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

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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 outcome[14]) 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 form 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, osteoarthrosis, 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, $\leq$2 mo; intermediate, between 2 and 12 mo; and long-term, $\geq$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 conditions[27–33]; 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 pain[39]; 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

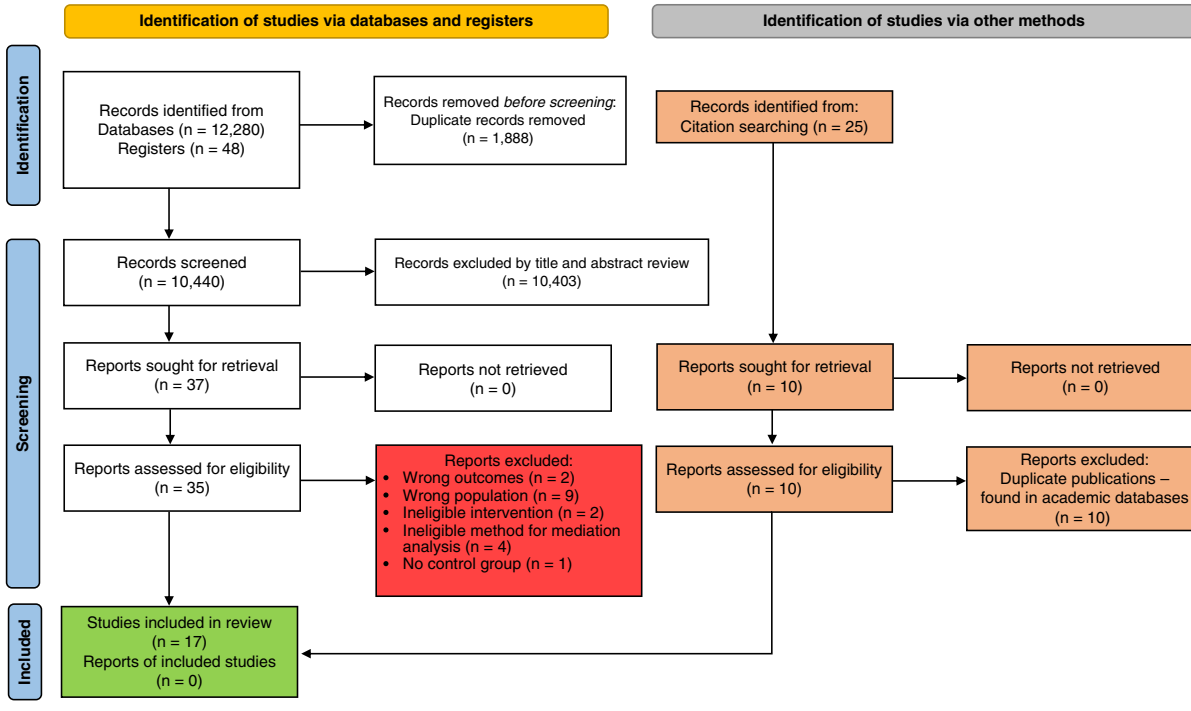

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram (2020) of the search process for studies examining the mechanisms of action of exercise-based, cognitive–behavioral, and mind–body interventions on pain and disability for participants with chronic primary musculoskeletal 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 al[17] 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] exposure[31] and psychologically informed physical therapy[40] 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
				−	Reapraisal	−	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.

