Mental health (i.e., cognitive bias regarding pain [e.g., worst-case thinking] and psychological distress [symptoms of anxiety and depression]) is an important and treatable correlate of pain intensity and activity intolerance that accounts for much of this variation. This study tested the degree to which psychological distress accentuates the role of cognitive bias in the relationship between pain intensity and activity intolerance.

Methods: We enrolled 125 adults with musculoskeletal illness in a cross-sectional study. Participants completed measures of activity intolerance related to pain (Patient-Reported Outcomes Measurement Information System [PROMIS] Pain Interference Computer Adaptive Test [CAT]) and in general (PROMIS Physical Function CAT]), measures of psychological distress (PROMIS Depression CAT and PROMIS Anxiety CAT), a numeric rating scale (NRS) for pain intensity, measures of pain-related cognitive bias (4-question versions of the Negative Pain Thoughts Questionnaire [NPTQ-4], Pain Catastrophizing Scale [PCS-4], and Tampa Scale for Kinesiophobia [TSK-4]), and a survey of demographic variables. We assessed the relationships of these measures through mediation and moderation analyses using structural equation modeling.

Results: Mediation analysis confirmed the large indirect relationship between pain intensity (NRS) and activity intolerance (PROMIS Pain Interference CAT and Physical Function CAT) through cognitive bias. Symptoms of depression and anxiety had an unconditional (consistent) relationship with cognitive bias (NPTQ), but there was no significant conditional effect/moderation (i.e., no increase in the magnitude of the relationship with increasing symptoms of depression and anxiety).

Conclusions: Psychological distress accentuates the role of cognitive bias in the relationship between pain intensity and activity intolerance. In other words, misconceptions make humans ill, more so with greater symptoms of depression or anxiety. Orthopaedic surgeons can approach their daily work with the knowledge that addressing common misconceptions and identifying psychological distress as a health improvement opportunity are important aspects of musculoskeletal care.

Level of Evidence: Prognostic Level III. See Instructions for Authors for a complete description of levels of evidence.

In the traditional biomedical model, illness is reduced to pathophysiology (objective somatic processes)[1,2]. The biopsychosocial model of illness is now recognized as more accurate and the new standard[1,2]. Pain intensity in particular is recognized as varying substantially for a given degree of actual or potential tissue damage. The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."[3] Given the evidence that thoughts and behaviors affect pain intensity[4], we consider pain as the unpleasant thoughts, emotions, and behaviors associated with, or resembling those associated with, actual or potential tissue damage. Pain can occur in the absence of objective, measurable pathophysiology. The observed variation in pain intensity independent of variations in actual or potential tissue damage is accounted for, in large part, by

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mental health (cognitive bias, stress, and distress) and social health (financial, employment, housing, and food security; healthy social roles; and connectedness)[5-7]. This also holds true for variation in activity intolerance in performing daily, social, or work-related tasks[5,6,8,9].

It might help to consider 1 study in detail to establish these points. Kim and colleagues[10] studied knee osteoarthritis in a population-based study of 660 people 65 years of age and older who had volunteered for a study of diseases in the elderly. About 5 of every 6 people had radiographic evidence of knee osteoarthritis, but only 1 in 6 (104 people, 16%) had sufficient symptoms to be categorized as having symptomatic knee osteoarthritis. Only about 38% (62 of 162) with radiographic evidence of severe and advanced osteoarthritis qualified as symptomatic, while about 14% (30 people) with normal or nearly normal radiographic findings qualified as symptomatic. (The approximations are due to ambiguity in interpreting the figure and an error in the table in this study[10].) Radiographically evident severity accounted for 20% of the variation in the magnitude of symptoms and activity intolerance related to knee osteoarthritis, and symptoms of depression accounted for 15% of the variation. The influence of a diagnosis of major depression was greater for lower radiographic grades of arthritis; there was no measured influence among the 77 people with the most severe grade of osteoarthritis. Keeping in mind that this study was population-based (meaning that it included people who were not seeking care), we interpret these data as indicating that the remarkable human capacity to accommodate pathology is hindered by symptoms of depression. What Kim and colleagues demonstrated is the extent to which mental health (and by reasonable inference social health[11]) accounts for symptom intensity and activity intolerance and—again by inference—a person's decision to seek care. There is evidence that symptom intensity and activity intolerance do not correlate with radiographic evidence of severity in people with trapeziometacarpal arthrosis seeking or not seeking care[12,13]. We are aware of similar data, not yet published, for patients seeking care for hip and knee osteoarthritis.

