How do psychologically based interventions for chronic musculoskeletal pain work?

Clinical Psychology Review 94 (2022) 102160

Contents lists available at ScienceDirect

Clinical Psychology Review

journal homepage: www.elsevier.com/locate/clinpsychrev

Review

How do psychologically based interventions for chronic musculoskeletal pain work? A systematic review and meta-analysis of specific moderators and mediators of treatment

Carlos Murillo [a,b], Tat-Thang Vo [c,d], Stijn Vansteelandt [d,e], Lauren E. Harrison [f], Barbara Cagnie [a], Iris Coppieters [a,b,g], Marjolein Chys [a], Inge Timmers [a,f,h,1], Mira Meeus [a,b,i,*,1]

[a] Department of Rehabilitation Sciences, Faculty of Health Sciences and Medicine, Ghent University, Belgium
[b] Pain in Motion international research group, www.paininmotion.be, University of Antwerp, Campus Drie EikenUniversiteitsplein 12610 Wilrijk, Belgium
[c] Department of Statistics, The Wharton School, University of Pennsylvania, Pennsylvania, United States
[d] Department of Applied Mathematics, Computer Science and Statistics, Ghent University, Belgium
[e] Department of Medical Statistics, London School of Hygiene and Tropical Medicine, United Kingdom
[f] Department of Anesthesiology, Perioperative, and Pain Medicine, Stanford University, California, United States
[g] Department of Physiotherapy, Human Physiology and Anatomy, Faculty of Physical Education and Physiotherapy, Vrije Universiteit Brussel, Belgium
[h] Department of Rehabilitation Medicine, Maastricht University, Netherlands
[i] MOVANT research group, Department of Rehabilitation Sciences and Physiotherapy, Faculty of Health Sciences and Medicine, University of Antwerp, Belgium

ARTICLE INFO

Keywords:
Chronic musculoskeletal pain
Psychologically based interventions
Mediation analysis
Moderation analysis
meta-analysis
Systematic review

ABSTRACT

Psychologically based interventions aim to improve pain-related functioning by targeting pain-related fears, cognitions and behaviors. Mediation and moderation analyses permit further examination of the effect of treatment on an outcome. This systematic review and meta-analysis aims to synthetize the evidence of specific mediators and moderators (i.e., treatment targets) of psychologically based treatment effects on pain and disability. A total of 28 mediation and 11 moderation analyses were included. Thirteen mediation studies were included in a meta-analysis, and the rest was narratively synthetized. Reductions in pain-related fear (indirect effect [IE]: −0.07; 95% confidence interval [CI]: −0.11, −0.04) and catastrophizing (IE: -0.07; 95%CI: −0.14, −0.00), as well as increases in self-efficacy (IE: -0.07; 95%CI: −0.11, −0.04), mediated effects of cognitive behavioral therapy on disability but not on pain intensity, when compared to control treatments. Enhancing pain acceptance (IE: -0.17; 95%CI: −0.31, −0.03) and psychological flexibility (IE: -0.30; 95%CI: −0.41, −0.18) mediated acceptance and commitment therapy effects on disability. The narrative synthesis showed conflicting evidence, which did not support a robust moderated effect for any of the examined constructs. Overall, the methodological quality regarding mediation was low, and some key pitfalls are highlighted alongside recommendations to provide a platform for future research.

1. Introduction

Musculoskeletal disorders account for the greatest proportion of chronic pain and represent a leading cause of persistent disability worldwide (Sebbag et al., 2019). Despite its increasing prevalence and enormous socioeconomic impact, the management of chronic musculoskeletal pain remains a challenge (Hay et al., 2017; Lewis & O'Sullivan, 2018). Over the last decades, biopsychosocial approaches have gained strength and replaced previous biomedical viewpoints (Gatchel, Peng, Peters, Fuchs, & Turk, 2007; Turk & Monarch, 2018), with increasing evidence supporting the negative impact pain-related fears, cognitions, and behaviors have on functional impairment (Lee et al., 2015; Martinez-Calderon, Flores-Cortes, Morales-Asencio, & Luque-Suarez, 2020c).

First introduced over 50 years ago and progressively implemented during the 1970s and 1980s, treatment approaches broadly referred to as cognitive-behavioral therapies (CBT; with a first wave centring on behavior and a second wave incorporating cognitions) are now well

* Corresponding author at: Universiteitsplein 1, 2610 Wilrijk, Belgium.
E-mail address: mira.meeus@uantwerpen.be (M. Meeus).
[1] These authors contributed equally to this manuscript.

https://doi.org/10.1016/j.cpr.2022.102160
Received 10 June 2021; Received in revised form 18 March 2022; Accepted 27 April 2022
Available online 2 May 2022

established as benchmark for the management of people with chronic pain (De Williams, Fisher, Hearn, & Eccleston, 2020; Morley, 2011). In the last decade, there has been growing interest in acceptance commitment therapy (ACT) and mindfulness-based therapies for pain management as alternatives to the more traditional cognitive -behavioral approaches (Morley, 2011; Veehof, Trompetter, Bohlmeijer, & Schreurs, 2016). Unlike traditional CBT which is focused on gaining control over pain beliefs and behaviors, ACT emphasizes accepting thoughts and feelings without attempting to change them (Hayes, Levin, Plumb-Vilardaga, Villatte, & Pistorello, 2013; McCracken & Vowles, 2014). Mindfulness-based therapies share some similarities with ACT such as pain acceptance, but also focus on awareness of thoughts, feelings, and bodily sensations (Day, 2017). While CBT, ACT and mindfulness are all presently popular interventions for reducing pain-related disability, yet only small to medium effect sizes have been observed (De Williams et al., 2020; Hughes, Clark, Colclough, Dale, & McMillan, 2017; Veehof et al., 2016) and current evidence does not support the efficacy of one modality over another (Hughes et al., 2017; van Tulder et al., 2000).

2. The underlying mechanisms of the psychologically based interventions for musculoskeletal pain

Recently, pain research has shifted from only examining the overall treatment effect (i.e., the total effect) to investigating the underlying mechanisms to identify treatment targets and enhance interventions, ultimately leading to improvement in outcomes (Morley, Williams, & Eccleston, 2013). Broadly, the mechanisms underlying treatment effects can be divided into specific and non-specific effects (Wampold, Minami, Tierney, Baskin, & Bhati, 2005). Specific effects refer to those factors that are actively targeted by the intervention. Non-specific effects, on the other hand, include contextual effects (e.g., therapeutic alliance or patient satisfaction) or natural disease fluctuations (Cashin, McAuley, Lamb, & Lee, 2021; Chatoor & Kurpnick, 2001), and reflect common mechanisms across different types of interventions (e.g., pharmacological, physical and psychological therapies; for an overview see Miller et al. (2021) and Rossettini, Carlino, and Testa (2018)). The current review will only focus on the specific effects in order to provide insights into psychologically based interventions for chronic musculoskeletal pain specifically.

Psychologically based interventions for chronic pain are based on various theoretical models, each with its own rationale. Each of these models, with differing levels of specificity, is framed around core principles and include treatment components targeting pain-specific psychosocial constructs or treatment processes. The traditional cognitive behavioral framework, for example, aims to reduce pain-related disabilities and increase patients' functioning by explicitly changing negative thoughts, beliefs, emotions and behaviors (Turk & Monarch, 2018; Vlaeyen & Morley, 2005). Thus, CBT interventions target maladaptive pain-related cognitions and behaviors through reconceptualizing catastrophic beliefs, addressing avoidance patterns, training certain coping skills (e.g., relaxation training) and promoting graded return to activity. Later extensions of the traditional cognitive-behavioral model, such as the fear avoidance model (Vlaeyen & Linton, 2012), have led to the incorporation of distinct treatment methods aiming to reduce pain-related disability by challenging negative expectations that lead to avoidance behaviors and exposing patients to feared movements/activities (i.e., exposure in vivo). Another conceptual framework incorporated into treatment for chronic pain, ACT, is theoretically rooted in the psychological flexibility model and emphasizes awareness and non-judgmental acceptance of the pain, while identifying valued life directions and teaching skills to support values-based goal setting. In ACT, there is no attempt to modify the pain experience or pain-related emotions, nor reconceptualization of maladaptive thoughts, but rather increasing psychological flexibility in presence of pain as a mean to improve patient's physical function (Hayes et al., 2013; McCracken & Vowles, 2014). Finally, mindfulness-based interventions, though theoretically distinct from ACT, share an underlying focus on pain acceptance and mindfulness. These interventions focus on promoting a nonjudgmental approach to pain where sensory aspects of pain are disengaged from emotional. Through mindful awareness and meditation, negative thoughts about pain can be pictured as discrete events rather than a manifestation of an underlying problem that requires maladaptive responses and behaviors (Day, 2017).

In summary, the respective theoretical models underlying CBT, ACT and mindfulness-based interventions hypothesize that changes in specific theoretically derived cognitive, behavioral and affective constructs mediate the treatment effect and need to be successfully targeted in order to maximize treatment (total) effects. Furthermore, various models also postulate that the pre-treatment status of these specific constructs can interact with the intervention and moderate treatment effect (Day, Ehde, & Jensen, 2015; Vlaeyen & Morley, 2005).

3. Methods to investigate the mechanisms underlying the interventions

Mediation analysis offers a method to examine whether or not an intermediate variable (i.e., a mediator) partially or fully accounts for the causal effect of a particular intervention on an outcome (i.e., indirect effect) (Kazdin, 2007; Windgassen, Goldsmith, Moss-Morris, & Chalder, 2016). Mediation analysis can be used to test and refine the theoretical hypothesis underlying an intervention. In particular, it can examine whether the intervention results in changes in the constructs that it was designed to target, and whether these changes result in improved treatment outcomes (Kazdin, 2007; Mansell, Kamper, & Kent, 2013). Hence, mediation analysis can ultimately help to understand which therapeutic components are (more) effective and should be enhanced, as well as which are ineffective or counterproductive and should consequently be eliminated (Kazdin, 2007; Maric, Wiers, & Prins, 2012). In addition to mediation analysis, *moderation analysis* can provide insights on the therapeutic mechanisms as well. Moderation analyses help to understand for whom a treatment is most effective; or in other words, to identify patient characteristics (i.e., moderators or effect modifiers) that modify the effect of treatment on outcome (i.e., moderated effect) (Kraemer, Frank, & Kupfer, 2006). Moderators can also be examined in combination with mediators to explore whether the underlying therapeutic processes differ across subgroups of patients and/or whether their strength interacts with a particular moderator (MacKinnon, Fairchild, & Fritz, 2007; Preacher, Rucker, & Hayes, 2007).

Over the last years, important advances in the context of mediation analysis have been made in order to provide more robust causal interpretation of the findings. Mediation research has been highly influenced by the seminal work of Baron and Kenny (1986), which includes a series of causal-steps tests within a regression-based framework to assess the presence of an indirect effect. Subsequent extensions of this work, which include the so-called difference- (i.e., total – direct effect) and product-of-coefficient (i.e., path a x b) methods, are currently the most popular mediation approaches (MacKinnon et al., 2007). These approaches however raise validity concerns when one or both of the mediator and outcome models is/are non-linear or when exists potential interactions between the treatment and the mediator (MacKinnon, Valente, & Gonzalez, 2020; VanderWeele, 2016). Structural equation modeling (derived from path analysis) is another possible approach to calculate indirect effect (De Stavola, Daniel, Ploubidis, & Micali, 2015); but its interpretation depends on the adequate models specification and unmeasured confounding (VanderWeele, 2016). The recently proposed counterfactual-based framework has gained support as it overcomes the limitations linked to the beforementioned traditional and structural equation modeling approaches. Some of the strengths of this framework are definition of the total and indirect effects with causal interpretation, clarification of the assumptions required for their identification (with a greater consideration of the need for confounding control) and

formulation of appropriate methods for their estimation (VanderWeele, 2016).

While moderation and mediation analyses have widely been used in basic and applied psychology research (Kazdin, 2007), this methodology is now gaining popularity in pain research (Miles et al., 2011; Wertli et al., 2014; Wertli et al., 2014). It is therefore timely to review mediation studies in the context of pain, both in terms of their findings and their methodologies. Consequently, this systematic review and meta-analysis aims to synthetize the evidence of specific (i.e., targeted) (1) mediators and (2) moderators of psychologically based interventions on pain and related disability to better understanding of how these interventions work in order to further optimize treatment approaches for musculoskeletal pain. Additionally, this review aims to provide a comprehensive comparative synthesis of the methodology related to mediation and moderation analysis to bring a better interpretation of the strengths and pitfalls of the current evidence and provide a platform for future research.

4. Methods

4.1. Protocol and registration

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)(Page et al., 2021). The protocol for this review was prospectively registered on PROSPERO (CRD42020188322).

4.2. Eligibility criteria

A modified PICOS statement (including mediator/moderator) was adopted to inform eligibility criteria. ***Population*** was defined as adults with chronic musculoskeletal pain as defined by the ACCTION-American Pain Society Pain Taxonomy (AAPT) (Dworkin et al., 2016) (e.g., spinal pain, temporomandibular disorders, widespread pain, osteoarthrosis and arthritis). Trials with mixed chronic pain population were included when patients with musculoskeletal pain represented more than 75% of the sample (Ghogomu et al., 2014). ***Intervention*** of interest was defined as any treatment with therapeutic components targeting pain-related cognitions, emotions and behaviors (e.g., CBT, exposure in vivo, ACT or mindfulness). Passive (e.g., waiting list) and active (e.g., standardized usual care or any other conservative therapy) treatment ***comparators*** were included as control interventions. Only cognitive-behavioral ***mediators and moderators*** of treatment were included (i.e., those hypothesized to be specifically targeted and hence affected by the treatment, such as pain catastrophizing, pain-related fear, pain acceptance)(Maric et al., 2012). Non-specific mediators (e.g., change in patient's symptoms or therapeutic alliance) and moderators (e.g., age, gender), which are common across the different therapies for pain, were thus excluded (Chatoor & Kurpnick, 2001). The ***outcomes*** of interest were pain intensity and pain-related disability/functioning, as assessed by both disease-specific (e.g., Roland-Morris Questionnaire or fibromyalgia impact questionnaire) and generic measures (e.g., SF-36 physical function subscale or Multidimensional Pain Inventory). Regarding ***study design***, we included randomized control trials (RCTs) that had formally conducted a mediation analysis (e.g., counterfactual-based mediation approaches, product of coefficient approach, difference in coefficient approach, latent growth modeling approach, Baron and Kenny's causal steps of mediation, structural equation modeling approach and Sobel's first-order mediation test) and/or a moderation analysis (e.g., regression analysis with the inclusion of a treatment-moderator interaction term). Secondary analyses of previously published RCTs were also included. Studies not published in English were excluded. Further details on the eligibility criteria can be found in **Table A.1.**

4.3. Information sources and search strategy

Sensitive topic-based search strategies were performed in PubMed, EMBASE, Scopus, Cochrane Library, PsycINFO and Web of Science from inception until the March 20, 2020 and later updated on June 9, 2021. A combination of indexing and free-text terms was derived from scoping searches and discussion with experts (subject specific [CM, MM, IT and LH] and methodological [MM]) (see full search strategy in **Table A.2**). Search was restricted to title and abstract. The reference lists of all included articles as well as previous reviews with similar topics (Gilpin, Keyes, Stahl, Greig, & McCracken, 2017; Wertli, Burgstaller, et al., 2014; Wertli, Rasmussen-Barr, et al., 2014) were hand-searched to identify further potentially relevant studies that were not obtained through the database search (Lefebvre et al., 2019). Additionally, trial register ClinicalTrials.gov was searched and authors of completed but unpublished trials were contacted to enquire about the study results and reduce the risk of publication bias (Lefebvre et al., 2019).

4.4. Study selection

The studies identified through database and hand-search were assessed for eligibility using a 2-stage process. First, two independent reviewers (CM and MC) screened all identified records based on title and abstract. Second, full texts of the remaining articles were assessed independently by the same reviewers following the eligibility criteria for inclusion. Any disagreements were resolved through discussion at each stage, and, if consensus was not reached, an additional reviewer was consulted (MM, LH or SV).

4.5. Data extraction process

Data were extracted by one reviewer (CM) using a data extraction form and checked by a second reviewer (T-TV, IT or MC). The extracted data included (i) author and year of publication, (ii) general information on the study sample (i.e., sample size, gender and musculoskeletal disorder), (iii) details of the experimental and control interventions according to the TIDieR checklist (Hoffmann et al., 2014), (iv) information on the assessment of the mediator(s)/moderator(s) and outcome(s) (i.e., construct, measurement tool and time of measurement) and (v) information on the planning and design of the mediation/moderation analysis (i.e., whether analyses were preplanned or rather post-hoc and rationale for the selection of the mediators/moderators, outcomes and analysis). Protocol publications and trial registrations (if available) were consulted to examine for deviations from the planned analyses.

To further describe the methodological characteristics of the reported mediation analysis, we then extracted the information on (vi) the statistical approach used to investigate mediation, (vii) the method used for handling missing data, (viii) whether eligible studies adjusted for mediator-mediator and mediator-outcome confounders (and if so, what confounders were adjusted) and (ix) how the different (mediator and outcome) models involved in the analysis were constructed and assessed (e.g., whether the potential treatment-mediator and other kinds of interaction were assessed across the mediation studies, and whether the goodness-of-fit statistics indicated good fit to the data). Finally, we also extracted all statistical results that were needed for the subsequent meta-analysis. For instance, if a trial considered a product of coefficient approach to assess mediation, we retained the total treatment effect estimate and the regression coefficient estimates of (i) the treatment in the mediator model, (ii) of the mediator in the outcome model (adjusting for the treatment and mediator-outcome confounders), and their product as an estimate for the indirect effect of interest. The corresponding standard errors of the above estimates were also extracted. If the required information was not available in the article, a data-sharing request was sent to the authors by email. Two reminders were also sent in case of no reply after the first contact.