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	−		PM
				+	Sleep	+		−
				+	Stress	+		−
				+	Anxiety	+	Disability at 12 mo	−
				+	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	PM
				NR	Catastrophizing	NR	Disability at 10 wk	PM
Wicksell et al[28]	CWAD	ACT + TAU vs. TAU	2 mo	−	Anxiety	−	Disability at 2 mo	−
				+	Depression	+		−
				+	Fear	−		−
				+	Pain	−		−
				+	Psychological flexibility	−		−
				−	Self-efficacy	−		−
				−	Anxiety	−	Disability at 6 mo	−
				−	Depression	+		−
				+	Fear	−		PM
				+	Pain	+		PM
				−	Psychological flexibility	+		−
				−	Self-efficacy	−		−
Leeuw et al[30]	CLBP	Exposure in vivo vs. Operant therapy	2 mo	+	Catastrophizing	+	Disability at 12 mo	−
				−	Perceived harmfulness	−		−
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
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

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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	+		−
				+	Working alliance	+		−
Smeets et al[25]	CLBP	Aerobic + strength + problem-solving training vs. waitlist	10 wk	NR	Catastrophizing	NR	Pain at 10 wk	PM
				NR		NR	Disability at 10 wk	PM
Fordham et al[38]	CLBP	CBT + exercises vs. exercises	6 wk	NR	Fear	NR	Pain at 3 mo	−
				NR	Mental functioning	NR		−
				NR	Physical activity	NR		PM
				NR	Self-efficacy	NR		PM
				NR	Fear	NR	Disability at 3 mo	−
				NR	Mental functioning	NR		−
				NR	Physical activity	NR		−
				NR	Self-efficacy	NR		−
				NR	Fear	NR	Pain at 6 mo	−
				NR	Mental functioning	NR		−
				NR	Physical activity	NR		PM
				NR	Self-efficacy	NR		PM
				NR	Fear	NR	Disability at 6 mo	PM
				NR	Mental functioning	NR		−
				NR	Physical activity	NR		PM
				NR	Self-efficacy	NR		PM
				NR	Fear	NR	Pain at 12 mo	−
				NR	Mental functioning	NR		−
				NR	Physical activity	NR		PM
				NR	Self-efficacy	NR		PM
				NR	Fear	NR	Disability at 12 mo	PM
				NR	Mental functioning	NR		−
				NR	Physical activity	NR		PM
				NR	Self-efficacy	NR		PM
Foy et al[39]	NP	Intensive lifestyle intervention vs. support and education	12 mo	+	Weight	+	Pain at 12 mo	PM
				+	Weight	+	Disability at 12 mo	PM
Mansell et al[40]	CLBP	PIPT vs. current best care	NR, pragmatic study	+	Pain	+	Disability at 4 mo	PM
				+	Pain-related distress	+		PM
Mansel et al[41]	CLBP	PIPT vs. TAU	2 mo	+	Fear of movement-related pain	+	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.

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: preregistration[48]; 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.

REFERENCES

1. Metrics GH. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392:1789–1858.
2. Treede RD, Rief W, Barke A, et al. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). *Pain*. 2019; 160:19–27.
3. Nicholas M, Vlaeyen JWS, Rief W, et al. The IASP classification of chronic pain for ICD-11: chronic primary pain. *Pain*. 2019;160:28–37.
4. Vos T, Lim SS, Abbafati C, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396:1204–1222.
5. Foster NE, Anema JR, Cherkin D, et al. Prevention and treatment of low back pain: evidence, challenges, and promising directions. *Lancet*. 2018;391:2368–2383.
6. Chou R, Loeser JD, Owens DK, et al. Interventional therapies, surgery, and interdisciplinary rehabilitation for low back pain:

an evidence-based clinical practice guideline from the American Pain Society. *Spine (Phila Pa 1976)*. 2009;34:1066–1077.
7. Skelly AC, Chou R, Dettori JR, et al. Noninvasive nonpharmacological treatment for chronic pain: a systematic review. Rockville, MD: Agency for Healthcare Research and Quality (US); 2020.
8. Williams ACdC, Fisher E, Hearn L, et al. Psychological therapies for the management of chronic pain (excluding headache) in adults. *Cochrane Database Syst Rev*. 2020;8:CD007407.
9. Lin I, Wiles L, Waller R, et al. What does best practice care for musculoskeletal pain look like? Eleven consistent recommendations from high-quality clinical practice guidelines: systematic review. *Br J Sports Med*. 2020;54:79–86.
10. Hutting N, Johnston V, Staal JB, et al. Promoting the use of self-management strategies for people with persistent musculoskeletal disorders: the role of physical therapists. *J Orthop Sports Phys Ther*. 2019;49:212–215.
11. Alperstein D, Sharpe L. The efficacy of motivational interviewing in adults with chronic pain: a meta-analysis and systematic review. *J Pain*. 2016;17:393–403.
12. Burns JW. Mechanisms, mechanisms, mechanisms: it really does all boil down to mechanisms. *Pain*. 2016;157:2393–2394.
13. Lee H, Lamb SE. Advancing physical therapist interventions by investigating causal mechanisms. *Phys Ther*. 2017;97:1119–1121.
14. Lee H, Herbert RD, Lamb SE, et al. Investigating causal mechanisms in randomised controlled trials. *Trials*. 2019;20:524.
15. Whittle R, Mansell G, Jellema P, et al. Applying causal mediation methods to clinical trial data: what can we learn about why our interventions (don't) work? *Eur J Pain*. 2017;21:614–622.
16. Lee H, Mansell G, McAuley JH, et al. Causal mechanisms in the clinical course and treatment of back pain. *Best Pract Res Clin Rheumatol*. 2016;30:1074–1083.
17. Mansell G, Kamper SJ, Kent P. Why and how back pain interventions work: what can we do to find out? *Best Pract Res Clin Rheumatol*. 2013;27:685–697.
18. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
19. Page MJ, McKenzie JE, Bossuyt PM, et al. Updating guidance for reporting systematic reviews: development of the PRISMA 2020 statement. *J Clin Epidemiol*. 2021;134:103–112.
20. Geneen LJ, Moore RA, Clarke C, et al. Physical activity and exercise for chronic pain in adults: an overview of Cochrane Reviews. *Cochrane Database Syst Rev*. 2017;4:CD011279–CD011279.
21. Henschke N, Ostelo RW, van Tulder MW, et al. Behavioural treatment for chronic low-back pain. *Cochrane Database Syst Rev*. 2010;2010:Cd002014.
22. Hayden JA, van Tulder MW, Malmivaara A, et al. Exercise therapy for treatment of non-specific low back pain. *Cochrane Database Syst Rev*. 2005. doi: 10.1002/14651858.CD000335.
23. Lee H, Hubscher M, Moseley GL, et al. How does pain lead to disability? A systematic review and meta-analysis of mediation studies in people with back and neck pain. *Pain*. 2015;156:988–997.
24. Cashin AG, Lee H, Lamb SE, et al. An overview of systematic reviews found suboptimal reporting and methodological limitations of mediation studies investigating causal mechanisms. *J Clin Epidemiol*. 2019;111:60–68.e1.
25. Smeets RJ, Vlaeyen JW, Kester AD, et al. Reduction of pain catastrophizing mediates the outcome of both physical and cognitive-behavioral treatment in chronic low back pain. *J Pain*. 2006;7:261–271.
26. Sherman KJ, Wellman RD, Cook AJ, et al. Mediators of yoga and stretching for chronic low back pain. *Evid Based Complement Alternat Med*. 2013;2013:130818.
27. O'Neill A, O'Sullivan K, O'Keeffe M, et al. Development of pain in older adults: a latent class analysis of biopsychosocial risk factors. *Pain*. 2018;159:1631–1640.
28. Wicksell RK, Olsson GL, Hayes SC. Psychological flexibility as a mediator of improvement in acceptance and commitment therapy for patients with chronic pain following whiplash. *Eur J Pain*. 2010;14:1059.e1–1059.e11.
