

What Are the Mechanisms of Action of Cognitive-Behavioral, Mind-Body, and Exercise-based Interventions for Pain and Disability in People With Chronic Primary Musculoskeletal Pain?

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What Are the Mechanisms of Action of Cognitive–Behavioral, Mind–Body, and Exercise-based Interventions for Pain and Disability in People With Chronic Primary Musculoskeletal Pain?

A Systematic Review of Mediation Studies From Randomized Controlled Trials

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Objectives: This systematic review examined studies that used mediation analysis to investigate the mechanisms of action of cognitive–behavioral, mind–body, and exercise-based interventions for pain and disability in people with chronic primary musculoskeletal pain.

Materials and Methods: We searched 5 electronic databases for articles that conducted mediation analyses of randomized controlled trials to either test or estimate indirect effects.

Results: We found 17 studies (n=4423), including 90 mediation models examining the role of 22 putative mediators on pain or disability, of which 4 had partially mediated treatment effect; 8 had mixed results, and 10 did not mediate treatment effect. The conditions studied were chronic whiplash-associated pain, chronic low back pain, chronic knee pain, and mixed group of chronic primary musculoskeletal pain.

Discussion: We observed that several of the studies included in our systematic review identified similar mechanisms of action, even between different interventions and conditions. However, methodological

limitations were common. In conclusion, there are still substantial gaps with respect to understanding how cognitive–behavioral, mind–body, and exercise-based interventions work to reduce pain and disability in people with chronic primary musculoskeletal pain.

Key Words: chronic pain, mediation, mechanisms of action, exercise, cognitive-behavioral

(*Clin J Pain* 2022;38:502–509)

Chronic primary musculoskeletal pain is among the most burdensome health conditions worldwide.^{1–3} Since 1990, chronic low back pain (CLBP) and other chronic primary musculoskeletal painful conditions have been the leading causes of years lived with disability in most countries.^{1,4} Although active treatment approaches, such as cognitive–behavioral, mind–body, and exercise-based interventions are effective in reducing pain and disability,^{5–8} most interventions are not superior to each other and the effect sizes are often small.^{9–11} A possible explanation is that most interventions do not sufficiently target relevant mediators, or may work through similar mechanisms despite their complex proposed mechanisms of action.¹²

The existence of evidence showing that complex interventions with very different proposed mechanisms of action are equally effective for chronic musculoskeletal pain (eg, cognitive–behavioral, mind–body, and exercise-based interventions) can be misleading and confusing for clinical researchers and clinicians. Therefore, better understanding of the underlying mechanisms of cognitive–behavioral, mind–body, and exercise-based treatment effects is important for the optimization and refinement of these complex interventions and may also assist clinicians in their clinical reasoning.¹³

Studying the role of mediators (ie, a variable by which one intervention affects an outcome¹⁴) in randomized clinical trials can generate evidence about the mechanisms of action for interventions.^{14,15} Although systematic reviews of mediation studies exist for CLBP,^{16,17} no review has tested the mechanisms of cognitive–behavioral, mind–body, and exercise-based interventions for chronic primary musculoskeletal pain in general. Understanding treatment mechanisms would save valuable research resources by identifying more promising

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clinical hypotheses to be tested in randomized clinical trials. Further, better understanding of mechanisms of action would allow interventions for pain conditions to precisely target mediators of treatment effect, based on empirical evidence rather than presumptive theories about how interventions work. Finally, a review with a broader scope might provide insights into the shared mechanisms of action across interventions and conditions.

This review aimed to identify and synthesize the results of studies that conducted mediation analyses of randomized controlled trials that test the indirect effects of cognitive-behavioral, mind-body, and exercise-based interventions for pain and disability in people with chronic primary musculoskeletal pain.

MATERIAL AND METHODS

Protocol and Registration

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.^{18,19} The review protocol was prospectively registered on PROSPERO (CRD42020198188), accessible at https://www.crd.york.ac.uk/prospERO/display_record.php?ID=CRD42020198188, and on the Open Science Framework (<https://cutt.ly/4xwuBIL>). Deviations from the preregistered protocol are documented in the following sections.