4.6. Risk of bias assessment in individual studies

To assess the general methodology related biases, we considered the revised Cochrane risk of bias tool (RoB 2.0) for RCTs (Sterne et al., 2019). This step was conducted by two reviewers (CM and MC) who resolved any disagreements through discussion, and if needed, by consulting a third reviewer (MM).

Next, as the risk of some mediation-specific biases was not yet discussed in the RoB 2.0 tool, we added several new bias domains that are more specific for mediation analyses. These include (i) the bias due to the temporal order of the treatment, mediator and outcome, (ii) the appropriateness of the statistical approach used to investigate mediation, (iii) the bias due to mediator-outcome and other types of confounding and (iv) the modeling bias. Within each new bias domain, there are signaling questions to assess the risk of the corresponding bias. A decision tree is then provided to summarize the different questions' responses to derive a final conclusion regarding the risk of the considered bias, analogous to the standard RoB 2.0 tool (see **Appendix B.** for the complete risk of bias tool for mediation analyses). The above extension was first proposed by two mediation experts (T-TV and SV), then applied to the current review by two reviewers (CM and T-TV). SV acted as third reviewer in case of disagreement. In terms of the risk of bias assessment related to moderation analysis, an additional item was added to further evaluate the risk of bias due to measurement of the moderator and modelled within the Cochrane RoB 2.0 tool (see item 4.0 in **Appendix B.**). The selection of this item was informed by the checklist developed by Pincus et al. (2011).

4.7. Data synthesis and analysis

We first summarized the characteristics of the eligible mediation and moderation studies. Studies were classified by mediator/moderator construct (i.e., pain catastrophizing, pain-related fear and avoidance, coping, somatization, self-efficacy and pain acceptance and psychological flexibility) as well as outcome (i.e., pain intensity and disability). We categorized comparator interventions as "usual care" when patients received standard or guided therapy (i.e., with a pre-specified protocol within the trial context). Unsupervised treatment as usual control groups were classified as waiting list.

Mediation analyses. For each mediator construct, we meta-analyzed the indirect effect estimates and the total effect estimates. The comparator intervention was consistent across all the included studies for each meta-analysis (usual care or waiting list). To ensure comparability between different outcome and mediator measures within a specific meta-analysis, the estimate was reversed if necessary. In specific, for pain, cognitions/fears and disability measures, all results were adapted to represent more symptoms/disability/fears with higher values (e.g., estimates regarding physical functioning scale were reversed). In contrast, for pain acceptance and psychological inflexibility measures, all results were adapted to represent higher flexibility/acceptance with higher values (e.g., the psychological inflexibility in pain scale was reversed).

Across all studies, the indirect and total effect estimates as well as their corresponding SE were standardized by calculating their ratio to the standard deviation of the outcome at follow-up (Preacher & Kelley, 2011). A parameter-based meta-analytic structural equation modeling (MASEM) approach was followed, where the standardized effect estimates were pooled by fitting a standard random-effect meta-analysis model using restricted maximum likelihood (Cheung & Cheung, 2016). The between-trial heterogeneity in each meta-analysis was quantitatively assessed by using (i) the between-trial variance estimate, (ii) the I^2 statistic and (iii) the Cochran Q heterogeneity test (Higgins, Thompson, Deeks, & Altman, 2003). Following recent recommendations, we did not switch to a fixed-effect meta-analysis model even when the above statistics indicated no statistical heterogeneity across studies (Lefebvre et al., 2019). The calculated standardized estimated of the total and indirect effect, confidence intervals (CIs) and proportion mediated (i.e., indirect effect / total effect), were summarized in a forest-plot for each mediator. All analyses were performed using R package *Metafor* (version 3.4.0)(Viechtbauer, 2010).

For some mediators, implementing a meta-analysis was not possible due to the fact that some eligible studies did not report the standard error (SE) of the indirect effect estimate or did not provide enough details on how the indirect effect (IE) estimate was standardized. In some other studies, the primary aim was to evaluate the presence of an indirect effect via the assessed mediator (e.g., by using the causal step-Baron & Kenny approach), but the magnitude of such indirect effect was not quantified. Similarly, some studies did not consider a formal mediation analysis upon noting that the impact of the treatment on the mediator was not statistically significant. In such cases, where possible, we reanalyzed the raw data from these studies by using the R packages *mediation* (Tingley, Yamamoto, Hirose, Keele, & Imai, 2014) and *medflex* (Steen, Loeys, Moerkerke, & Vansteelandt, 2017) and incorporated the obtained findings in the meta-analysis. For those studies without raw data nor sufficient reported data to allow a meta-analysis, findings were summarized in accordance with the Synthesis Without Meta-analysis reporting guideline (Campbell et al., 2020). The vote counting method was used to summarize the direction of the indirect and total effects for a given mediator/outcome and results were presented in a harvest plot as described in the Cochrane handbook (McKenzie & Brennan, 2019). Synthesis without meta-analysis was also used for the few studies that compared mediated effects between different psychologically based interventions/modalities.

Moderation analyses. Quantitative data synthesis and formal meta-analysis were not possible for the eligible moderation studies, due to the limited number of studies and due to an important heterogeneity related to the intervention, moderator and outcome observed among these studies. Their findings were hence only narratively synthesized, and the direction of the moderated and total effect was summarized in a harvest plot.

4.8. Certainty of evidence

Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria (Balshem et al., 2011) were used to assess the certainty of evidence for the results in the meta-analyses. As all data came from RCTs, high certainty was assumed, and evidence certainty was downgraded 1 category for each of the following GRADE criteria. (i) Risk of bias (>25% of participants came from studies judged as high/unclear risk of methodological bias and/or bias related to mediation analysis, (ii) inconsistency of the results (determined by a significant heterogeneity in pooled indirect effect [$I^2 > 50\%$]), (iii) indirectness of evidence (interventions, populations, comparators, outcomes or mediators were not directly comparable), (iv) imprecision of the results (determined by width of the CIs) and (v) publication bias. Formal publication bias assessment through funnel plots was not considered due to the insufficient number of studies included in each meta-analyses to reliably detect sources of asymmetry (Sterne et al., 2011).

5. Results

5.1. Study selection

Database searches resulted in the identification of 22,808 citations. We obtained 9941 potential citations after the removal of duplicate records, and 38 additional articles were identified through handsearching. After the first screening of titles and abstracts, 152 publications were retrieved for full-text screening. Finally, 37 studies were included with a total of 28 mediation analyses ($n = 4652$) (Cederberg, Cernvall, Dahl, von Essen, & Ljungman, 2016; Chalder, Goldsmith, White, Sharpe, & Pickles, 2015; Coronado et al., 2020; Durá-Ferrandis, Ferrando-García, Galdón-Garrido, & Andreu-Vaillo, 2017; Fordham, Ji,

Hansen, Lall, & Lamb, 2017; Garland et al., 2019; Hedman-Lagerlof et al., 2019; Leeuw et al., 2008; Lin, Klatt, McCracken, & Baumeister, 2018; Luciano et al., 2014; Mansell, Hill, Main, Von Korff, & Van Der Windt, 2017; Mansell, Hill, Main, Vowles, & van der Windt, 2016; Mansell, Storheim, Løchting, Werner, & Grotle, 2017; Molinari et al., 2019; O'Neill, O'Sullivan, O'Sullivan, Purtill, & O'Keeffe, 2020; Pérez-Aranda et al., 2019; Simister et al., 2018; Smeets, Vlaeyen, Kester, & Knottnerus, 2006; Sodermark et al., 2020; Spinhoven et al., 2004; Taylor et al., 2018; Trompetter, Bohlmeijer, Fox, & Schreurs, 2015; Turner, Holtzman, & Mancl, 2007; van Koulil et al., 2011; Wetherell et al., 2011; Wiborg, Knoop, Frank, & Bleijenberg, 2012; Wicksell et al., 2013; Wicksell, Olsson, & Hayes, 2010) and 11 moderation analyses (n = 1925) (Broderick et al., 2016; Buckelew et al., 1996; Day et al., 2019; Flink, Boersma, & Linton, 2010; Lawford et al., 2018; Leeuw et al., 2008; Litt, Shafer, & Kreutzer, 2010; Macedo et al., 2014; Probst, Baumeister, McCracken, & Lin, 2019; Turner et al., 2007; Underwood, Mistry, Lall, & Lamb, 2011) Further details on the screening process can be found in the flow chart illustrated in Fig. 1 and excluded full-text articles with reasons can be found in **Table A.3**.

5.2. Characteristics of the included studies

Low back pain was the most common musculoskeletal disorder (12/37 studies), followed by mixed chronic pain (9/37 studies), fibromyalgia (8/37 studies), knee and hip osteoarthrosis (3/37 studies), chronic fatigue syndrome (2/37 studies), temporomandibular disorders (2/37 studies), post-surgical pain (1/37 studies) and whiplash associated disorders (1/37 studies).

CBT was examined in 26/37 trials (18 mediation and 10 moderation analyses; n = 3655 and 1685 respectively), ACT in 10/37 trials (8 mediation and 1 moderation analyses, n = 837 and 302 respectively) and Mindfulness-based therapy in 3/37 trials (2 mediation and 1 moderation analyses; n = 300 and 69 respectively). Thirty-four studies included a control comparator, of which 16 studies used a passive control group such as waiting list (14 mediation and 4 moderation analysis) and 20 studies used an active control such as usual care or sham intervention (16 mediation and 5 moderation analysis). On the other hand, three studies compared mediators across different CBT modalities and 1 study did so between CBT and ACT. Only one study compared moderators across different experimental interventions (CBT, mindfulness and mindfulness CBT). The detailed intervention characteristics of the individual included studies are summarized in **Table C.1 and C.2**.

All included mediators and moderators were self-reported and continuous measures. A median of 3 (interquartile range [IQR]: 3.25) specific mediators were assessed by study. Half of the studies allowed for a temporal mediator-outcome precedence. Regarding the moderators, a median of 2 (IQR: 2) specific moderators were assessed per study and in all studies but one these were measured prior to treatment allocation. In over half of the studies (18/28 and 7/11), non-specific mediators/moderators of treatment were also examined. Self-reported symptoms (e.g., depression, anxiety, pain intensity, disability and sleep problems) were the most common non-specific mediators/moderators.

Seven studies tested a single mediator model whereas multiple mediators were examined in the remaining 21 studies. Two studies considered both parallel and serial mediation analyses. The other nineteen followed a parallel mediation model, of which ten studies investigated the indirect effect via each mediator by performing separate analyses for each mediator, and 4 studies including all mediators in one analysis. The remaining 7 studies followed a two-step approach where the mediators were first separately analyzed and those with indirect effect statistically significance were then fitted in one common model. Around half of the included studies (14/28) did not adjust for mediator-outcome confounders and only one third of them evaluated the goodness-of-fit of the mediation model.

Over half of the included mediation studies (15/28) reported missing

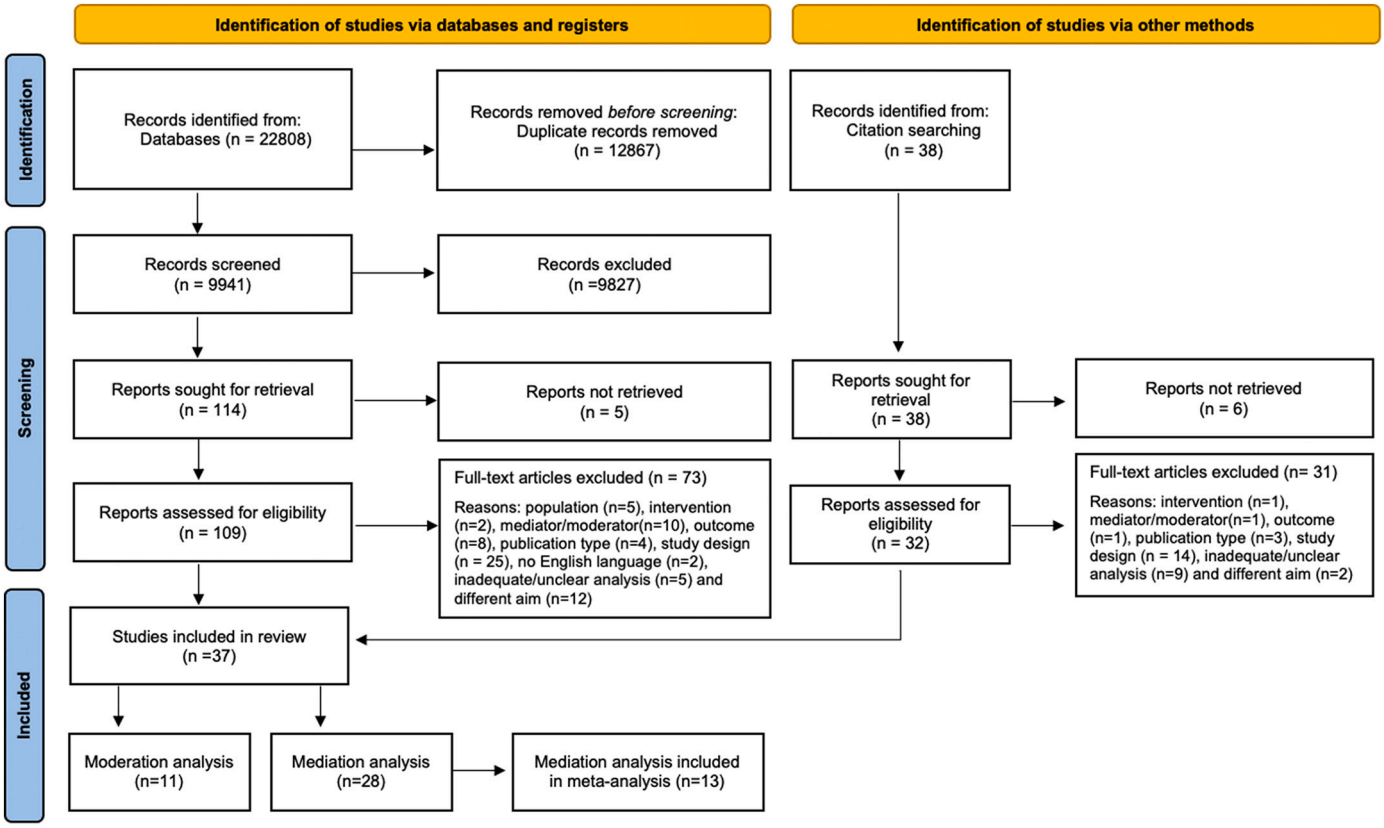


Fig. 1. Flow chart of screening process.

mediator and outcome data of >20%, and only two studies reported missing data of <5%. Complete-case analysis was the most common method to handle missing mediator and outcome data (i.e., used in 5/28 and 9/28 studies with missing data of 5–20% and > 20%, respectively). Regarding moderation analysis, missing outcome data was greater than 20% in 4 studies.

Detailed information on the mediation and moderation analyses of each individual study can be found in Table 1 and Table 2 respectively. A summary and descriptive statistics of the methodological characteristics of the included mediation and moderation studies can be found in Table 3 and **Table C.3**.

5.3. Results of the risk of bias assessment

The summary of the risk of bias assessment for the included mediation and moderation studies is presented in Fig. 2 (see full assessment in **Tables C.4 and C.5**). Regarding the results from the RoB 2.0, 6 mediation studies were evaluated as low risk of bias, 11 as some concerns, and 11 as high risk of bias. Additionally, biases linked to the statistical procedure selected for the mediation analysis were scored as high risk for all studies.

On the other hand, two moderation studies were scored as low risk of bias in the RoB 2.0, 6 as high risk of bias and the other 3 as some concerns.

5.4. Results from mediation studies

5.4.1. Results of the meta-analysis and narrative synthesis: mediated effects of psychologically based interventions vs control treatment

Thirteen (n = 1518)(Cederberg et al., 2016; Chalder et al., 2015; Coronado et al., 2020; Luciano et al., 2014; O'Neill et al., 2020; Pérez-Aranda et al., 2019; Simister et al., 2018; Smeets et al., 2006; Taylor et al., 2018; Trompetter et al., 2015; Turner et al., 2007; Wicksell et al., 2010; Wicksell et al., 2013) and 4 (n = 447)(Coronado et al., 2020; O'Neill et al., 2020; Smeets et al., 2006; Turner et al., 2007) studies were included in the meta-analysis for the outcomes disability and pain intensity, respectively (Figs. 3 to 5**)**. Three studies were re-analyzed (2 single-mediator analyses (Cederberg et al., 2016; Luciano et al., 2014) and 1 parallel multiple-mediator analysis (Smeets et al., 2006)). Results of the mediation studies excluded from the meta-analysis are summarized in a harvest plot (Fig. 6**)**. Full details on GRADE evidence assessment of the studies included in the meta-analysis can be found in **Table C.6**.