The degree of activity intolerance due to pain can be measured using the Patient-Reported Outcomes Measurement Information System (PROMIS)[14] Pain Interference Computer Adaptive Test (CAT)[15,16]. Activity intolerance related to pain has substantial correlation with psychological distress (symptoms of anxiety and depression)[15,16] and cognitive bias regarding pain (e.g., catastrophic thinking and kinesiophobia)[15,17-19]. There is evidence that cognitive biases such as catastrophic thinking and fear of movement *mediate* the effect of pain intensity on activity intolerance[20], meaning that they add an indirect effect on top of any direct effect. There is also evidence that cognitive biases *moderate* the influence of psychological distress on activity intolerance[21]. In a prior analysis of people presenting for musculoskeletal specialty care, the relationship between pain-related anxiety and activity intolerance related to pain was stronger in the presence of greater degrees of cognitive bias (in this case greater intolerance of uncertainty)[21]. In our opinion, it is more intuitive to interpret these statistical associations as indicating that the bias-prone human mind might be more influenced by biases such as intolerance of uncertainty when in distress (greater symptoms of anxiety). We were inspired to continue this line of research.

Accounting for psychosocial factors brings us closer to an explanation for the limited correlation between actual or potential tissue damage and pain interference that is often observed, especially in patients with persistently painful conditions[22]. There is an opportunity for orthopaedic surgeons to be the most qualified and able to identify the mental and social health opportunities manifested in these variations—they are the experts regarding pathophysiology, and they can also become experts regarding the relative influence of thoughts and emotions. Considering the availability of therapies that can reduce pain intensity and activity intolerance by addressing mental and social health[23-25], a better understanding of the role that mental and social health play in the experience of pain and its relationship to physical function has the potential to shed additional light on the most effective treatments for patients with musculoskeletal pain.

This study addresses the degree to which psychological distress potentiates the influence of cognitive bias on activity tolerance. The influence of pain-related cognitive biases on the relationship between pain intensity and activity intolerance (i.e., the mediation effect) was measured first. Then the degree to which psychological distress moderates the influence of cognitive bias (i.e., the moderation effect) was measured.

Materials and Methods

This was a cross-sectional study. Recruitment took place at several orthopaedic offices in a large urban area during November 2019. A research assistant approached patients visiting a musculoskeletal specialist and explained, prior to or after the appointment with the physician, the nature of this study and obtained verbal informed consent for participation. Participants completed questionnaires on a tablet using REDCap (Research Electronic Data Capture), a secure web-based application designed to support data capture for research studies[26]. The investigation was approved by our institutional review board and was carried out in accordance with the latest version of the Declaration of Helsinki.

The inclusion criteria were (1) all new and returning patients in an orthopaedic office, (2) an age of 18 to 89 years, (3) fluency in the English language, and (4) cognitive capacity to complete a questionnaire. Among the 134 patients who completed the questionnaire, 9 (7%) were excluded because of incomplete data. The remaining 125 participants had a mean age (and standard deviation [SD]) of 46 ± 16 years, and slightly more than half were women (Table I). We had no missing data.

Questionnaires

We used the PROMIS[14] Pain Interference CAT[27] to measure intolerance of painful activities[28], the PROMIS Physical Function[29] CAT to measure general activity tolerance irrespective of pain, the PROMIS Depression CAT to measure symptoms of depression, and the PROMIS Anxiety CAT to measure

TABLE I Demographics

Variable	No. (%)*
Total patients included	125 (100%)
Male	57 (46%)
Race	
White	87 (67%)
Latino/Hispanic	22 (18%)
Black/African American	9 (7%)
Other	7 (6%)
Level of education	
High school diploma or less	18 (14%)
Some college	40 (32%)
Bachelor's degree	43 (34%)
Graduate or professional degree	24 (19%)
Age *(yr)*	46 ± 16 (18-78)
Diagnosis cluster	
Upper extremity	68 (54%)
Lower extremity	38 (30%)
Other	19 (15%)
Trauma	71 (57%)
Discrete atraumatic pain	93 (74%)
≥1 difficult life event	66 (53%)

*Except for age, which is given as the mean and SD (range).

symptoms of anxiety. The PROMIS instruments have a scaled score with 50 representing the United States population norm and every 10 points higher representing 1 SD of increase in the score.