Eligibility Criteria

We included randomized, controlled trials of cognitive-behavioral, exercise-based, and mind-body interventions on pain and disability in individuals with chronic primary musculoskeletal pain that conducted mediation analyses. Although we preplanned the inclusion of mind-body therapies in the review protocol as cognitive-behavioral interventions, we acknowledge that using “cognitive-behavioral interventions” as an umbrella term for all psychological approaches might be confusing. Therefore, we decided to synthesize the results of mind-body interventions as a separate intervention category.

Studies that included individuals 18 years or older with chronic primary musculoskeletal pain longer than 3 months according to the ICD-11 chronic pain classification,³ including neck pain, thoracic pain, low back pain, and limb pain (ie, shoulder pain, elbow pain, hip pain and knee pain) were included. Studies that included patients with specific pathology (eg, fracture, cauda equina syndrome, malignancy, full thickness rotator cuff tear, osteoarthritis, or spinal stenosis) and orofacial painful conditions were excluded. Studies with mixed populations and varying pain duration were only included if 75% or more of the participants who met the condition and duration criteria.

Interventions that used cognitive-behavioral (including cognitive-behavioral therapy, acceptance and commitment therapy, cognitive functional therapy, graded activity, operant therapy, exposure therapy, respondent therapy, and lifestyle interventions), mind-body (including yoga, meditation, qigong, virtual reality, guided imagery, Tai Chi, and mindfulness-based interventions), and exercise-based approaches (including general or specific exercises, motor control exercises, McKenzie, pilates, stretching), in comparison to passive or active controls, for pain or disability in patients with chronic musculoskeletal pain were included. Education was defined as a cognitive-behavioral intervention if it pertained to cognitive and psychological aspects associated with pain such as knowledge, beliefs, fear, stress, or relaxation, with a didactic mode of delivery (eg, a lecture or a session).

We included studies that formally conducted a mediation analysis (eg, product of coefficient test, difference in coefficient test, Baron and Kenny’s causal steps of mediation, structural equation modeling, causal mediation analysis) or significance tests of mediation (eg, Sobel’s first-order test). We did not exclude studies based on the mediators that were studied.

Studies without a control group and nonstandard randomized designs (eg, stepped wedged designs), studies not written in English, or studies that did not test or estimate indirect effects were excluded. Only studies published in peer-reviewed journals were included. Conference proceedings, preprints, dissertations and nonoriginal research were excluded.

Search Strategy

On November 22, 2021, an electronic search was conducted in the following databases: PubMed, CINAHL (via EBSCOhost), EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and PsychINFO (via EBSCOhost). All databases were searched from their inception. The search strategies outlined by the Cochrane Back Review Group were used to identify studies including low back pain and neck pain. The search strategy of other systematic reviews were used to identify studies including other musculoskeletal painful conditions,²⁰ cognitive-behavioral and mind-body interventions,^{8,21} exercise-based interventions,²² and studies that conducted mediation analyses.^{23,24} The full search strategy is available in the supplementary file (Supplemental Digital Content 1, <http://links.lww.com/CJP/A883>).

The search results were downloaded into EndNote (EndNote X9 Thomson Corporation) and duplicates were removed. R.K.A. and J.C. independently screened titles and abstracts and selected articles for full-text review using the inclusion/exclusion criteria and independently reviewed the full texts to determine eligibility. R.K.A. and J.C. resolved disagreements through discussion and reaching consensus. H.L. was consulted for consensus if disagreements persisted. We hand-searched the reference lists of included studies for eligible articles.

Data Extraction

Two reviewers (R.K.A. and J.C.) independently extracted data using a data extraction form developed for the study. We extracted information about the study, including the year of publication, journal, and sample size; participant characteristics (age, sex, pain condition, and duration); characteristics of the intervention (type and content); mediators and outcome variables (construct, measurement tool, time of measurement); mediation analysis approach; measures taken to control for confounding; testing of moderated mediation paths; standardized or unstandardized coefficients, precision of estimates, and significance levels of the relevant paths (treatment-mediator, mediator-outcome, total, direct and indirect effects); and the authors’ conclusion(s).