29. Turner JA, Holtzman S, Mancl L. Mediators, moderators, and predictors of therapeutic change in cognitive-behavioral therapy for chronic pain. *Pain*. 2007;127:276–286.
30. Leeuw M, Goossens ME, van Breukelen GJ, et al. Exposure in vivo versus operant graded activity in chronic low back pain patients: results of a randomized controlled trial. *Pain*. 2008;138:192–207.
31. Robinson JP, Theodore BR, Dansie EJ, et al. The role of fear of movement in subacute whiplash-associated disorders grades I and II. *Pain*. 2013;154:393–401.
32. Williams A, Lee H, Kamper SJ, et al. Causal mechanisms of a healthy lifestyle intervention for patients with musculoskeletal pain who are overweight or obese. *Clin Rehabil*. 2019;33:1088–1097.
33. Kemani MK, Hesser H, Olsson GL, et al. Processes of change in acceptance and commitment therapy and applied relaxation for long-standing pain. *Eur J Pain*. 2016;20:521–531.
34. Garland EL, Manusov EG, Froeliger B, et al. Mindfulness-oriented recovery enhancement for chronic pain and prescription opioid misuse: results from an early-stage randomized controlled trial. *J Consult Clin Psychol*. 2014;82:448–459.
35. Garland EL, Hanley AW, Riquino MR, et al. Mindfulness-oriented recovery enhancement reduces opioid misuse risk via analgesic and positive psychological mechanisms: a randomized controlled trial. *J Consult Clin Psychol*. 2019;87:927–940.
36. Hall AM, Kamper SJ, Emsley R, et al. Does pain-catastrophising mediate the effect of tai chi on treatment outcomes for people with low back pain? *Complement Ther Med*. 2016;25:61–66.
37. Cheing G, Vong S, Chan F, et al. Testing a path-analytic mediation model of how motivational enhancement physiotherapy improves physical functioning in pain patients. *J Occup Rehabil*. 2014;24:798–805.
38. Fordham B, Ji C, Hansen Z, et al. Explaining how cognitive behavioral approaches work for low back pain: mediation analysis of the back skills training trial. *Spine*. 2017;42:E1031–E1039.
39. Foy CG, Lewis CE, Hairston KG, et al. Intensive lifestyle intervention improves physical function among obese adults with knee pain: findings from the Look AHEAD trial. *Obesity (Silver Spring)*. 2011;19:83–93.
40. Mansell G, Hill JC, Main C, et al. Exploring what factors mediate treatment effect: example of the STarT Back Study High-Risk Intervention. *J Pain*. 2016;17:1237–1245.
41. Mansell G, Hill JC, Main CJ, et al. Mediators of treatment effect in the back in action trial: using latent growth modeling to take change over time into account. *Clin J Pain*. 2017;33:811–819.
42. O'Neill A, O'Sullivan K, O'Sullivan P, et al. Examining what factors mediate treatment effect in chronic low back pain: a mediation analysis of a cognitive functional therapy clinical trial. *Eur J Pain*. 2020;24:1765–1774.
43. Wicksell RK, Kemani M, Jensen K, et al. Acceptance and commitment therapy for fibromyalgia: a randomized controlled trial. *Eur J Pain*. 2013;17:599–611.
44. Hayes SC, Hofmann SG. The third wave of cognitive behavioral therapy and the rise of process-based care. *World Psychiatry*. 2017;16:245–246.
45. Hofmann SG, Hayes SC. The future of intervention science: process-based therapy. *Clin Psychol Sci*. 2019;7:37–50.
46. Taylor SS, Oddone EZ, Coffman CJ, et al. Cognitive mediators of change in physical functioning in response to a multifaceted intervention for managing osteoarthritis. *Int J Behav Med*. 2018;25:162–170.
47. Vo TT, Superchi C, Boutron I, et al. The conduct and reporting of mediation analysis in recently published randomized controlled trials: results from a methodological systematic review. *J Clin Epidemiol*. 2020;117:78–88.
48. Lee H, Lamb SE, Bagg MK, et al. Reproducible and replicable pain research: a critical review. *Pain*. 2018;159:1683–1689.