Pain intensity was measured using an 11-point ordinal scale (numeric rating scale [NRS])[30] ranging from 0 ("no pain") to 10 ("the worst pain imaginable"). Participants completed a checklist of difficult life events derived from the Holmes-Rahe Life Stress Inventory[31].

We measured cognitive biases related to pain using 3 measures: the 4-question versions of the Negative Pain Thoughts Questionnaire (NPTQ-4)[32], the Pain Catastrophizing Scale (PCS-4)[33,34], and the Tampa Scale for Kinesiophobia (TSK-4)[35] (see Appendix 1).

Structural Equation Modeling

To study the relationship of the correlated measures of pain intensity, psychological distress (depression and anxiety), and cognitive bias (NPTQ, PCS, and TSK scores) and their relationship with activity intolerance, we performed mediation and moderation analyses using structural equation modeling (Fig. 1).

Mediation

We expected that pain intensity correlates with activity intolerance (the *direct effect*; Fig. 1, path C) and that part of this relationship is mediated by cognitive bias (the *indirect effect*, measured with the NPTQ, PCS, and TSK; Fig. 1, paths A and B). To determine the magnitude of the mediated indirect effect, and its proportion of the total effect, we created 6 structural equation models with each including a single cognitive bias measure. We report robust standard errors using the Huber/White/sandwich estimator to overcome potential heteroscedasticity (the circumstance in which the variability of a dependent variable is unequal across the range of values of an independent variable).

Moderation

We also assessed whether the indirect relationship of the NPTQ score is influenced by symptoms of psychological distress (depression or anxiety). Moderation means that the strength of the influence of psychological distress on the mediation effect of the NPTQ score on pain intensity becomes larger at higher levels of distress as assessed using slope analysis. We report unstandardized, mean-centered coefficients, robust standard errors, and bootstrap confidence intervals (CIs) (n = 5,000).

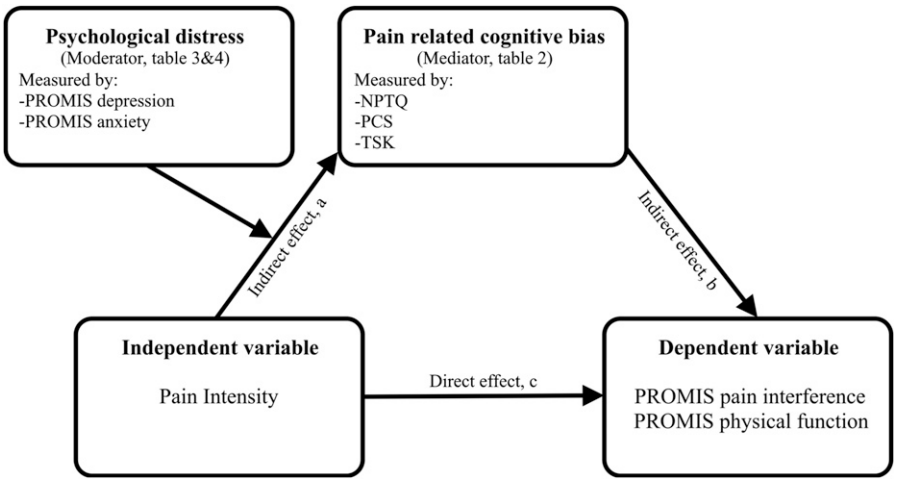

Fig. 1
Diagram of the mediation model.