5.4.2. Pain catastrophizing

Ten trials (Chalder et al., 2015; Coronado et al., 2020; Durá-Ferrandis et al., 2017; Hedman-Lagerlof et al., 2019; Mansell et al., 2016; Mansell, Storheim, et al., 2017; Smeets et al., 2006; Spinhoven et al., 2004; Taylor et al., 2018; Turner et al., 2007) investigated indirect (i.e., mediated) effects of pain catastrophizing on disability changes after CBT compared to control treatment and 5 trials (Coronado et al., 2020; Durá-Ferrandis et al., 2017; Smeets et al., 2006; Spinhoven et al., 2004; Turner et al., 2007) did so for changes in pain intensity. Two ACT trials examined pain catastrophizing as mediator of treatment compared to control therapy (Simister et al., 2018; Trompetter et al., 2015).

Meta-analysis: Five CBT trials (n = 767) (Chalder et al., 2015; Coronado et al., 2020; Smeets et al., 2006; Taylor et al., 2018; Turner et al., 2007) met the criteria to be included in the meta-analysis for the outcome disability and four (n = 494) (Coronado et al., 2020; Smeets et al., 2006; Turner et al., 2007) to be included for the outcome pain intensity, compared to usual care. The random-effect meta-analysis detected a significant mediated effect on disability via reductions in pain catastrophizing (indirect effect estimate: -0.07 [95% CI -0.14, −0.00]) (Fig. 3). This indicates that disability reduces by 0.07 standard deviations via the pain catastrophizing pathway. The total effect of CBT on disability was found to be moderate (−0.51 [95% CI -0.63, −0.40]), and the estimated proportion of this total effect that was mediated by pain catastrophizing was 20%. Heterogeneity across studies was large for the mediated effect and low for total effects. By contrast, no evidence was found that reductions in pain catastrophizing mediated pain relief (indirect effect estimate: -0.05 [95% CI -0.10, 0.01]) **(**Fig. 4). Heterogeneity across these studies was large for both the mediated effect and the total effect. Certainty of evidence determined by GRADE was very low for both outcomes.

Narrative synthesis: Seven studies were not included in the meta-analysis for the reasons reported in the data synthesis methods. Most of the CBT studies (3/5) excluded support the findings from the meta-analysis for outcome disability (Hedman-Lagerlof et al., 2019; Mansell et al., 2016; Spinhoven et al., 2004) (Fig. 6). The two CBT studies excluded from the meta-analysis for pain intensity reported conflicting findings (Durá-Ferrandis et al., 2017; Spinhoven et al., 2004). Regarding ACT, Trompetter et al. (2015) reported that reductions in catastrophizing mediated treatment effects on disability but not pain intensity and Simister et al. (2018) did not report the results of the mediation analysis for pain catastrophizing.

5.4.2.1. Pain-related fear and avoidance. Eight (Chalder et al., 2015; Coronado et al., 2020; Fordham et al., 2017; Hedman-Lagerlof et al., 2019; Mansell et al., 2016; Mansell, Hill, et al., 2017; O'Neill et al., 2020; Turner et al., 2007) and four (Coronado et al., 2020; Fordham et al., 2017; O'Neill et al., 2020; Turner et al., 2007) CBT trials examined the indirect effects of pain-related fear and avoidance on disability and pain intensity changes, respectively, compared to control therapy. Two ACT trials examined the indirect effects of pain-related fear and avoidance on disability compared to control therapy (Simister et al., 2018; Wicksell et al., 2010).

Meta-analysis: Four CBT trials (n = 560) (Chalder et al., 2015;Coronado et al., 2020 ; O'Neill et al., 2020 ; Turner et al., 2007) were included in the meta-analysis with outcome disability and three (n = 287) (Coronado et al., 2020; O'Neill et al., 2020; Turner et al., 2007) were included for outcome pain intensity, with usual care as comparator. The random-effect meta-analysis detected a significant mediated effect of pain-related fear on disability (indirect effect estimate: -0.07 [95% CI -0.12, −0.02]), which indicates that disability reduces by 0.07 standard deviations through this mediator (Fig. 3). The total effect of CBT on disability (compared to control treatment) was found to be moderate (−0.41 [95% CI -0.56, −0.25]), and the proportion mediated relative to the total effect was 15%. Heterogeneity between studies was moderate for the mediated effect and large for total effect. Pain-related fear did not significantly mediate pain relief after therapy (indirect effect estimate: -0.02 [95% CI -0.06, 0.01]) (Fig. 4). Heterogeneity between studies was low for the mediated effect and total effect. Certainty of evidence determined by GRADE was low for both outcomes.

Narrative synthesis: Findings from the four CBT studies not included in the meta-analysis for disability supported a mediated effect of pain-related fear or avoidance and were, therefore, in line with the results of the meta-analysis (Fordham et al., 2017; Hedman-Lagerlof et al., 2019; Mansell et al., 2016; Mansell, Hill, et al., 2017) (Fig. 6). On the other hand, the CBT study excluded from the meta-analysis for pain intensity reported a mediated effect of this mediator (Fordham et al., 2017). Lastly, both ACT trials found no evidence of mediated effects of pain-related fear on changes in disability (Simister et al., 2018; Wicksell et al., 2010).

5.4.2.2. Self-efficacy. Nine (Chalder et al., 2015; Coronado et al., 2020; Durá-Ferrandis et al., 2017; Fordham et al., 2017; O'Neill et al., 2020; Smeets et al., 2006; Spinhoven et al., 2004; Taylor et al., 2018; Turner et al., 2007) and six (Coronado et al., 2020; Durá-Ferrandis et al., 2017; Fordham et al., 2017; O'Neill et al., 2020; Smeets et al., 2006; Turner et al., 2007) trials examined the indirect effects of self-efficacy on disability and pain intensity, respectively, for CBT compared to control

Table 1
Description of mediators, outcomes and mediation approach of the included studies performing mediation analysis.

Study	Sample	Mediator (s)			Mediator-outcome confounders	Outcome (s)		Mediation analysis approach	Drop-out rate and method for handling missing data
		Specific mediators (measure) [n]	Non-specific mediators	Timepoint[1]		Construct (measure)	Timepoint[1]		
CBT trials									
Chalder et al. (2015) †	CFS (*n* = 641, 80.0% ♀)	Self-efficacy (**SES**), catastrophizing, pain-related fear, symptoms focussing, damage beliefs, embarrassment avoidance beliefs, all-or-nothing behavior and avoidance/resting behavior (**CBRQ**). **[8]**	Anxiety and depression (**HADS**), sleep problems **(JSS)** and exercise tolerance **(Self-paced step** and **6-min walk test)**	Mid-therapy	Mediator and outcome baseline values and other baseline variables (symptoms status and demographic data)	Disability (**SF-36-physical**)	6-month	Paralell (separate) MA Product-of-coefficient	CBT (16%), CBT-APT (10%), CBT-GA (16%), UC (13%) Complete-case analysis[3]
Coronado et al. (2020) †	Post-surgical (*n* = 86, 55.8% ♀)	Pain catastrophizing (**PCS**), self-efficacy (**PSEQ**) and pain-related fear (**TSK-17**). **[3]**	No	≈1- and 4-month	Mediator and outcome baseline values	Disability (**ODI** and **SF-12 physical)** Pain intensity (**BPI**)	≈4-month	Parallel (one analysis) MA Product-of-coefficient	CBT (11.6%) and UC (2.3%) Complete-case analysis and multiple imputation
Durá-Ferrandis et al. (2017) †	TMD (*n* = 72, 88.9% ♀)	Pain catastrophizing (**PCS**), coping (**CAD-distraction**) and self-efficacy (**CAD-self control)** and **SOPA-35-control**). **[4]**	Disability beliefs (**SOPA-disability**) and distress (**BSI-18**)	Post-therapy	No	Disability (**MPI-interference**) Pain intensity (**CPGS-pain**)	Post-therapy	Parallel (one analysis) and serial MA Product-of-coefficient	CBT (26.8%) and UC (29.27%) Complete-case analysis
Fordham et al. (2017) †	LBP (*n* = 701, 59.9% ♀)	Self-efficacy (**PSEQ**) and pain-related fear (**FABQ**). **[2]**	Disability (**SF-12 physical)** and mental functioning (**SF-12 mental)**	≈1-, 4- and 10-month	No	Disability (**RMDQ** and **CPGS-interference**) Pain intensity (**CPGS-pain**)	≈1-, 4- and 10-month	Parallel (two-step) and serial MA Product-of-coefficient	CBT (16.0%) and WL (18.9%) Complete-case analysis
Hedman-Lagerlof et al. (2019) †	FM (=140, 97.9% ♀)	Pain-related fear (**PIPS-avoidance**), mindfulness non-reactivity (**FFMQ-non reactivity**) and pain catastrophizing (**PRS**). **[3]**	No	Every-week	No	Disability (**FIQ**)	Every-week	Parallel (two-step) MA Product-of-coefficient	CBT (5.7%) and WL (0%) MLE
Leeuw et al. (2008)[2]	LBP (*n* = 85, 49.2% ♀)	Pain catastrophizing (**PCS**) and pain-related fear (**PHODA**). **[2]**	No	Post-therapy and 6-month	Mediator baseline values, other baseline variables (financial compensation, pain duration and gender) and post-therapy mediator-outcome confounders (post-therapy mediator value)	Disability (**QBPDS** and **PSC**)	Post-therapy and 6-month	Single MA Product-of-coefficient	CBT-EXP (9.5%) and CBT-GA (18.3%) MLE
Mansell et al. (2016) †	LBP (*n* = 236, 56.4% ♀)	Mediators grouped in **[1]** latent variable. Pain catastrophizing (**PCS**) and pain-related fear (**TSK-17**).	Anxiety and depression (**HADS**) and pain intensity (**NRPS**)	≈1-month	No [3]	Disability (**RMDQ**)	≈1-month	Parallel (one analysis) MA Product-of-coefficient	CBT (41.8%) and UC (43.0%) Complete-case analysis
Mansell, Hill, et al. (2017) †	LBP (n = 240, 62.5% ♀)	Pain-related fear (**TSK-10**). **[1]**	No	Post-therapy, 4-, 10- and 22-month	No	Disability (**RMDQ**)	Post-therapy, 4–10- and 22-month	Single MA Latent growth modeling	CBT (21%) and WL (24.1%) Simple imputation
Mansell, Storheim, et al. (2017) †	LBP (*n* = 216, 54.2% ♀)	Pain catastrophizing (**PCS**), Illness perceptions (**IPQ-9**), Pain beliefs (**BPMQ-12**). **[3]**	No	Post-therapy	Other baseline variables (pain intensity and duration, and provider)	Disability (**RMDQ**)	Post-therapy	Parallel (separate) MA Product-of-coefficient	CBT (22%) and UC (18.9%) Unclear
Molinari et al. (2019) †	FM (*n* = 80, 100% ♀)	Positive and negative affect (**PANAS-positive and negative**). **[2]**	Treatment expectancies (**SPT-negative and positive**) and depression (**BDI**)	Post-therapy	Outcome baseline value	Disability (**FIQ**)	Post-therapy	Parallel (one analysis) MA Product-of-coefficient	Mindfulness (37.5%) and UC (30.0%) Complete-case analysis
O'Neill et al. (2020) †	LBP (*n* = 206, 73.8% ♀)	Self-efficacy (**PSEQ**), pain-related fear (**FABQ-physical activity**), coping (**CSQ-coping**). **[3]**	Sleep problems, anxiety and depresion (**Yes/No**	≈3-month	Outcome baseline value[3]	Disability (**ODI**) Pain intensity **(NRPS)**	≈9-month	Parallel (separate) MA	CBT (31.1%) and UC (25%)

(*continued on next page*)

Table 1 (*continued*)

Study	Sample	Mediator (s)			Mediator-outcome confounders	Outcome (s)		Mediation analysis approach	Drop-out rate and method for handling missing data
		Specific mediators (measure) [n]	Non-specific mediators	Timepoint[1]		Construct (measure)	Timepoint[1]		
			question) and stress (**DASS-stress**)					Natural/indirect effect	Complete-case analysis[4]
Smeets et al. (2006) †	LBP (*n* = 223, 47.1% ♀)	Pain castastrophizing and self-efficacy (**PCL-catastrophizing** and **internal control**). **[2]**	No	Post-therapy	Mediator and Outcome baseline values and other baseline variables (age, gender, treatment center and disability duration)	Disability (**RMDQ** and **PSC**) Pain intensity (**VAS**)	Post-therapy	Parallel (separate) MA Causal step-Baron & Kenny	CBT (5.2%), CBT + UC (9.8%), UC (1.9%) and WL (2.0%) Complete-case analysis
Sodermark et al. (2020)[2]	Mixed chronic pain (*n* = 115, 83.3% ♀)	Mediators grouped in **[2]** latent variables. (1) Pain catastrophizing (**PCS**), pain-related fear (**TSK-11**) and pain acceptance (**CPAQ**). (2) Emotional regulation (**DERS**), self-compassion (**SCS**) and depression (**BADS**).	No	Post-therapy	Mediator and Outcome baseline values	Disability (**MPI**)	9-month	Parallel (separate) MA Product-of-coefficient [5]	CBT (79%) and hybrid CBT (84%) MLE
Spinhoven et al. (2004) †	LBP (*n* = 148, 63.5% ♀)	Pain catastrophizing, self-efficay and coping (**PCCL-catastrophizing, internal control and coping**). **[3]**	Treatment expectancies (**PCCL external pain control**)	Post-therapy	No	Disability (**PBS**) Pain intensity (**McGill PQ-Pain**)	Post-therapy	Parallel (separate) MA Causal step-Baron & Kenny	CBT (14.6%), CBT + Disc (10.3%) and WL (3.2%) Complete-case analysis
Taylor et al. (2018) †	Knee/hip OA (*n* = 300, 9.3% ♀)	Pain catastrophizing (**PCS**), self-efficacy (**ASES** and **CSQ**-two items). **[3]**	No	Mid-therapy	Other baseline variables (race) and post-therapy mediator-outcome confounders (depression and physical activity)	Disability (**WOMAC-function**)	Post-therapy	Parallel (two-step) MA Product-of-coefficient	CBT (9.9%) and UC (8.1%) Complete-case analysis
Turner et al. (2007) †	TMD (*n* = 158, 81.0% ♀)	Pain catastrophizing (**PCS-rumination** and **CSQ-catastrophizing**), self-efficacy (**ASES** and **SOPA-57-control**), coping (**CPCI-relaxation**) and pain-related fear (**SOPA-57-harm**). **[6]**	Disability (**SOPA-57-disability**)	3-month	Mediator baseline value	Disability (**MFIQ** and **CPGS-interference**) Pain intensity (**CPGS-pain**)	9-month	Parallel (two-step) MA Causal step-Baron & Kenny and Product-of-coefficient	CBT (13.9%) and UC (11.4%) Complete-case analysis
van Koulil et al. (2011) †	FM (n = 158, 93% ♀)	Coping (**PCI-resting**) and activity pacing (**APS**). **[2]**	No	Post-therapy	Mediator and outcome baseline values	Disability (**IRGL-mobility**)	Post-therapy	Single MA Joint significance test	CBT-EXP (5.0%), CBT-APT (13.8%) and WL (4.6%) MLE and LOCF
Wetherell et al. (2011)[2]	Mixed chronic pain (n = 114, 50.9% ♀)	Pain acceptance (**CPAQ**) and self-efficacy (**SOPA-57-control**). **[2]**	No	Post-therapy	Outcome baseline value and other baseline variables (depression)	Disability (**BPI-interference**)	Post-therapy	Single MA Product-of-coefficient	CBT (26.3%) and ACT (22.8%) MLE
Wiborg et al. (2012) †	CFS (*n* = 169, 79.29% ♀)	Somatization (**SCL-90-somatization**). **[1]**	Disability (**CIS-activity**)	Post-therapy	Other baseline variables (gender, age and illness duration)	Disability (**SIP** and **SF-36-physical**)	Post-therapy	Parallel (two-step) MA Product-of-coefficient	CBT (8.3%) and WL (30.9%) Complete-case analysis
ACT trials									
Cederberg et al. (2016) †	Mixed chronic pain (*n* = 90, 64.4% ♀)	Pain acceptance (**CPAQ**). **[1]**	Anxiety and Depression (**HADS**)	Post-therapy	Post-therapy Mediator-Outcome confounders (Pain intensity and post-therapy outcome value)	Disability (**ÖMPQ**)	6- and 12-month	Parallel (separate) MA Product-of-coefficient	ACT (67.3%) and AR (60.5%) Complete-case analysis
Lin et al. (2018) †	Mixed chronic pain (n =	Mediators grouped in **[1]** latent variable Pain acceptance (**CPAQ-**	No	Post-therapy	No	Disability (**MPI-interference, BPI-**	≈4-month	Single MA Product-of-coefficient	Guided-ACT (46.0%), unguided-ACT

(*continued on next page*)

Table 1 (*continued*)