Data Synthesis and Analysis

The beta-coefficients of the indirect, treatment-mediator (ie, Path a), mediator-outcome (ie, Path b), and total effects were synthesized. We organized the data by the type of intervention (exercise-based, mind-body, cognitive-behavioral, or combined), follow-ups (short-term, ≤ 2 mo; intermediate, between 2 and 12 mo; and long-term, ≥ 12 mo), outcome (pain or disability),

mediator, and condition. We decided against pooling the data, since the included studies had different interventions and targeted different conditions.

Study Quality Assessment

The quality of the included studies were assessed through criteria outlined by Mansell et al.¹⁷ This criteria was used for quality assessment, instead of the Cochrane risk of bias tool, because currently there is no available criteria for the evaluation of risk of bias in mediation studies and Mansell and colleagues' tool is the best available for the purpose of this study. Moreover, other systematic reviews of mediation studies used this criteria for quality assessment.^{16,23}

Two independent reviewers (R.K.A. and J.C.) scored each of the 7 criteria: 1 (yes) or 0 (no). The sum of these scores was used to reflect the overall quality for each study. The 7 criteria are shown in Table 5.

RESULTS

Study Selection

A total of 12,353 records were identified through the database search and hand-searching of reference lists (Fig. 1). After duplicate removal, a total of 10,440 records were screened. After title and abstract screening, 37 studies remained for full-text screening; 17 studies met the inclusion criteria and were included in the systematic review (Fig. 1). A description of the characteristics of excluded studies is provided in Tables S1 in the supplementary file (Supplemental Digital Content 1, <http://links.lww.com/CJP/A883>).

Description of Studies

From 17 included studies (n = 4423), 2 studies, comprising 221 participants, estimated the effect of exercise-based interventions on pain and disability through 3 putative mediators in patients with CLBP^{25,26}; 7 studies, comprising 853 participants, estimated the effect of cognitive-behavioral interventions on pain and disability through 15 putative mediators under 3 different conditions²⁷⁻³³; 4 studies, comprising 430 participants, estimated the effect of mind-body interventions on pain and disability through 8 putative mediators under 2 different conditions^{26,34-36}; and 6 studies, comprising 3020 participants, estimated the effect of a combined (eg, exercise-based plus cognitive-behavioral interventions) approach on pain and disability through 10 putative mediators under 2 different conditions.³⁷⁻⁴¹ As some of the included studies had more than 2 arms, they were included in more than 1 intervention category. In total, these studies tested 90 mediation models examining the role of 22 putative mediators on pain or disability at different follow-up points, of which 4 partially mediated treatment effect; 8 had mixed results; and 10 did not significantly mediate the treatment effect. A summary of the estimated mediators and of the results of mediation analysis (treatment-mediator, mediator-outcome, and indirect effects) is provided in Tables 1-4.

Two studies included participants with chronic whiplash-associated pain^{28,31}; 9 studies included participants with CLBP^{25,26,30,36-38,40-42}; 1 study included participants with chronic knee pain³⁹; and 4 studies included participants with chronic primary musculoskeletal pain.³²⁻³⁵

Thirteen of the mediators were psychological constructs and 4 studies estimated the mediating role of physical, lifestyle, and social constructs. Characteristics of the