TABLE II Mediation Analysis of Cognitive Bias on the Effect of Pain Intensity on Activity Intolerance

	Regression Coefficient* (95% CI)	P Value	Robust Standard Error	Proportion of Total Effect†	Variation Explained by Model (R^2)
Effect on pain interference					
Total effect of pain intensity on pain interference	0.49 (0.34 to 0.65)	<0.001	0.080		
Indirect effect mediated through NPTQ	0.21 (0.11 to 0.30)	<0.001	0.048	0.43	0.42
Indirect effect mediated through PCS	0.20 (0.11 to 0.29)	<0.001	0.044	0.41	0.33
Indirect effect mediated through TSK	0.13 (0.05 to 0.20)	0.001	0.037	0.27	0.34
Effect on physical function					
Total effect of pain intensity on physical function	−0.37 (−0.53 to −0.20)	<0.001	0.084		
Indirect effect mediated through NPTQ	−0.19 (−0.29 to −0.09)	<0.001	0.050	0.51	0.29
Indirect effect mediated through PCS	−0.16 (−0.25 to −0.06)	0.001	0.047	0.43	0.19
Indirect effect mediated through TSK	−0.14 (−0.23 to −0.07)	<0.001	0.042	0.38	0.26

*All coefficients are standardized. †Proportion of the total effect of the mediated indirect effect. Each indirect effect of NPTQ, PCS, and TSK scores is determined in a separate model.

Potential Confounders

To assess the effect of any potential confounding variables, we included any demographic variable with $p < 0.10$ in the bivariate analysis (see Appendix 2) in a separate analysis using a generalized structural equation model. The bivariate analyses were performed using independent samples t tests, Pearson correlations, and 1-way independent analysis of variance (ANOVA).

Power Analysis

Based on a previous simulation study, a priori power analysis indicated that 90 patients would provide 0.80 power, assuming that pain intensity would explain 13% of the variation in NPTQ scores and NPTQ scores would explain 13% of the variation in PROMIS Pain Interference CAT scores, with alpha set at 0.05 (Sobel first-order test for direct, indirect, and total effects; standard errors obtained with the delta method). Because we aimed to also include a moderator analysis, and to account for incomplete responses, we planned to enroll 130 patients.

Results

All 3 measures of cognitive bias (NPTQ, PCS, and TSK) mediated the relationship of pain intensity with activity intolerance (PROMIS Pain Interference and PROMIS Physical Function CAT scores). The NPTQ score had the largest indirect effect and proportion of the total effect, followed by the PCS score and then the TSK score, but the CIs overlapped, indicating no statistical difference. The models explained 33% to 42% of the variation in the PROMIS Pain Interference CAT score (R^2) and 19% to 29% of the variation in the PROMIS Physical Function CAT score (Table II).

The PROMIS Depression CAT score had a significant unconditional effect (the effect was the same at all levels) on the NPTQ score. However, its moderation effect (conditional, meaning that the effect was greater at higher levels) was limited, as illustrated by a nonsignificant interaction term of PROMIS Depression CAT and pain intensity (NRS) scores (Table III). As expected, we found only a limited increase in slope from 0.34 at 1 SD below the mean to 0.57 at 1 SD above the mean for pain intensity (NRS), and from −0.36 to −0.62 for the PROMIS Physical Function CAT score, with wide CIs (Fig. 2). The index (a measure of the magnitude of change in the slopes) was nonsignificant (Table III).

The PROMIS Anxiety CAT score also had a significant unconditional effect on the NPTQ score and a stronger moderator (conditional) effect that had a borderline nonsignificant index of the magnitude of change in slopes (Fig. 3 and Table IV).

No demographic variables were associated with the PROMIS Pain Interference CAT score. Only injury location was associated with the PROMIS Physical Function CAT score in the bivariate analysis. Generalized structural equation modeling showed little effect of anatomical location on our mediation analysis (see Appendix 3).

Discussion

Psychological factors (e.g., cognitive bias and psychological distress [symptoms of anxiety and depression]) are important and treatable correlates of pain intensity and activity intolerance associated with musculoskeletal pathology[6,15-19,23,24]. A better understanding of these relationships can improve the development of more comprehensive treatment options for people with symptoms and activity intolerance ascribed to musculoskeletal pathology. This study assessed whether the influence of cognitive bias on the relationship between pain intensity and activity intolerance is influenced (moderated) by symptoms of depression and anxiety.