Study	Sample	Mediator (s)			Mediator-outcome confounders	Outcome (s)		Mediation analysis approach	Drop-out rate and method for handling missing data
		Specific mediators (measure) [n]	Non-specific mediators	Timepoint[1]		Construct (measure)	Timepoint[1]		
	302, 84.1% ♀)	**willingness and activity engagement** and **AAQ-II**).				**interference**) Pain intensity **(NRPS)**			(44.6%) and WL (22.8%) Single imputation
Luciano et al. (2014)	FM (n = 156, 96.2% ♀)	Pain acceptance (**CPAQ**). **[1]**	No	Post-therapy	No	Disability **(FIQ)** Pain intensity **(VAS)**	6-month	Single MA Product-of-coefficient	ACT (11.8%), UC (15.4%) and WL (11.3%) Complete-case analysis
Simister et al. (2018)	FM (n = 67, 95% ♀)	Pain acceptance **(CPAQ), fusion (CFQ)**, **valued living (VLQ),** Pain catastrophizing **(PCS),** pain-related fear and avoidance **(TSK-11)** and mindfulness **(FFMQ). [5]**	No	Post-therapy	No	Disability **(FIQ)**	3-month	Parallel (separate) MA Product-of-coefficient.	ACT (24.2%) and UC (26.5%) Single imputation
Trompetter et al. (2015) †	Mixed chronic pain (n = 240, 76.1% ♀)	Psychological flexibility (**PIPS**) and pain catastrophizing (**PCS**). **[2]**	No	Post-therapy	No	Disability (**MPI-interference)** Pain intensity **(NRPS)**	3-month	Parallel (two-step) MA Product-of-coefficient	ACT (28.0%), ExpW (35.44%) and WL (19.5%) Single imputation
Wetherell et al. (2011)[2]	Mixed chronic pain (n = 114, 50.9% ♀)	Pain acceptance (**CPAQ**) and self-efficacy (**SOPA-57-control**). **[2]**	No	Post-therapy	Outcome baseline value and other baseline variables (depression)	Disability (**BPI-interference)**	Post-therapy	Parallel (separate) MA Product-of-coefficient	ACT (22.8%) and CBT (26.3%) MLE
Wicksell et al. (2010) †	CWAD (n = 21, 76.2% ♀)	Pyschological flexibility (**PIPS-total and subscales**), self-efficacy (**SES**), pain-related fear and avoidance (**TSK-17**). **[5]**	Pain intensity (**VAS**), anxiety and depression (**HADS**)	Post-therapy	No	Disability (**PDI**)	Post-therapy and 4-month	Parallel (two-step) MA Product-of-coefficient	ACT (4.8%) and WL (4.8%) Single imputation
Wicksell et al. (2013)	FM (n = 40, 100% ♀)	Psychological flexibility (**PIPS**). **[1]**	No	Post-therapy	No	Disability (**PDI** and **FIQ**)	3–4-month	Single MA Product-of-coefficient	ACT (17.4%) and WL (17.6%) Complete-case analysis
Mindfulness trials									
Garland et al. (2019)	Mixed chronic pain (n = 95, 66% ♀)	Mediators grouped in **[1]** latent variable. Positive affect (**PANAS-positive**), meaning in life (**MLQ-presence of meaning**), and self-transcendence (**NADA**).	No	Post-therapy	No	Pain intensity (**BPI**)	Post-therapy	Single MA Product-of-coefficient.	Mindfulness (24.0%) and support (15.6%) MLE
Pérez-Aranda et al. (2019)	FM (n = 255, 98.7% ♀)	Pyschological flexibility (**PIPS**), self-compassion (**SCS**) and Mindfulness **(FFMQ observe, describe, act with awareness, nonjudge and nonreact)**. **[3]**	No	Post-therapy	No	Disability **(FIQ)**	12-month	Parallel (separate) MA Product-of-coefficient	Mindfulness (34.7%), sham (32.0%) and WL (34.7%) Complete-case analysis

CBT, Cognitive behavioral therapy; CFS, chronic fatigue syndrome; SES, Self-efficacy scale; CBRQ, Cognitive and Behavioral Response Questionnaire; HADS, Hospital Anxiety and Depression Scale; JSS, Jenkins Sleep Scale; SF, Short Form Health Survey; MA, Mediation analysis; APT; Activity pacing therapy; GA, Graded activity; UC, Usual care; PCS, Pain Catastrophizing Scale; PSEQ, Pain Self-efficacy Questionnaire; TSK, Tampa Scale of Kinesiophobia; ODI, Oswestry Disability Index; BPI, Brief Pain Inventory; TMD, temporomandibular disorders; CAD, Coping Pain Questionnaire; SOPA, Survey of Pain Attitudes; BSI, Brief symptoms inventory; MPI, Multidimensional Pain Inventory; CPGS, Chronic Pain Grade Scale; LBP, low back pain; FABQ, Fear Avoidance Beliefs Questionnaire; RMDQ, Roland Morris Disability Questionnaire; WL, waiting list; PIPS, Psychological Inflexibility in Pain Scale; FFMQ, Five Facet Mindfulness Questionnaire; PRS, Pain Reactivity Scale; FIQ, Fibromyalgia Impact Questionnaire; MLE, maximum likelihood estimation; PHODA, Photograph Series of Daily Activities; QBPDS, Quebec Back Pain Disability Scale; PSC, Patient Specific Complaints; EXP; exposure in vivo; NRPS, Numerical Rating Pain Scale; IPQ, Illness and Perceptions Questionnaire; Back Pain Myths Questionnaire; CSQ, Coping Strategies Questionnaire; DASS, Depression and Anxiety and Stress Scale; PCL, Pain Cognition List; VAS, visual analogue scale; DERS, Difficulties in Emotion Regulation Scale; SCS, self-compassion scale; BADS, Behavioral Activation for Depression Scale; PCCL, Pain Coping and Cognition List; PBS, Pain Behavior Scale; McGill PQ; McGill Pain Questionnaire; Disc, Discussion; OA, osteoarthrosis; ASES, Arthritis Self-Efficacy Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; CPCI, Chronic Pain Coping Inventory; MFIQ, Mandibular Function Impairment; FM, fibromyalgia; PCI, Pain Coping Inventory; APS, Activity Pacing Scale; IRGL, Impact of Rheumatic Diseases on General Health and Lifestyle; LOCF, last observation carried forward; CPAQ, Chronic Pain Acceptance Questionnaire; ACT, acceptance and commitment therapy; SIP, Sickness Impact Profile; SCL, Symptom Checklist; CIS, Checklist Individual Strength; ÖMPQ, Örebro Musculoskeletal Pain Questionnaire; AR, applied relaxation; AAQ-II, Acceptance and Action Questionnaire-II; MPI, Multidimensional Pain Inventory; BPI, Brief Pain Inventory; FM, fibromyalgia; CFQ, Cognitive Fusion Questionnaire; VLQ, Valued Living Questionnaire; ExpW, Expressive writing; SOPA, Survey of Pain Attitudes; CWAD, chronic whiplash associated disorders; PDI, Pain Disability Index; PANAS, Positive and Negative Affect Scale; Meaning in Life Questionnaire; NADA, Nondual Awareness Dimensional Assessment; SPT, Subjective Probability Task; BDI, Beck Depression Index.

Notes: † Secondary analysis of a previously published RCT; [1] Timepoints (follow-ups) were normalized to the end of therapy; [2] No control group; [3] Sensitivity analysis is performed to assess the risk of unmeasured confounders; [4] Sensitivity analysis is performed to assess the impact of missing data on the results; [5] Moderated mediation was also tested.

therapy. One ACT trial examined self-efficacy as mediator of treatment (Wicksell et al., 2010).

Meta-analysis: Six CBT trials (n = 998)(Chalder et al., 2015; Coronado et al., 2020; O'Neill et al., 2020; Smeets et al., 2006; Taylor et al., 2018; Turner et al., 2007) were included in the meta-analysis with outcome disability and four (n = 452)(Coronado et al., 2020; O'Neill et al., 2020; Smeets et al., 2006; Turner et al., 2007) were included for outcome pain intensity, with usual care as comparator. The random-effect meta-analysis detected a significant mediated effect of self-efficacy on disability (indirect effect estimate: -0.07 [95% CI -0.11, −0.04]) (Fig. 3). This mediated effect accounted for 17% of the total effect (−0.44 [95% CI -0.56, −0.33]). Heterogeneity between studies was low for the mediated effect and total effect. Self-efficacy did not significantly mediate pain relief after CBT (indirect effect estimate: -0.03 [95% CI -0.06, 0.01]) (Fig. 4). Heterogeneity between studies was low for the mediated effect and total effect. Certainty of evidence determined by GRADE was low for both outcomes.

Narrative synthesis: Overall, the three CBT studies excluded from the quantitative sysnthesis reported consistent findings with those observed in the meta-analysis for mediated effect of self-efficacy on diability (Durá-Ferrandis et al., 2017; Fordham et al., 2017; Spinhoven et al., 2004) (Fig. 6). The two studies excluded from the meta-analysis for pain intensity reported a mediated effect of this mediator, contrary to the results of the meta-analysis (Durá-Ferrandis et al., 2017; Fordham et al., 2017). The ACT trial did not find evidence for mediated effect of self-efficacy on disability (Wicksell et al., 2010).

5.4.2.3. Pain acceptance & psychological flexibility. Eight trials (Cederberg et al., 2016; Lin et al., 2018; Luciano et al., 2014; Simister et al., 2018; Trompetter et al., 2015; Wetherell et al., 2011; Wicksell et al., 2010; Wicksell et al., 2013) examined the indirect effects of pain acceptance or psychological flexibility for ACT on disability compared to control therapy and three trials (Lin et al., 2018; Luciano et al., 2014; Trompetter et al., 2015) did so for pain intensity. One mindfulness study examined psychological flexibility as mediator of treatment on disability (Pérez-Aranda et al., 2019).

Meta-analysis: 6 studies met the criteria to be included in the meta-analysis to examine the indirect effects of pain acceptance (n = 213, compared to usual care) (Cederberg et al., 2016; Luciano et al., 2014; Simister et al., 2018) and psychological flexibility (n = 312, compared to waiting list) (Pérez-Aranda et al., 2019; Trompetter et al., 2015; Wicksell et al., 2010; Wicksell et al., 2013) were included for the meta-analysis on disability. The random-effect meta-analysis detected a significant mediated effect on disability through increases in pain acceptance (indirect effect estimate: -0.17 [95% CI -0.31, −0.03]) (Fig. 5). This mediated effect accounted for 16% of the total effect of ACT (−1.04 [95% CI -1.88, −0.20]). Heterogeneity between studies was low for the mediated effect and large for total effect. A significant mediated effect on disability was also observed via increases in psychological flexibility (indirect effect estimate: -0.30 [95% CI -0.41, −0.18]) (Fig. 5). This mediated effect accounted for 75% of the total effect of ACT (−0.40 [95% CI -0.70, −0.10]). Heterogeneity between studies was large for the mediated effect and moderate for total effect. Certainty of evidence determined by GRADE was very low for both mediators of ACT.

Narrative synthesis: One ACT trial could not be included in the meta-analysis and reported that increases in pain acceptance mediated reductions in disability (Lin et al., 2018)(Fig. 6). Regarding pain intensity, Lin et al. (2018) and Trompetter et al. (2015) found that increases in acceptance and psychological flexibility mediated reductions in pain intensity after ACT while Luciano et al. (2014) found no evidence for mediated effect for pain acceptance on this outcome.

5.4.2.4. Other mediators: general coping, somatization and mindfulness measures. Six CBT trials examined the mediated effects of general coping, measured with several measures, on disability or pain intensity

Table 2
Description and measurement of moderators and outcomes in included studies performing moderation analysis.

Study	Sample	Moderator(s)		Outcome(s)		Test of interaction moderator-treatment	Drop-out rate and method for handling missing data
		Construct (measure) [n]	Non-specific moderator (s)	Construct (measure)	Timepoint[2]		
CBT trials							
Buckelew et al. (1996)	FM (n = 119, 89.9%♀)	Self-efficacy **(ASES)**. **[1]**	No	Disability **(AIMS)** Pain intensity **(VAS)**	Post-therapy	Yes	Total (8.4%) Unclear
Broderick et al. (2016) †	Knee/hip OA (n = 257, 76.7% ♀)	Coping **(MPI-interpersonal distress and dysfunctional)**. **[2]**	Demographic data, x-ray severity, treatment expectancies **(CEQ)** and depression **(BDI)**.	Disability **(AIMS and WOMAC)** Pain intensity **(BPI)**	Post-therapy	Yes	CBT (28.3%) and WL (29.5%) MLE
Day et al. (2019) †	LBP (n = 69, 52% ♀)	Pain catastrophizing **(PCS)**, mindfulness **(FFMQ-observe and non-reactivity)**. **[3]**	No	Disability **(PROMIS interference** and **physical function)** Pain intensity **(NRPS)**	Post-therapy	Yes	Mindfulness (39.1%), mindfulness CBT (21.7%) and CBT (30.4%) LOCF
Flink et al. (2010) †	LBP (n = 46, 52.9% ♀)	Pain catastrophizing **(PCS)**. **[1]** [1]	Anxiety and depression **(HADS)**	Disability **(QBPDS)**	Post-therapy	Yes	CBT (38.1%) and WL (16%) Complete-case analysis
Lawford et al. (2018) †	Knee OA (n = 148, 56.1% ♀)	Pain catastrophizing **(PCS)** and self-efficacy **(ASES)**. **[2]**	Demographic data and treatment expectancies **(5-point scale)**	Disability **(WOMAC-function)** Pain intensity during walking **(NRPS)**	Post-therapy and 6-month	Yes	CBT (10.8%) and UC (9.5%) Unclear
Leeuw et al. (2008)	LBP (n = 85, 49.2% ♀)	Pain-related fear **(PHODA)**. **[1]**	No	Disability **(QBPDS** and **PSC)** Pain intensity **(VAS)**	Post-therapy and 6-month	Yes	CBT-EXP (9.5%) and CBT-GA (18.3%) MLE
Litt et al. (2010)	TMD (n = 101, 84.2% ♀)	Pain catastrophizing **(PRSSS-catastrophizing)**, Self-efficacy **(CPSS)**, coping **(PRSSS-coping** and **MBSS-monitoring)** and somatization **(SCL-90-somatization)**. **[5]**	Treatment expectancies **(PSOCQ)** and optimisim (Not reported).	Disability **(MPI-interference)** Pain intensity **(MPI-pain)**	Post-therapy, 2, 4, 7, 10-month	Yes	CBT (26.5%) and UC (28.8%) MLE
Macedo et al. (2014) †	LBP (n = 172, 59.3% ♀)	Self-efficacy **(PSEQ)**, pain-related fear **(PASS)** and coping **(CSQ)**. **[3]**	Physical activity level **(IPAQ)**, walking tolerance **(SWT)**, clinical instability **(LSIQ)** and disability **(ÖMPQ)**	Disability **(PSFS)**	Post-therapy and 10-month	Yes	CBT (7.0%) and UC (12.8%) Unclear
Turner et al. (2007) †	TMD (n = 158, 81.0% ♀)	Somatization **(SCL-90-somatization)**. **[1]**	Demographic data, symptoms (pain duration and number of painful sites), depression **(BDI)** and tendency to experience negative affect **(NEO-Neuroticism and Openness)** and stress **(PSS)**	Disability **(MFIQ** and **CPGS-interference)** Pain intensity **(CPGS-pain)**	9-month	Yes	CBT (13.9%) and UC (11.4%) Complete-case analysis
Underwood et al. (2011) †	LBP (n = 701, 59.9% ♀)	Self-efficay **(PSEQ)** and pain-related fear **(FABQ)**. **[2]**	Demographic data, symptoms (pain frecuency, duration and troublesomeness), anxiety and depression **(HADS)**	Disability **(RMDQ** and **CPGS-disability)** Pain intensity **(CPGS-pain)**	10-month	Yes	CBT (16.0%) and WL (18.9%) Complete-case analysis
ACT trials							
Probst et al. (2019) †	Mixed chronic pain (n = 302, 84.1% ♀)	Pain acceptance **(AAQ-II)**. **[1]**	No	Disability **(MPI-interference)**	Post-therapy and ≈4-month	Yes	Guided-ACT (46.0%), unguided-ACT (44.6%) and WL (22.8%) Single imputation
Mindfulness trials							
Day et al. (2019) †	LBP (n = 69, 52% ♀)	Pain catastrophizing **(PCS)**, mindfulness **(FFMQ-observe and non-reactivity)**. **[3]**	No	Disability **(PROMIS interference and physical function)** Pain intensity **(NRPS)**	Post-therapy	Yes	Mindfulness (39.1%), mindfulness CBT (21.7%) and CBT (30.4%) LOCF

CBT, Cognitive behavioral therapy; FM; fibromyalgia; ASES, Arthritis Self-Efficacy Scale; AIMS, Arthritis Impact Measurement Scales; VAS, Visual Analogue Scale; OA, osteoarthrosis; MPI, Multidimensional Pain Inventory; CEQ, Credibility/Expectancy Questionnaire; BDI, Beck Depression Inventory; BPI, Brief Pain Inventory; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; WL, waiting list; MLE, maximum likelihood estimation; LBP, low back pain; PCS, Pain Catastrophizing Scale; FFMQ, Five Facet Mindfulness Questionnaire; PROMIS; Patient-Reported Outcomes Measurement Information System; NRPS, Numerical Rating Pain Scale; LOCF, last observation carried forward; HADS, Hospital and Anxiety Scale; QBPDS, Quebec Back Pain Disability Scale; UC, Usual care; PHODA, Photograph Series of Daily Activities; QBPDS, Quebec Back Pain Disability Scale; PSC, Patient Specific Complaints; EXP, exposure in vivo; GA, graded activity; TMD, temporomandibular disorders; CPSS, Chronic Pain Self-Efficacy Scale; PRSSS, Pain-Related Self-Statements Scale; MBSS, Miller Behavioral Style Scale; SCL, Symptom Checklist; PSOCQ, Pain Stages of Change Questionnaire; PSEQ, Pain Self-efficacy Questionnaire; PASS, Pain Anxiety Symptoms Scale; CSQ, Coping Strategies Questionnaire; ÖMPQ, Örebro Musculoskeletal Pain Questionnaire; IPAQ, International Physical Activity Questionnaire; LSIQ, Lumbar Spine Instability Questionnaire; SWT, Shuttle Walk Test; PSFS, Patient-Specific Functional Scale; NEO, NEO Five-Factor; Inventory; PSS, Perceived Stress Scale; MFIQ, Mandibular Function Impairment Questionnaire; CPGS, Chronic Pain Grade Scale; FABQ, Fear Avoidance Beliefs Questionnaire; RMDQ, Roland Morris Disability Questionnaire; AAQ-II, Acceptance and Action Questionnaire-II.
Notes: † Secondary analysis of a previously published RCT; [1] Baseline measurement prior randomization. [2] Timepoints (follow-ups) were normalized to the end of therapy.