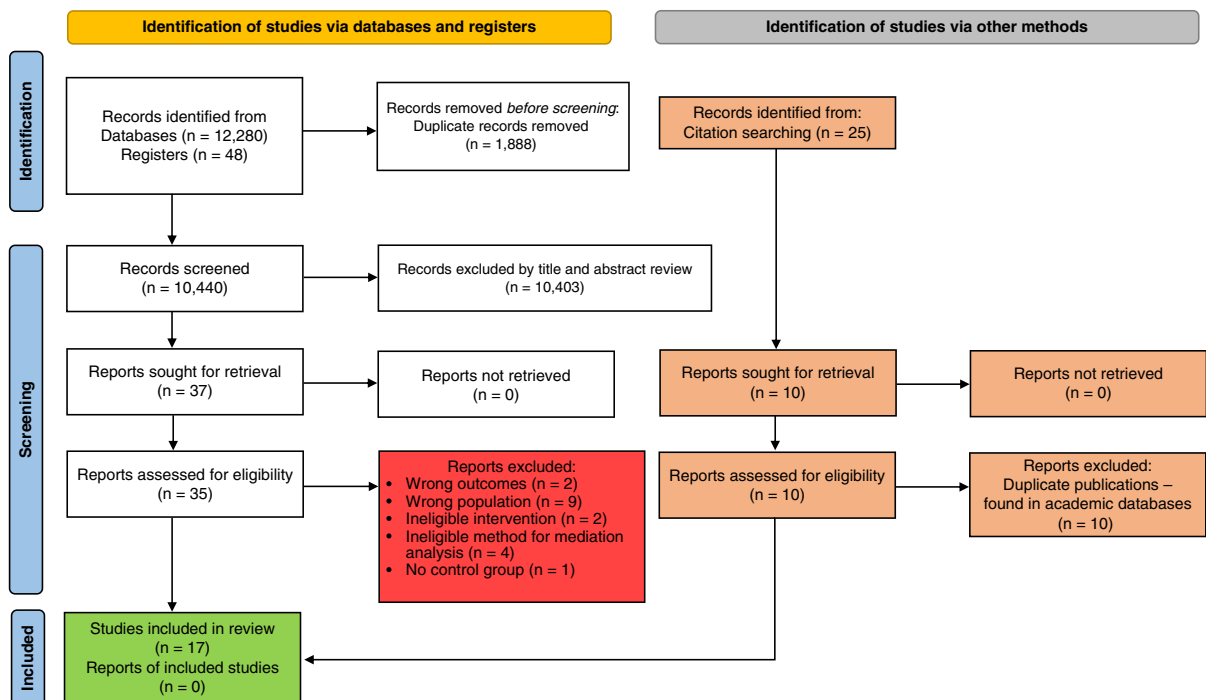


FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram (2020) of the search process for studies examining the mechanisms of action of exercise-based, cognitive-behavioral, and mind-body interventions on pain and disability for participants with chronic primary musculoskeletal pain.

TABLE 1. Summary of Mediation Models From Exercise-based Interventions Assessed in the Included Studies

References	Condition	Intervention vs. Comparator	Intervention Period	Path a	Mediator	Path b	Outcome	Indirect Effect
Smeets et al ²⁵	CLBP	Aerobic + strength training vs. waitlist	10 wk	NR	Catastrophizing	NR	Pain at 10 wk	PM
				NR	Catastrophizing	NR	Disability at 10 wk	PM
Sherman et al ²⁶	CLBP	Stretching vs. self-care book	3 mo	+	Physical activity	-	Disability at 3 mo	-
				+	Self-efficacy	+		PM
				+	Sleep	+		PM

CLBP indicates chronic low back pain; FM, full mediation; NM, no mediation; NR, not reported; PM, partial mediation.

included studies are provided in Tables S2–S5 (Supplemental Digital Content 2, <http://links.lww.com/CJP/A884>).

Quality Assessment

All included studies cited a theoretical framework. Most of the studies controlled for confounding (15/17) and used measures of the exposure that preceded the mediator (12/17) and used measures of the mediator that preceded the outcome (12/17). However, sample size estimations and psychometric properties of the measurement tools were rarely reported (2/17 and 3/17, respectively). The quality assessment ratings are presented in Table 5.

DISCUSSION

This systematic review identified 17 studies, including 4423 participants, which included a total of 90 mediation models examining the role of 22 putative mediators on pain or disability. Four mediators partially mediated treatment effect; 8 had mixed results; and 10 did not significantly mediate the treatment effect. Most studies assessed psychological mediators (13/17), while 4 studies investigated physical, lifestyle, and social constructs.

There were relatively few studies that conducted mediation analyses on exercise-based interventions (2) compared with the other types of intervention, which makes it difficult to understand the mechanisms of action of these interventions. This discrepancy may reflect the established

tradition in psychological science to investigate how interventions work. Evidence-based psychological interventions rely on theoretical assumptions and conceptual models for explaining how interventions exert their effects.^{44,45} These findings are supported in the reviews by Mansell et al¹⁷ and Lee et al,¹⁶ where most putative mediators evaluated for low back pain were psychological constructs.