This study has a number of limitations. First, because it had a cross-sectional design, we cannot draw conclusions regarding directionality or cause. There is precedent, however, for using cross-sectional data to assess hypotheses that assume directionality when there is evidence in previous studies that support those assumptions[21,36,37]. We interpret our findings as

TABLE III Moderation Effect of Depression on the Mediation of Cognitive Bias on the Relationship Between Pain Intensity and Activity Intolerance

	Regression Coefficient (95% CI)	P Value	Bootstrap Standard Error	Robust Standard Error
Effect of depression on NPTQ				
Pain	0.52 (0.26 to 0.77)	<0.001		0.13
Depression	0.21 (0.14 to 0.28)	<0.001		0.036
Interaction, pain × depression	0.0147 (−0.011 to 0.0403)	0.26		0.013
Conditional indirect effect of depression on pain interference				
−1 SD	0.34 (0.084 to 0.63)		0.14	
Mean	0.45 (0.21 to 0.73)		0.14	
+1 SD	0.57 (0.17 to 0.97)		0.57	
Index	0.013 (−0.013 to 0.035)		0.013	
Conditional indirect effect of depression on physical function				
−1 SD	−0.36 (−0.68 to −0.079)		0.15	
Mean	−0.49 (−0.84 to −0.20)		0.16	
+1 SD	−0.62 (−1.1 to −0.15)		0.24	
Index	−0.014 (−0.040 to 0.014)		0.014	

indicating that cognitive bias leads to greater symptom intensity and activity intolerance. While the reverse is possible—namely, that patients with greater activity tolerance tend to have more adaptive thoughts as a consequence rather than a cause of their better physical function—this seems unlikely given what is already known about the relationship between cognitive bias and activity intolerance[33,38,39]. Nevertheless, directional relationships and treatment strategies are best addressed in longitudinal and interventional studies. Second, there may have been patients with substantial symptoms of depression and anxiety who declined to participate, contributing to selection bias. This seems unlikely as very few people declined participation in our setting. Third, the external validity may be limited because we were limited to English-speaking patients with musculoskeletal pain visiting male, White orthopaedic surgeons who are specialists rather than generalists. Fourth, our study population was a mixed sample of new

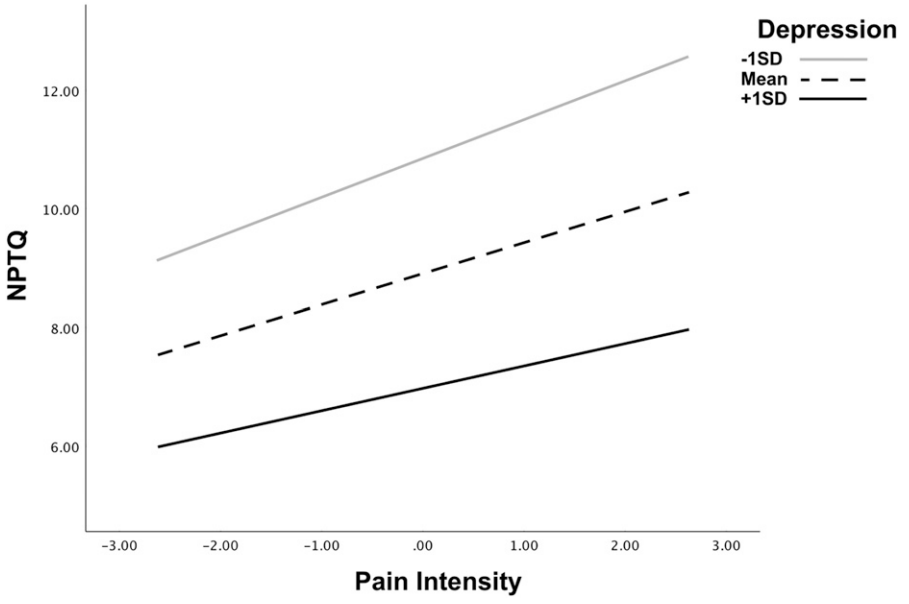

Fig. 2

The slopes of the relationship between pain intensity (NRS) and NPTQ scores for various PROMIS Depression CAT scores show a limited, nonsignificant increase in slope. Pain intensity (on the x axis) was mean-centered, meaning that we subtracted the mean from all pain scores so the new mean of pain intensity score becomes 0. This is recommended in moderation analysis to reduce the artificially introduced collinearity with the interaction term (i.e., pain intensity score multiplied by PROMIS Depression CAT score).