and reported conflicting findings (Chalder et al., 2015; Durá-Ferrandis et al., 2017; O'Neill et al., 2020; Spinhoven et al., 2004; Turner et al., 2007; van Koulil et al., 2011). Three studies found that disability reduced via descreases in coping whereas three studies did not find evidence for such a mediated effect. No evidence for mediated effect of coping on pain intensity was observed in three studies. Regarding pain vigilance and somatization, Chalder et al. (2015) reported a mediated effect for CBT effects on disability when compared to usual care whereas Wiborg et al. (2012) did not find evidence for such a mediated effect. Two studies examined the indirect effect of changes in measures of mindfulness on disability after CBT (Hedman-Lagerlof et al., 2019) and mindfuness-based therapy (Pérez-Aranda et al., 2019) and reported inconclusive results. Additionally, positive and negative affect were found to mediate changes in disability (Molinari et al., 2019) and pain intensity (Garland et al., 2019) after CBT and mindfulness respectively. Results of the studies examining the mediated effects of general coping, somatization and mindfulness measures are summarized in a harvest plot (Fig. 6**).**

5.4.2.5. Results of the narrative synthesis: mediated effects between different psychologically based interventions. Four studies compared the mediated effects between interventions with different theoretical frameworks. Chalder et al. (2015) examined the mediated effect of CBT (focused on cognitive restructuring) and graded activity on disability compared to activity pacing. Pain catastrophizing, pain-related fear, pain vigilance, damage beliefs and other measures of coping were found to mediate the effects of CBT and graded activity when compared to activity pacing. Pain-related fear and avoidance accounted for the largest proportion of the total effect (37% and 51% respectively). Leeuw et al. (2008) showed that pain-related fear and catastrophizing mediated the effects of exposure in vivo on disability compared to graded activity, accounting for 75% of the total effect. Sodermark et al. (2020) reported that a latent variable consisted of pain-related fear, catastrophizing and acceptance mediated the effects of a hybrid CBT intervention (including techniques addressing comorbid depression) on disability compared to traditional CBT. Lastly, Wetherell et al. (2011) compared the mediated effects of pain acceptance and self-efficacy on disability between CBT and ACT and reported no mediated effects for any of them. A summary of the narrative synthesis of the results from these studies can be found in **Table C.7.**

5.5. Moderation studies

5.5.1. Results of the narrative synthesis

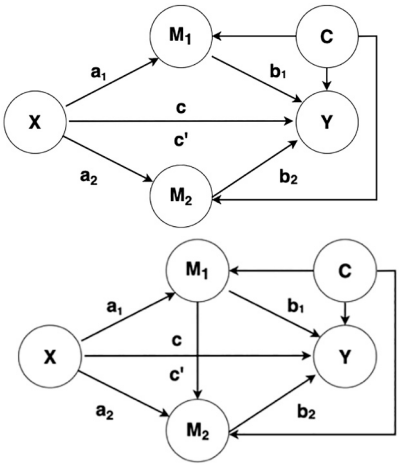
Results of the studies that compared moderated effects of psychologically based interventions vs control treatment are summarized in a harvest plot (Fig. 7**)**. Two studies (Day et al., 2019; Leeuw et al., 2008) compared moderated effects between different psychologically based interventions.

5.5.1.1. Pain catastrophizing. Conflicting results were reported from 3 CBT trials. Flink et al. (2010) found low pre-treatment pain catastrophizing to be a moderator of reduction in disability after CBT compared to control, while the other two trials did not observe any evidence of moderated effect for changes disability as well as pain intensity (Lawford et al., 2018; Litt et al., 2010).

5.5.1.2. Pain-related fear and avoidance. Evidence from 2 CBT trials did not support pre-treatment pain-related fear as moderator of CBT effect for pain intensity or disability compared to control therapy (Macedo et al., 2014; Underwood et al., 2011). Also, Leeuw et al. (2008) did not find evidence of an interaction between pre-treatment pain-related fear an either exposure in vivo or graded activity for both outcomes.

5.5.1.3. Self-efficacy. Five CBT trials examined if pre-treatment self-

Table 3
Summary of the methodological characteristics of included mediation studies.

Domain		All studies n of studies (%)	Meta-analysis n of studies (%)
Planning of mediation analysis			
1.1	Implementation of mediation analysis		
	• Primary analysis	5 (17.85)	3 (23.08)
	• Secondary analysis of a previously published trial	23 (82.14)	10 (76.92)
1.2	Protocol		
	• No published protocol	23 (82.14)	11 (84.62)
	• Published protocol, but mediation analysis is not planned a priori	3 (10.71)	1 (7.69)
	• Published protocol and mediation analysis is preplanned a priori (w.r.t the mediators, outcome and approach used)	2 (7.14)	1 (7.69)
1.3	If planned a priori, there was a deviation from protocol (w.r.t the mediators, outcome and approach used)		
	• No deviation	1 (3.57)	0 (0)
	• Deviation	1 (3.57)	1 (7.69)
1.4	ITT treatment effect was statistically significant in all of the outcomes included in the mediation analysis	22 (78.57)	11 (84.62)
1.5	Authors stated that the mediation analysis was conducted when ITT treatment effect was statistically significant	8 (28.57)	6 (46.15)
Mediator(s) and outcome characteristics			
2.1	Number of specific mediators assessed (median)	3	3
2.2	Rationale for the mediator selection		
	• Based on a theoretical framework	26 (92.86)	12 (92.31)
	• Based on results of previous studies	23 (82.14)	11 (84.62)
	• Not specified	2 (7.14)	1 (7.69)
2.3	Studies including non-specific mediators	11 (39.28)	6 (46.15)
2.4	Mediators measured by several scales (latent variable)	4 (14.28)	0 (0)
2.5	Mediators repeatedly measured (and all measurements included into the analysis)	5 (17.85)	1 (7.69)
2.6	Outcome measured by several scales	0 (0)	0 (0)
2.7	Outcome repeatedly measured (and all measurements included into the analysis)	6 (21.42)	2 (15.38)
2.8	Was the proposed mediator(s) measured before outcome assessment?	14 (50.00)	11 (84.62)
Statistical power			
3.1	Sample size calculated	0 (0)	0 (0)
3.2	Authors discuss impact of sample size on the results	8 (28.57)	4 (30.77)
Missing data and handling missing data			
4.1	Percentage missing data		
	• No missing data	0 (0)	0 (0)
	• <5% missing data	2 (7.14)	0 (0)
	• 5-20% missing data	13 (46.42)	9 (69.23)
	• >20% missing data	13 (46.42)	4 (30.77)
4.2	Approach used to handle missing data		
	• ITT: single imputation	5 (17.85)	3 (23.08)
	• ITT: multiple imputation	1 (3.57)	1 (7.69)
	• ITT: last observation carried forward	1 (3.57)	0 (0)
	• ITT: full information maximum likelihood	6 (21.42)	0 (0)
	• Complete-case analysis	15 (53.57)	10 (76.92)
	• Unclear/NI	2 (7.14)	0 (0)
4.3	Performing sensitivity analysis to assess the impact of missing data on the findings	3 (10.71)	2 (15.38)
Mediational Analysis approach			
5.1	Single mediator analysis	7 (25.00)	2 (15.38)
	• Traditional approaches	7 (25.00)	2 (15.38)
	• Causal approaches	0 (0)	0 (0)
	• Other approaches	0 (0)	0 (0)
5.2	Multiple mediators' analysis	21 (75.00)	11 (84.62)
	• Traditional approaches	20 (71.42)	10 (76.92)
	• Causal approaches	1 (3.57)	1 (7.69)
	• Other approaches	0 (0)	0 (0)
5.4	Model for multiple mediators' analysis		
	• Parallel model	21 (75.00)	11 (84.62)
	• Separate analysis for each mediator	10 (35.71)	6 (46.15)
	• One common model for all mediators	4 (14.28)	1 (7.69)
	• Two-step approach	7 (29.00)	4 (30.77)
	• Serial model	2 (7.14)	0 (0)
	 **Note:** In **(A) parallel mediation analysis** does not assume a causal relationship between mediators. By contrast, **(B) serial (sequential) mediation analysis** assumes a causal relationship from one mediator to the other. The serial approach is sensitive to misspecification of the causal order between mediators and to the presence of unmeasured common causes of the mediators.	
Mediator-outcome confounding adjustment			
6.1	Confounder adjustment was performed		
	• No adjustment	14 (50.00)	6 (46.15)
	• Baseline value of the mediator(s)	7 (25.00)	4 (30.77)
	• Baseline value of the outcome	8 (28.57)	4 (30.77)
	• Baseline covariates that are not of the two types above	7 (29.00)	3 (23.08)
	• Post-intervention mediator-outcome confounders	2 (7.14)	1 (7.69)
6.2	Number of confounders adjusted for (median)	3	1
6.3	Sensitivity analysis to assess the risk of unmeasured confounders	1 (3.57)	1 (7.69)
Model construction			
7.1	Treatment-mediator interaction evaluated	3 (10.71)	2 (15.38)
7.2	Goodness-of-fit statistics or residual diagnostics of the involved models reported	9 (32.14)	2 (15.38)

efficacy moderates CBT effects on disability or pain intensity compared to control therapy and reported conflicting findings. In terms of disability, Buckelew et al. (1996) reported that high pre-treatment self-efficacy moderated CBT effects and four studies did not find evidence of an interaction with treatment (Lawford et al., 2018; Litt et al., 2010; Macedo et al., 2014; Underwood et al., 2011). Regarding pain intensity, two studies (Lawford et al., 2018; Litt et al., 2010) reported that high pre-treatment self-efficacy moderated CBT effects and the other two studies (Buckelew et al., 1996; Underwood et al., 2011) did not find evidence of an interaction with treatment.

5.5.1.4. Pain acceptance & psychological inflexibility. Only one study examined whether or not pre-treatment pain acceptance was a moderator of ACT, reporting superior effects of ACT on disability compared to control treatment when patients reported higher pre-treatment pain acceptance (Probst et al., 2019).

5.5.1.5. Other moderators: general coping, somatization and mindfulness measures. Two CBT trials examined if pre-treatment somatization moderates CBT effects on disability or pain intensity compared to control therapy. Litt et al. (2010) reported a moderated effect of low pre-treatment somatization on reductions in disability and pain for CBT, whereas Turner et al. (2007) did not observe an interaction effect for any of the two outcomes. Three CBT trials examined whether or not pre-treatment coping was a moderator of treatment effect and reported no evidence of moderated effect (Broderick et al., 2016; Litt et al., 2010; Macedo et al., 2014). Finally, Day et al. (2019) reported that

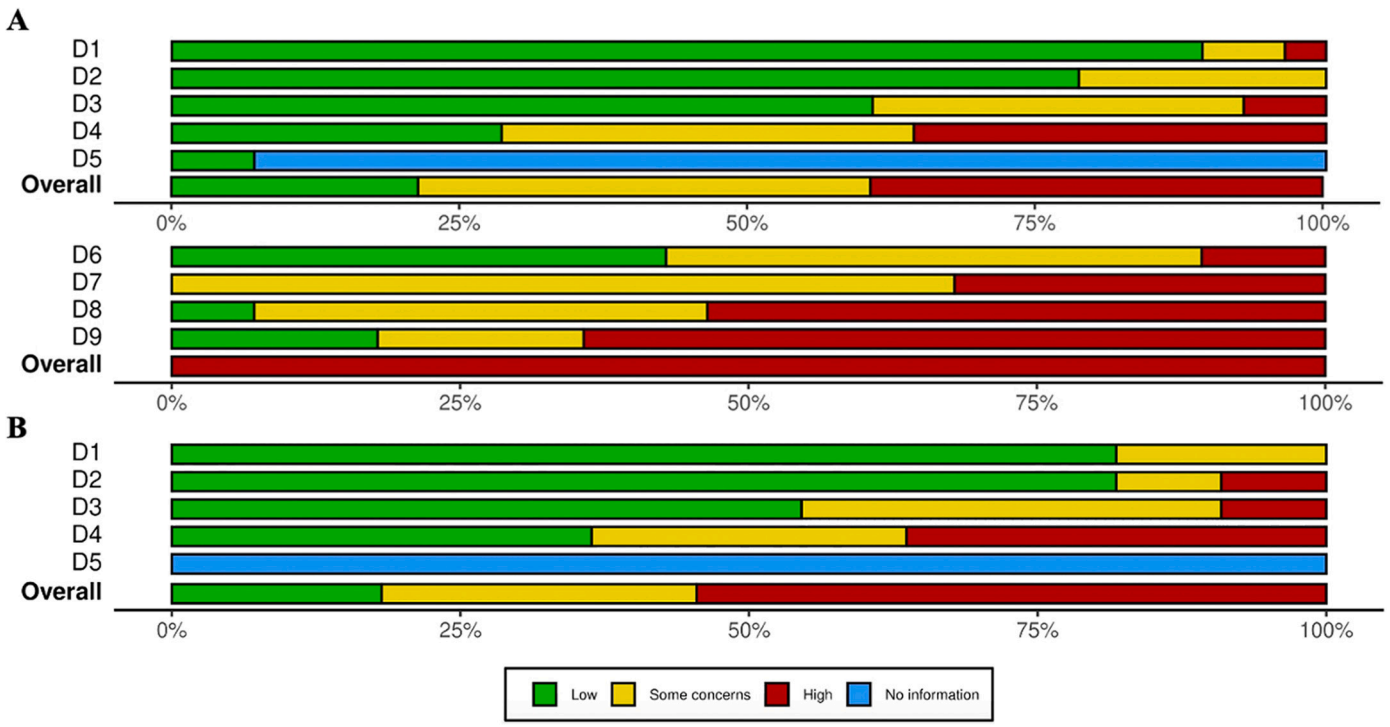


Fig. 2. Summary of the results of risk of bias assessment for (A) mediation and (B) moderation studies.
Domain 1 (D1): Risk of bias arising from the randomization process; **Domain 2 (D2)**: Risk of bias due to deviations from the intended interventions; **Domain 3 (D3)**: Risk of bias due to missing outcome data; **Domain 4 (D4)**: Risk of bias in measurement of the outcome; **Domain 5 (D5)**: Risk of bias in selection of the reported results.
Only for mediation studies: Domain 6 (D6): Risk of temporal order bias; **Domain 7 (D7)**: Risk of bias related to the appropriateness of the selected method for mediation analysis; **Domain 8 (D8)**: Risk of Confounding bias; **Domain 9 (D9)**: Risk of modeling bias.

mindfulness CBT had superior effects on disability in patients with higher pre-treatment mindful nonreactivity whereas mindfulness therapy had superior effects on disability in patients with lower baseline mindful nonreactivity.

6. Discussion

Psychologically based interventions for chronic pain focus on and address various pain-specific psychosocial constructs which are hypothesized to be associated with changes in pain-related functioning in accordance with distinct biopsychosocial theoretical models. This systematic and meta-analytic review aimed to provide a better understanding about how these interventions work by examining the specific mediators and moderators of treatment. We were able to include sufficient mediation studies to enable meta-analyses for several mediators (i.e., catastrophizing, pain-related fear and avoidance, self-efficacy, pain acceptance and psychological inflexibility) across both CBT and ACT trials, while synthesis without meta-analysis was performed for the moderation studies due to the small number of included studies. The results of the meta-analyses showed that reductions in pain-related fear and catastrophizing as well as increases in self-efficacy significantly mediated the effects of CBT on disability but not on pain intensity, when compared to control treatments. In a similar manner, enhancing pain acceptance and psychological flexibility was found to significantly mediate the effects of ACT on disability. The results from this meta-analysis also highlight that the proportion mediated did not exceed the 20% for most of the examined mediators. This suggests that both CBT and ACT operate through complex processes that cannot be explained through changes in only one construct. On the other hand, the narrative synthesis of specific moderators underscored conflicting findings, which did not support a robust moderated effect for any of the examined pain-specific psychosocial constructs, and further research is needed to draw valid conclusions in this vein.

6.1. Evidence from mediation analyses

Previous research has consistently shown that CBT is superior to usual care or waiting list in reducing pain-related fear and catastrophizing as well as increasing self-efficacy (i.e., treatment-mediator causal relationship or path-a in a mediation diagram) (Martinez-Calderon, Flores-Cortes, Morales-Asencio, Fernandez-Sanchez, & Luque-Suarez, 2020; Martinez-Calderon, Flores-Cortes, Morales-Asencio, & Luque-Suarez, 2020b; Schutze et al., 2018). Findings from the present review support that these changes are part of the underlying mechanisms of the effectiveness of CBT on primary outcomes, as they mediate gains in pain-related functioning. These results are largely consistent with the theoretical underpinnings of CBT and the cognitive behavioral framework (Turk & Monarch, 2018). CBT aims to reduce disability by targeting maladaptive pain-related cognitions and behaviors (e.g., pain-related fear and catastrophizing) and by improving pain management (e.g., self-efficacy). Controlling pain intensity, on the other hand, is not a primary therapeutic target of CBT interventions (Vlaeyen & Crombez, 2020). Previous work had already shown that pain-related fear, catastrophizing and self-efficacy are more strongly related to disability than with pain intensity; and the current findings support that by demonstrating the lack of a significant mediated effect on pain intensity (Jackson, Wang, Wang, & Fan, 2014; Martinez-Calderon, Flores-Cortes, Morales-Asencio, & Luque-Suarez, 2020c).