We observed that several of the studies included in our systematic review identified similar mechanisms of action despite different interventions (eg, self-efficacy was identified as a potential mediator for pain and disability by studies of exercise-based, mind–body, cognitive–behavioral, and combined interventions^{26,27,29,46}). According to the included studies with positive findings, even specific approaches with very different proposed mechanisms of action may work through similar mediators under different conditions (eg, fear was identified as a mediator for disability in acceptance and commitment therapy,²⁸ cognitive behavioral therapy,³⁸ exposure³¹ and psychologically informed physical therapy⁴⁰ in patients with CLBP and neck pain). These observations corroborate those of Mansell et al.¹⁷ Their review revealed that increased self-efficacy, reduced pain catastrophizing, accurate pain beliefs, increased pain coping, increased psychological flexibility, and reduced fear avoidance and distress were important mediators for all psychological interventions for CLBP.

The available research identified by this review was mostly of poor quality with high risk of bias. Although most

TABLE 2. Summary of Mediation Models From Mind–body Interventions Assessed in the Included Studies

References	Condition	Intervention vs. Comparator	Intervention Period	Path a	Mediator	Path b	Outcome	Indirect Effect
Garland et al ³⁵	CPMP	Mind–body therapy + mindfulness vs. support group	2 mo	+	Positive psychology health	+	Pain severity at 2 mo	PM
Garland et al ³⁴	CPMP	Mind–body therapy + mindfulness vs. support group	2 mo	+	Coping	+	Pain severity at 2 mo	PM
Hall et al ³⁶	CLBP	Tai chi vs. waitlist	10 wk	+	Nonreactivity	+	Pain at 10 wk	PM
				-	Reappraisal	-	Disability at 10 wk	-
Sherman et al ²⁶	CLBP	Yoga vs. self-care book	3 mo	+	Physical activity	-	Disability at 3 mo	-
				+	Self-efficacy	+		PM
				+	Sleep	+		PM

CLBP indicates chronic low back pain; CMP, chronic primary musculoskeletal pain; FM, full mediation; NM, no mediation; NR, not reported; PM, partial mediation.

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TABLE 3. Summary of Mediation Models From Cognitive-behavioral Interventions Assessed in Included Studies

References	Condition	Intervention vs. Comparator	Intervention Period	Path a	Mediator	Path b	Outcome	Indirect Effect
O'Neill et al ⁴²	CLBP	CFT vs. exercise + education	6-8 wk	+	Anxiety	+	Pain at 12 mo	-
				+	Coping	+		-
				+	Depression	+	-	
				+	Fear	+	-	
				-	Self-efficacy	-	Disability at 12 mo	PM
				+	Sleep	+		-
				+	Stress	+		-
				+	Anxiety	+		-
				+	Coping	+		-
				+	Depression	+		-
				+	Fear	+		-
				-	Self-efficacy	-		PM
				+	Sleep	+		-
+	Stress	+	-					
Smeets et al ²⁵	CLBP	CBT vs. Waitlist;	10 wk	NR	Catastrophizing	NR	Pain at 10 wk Disability at 10 wk	PM
				NR	Catastrophizing	NR		
Wicksell et al ²⁸	CWAD	ACT + TAU vs. TAU	2 mo	-	Anxiety	-	Disability at 2 mo	-
				+	Depression	+		-
				+	Fear	-	-	
				+	Pain	-	-	
				+	Psychological flexibility	-	-	
				-	Self-efficacy	-	Disability at 6 mo	-
				-	Anxiety	-		-
				-	Depression	+		-
				+	Fear	-		PM
				+	Pain	+	PM	
-	Psychological flexibility	+	-					
Leeuw et al ³⁰	CLBP	Exposure in vivo vs. Operant therapy	2 mo	-	Self-efficacy	-	Disability at 12 mo	-
				+	Catastrophizing	+		-
Robinson et al ³¹	CWAD	Exposure in vivo + Information Booklet (IB) vs. waitlist	1 mo	+	Fear of movement-related pain	+	Disability at 1 mo	PM
				-		Perceived harmfulness		
Williams et al ³²	CMP	Telephone-based HLC+ Education and Behavioral Change vs. Waitlist	6 mo	-	Diet	-	Pain at 6 mo	-
				-	Pain beliefs	-		-
				-	Physical activity	-	-	
				-	Weight	-	-	
				-	Diet	-	Disability at 6 mo	-
				-	Pain beliefs	-		-
				-	Physical activity	-		-
				-	Weight	-		-
Kemani et al ³³	CPMP	ACT vs. Applied Relaxation	3 mo	+	Catastrophizing	-	Pain interference at 3 mo	-
				-	Pain	-		-
				+	Psychological flexibility	+	PM	