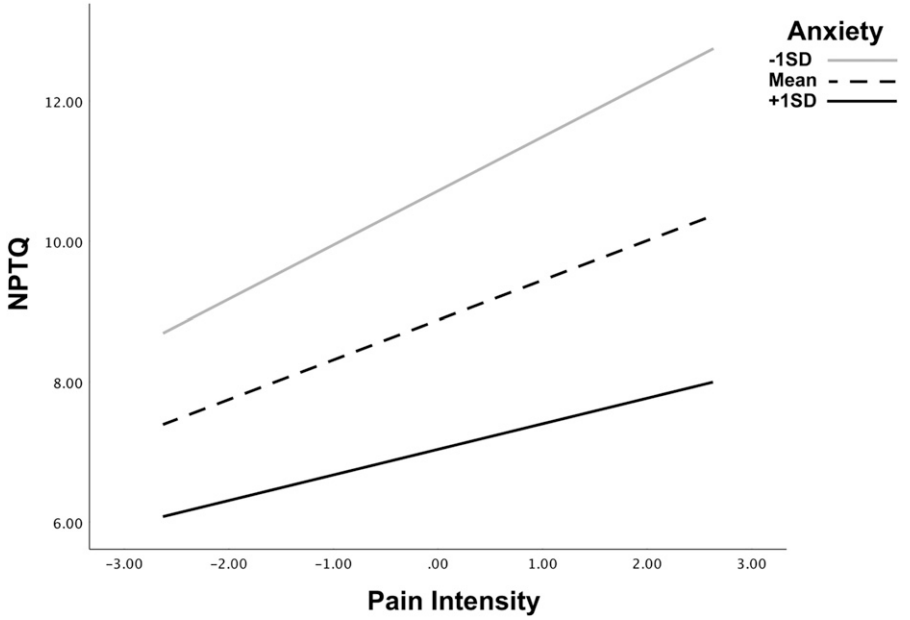

Fig. 3

The slopes of the relationship between pain intensity (NRS) and NPTQ score for various PROMIS Anxiety CAT scores illustrate some increase in slope with greater PROMIS Anxiety scores consistent with a moderation effect, but the effect did not reach statistical significance. Pain intensity (on the x axis) was mean-centered, meaning that we subtracted the mean from all pain scores so the new mean of pain intensity becomes 0. This is recommended in moderation analysis to reduce the artificially introduced collinearity with the interaction term (i.e., pain intensity score multiplied by PROMIS Anxiety CAT score).

and returning patients with various musculoskeletal diagnoses. The advantage of our broad inclusion criteria is that it is likely a reflection of the types of problems for which people seek musculoskeletal specialty expertise. Prior work has shown relatively little influence of the type of visit (new or return) or specific pathological conditions[9,17]. Nevertheless, studies of specific diagnoses might have different findings.

The observation that cognitive bias (measured with the NPTQ, PCS, and TSK) mediates the effect of pain intensity on activity intolerance as measured with the PROMIS Pain Interference and PROMIS Physical Function CATs is consistent with prior research that a large part of the variation in activity tolerance is accounted for by unhelpful cognitive biases regarding pain[6,20,40]. The observation of no significant differences

TABLE IV Moderation Effect of Anxiety on the Mediation of Cognitive Bias on the Relationship Between Pain Intensity and Activity Intolerance