CBT is characterized as being a multicomponent intervention in which several techniques are combined to effectively target the constructs hypothesized to be responsible for patient's persistent symptoms (Turk & Monarch, 2018). However, it is still uncommon to evaluate the mediated effects across different therapeutic components. This brings the disadvantage that no information can be gathered about which

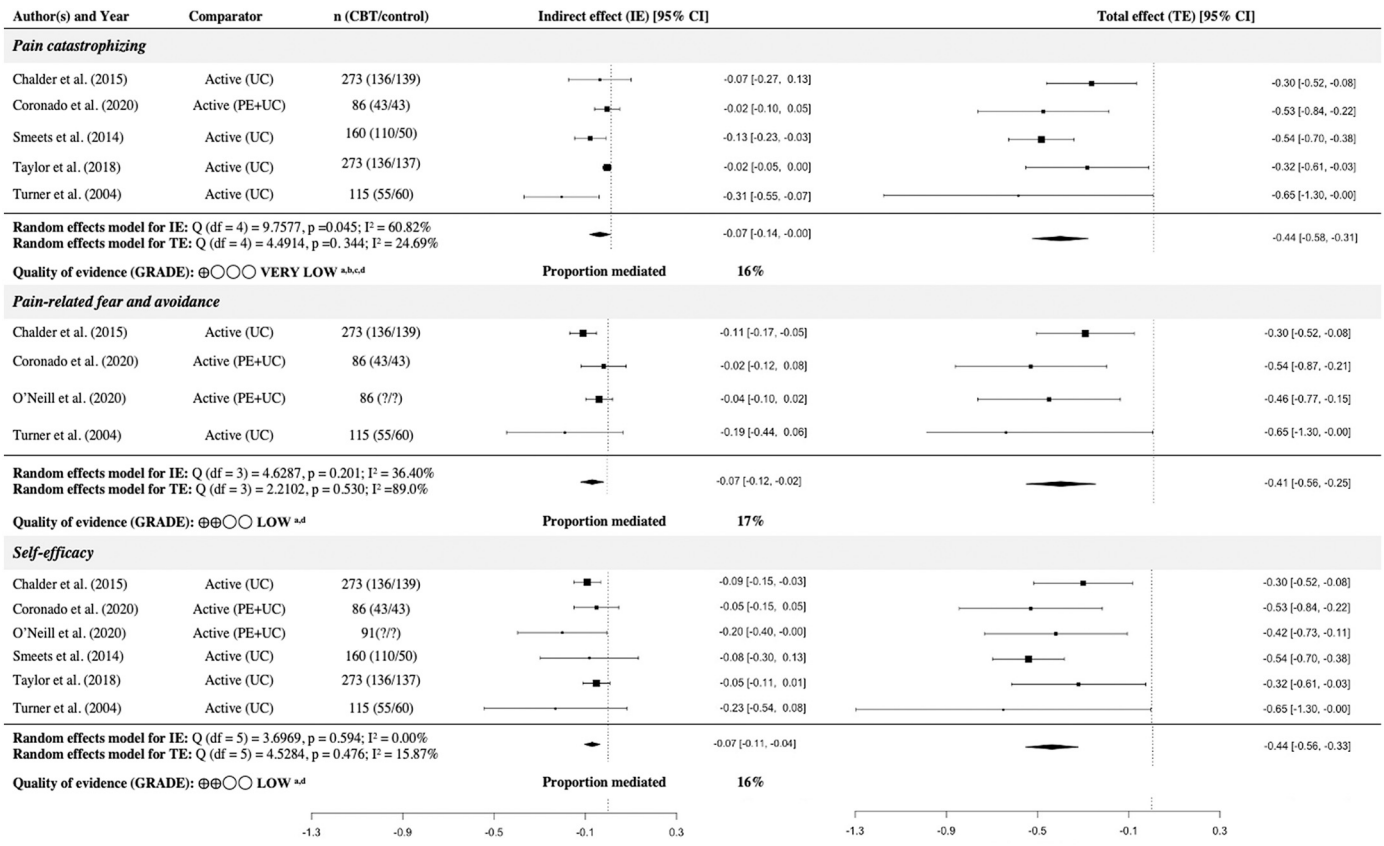


Fig. 3. Meta-analysis on the indirect and total effects of CBT care on disability. Between-trial heterogeneity Cochran Q heterogeneity test and I^2 statistic are reported.
GRADE:[a] downgraded due to risk of bias, [b] downgraded due to inconsistency, [c] downgraded due to imprecision, [d] downgraded due to possible publication bias.

therapeutic ingredient is the most relevant for treatment effectiveness and hence should be prioritized (Kazdin, 2007; Lee et al., 2016; Maric et al., 2012). Only few studies compared the strength of the mediated effect across different CBT approaches (e.g., graded activity, activity pacing and exposure in vivo), which were not enough to perform a meta-analyses. Also, another study examined whether or not adding a specific component (e.g., a group discussion) resulted in a stronger mediated effect. Study designs in which therapeutic components are added, removed or enhanced have recently been proposed in context of mediation analysis to examine which therapeutic components are more effective, but remain scarce in the pain literature to date (Kazdin, 2007).

Along similar lines, previous research has steadily reported that ACT is effective in enhancing pain acceptance and psychological flexibility (Hughes et al., 2017). Mediation results from the meta-analyses extend these findings by showing that increases in pain acceptance and psychological flexibility significantly mediate reductions in pain-related disability and therefore, support the psychological flexibility model (McCracken & Vowles, 2014). It was also observed that psychological flexibility mediated a greater proportion of the total effect compared to pain acceptance. This may be due to the fact that psychological flexibility measured with the psychological inflexibility in pain scale also evaluates cognitive fusion in addition to avoidance (opposite strategy to acceptance) (Trompetter et al., 2014). It was noticeable, though, that the evidence base for mechanisms underlying ACT is still stymied by an excessive focus on pain acceptance as a unique construct of change for ACT, and hence a lack of integration of all six interrelated processes which comprise the psychological flexibility model (i.e., acceptance, cognitive defusion, values-based action, committed action, present-focused awareness and self-as-observer) (Hayes et al., 2013; McCracken & Vowles, 2014). Thus, despite a growing number of studies supporting the potential of all these six processes in relation to chronic pain (McCracken & Morley, 2014; McCracken & Vowles, 2008, 2014; Wicksell, Olsson, & Melin, 2009), this theoretical counterbalance is not reflected in the design of the related mediation studies to date and future mediation research should, therefore, include valid measures of all the processes. That would furthermore enable a more systematic examination on which components are the most effective. Like ACT, mindfulness-based therapies aim to reshape how pain, and associated stressful thoughts and feelings, are experienced by enhancing pain acceptance and awareness, and bringing the focus into the present moment, helping to recognize what one can control/not control and mitigate catastrophic thoughts about future events (Day, 2017). However, few studies have examined their underlying mechanisms and further research is needed before clear conclusions are drawn.

Studies in which mediation analysis is performed to compare the underlying mechanisms between interventions with different theoretical frameworks (i.e., by examining the same putative mediators) are still lacking as evidenced in this review. This, however, is crucial to unravel whether different interventions work through separate underlying processes or by contrast whether they share, to greater or lesser extent, key mechanisms of change (Maric et al., 2012; Vlaeyen & Morley, 2005). For example, a few studies examined the causal pathways of constructs traditionally associated with more traditional CBT (e.g., self-efficacy or pain-related fear) in ACT trials and failed to find a consistent mediated effect for these non-ACT specific constructs. Similarly, only few studies -again not sufficient for a meta-analysis- examined mediated effects of ACT or mindfulness-related constructs in CBT trials. Hence, as assessed mediators hardly overlapped across CBT, ACT and mindfulness studies, this precludes any inferences on potential common or specific mechanisms. In fact, as there was such a disbalance between type of trials across the various mediators, we decided to immediately perform analyses per intervention instead of initiating with analyses collapsed across

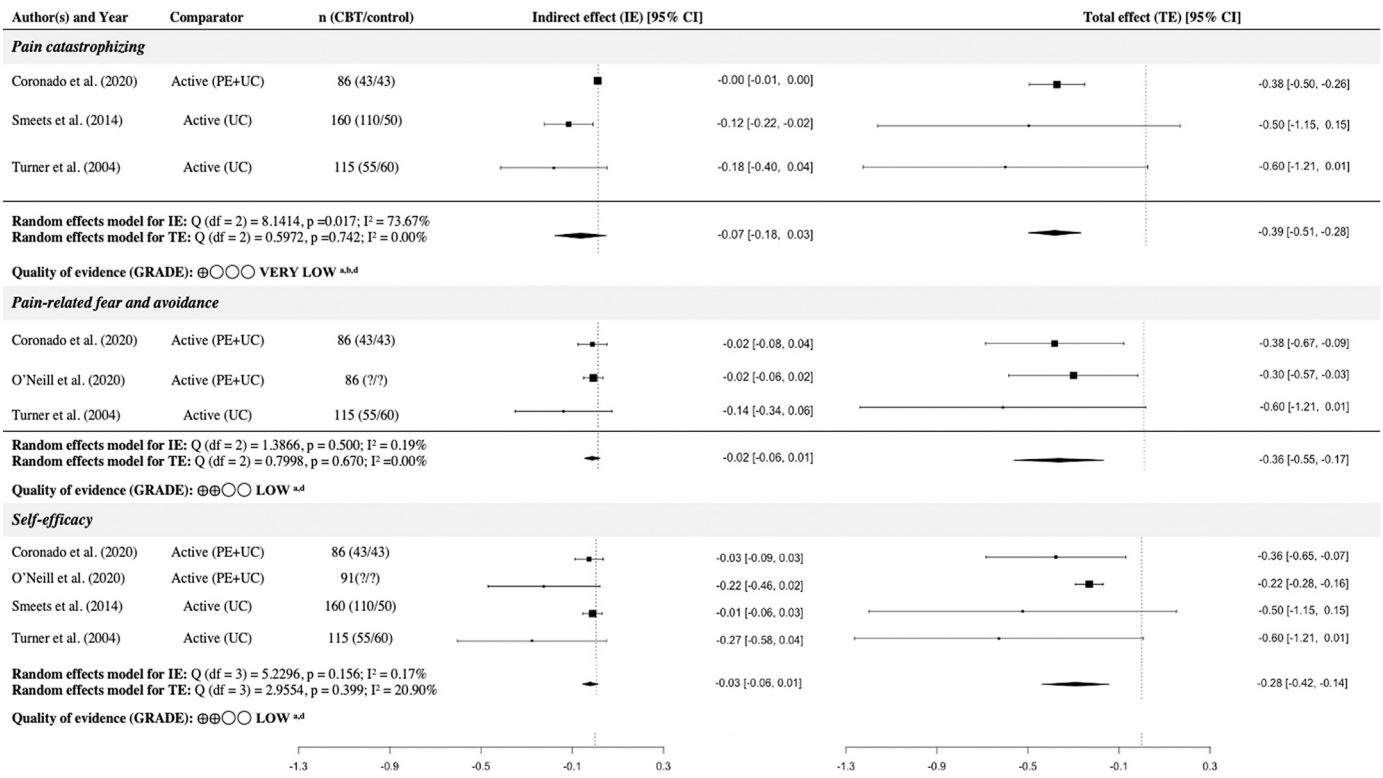


Fig. 4. Meta-analysis on the indirect and total effects of CBT on pain intensity. Between-trial heterogeneity Cochran Q heterogeneity test and I^2 statistic are reported.
GRADE:[a] downgraded due to risk of bias, [b] downgraded due to inconsistency, [c] downgraded due to imprecision, [d] downgraded due to possible publication bias.

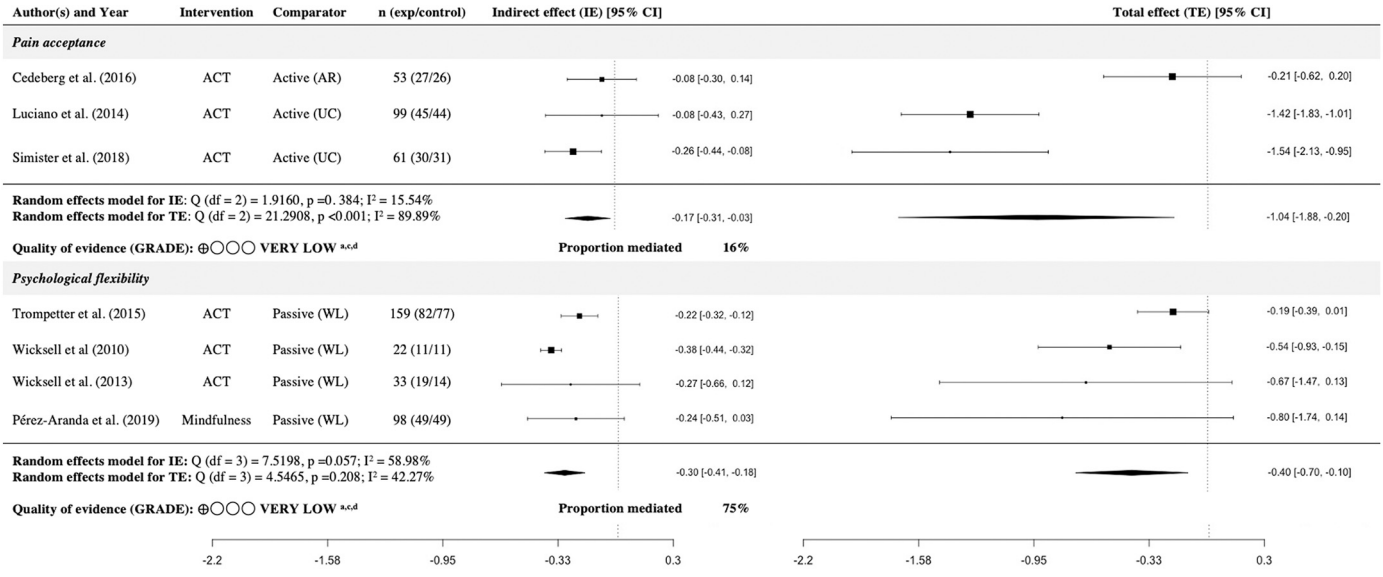


Fig. 5. Meta-analysis on the indirect and total effects of ACT on disability. Between-trial heterogeneity Cochran Q heterogeneity test and I^2 statistic are reported.
GRADE:[a] downgraded due to risk of bias, [b] downgraded due to inconsistency, [c] downgraded due to imprecision, [d] downgraded due to possible publication bias.

all interventions (as originally planned). Despite the different theoretical underpinnings and divergent therapeutic techniques, CBT, ACT and mindfulness-based interventions are all part of the behavioral and cognitive therapies family. Thus, it is likely that most of these interventions share common cognitive and behavioral mechanisms to at least some extent, and future research should address this gap in the knowledge (Jensen, 2011; Windgassen et al., 2016).