ACT indicates acceptance and commitment therapy; CBT, cognitive behavioral therapy; CLBP, chronic low back pain; CPMP, chronic primary musculoskeletal pain; CWAD, chronic whiplash-associated pain; FM, full mediation; NM, no mediation; NR, not reported; PM, partial mediation; TAU, treated as usual.

of the studies controlled for possible confounders (15/17) and ensured temporal precedence (intervention-mediator: 12/17, mediator-outcome 12/17), sample size estimations and psychometric properties of the measurement tools were rarely reported (2/17 and 3/17, respectively). In addition, the

conduct and reporting of mediation analysis were highly heterogeneous between studies, which is in line with the findings of Vo et al.⁴⁷

There is high probability of publication bias in the results. In view of the many positive mediation findings by individual

TABLE 4. Summary of Mediation Models From Combined Interventions Assessed in Included Studies

References	Condition	Intervention vs. Comparator	Intervention Period	Path a	Mediator	Path b	Outcome	Indirect Effect	
Cheing et al ³⁷	CLBP	Motivational enhanced PT vs. PT	2 mo	+	Outcome expectancy	+	Physical function at 2 mo	-	
				-	Pain	+		-	
Smeets et al ²⁵	CLBP	Aerobic + strength + problem-solving training vs. waitlist	10 wk	NR	Working alliance	+	Pain at 10 wk	PM	
				NR	Catastrophizing	NR			
Fordham et al ³⁸	CLBP	CBT + exercises vs. exercises	6 wk	NR	Fear	NR	Disability at 10 wk Pain at 3 mo	PM	
				NR		Mental functioning			NR
				NR		Physical activity			NR
				NR		Self-efficacy			NR
				NR		Fear			NR
				NR		Mental functioning			NR
				NR		Physical activity			NR
				NR		Self-efficacy			NR
				NR		Fear			NR
				NR		Mental functioning			NR
				NR		Physical activity			NR
				NR		Self-efficacy			NR
				NR		Fear			NR
				NR		Mental functioning			NR
				NR		Physical activity			NR
				NR		Self-efficacy			NR
				NR		Fear			NR
				NR		Mental functioning			NR
				NR		Physical activity			NR
				NR		Self-efficacy			NR
Foy et al ³⁹	NP	Intensive lifestyle intervention vs. support and education	12 mo	+	Weight	+	Pain at 12 mo	PM	
				+		Weight			+
				+		Pain			+
				+		Pain-related distress			+
				+		Fear of movement-related pain			+
				+		Weight			+
				+		Pain			+
				+		Pain-related distress			+
				+		Fear of movement-related pain			+
				+		Weight			+
Mansell et al ⁴⁰	CLBP	PIPT vs. current best care	NR, pragmatic study	+	Weight	+	Disability at 12 mo Disability at 4 mo	PM	
				+		Pain			+
Mansel et al ⁴¹	CLBP	PIPT vs. TAU	2 mo	+	Pain-related distress	+	Disability at 2 mo	PM	

CBT indicates cognitive behavioral therapy; CLBP, chronic low back pain; CNP, chronic knee pain; FM, full mediation; NM, no mediation; NR, not reported; PIPT, psychologically informed physical therapy; PM, partial mediation; PNE, pain neuroscience education; PT, physical therapy; TAU, treated as usual.

studies (ie, 4 mediators partially mediated treatment effect and 8 had mixed results), and the fact that mediation analyses are usually conducted as secondary aims or only exploratively, it is possible that mediation analysis was only conducted in studies that showed a significant treatment effect, and that primarily those with statistically significant results were published. Clinical researchers could help improve the overall methodological quality of mediation studies using adequate statistical methods in their randomized clinical trial protocols for conducting mediation analysis, and by designing clinical trials to answer mechanistic questions (ie, measuring relevant mediators using longitudinal and more frequent measures of mediators and outcomes, with adequate measurement tools).