	Regression Coefficient (95% CI)	P Value	Bootstrap Standard Error	Robust Standard Error
Effect of anxiety on NPTQ				
Pain	0.57 (0.32 to 0.82)	<0.001		0.13
Anxiety	0.19 (0.11 to 0.26)	<0.001		0.038
Interaction, pain × anxiety	0.021 (−0.0044 to 0.046)	0.11		0.013
Conditional indirect effect of anxiety on pain interference				
−1 SD	0.32 (0.037 to 0.61)		0.15	
Mean	0.50 (0.25 to 0.78)		0.14	
+1 SD	0.67 (0.27 to 1.1)		0.21	
Index	0.018 (−0.0063 to 0.041)		0.21	
Conditional indirect effect of anxiety on physical function				
−1 SD	−0.35 (−0.68 to −0.040)		0.16	
Mean	−0.54 (−0.90 to −0.24)		0.17	
+1 SD	−0.73 (−1.2 to −0.27)		0.25	
Index	−0.020 (−0.045 to 0.064)		0.13	

in the mediation effect of various measures of cognitive bias on the indirect effect of pain intensity on PROMIS Pain Interference and PROMIS Physical Function CAT scores suggests that they are comparably useful. There is some evidence that they are measuring a common underlying construct[17,41,42], which might fall under a rubric of the unhelpful cognitive bias that "pain indicates harm." It might be possible to measure this construct in a patient care (and perhaps even a research) setting using just 1 or 2 questions in a way that makes cognitive bias a comfortable topic of discussion while encouraging a healthy patient-clinician relationship—an area of ongoing investigation.

The finding that greater symptoms of anxiety and depression are associated with a greater influence of cognitive biases on the relationship between pain intensity and activity intolerance suggests that psychological distress may reinforce bias (perhaps by hindering cognitive debiasing strategies such as critical or analytical thinking). We consider this a confirmation of the findings of Fischerauer and colleagues, who reported that cognitive bias increased the influence of symptoms of anxiety on the relationship between pain intensity and activity tolerance[21]. On the other hand, they also found a conditional influence of intolerance of uncertainty on pain anxiety (a moderation effect), while we did not find a moderation effect of psychological distress on the influence of cognitive bias. In other words, the magnitude of the effect of anxiety and depression did not increase at greater levels of depression or anxiety. Although our slope analyses indicated some increase in the effect, it was not significant. There is a great deal of evidence that some of the relationship between pain intensity and activity intolerance is accounted for by symptoms of anxiety and depression (mediation)[10,21,29,43-47]. Both the study by Fischerauer and colleagues and our study suggest that this may be, in part, due to reinforcement of unhelpful cognitive biases by psychological distress. In other words, despair or worry can increase the degree to which thoughts are regarded as facts (cognitive fusion).

These findings contribute to the weight of evidence demonstrating that unhelpful cognitive biases regarding pain are associated with greater pain intensity for a given degree of actual or potential tissue damage and greater activity intolerance for a given pain intensity. These data further elucidate that psychological distress increases the impact of cognitive bias on symptoms and activity intolerance. In other words, perhaps it is easier to move on from the mind's automatic thoughts or "first draft" and reorient one's thinking when one's mood is more elevated and one is experiencing less apprehension about what is to come. This suggests that it is important to address despair and worry along with misconceptions resulting from cognitive biases and perhaps treatment of the psychological distress might take priority. Clinicians and patients can be aware that reduction in symptoms of depression and anxiety with cognitive behavioral therapy and its derivatives has the potential to help limit the impact of unhelpful cognitive biases regarding pain, which could alleviate pain and reduce activity intolerance as much as or more than many biomedical or surgical treatments.

Appendix

eA Supporting material provided by the authors is posted with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJS/G208). ■

Teun Cremers, BSc[1]
Michael Zoulfi Khatiri, BSc[1]
Koen van Maren, BSc[1]
David Ring, MD, PhD[1]
Teun Teunis, MD, PhD[2]
Amirreza Fatehi, MD[1]

[1]Department of Orthopedic Surgery, Dell Medical School, The University of Texas at Austin, Austin, Texas

[2]Plastic Surgery Department, University Medical Center Utrecht, University of Utrecht, Utrecht, the Netherlands

Email address for D. Ring: David.ring@austin.utexas.edu

ORCID iD for T. Cremers: 0000-0002-2651-5489
ORCID iD for M. Zoulfi Khatiri: 0000-0001-6838-423X
ORCID iD for K. van Maren: 0000-0002-8287-6940
ORCID iD for D. Ring: 0000-0002-6506-4879
ORCID iD for T. Teunis: 0000-0001-5660-0695
ORCID iD for A. Fatehi: 0000-0001-6033-7834

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