The current review is focused on the specific constructs (mediators) of the psychologically based interventions, which are those intended targets in accordance with a particular theoretical model. However, it should be noted that a proportion of the total effect is also explained by (often unmeasured) non-specific mechanisms common across all interventions for chronic pain, which were beyond the scope of the current review but are certainly important to be accounted for in the statistical

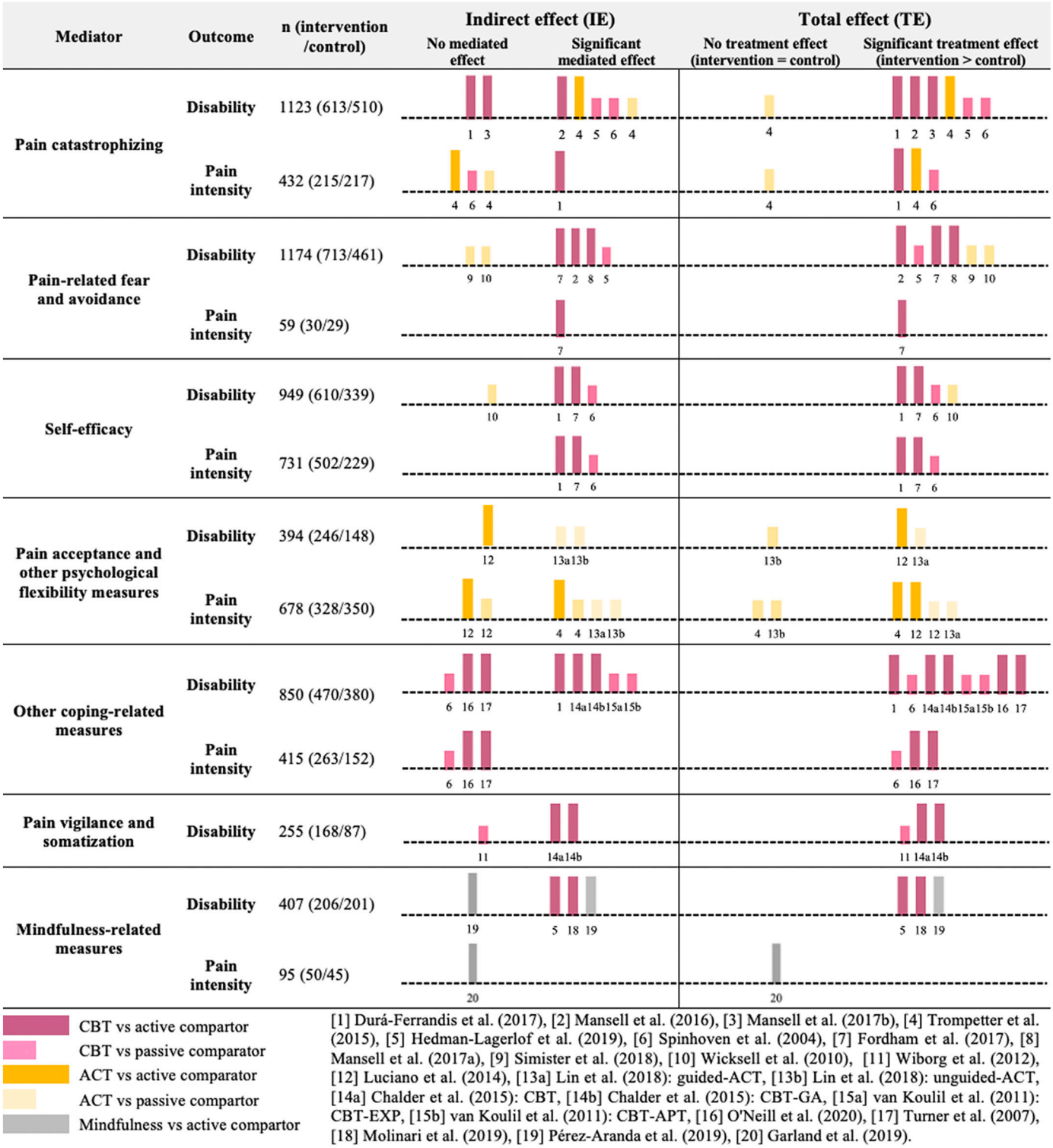


Fig. 6. Harvest plot. Summary of the narrative synthesis of results from mediation studies not included in the meta-analysis.

model. Non-specific effects can include both contextual effects (e.g., therapeutic alliance or patient satisfaction) as well as mechanisms that are unintentionally targeted by the intervention (Baier, Kline, & Feeny, 2020; Cashin et al., 2021; Chatoor & Kurpnick, 2001). The latest would be, for example, changes in symptoms of anxiety and depression (i.e., or more broadly emotional distress that often co-occurs with chronic pain) (Burke, Mathias, & Denson, 2015; Craig et al., 2016), which were found to mediate treatment outcome in some included studies. In most of the cases, these can be considered non-specific because despite CBT and ACT have been shown to be effective in managing other psychological disorders (e.g., major depressive disorder), specific techniques focusing on reducing anxiety and depression have rarely been integrated within the pain management intervention (Goesling, Clauw, & Hassett, 2013; Linton & Bergbom, 2011). Among all included studies, only one intentionally targeted these constructs during treatment through specific techniques (Sodermark et al., 2020).

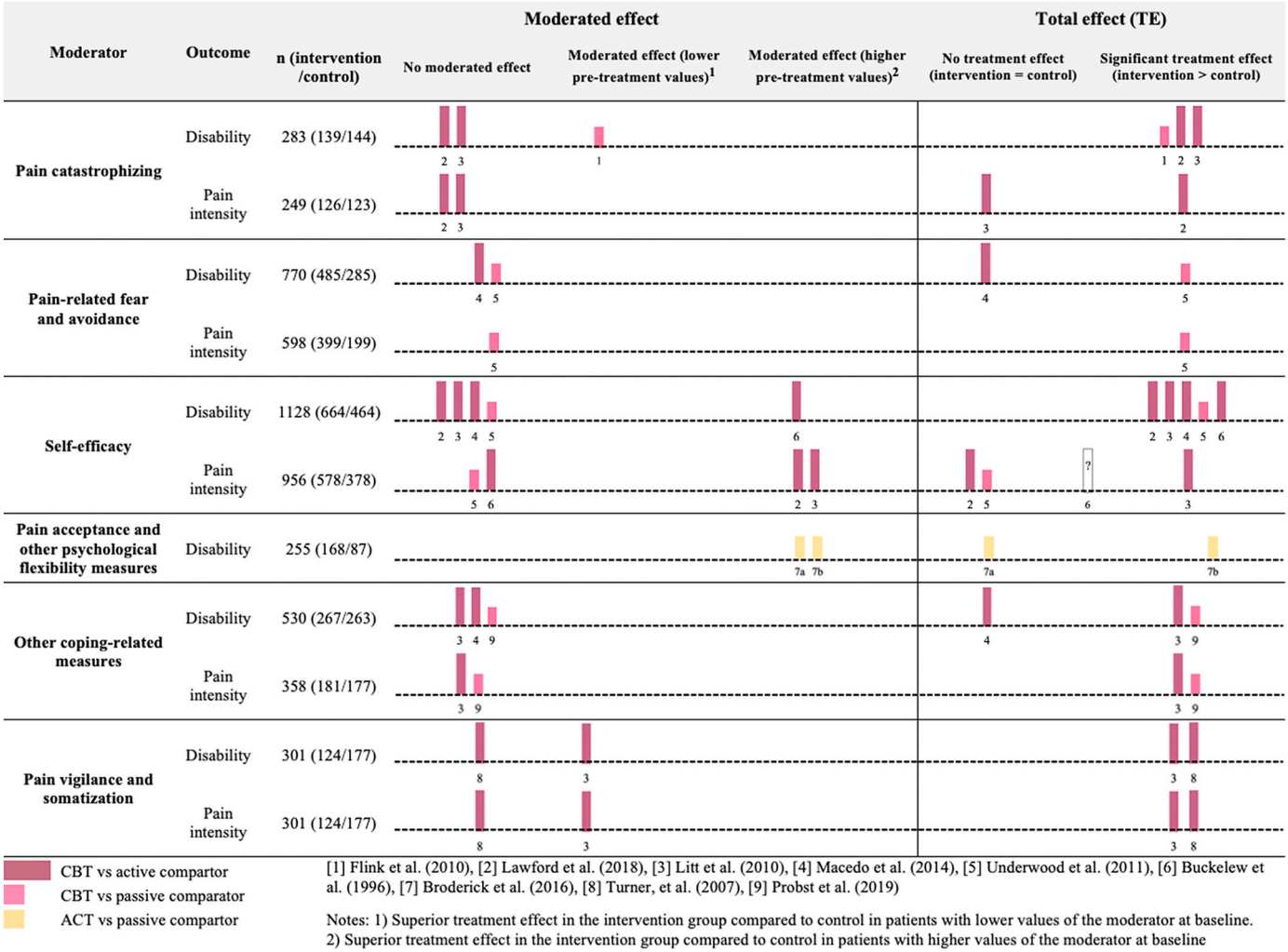


Fig. 7. Harvest plot. Summary of the narrative synthesis of results from moderation studies.

6.2. *Evidence from moderation analyses*

It is well-known that patients respond differently to the same therapeutic intervention and one-size approach does not fit all patients, yet research on moderators of treatment is lacking and it is mainly focused on non-specific factors (Gilpin et al., 2017; Kravitz, Duan, & Braslow, 2004; Moore et al., 2010). Whereas non-specific factors provide important prognostic information about which patients are more likely to respond positively to treatment, specific moderators demonstrate how patients' pre-treatment status interacts with treatment type, yielding the potential for new personalized therapeutic pathways. CBT, ACT and mindfulness theoretical frameworks postulate that pre-treatment differences in the process targeted by the intervention can predict a patient's treatment response and hence act as moderators (Day et al., 2015; Kazdin, 2007; Turk & Monarch, 2018; Vlaeyen & Morley, 2005). Under this premise, it is suggested that, for example, patients with greater pain-related fear and/or avoidance would benefit more from exposure in vivo as this construct is explicitly targeted in this intervention.

Conflicting findings from a limited number of studies overall fail to support these postulates and future research in this vein is needed in order to draw meaningful conclusions. One of the reasons that may explain the inconsistent findings is the variability in terms of the measures of the putative moderators and treatment under investigation. Another possibility is that the hypothesized moderators are particularly sensitive to the idiosyncrasies of the treatment sample (e.g., specifically recruiting patients who present with high levels of fear, which may limit subsequent variance across the sample).

Of note, mediation and moderation analyses have remained largely independent in research to date, as likewise found in this review. However, future research should also aim to combine these two approaches (i.e., moderated mediation or mediated moderation), as simultaneous investigation of the mediated and moderated effects of treatment allows for testing more complex research hypotheses (e.g., whether the mediated effect differs across subgroups of patients, or whether its strength interacts with a particular moderator) (Fairchild & MacKinnon, 2009; Muller, Judd, & Yzerbyt, 2005; Preacher et al., 2007).

6.3. *Methodological considerations*

Although the concepts of mediation and moderation are gaining traction and are becoming more and more popular, the corresponding analyses are relatively complex and are often not of primary interest in RCTs. Most of the mediation and moderation analyses included in the present review (83% and 64% respectively) were secondary analyses of previously published trials and only two studies specified a pre-planned mediation analysis in the protocol. These analyses were often performed when the primary trial showed a statistically significant (total) ITT effect (79% and 50% of the included mediation and moderation analyses respectively). This may be the result of the misconception that mediation analysis should be only performed when the treatment effect is statistically significant (e.g., authors stated that significant ITT was a required condition to perform the mediation analysis in 29% of the

included studies), which can lead to an overestimation of the indirect effects in our meta-analysis (Vo et al., 2020). By contrast, only few mediation and moderation analyses in our review were conducted to explain why no (evidence of a) treatment effect was found, despite the fact that relevant underlying therapeutic mechanisms can still be present (Fairchild & McDaniel, 2017; O'Rourke & MacKinnon, 2018). Planning mediation and moderation analyses a priori can help to improve the validity of the results by increasing statistical power and reducing some of the methodological pitfalls, which have been likewise observed in previous reviews (Cashin et al., 2019; Champoux & Peters, 1987; Vo et al., 2020). Below, we discuss some of the common misconceptions and biases encountered among the eligible studies in this review, and we will provide methodological recommendations.

If interventions are hypothesized to operate through several mechanisms, it would be of added value to model them within a multiple- rather than a single-mediator analysis (Kazdin, 2007; Maric et al., 2012). Some of the included studies with multiple mediators performed a series of single mediation analyses (i.e., assuming that the mediators to be independent) rather than one multiple mediation analysis. As the mediator constructs discussed in this review are often correlated, this practice may generate biased results due to some mediators may confound the association between other mediators and outcome (treatment-induced mediator-outcome confounding) (Elvery, Jensen, Ehde, & Day, 2017; French, France, Vigneau, French, & Evans, 2007; VanderWeele, 2016; VanderWeele & Vansteelandt, 2014). When the independence between mediators cannot be presumed, several alternative methods can be implemented. Firstly, multiple mediators can be considered jointly (VanderWeele & Vansteelandt, 2014). Secondly, if causal ordering of the mediators can be confidently presumed, then serial (sequential) mediation analysis may provide more complete insight through what pathways the interventions primarily works (VanderWeele & Vansteelandt, 2014). Finally, if the causal structure between the mediators is unclear or unknown, recent extensions within the counterfactual-based framework should be potentially considered (Vansteelandt & Daniel, 2017).

Three studies used the mediation approach originally proposed by Baron and Kenny (1986), which includes a series of tests for links in the causal chain to assess the presence of an indirect effect. This approach is conservative and has limited statistical power because of the unnecessary requirement of a non-zero ITT effect to investigate mediation (MacKinnon et al., 2007). The product-of-coefficients (path a x b) method was the most common approach in the present review. This approach is valid when the considered mediators and outcomes obey simple linear models without treatment-mediator or mediator-mediator interaction; and remains valid for testing for the presence of indirect effects when the mediators and outcomes obey generalized linear models without treatment-mediator interaction. For assessing the magnitude of the indirect effect, it raises validity concerns when one or both of the mediator and outcome models is/are nonlinear, or when there are potential interactions between the treatment and the mediator (s)(MacKinnon et al., 2020; VanderWeele, 2016). To accommodate this, a counterfactual-based framework to mediation has been recommended, which includes the aforementioned traditional approaches as special cases, and in addition offers a great variety of potential models accommodating complicated hypothesis testing (Fairchild & McDaniel, 2017; VanderWeele, 2016).

Half of the included studies did not assure mediator-outcome temporal precedence (i.e., mediator is assessed prior to the outcome), rendering a causal interpretation of the findings potentially questionable (Fairchild & McDaniel, 2017). Half of the studies also did not adjust for mediator-outcome confounders, despite the confounding assumptions are extremely important in mediation analysis and their violations can originate spurious results regardless of the statistical approach used (Fairchild & McDaniel, 2017;VanderWeele, 2016 ; Vo et al., 2020). Randomization permits to control for treatment-outcome and treatment mediator confounding. However, it does not allow to control for mediator-outcome confounding, which can considerably bias estimates of the indirect effects in a mediation analysis (VanderWeele, 2016; Vo et al., 2020). Sensitivity analyses, which can help to determine the possible degree of bias due to unmeasured confounding, were included in only one study. Also, those studies which included adjustment did not overlap in the set of adjusted confounders. This contributes to further heterogeneity in the findings.

Additionally, the reporting of mediation analyses and findings was suboptimal. Often, details about the exact models and analyses were missing (e.g., the mediation model and outcome model and the included interactions were not described in detail), and the reporting of results often lacked detailed information (e.g., results on path-a, −b and c' were often omitted as well as information whether or not coefficients were standardized or not). This obstacle has been reported in previous reviews on mediation and stresses the need for the implementation of valid reporting guidelines (Cashin et al., 2019; Lee et al., 2021; Vo et al., 2020).

Lastly, it should be noted that we only included RCTs in which an experimental intervention was compared to a control intervention (or other experimental intervention). There are also lots of studies that perform mediation analyses in cohort studies, or that take together both intervention groups (i.e., especially when there was no significant total effect) (Åkerblom, Perrin, Fischer, & McCracken, 2015; Cassidy, Atherton, Robertson, Walsh, & Gillett, 2012; Gilliam, Craner, Morrison, & Sperry, 2017; Greenberg, Mace, Bannon, Kulich, & Vranceanu, 2021). We originally intended to present this literature alongside with its limitations; but we decided to not include this information in the current review to provide a clearer, more focused overview of controlled trials here. Such single-arm or cohort studies should thus be covered in future reviews, even though it should be noted that causal inference from such approaches is linked to higher uncertainty since the intervention assignment is unknown and due to unmeasured confounding, which biases the estimation of the treatment-outcome/mediator relationship (i.e., whether or not changes in the mediator(s) are caused by the specific treatment or by other factors such as passage of time).

6.4. *Strengths and limitations*

This leading-edge systematic review has several strengths. Previous reviews have focussed exclusively on patients with low back pain and have encompassed non-specific factors as well as all kinds of conservative interventions for pain (Miles et al., 2011; Wertli, Burgstaller, et al., 2014; Wertli, Rasmussen-Barr, et al., 2014). By contrast, the current review addresses the mediated and moderated effect of specific constructs targeted by psychologically based interventions. This facilitates a concise and comprehensive interpretation of the causal pathways of the interventions of interest in relation to their corresponding theoretical models. Only few meta-analyses of mediation RCTs have been conducted in the field of health sciences (Curtiss, Andrews, Davis, Smits, & Hofmann, 2017; Gu, Strauss, Bond, & Cavanagh, 2015; Parsons, Zachariae, Landberger, & Young, 2021), and this is the first one in chronic musculoskeletal pain. To the best of our knowledge, no tool has been developed to assess specific biases related to mediation analyses. Some appraisal tools and reporting checklists of mediation analyses are available in the literature (Gu et al., 2015; Mansell et al., 2013). These checklists, however, are often overly simplistic and do not take into account recent developments in the field of mediation analysis. The tool that we developed in this study overcomes these limitations. Additionally, by carrying out a comprehensive comparative synthesis of mediators/moderators, confounders and statistical approaches of the included studies, we aimed to inform on the strengths and pitfalls of the current evidence and provide a platform for future research.

Although a quantitative synthesis of moderators of treatment was also pre-planned, we were unable to do so due to the small number of included studies and the heterogeneity of the moderators evaluated. On the other hand, findings from the current meta-analysis of mediation

studies, however, came from an overall low certainty evidence and should hence be interpreted within the context of some limitations. The main limitation was the small number of included studies. Despite the systematic search retrieving 29 mediation analyses, only 13 and 4 studies could be included in the meta-analysis for the outcomes pain-related disability and pain intensity, respectively. This is due to the large variety of mediators assessed across different studies together with the diverse statistical approaches used. In addition, poor reporting as well as insufficient information and data was observed in some included studies prevented from the inclusion of more studies into the meta-analysis. Another limitation that should be acknowledged is the between-trial heterogeneity in some meta-analysis due to the variety across the studies in terms of interventions. This issue is particularly noticeable in the meta-analyses for CBT as there is not one standardized protocol, and intervention delivery, duration and components (ranging from very behaviorally focused such as exposure in vivo to very cognitively focused such as cognitive restructuring) varied across interventions. Similarly, slight variations with respect to the comparators was also observed, where for example, some studies included some form of traditional (biomechanical) pain education in addition to standard usual care.