This systematic review presents preliminary evidence on the mechanisms of action of cognitive-behavioral, mind-body, and

exercise-based interventions so far, with meaningful opportunities to move the field forward by establishing strengths and limitations of the field. Better evidence of causal mechanisms of interventions can help develop more fine-grained clinical hypotheses to be tested in randomized clinical trials and lead to more effective interventions.

Strengths and Limitations of This Review

This review has several limitations. It is possible that post hoc mediation analyses were only conducted in studies that showed a significant treatment effect, and that primarily those with statistically significant results were published. Study heterogeneity is another important issue. We may have fostered heterogeneity by categorizing together studies of different interventions. However, we think that this is also the main strength of this study.

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TABLE 5. Quality Assessment

	1. Theoretical Framework	2. Report of Psychometric Characteristics	3. Power Calculation for Mediation Analysis	4. Were Acceptable Statistically Methods of Data Analysis Used?	5. Changes in Exposure Precedes Changes in Mediator?	6. Changes in Mediator Precedes Changes in Outcome?	7. Controlled for Confounding?
Smeets et al ²⁵	1	0	0	1	1	1	1
Hall et al ³⁶	1	0	0	1	1	1	1
Sherman et al ²⁶	1	0	0	1	1	1	1
Cheing et al ³⁷	1	0	0	1	0	1	0
Fordham et al ³⁸	1	0	0	1	0	1	1
Foy et al ³⁹	1	0	0	1	1	1	1
Mansell et al ⁴⁰	1	0	0	1	1	1	1
Mansell et al ⁴¹	1	0	0	1	1	1	1
O'Neill et al ⁴²	1	0	0	1	0	0	1
Wicksell et al ²⁸	1	1	0	1	0	0	0
Garland et al ³⁵	1	0	0	1	1	1	1
Garland et al ³⁴	1	1	0	1	1	1	1
Leeuw et al ³⁰	1	0	0	1	0	0	1
Wicksell et al ⁴³	1	0	0	1	1	1	1
Robinson et al ³¹	1	1	0	1	1	1	1
Williams et al ³²	1	0	1	1	1	1	1
Kemani et al ³³	1	0	1	1	1	1	1

1, Did the study cite a theoretical framework? 2, Were the psychometric characteristics of the mediator and outcome variables reported? (Computed from the present study or a reference provided.) 3, Did the study report a power calculation? If so, was the study adequately powered to detect mediation? 4, Were statistically appropriate/acceptable methods of data analysis used? This includes the product of coefficient approach with bootstrapped confidence intervals, structural equation modelling, path analysis, latent growth modelling, and causal mediation analysis. 5, Did the study ascertain whether changes in the exposure variable preceded changes in the mediator variable? 6, Did the study ascertain whether changes in the mediating variables preceded changes in the outcome variables? 7, Did the study control for possible confounding factors, for example, baseline values?

We were able to identify and summarize, in a single paper, the evidence of the mechanisms of action for very different interventions, which gave us an overview of the field. Other strengths of this review included: preregistration⁴⁸; a comprehensive search strategy; and use of 2 reviewers who independently screened, extracted the data, and evaluated the studies.

CONCLUSIONS

Our results suggest that there are substantial gaps with respect to understanding how cognitive-behavioral, mind-body, and exercise-based interventions work for pain and disability in people with chronic primary musculoskeletal pain.

We found a total of 90 mediation models examining the role 22 putative mediators on pain or disability, of which 4 partially mediated the treatment effects; 8 had mixed results and 10 did not significantly mediate treatment effect. Methodological limitations were common and most of the included studies were at high risk of bias.

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