7. Conclusions

The investigation of the mechanisms underlying the effects of psychologically based interventions on pain and related disability is a complex yet crucial journey in order to refine theoretical models, inform the direction of future research and ultimately improve outcomes. The available evidence supports the idea that reductions in pain catastrophizing, pain-related fear and avoidance as well as increases in self-efficacy mediate the effects of cognitive behavioral therapy on pain-related disability, but not on pain intensity. Similarly, increases of pain acceptance and psychological flexibility mediate the effects of acceptance and commitment therapy on pain-related disability. Limitations notwithstanding, findings seem to be consistent with the theoretical models and support targeting these constructs in treatment, but further research is needed to understand the shared and specific mechanisms of these interventions. Further examination is also needed to unravel whether or not pre-treatment status of these constructs also acts as moderator of treatment.

Role of funding sources statement

CM is supported by Fonds Wetenschappelijk Onderzoek (FWO). G001419N.

Authors contribution statement

CM, IT, BC, IC and MM conceptualised the review. CM, MM, IT and LH design the search strategy. CM and MC conducted literature searches and screened the retrieved articles. CM, T-TV, IT and MC extracted the data. Risk of bias was assessed by CM, MC and T-TV, and SV, LH and MM acted as third reviewer. T-TV and SV developed the extension to assess risk of mediation-specific biases. CM, T-TV and SV performed the formal analysis. CM prepared an initial draft and all the authors revised and approved the final manuscript.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cpr.2022.102160.

References

Åkerblom, S., Perrin, S., Fischer, M. R., & McCracken, L. M. (2015). The mediating role of acceptance in multidisciplinary cognitive-behavioral therapy for chronic pain. *The Journal of Pain, 16*, 606–615. https://doi.org/10.1016/j.jpain.2015.03.007

Baier, A. L., Kline, A. C., & Feeny, N. C. (2020). Therapeutic alliance as a mediator of change: A systematic review and evaluation of research. *Clinical Psychology Review, 101921*. https://doi.org/10.1016/j.cpr.2020.101921

Balshem, H., Helfand, M., Schünemann, H. J., Oxman, A. D., Kunz, R., Brozek, J., … Norris, S. (2011). GRADE guidelines: 3. Rating the quality of evidence. *Journal of Clinical Epidemiology, 64*, 401–406. https://doi.org/10.1016/j.jclinepi.2010.07.015

Baron, R. M., & Kenny, D. A. (1986). The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology, 51*, 1173. https://doi.org/10.1037//0022-3514.51.6.1173

Broderick, J. E., Keefe, F. J., Schneider, S., Junghaenel, D. U., Bruckenthal, P., Schwartz, J. E., … Gould, E. (2016). Cognitive behavioral therapy for chronic pain is effective, but for whom? *Pain, 157*, 2115–2123. https://doi.org/10.1097/j.pain.0000000000000626

Buckelew, S. P., Huyser, B., Hewett, J. E., Johnson, J. C., Conway, R., Parker, J. C., & Kay, D. R. (1996). Self-efficacy predicting outcome among fibromyalgia subjects. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology, 9*, 97–104. https://doi.org/10.1002/1529-0131(199604)9:2<97::AID-ANR1790090205>3.0.CO;2-F

Burke, A. L., Mathias, J. L., & Denson, L. A. (2015). Psychological functioning of people living with chronic pain: A meta-analytic review. *British Journal of Clinical Psychology, 54*, 345–360. https://doi.org/10.1111/bjc.12078

Campbell, M., McKenzie, J. E., Sowden, A., Katikireddi, S. V., Brennan, S. E., Ellis, S., … Thomas, J. (2020). Synthesis without meta-analysis (SWiM) in systematic reviews: Reporting guideline. *Bmj, 368*. https://doi.org/10.1136/bmj.l6890

Cashin, A. G., Lee, H., Lamb, S. E., Hopewell, S., Mansell, G., Williams, C. M., … McAuley, J. H. (2019). An overview of systematic reviews found suboptimal reporting and methodological limitations of mediation studies investigating causal mechanisms. *Journal of Clinical Epidemiology, 111*(60–68), Article e1. https://doi.org/10.1016/j.jclinepi.2019.03.005

Cashin, A. G., McAuley, J. H., Lamb, S. E., & Lee, H. (2021). Disentangling contextual effects from musculoskeletal treatments. *Osteoarthritis and Cartilage, 29*, 297–299. https://doi.org/10.1016/j.joca.2020.12.011

Cassidy, E. L., Atherton, R. J., Robertson, N., Walsh, D. A., & Gillett, R. (2012). Mindfulness, functioning and catastrophizing after multidisciplinary pain management for chronic low back pain. *Pain, 153*, 644–650. https://doi.org/10.1016/j.pain.2011.11.027

Cederberg, J. T., Cernvall, M., Dahl, J., von Essen, L., & Ljungman, G. (2016). Acceptance as a mediator for change in acceptance and commitment therapy for persons with chronic pain? *International Journal of Behavioral Medicine, 23*, 21–29. https://doi.org/10.1007/s12529-015-9494-y

Chalder, T., Goldsmith, K. A., White, P. D., Sharpe, M., & Pickles, A. R. (2015). Rehabilitative therapies for chronic fatigue syndrome: A secondary mediation analysis of the PACE trial. *The Lancet Psychiatry, 2*, 141–152. https://doi.org/10.1016/S2215-0366(14)00069-8

Champoux, J. E., & Peters, W. S. (1987). Form, effect size and power in moderated regression analysis. *Journal of Occupational Psychology, 60*, 243–255. https://doi.org/10.1111/j.2044-8325.1987.tb00257.x

Chatoor, I., & Kurpnick, J. (2001). The role of non-specific factors in treatment outcome of psychotherapy studies. *European Child & Adolescent Psychiatry, 10*, S19. https://doi.org/10.1007/s007870170004

Cheung, M. W. L., & Cheung, S. F. (2016). Random-effects models for meta-analytic structural equation modeling: Review, issues, and illustrations. *Research Synthesis Methods, 7*, 140–155. https://doi.org/10.1002/jrsm.1166

Coronado, R. A., Ehde, D. M., Pennings, J. S., Vanston, S. W., Koyama, T., Phillips, S. E., … Archer, K. R. (2020). Psychosocial mechanisms of cognitive-behavioral-based physical therapy outcomes after spine surgery: Preliminary findings from mediation analyses. *Physical Therapy*. https://doi.org/10.1093/ptj/pzaa112

Craig, A., Tran, Y., Guest, R., Gopinath, B., Jagnoor, J., Bryant, R. A., … Middleton, J. W. (2016). Psychological impact of injuries sustained in motor vehicle crashes: Systematic review and meta-analysis. *BMJ Open, 6*. https://doi.org/10.1136/bmjopen-2016-011993

Curtiss, J., Andrews, L., Davis, M., Smits, J., & Hofmann, S. G. (2017). A meta-analysis of pharmacotherapy for social anxiety disorder: An examination of efficacy, moderators, and mediators. *Expert Opinion on Pharmacotherapy, 18*, 243–251. https://doi.org/10.1080/14656566.2017.1285907

Day, M. A. (2017). The development of MBCT for chronic pain. In *Mindfulness-Based Cognitive Therapy for Chronic Pain: A Clinical Manual and Guide*. John Wiley & Sons.

Day, M. A., Ehde, D. M., & Jensen, M. P. (2015). Psychosocial pain management moderation: The limit, activate, and enhance model. *The Journal of Pain, 16*, 947–960. https://doi.org/10.1016/j.jpain.2015.07.003

Day, M. A., Thorn, B. E., Ehde, D. M., Burns, J. W., Barnier, A., Mattingley, J. B., … Jensen, M. P. (2019). Moderators of mindfulness meditation, cognitive therapy, and mindfulness-based cognitive therapy for chronic low back pain: A test of the limit, activate, and enhance model. *The Journal of Pain.*. https://doi.org/10.1016/j.jpain.2019.06.006

De Stavola, B. L., Daniel, R. M., Ploubidis, G. B., & Micali, N. (2015). Mediation analysis with intermediate confounding: Structural equation modeling viewed through the causal inference lens. *American Journal of Epidemiology, 181*, 64–80. https://doi.org/10.1093/aje/kwu239

De Williams, A. C., Fisher, E., Hearn, L., & Eccleston, C. (2020). Psychological therapies for the management of chronic pain (excluding headache) in adults. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD007407.pub2

Durá-Ferrandis, E., Ferrando-García, M., Galdón-Garrido, M. J., & Andreu-Vaillo, Y. (2017). Confirming the mechanisms behind cognitive-behavioural therapy effectiveness in chronic pain using structural equation modeling in a sample of patients with temporomandibular disorders. *Clinical Psychology & Psychotherapy, 24*, 1377–1383. https://doi.org/10.1002/cpp.2114

Dworkin, R. H., Bruehl, S., Fillingim, R. B., Loeser, J. D., Terman, G. W., & Turk, D. C. (2016). Multidimensional diagnostic criteria for chronic pain: Introduction to the ACTTION–American pain society pain taxonomy (AAPT). *The Journal of Pain, 17*, T1–T9. https://doi.org/10.1016/j.jpain.2016.02.010

Elvery, N., Jensen, M. P., Ehde, D. M., & Day, M. A. (2017). Pain catastrophizing, mindfulness, and pain acceptance. *The Clinical Journal of Pain, 33*, 485–495. https://doi.org/10.1097/AJP.0000000000000430

Fairchild, A. J., & MacKinnon, D. P. (2009). A general model for testing mediation and moderation effects. *Prevention Science, 10*, 87–99. https://doi.org/10.1007/s11121-008-0109-6

Fairchild, A. J., & McDaniel, H. L. (2017). Best (but oft-forgotten) practices: Mediation analysis. *The American Journal of Clinical Nutrition, 105*, 1259–1271. https://doi.org/10.3945/ajcn.117.152546

Flink, I. K., Boersma, K., & Linton, S. J. (2010). Catastrophizing moderates the effect of exposure in vivo for back pain patients with pain-related fear. *European Journal of Pain (London, England), 14*, 887–892. https://doi.org/10.1016/j.ejpain.2010.02.003

Fordham, B., Ji, C., Hansen, Z., Lall, R., & Lamb, S. E. (2017). Explaining how cognitive behavioral approaches work for low back pain. *Spine, 42*. https://doi.org/10.1097/BRS.0000000000002066. E1031-E39.

French, D. J., France, C. R., Vigneau, F., French, J. A., & Evans, R. T. (2007). Fear of movement/(re) injury in chronic pain: A psychometric assessment of the original English version of the Tampa scale for kinesiophobia (TSK). *Pain, 127*, 42–51. https://doi.org/10.1016/j.pain.2006.07.016

Garland, E. L., Hanley, A. W., Riquino, M. R., Reese, S. E., Baker, A. K., Salas, K., , … Atchley, R., et al. (2019). Mindfulness-oriented recovery enhancement reduces opioid misuse risk via analgesic and positive psychological mechanisms: A randomized controlled trial. *Journal of Consulting and Clinical Psychology, 87*, 927–940. https://doi.org/10.1037/ccp0000390

Gatchel, R. J., Peng, Y. B., Peters, M. L., Fuchs, P. N., & Turk, D. C. (2007). The biopsychosocial approach to chronic pain: Scientific advances and future directions. *Psychological Bulletin, 133*, 581. https://doi.org/10.1037/0033-2909.133.4.581

Ghogomu, E. A., Maxwell, L. J., Buchbinder, R., Rader, T., Pardo, J. P., Johnston, R. V., … Singh, J. A. (2014). Updated method guidelines for cochrane musculoskeletal group systematic reviews and meta-analyses. *The Journal of Rheumatology, 41*, 194–205. https://doi.org/10.3899/jrheum.121306

Gilliam, W. P., Craner, J. R., Morrison, E. J., & Sperry, J. A. (2017). The mediating effects of the different dimensions of pain catastrophizing on outcomes in an interdisciplinary pain rehabilitation program. *The Clinical Journal of Pain, 33*, 443–451. https://doi.org/10.1097/AJP.0000000000000419

Gilpin, H. R., Keyes, A., Stahl, D. R., Greig, R., & McCracken, L. M. (2017). Predictors of treatment outcome in contextual cognitive and behavioral therapies for chronic pain: A systematic review. *The Journal of Pain, 18*, 1153–1164. https://doi.org/10.1016/j.jpain.2017.04.003

Goesling, J., Clauw, D. J., & Hassett, A. L. (2013). Pain and depression: An integrative review of neurobiological and psychological factors. *Current Psychiatry Reports, 15*. https://doi.org/10.1007/s11920-013-0421-0

Greenberg, J., Mace, R. A., Bannon, S. M., Kulich, R. J., & Vranceanu, A. M. (2021). Mind-body activity program for chronic pain: Exploring mechanisms of improvement in patient-reported, performance-based and ambulatory physical function. *Journal of Pain Research, 14*, 359–368. https://doi.org/10.2147/JPR.S298212

Gu, J., Strauss, C., Bond, R., & Cavanagh, K. (2015). How do mindfulness-based cognitive therapy and mindfulness-based stress reduction improve mental health and wellbeing? A systematic review and meta-analysis of mediation studies. *Clinical Psychology Review, 37*, 1–12. https://doi.org/10.1016/j.cpr.2015.01.006

Hay, S. I., Abajobir, A. A., Abate, K. H., Abbafati, C., Abbas, K. M., Abd-Allah, F., … Abera, S. F. (2017). Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. *The Lancet, 390*, 1260–1344. https://doi.org/10.1016/S0140-6736(17)32130-X

Hayes, S. C., Levin, M. E., Plumb-Vilardaga, J., Villatte, J. L., & Pistorello, J. (2013). Acceptance and commitment therapy and contextual behavioral science: Examining the progress of a distinctive model of behavioral and cognitive therapy. *Behavior Therapy, 44*, 180–198. https://doi.org/10.1016/j.beth.2009.08.002

Hedman-Lagerlof, M., Andersson, E., Hedman-Lagerlof, E., Wicksell, R. K., Flink, I., & Ljotsson, B. (2019). Approach as a key for success: Reduced avoidance behaviour mediates the effect of exposure therapy for fibromyalgia. *Behaviour Research and Therapy, 122*. https://doi.org/10.1016/j.brat.2019.103478

Higgins, J. P., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *Bmj, 327*, 557–560. https://doi.org/10.1136/bmj.327.7414.557

Hoffmann, T. C., Glasziou, P. P., Boutron, I., Milne, R., Perera, R., Moher, D., … Johnston, M. (2014). Better reporting of interventions: Template for intervention description and replication (TIDieR) checklist and guide. *Bmj, 348*. https://doi.org/10.1136/bmj.g1687

Hughes, L. S., Clark, J., Colclough, J. A., Dale, E., & McMillan, D. (2017). Acceptance and commitment therapy (ACT) for chronic pain. *The Clinical Journal of Pain, 33*, 552–568. https://doi.org/10.1097/AJP.0000000000000425

Jackson, T., Wang, Y., Wang, Y., & Fan, H. (2014). Self-efficacy and chronic pain outcomes: A meta-analytic review. *The Journal of Pain, 15*, 800–814. https://doi.org/10.1016/j.jpain.2014.05.002

Jensen, M. P. (2011). Psychosocial approaches to pain management: An organizational framework. *PAIN®, 152*, 717–725. https://doi.org/10.1016/j.pain.2010.09.002

Kazdin, A. E. (2007). Mediators and mechanisms of change in psychotherapy research. *Annual Review of Clinical Psychology, 3*, 1–27. https://doi.org/10.1146/annurev.clinpsy.3.022806.091432

van Koulil, S., Kraaimaat, F. W., van Lankveld, W., van Helmond, T., Vedder, A., van Hoorn, H., , … van Riel, P. L., et al. (2011). Cognitive-behavioral mechanisms in a pain-avoidance and a pain-persistence treatment for high-risk fibromyalgia patients. *Arthritis Care & Research, 63*, 800–807. https://doi.org/10.1002/acr.20445

Kraemer, H. C., Frank, E., & Kupfer, D. J. (2006). Moderators of treatment outcomes: Clinical, research, and policy importance. *JAMA, 296*, 1286–1289. https://doi.org/10.1001/jama.296.10.1286

Kravitz, R. L., Duan, N., & Braslow, J. (2004). Evidence-based medicine, heterogeneity of treatment effects, and the trouble with averages. *The Milbank Quarterly, 82*, 661–687. https://doi.org/10.1111/j.0887-378X.2004.00327.x

Lawford, B. J., Hinman, R. S., Kasza, J., Nelligan, R., Keefe, F., Rini, C., & Bennell, K. L. (2018). Moderators of effects of internet-delivered exercise and pain coping skills training for people with knee osteoarthritis: Exploratory analysis of the IMPACT randomized controlled trial. *Journal of Medical Internet Research, 20*, Article e10021. https://doi.org/10.2196/10021

Lee, H., Cashin, A. G., Lamb, S. E., Hopewell, S., Vansteelandt, S., VanderWeele, T. J., … Golub, R. M. (2021). A guideline for reporting mediation analyses of randomized trials and observational studies: The AGReMA statement. *JAMA, 326*, 1045–1056. https://doi.org/10.1001/jama.2021.14075

Lee, H., Hübscher, M., Moseley, G. L., Kamper, S. J., Traeger, A. C., Mansell, G., & McAuley, J. H. (2015). How does pain lead to disability? A systematic review and meta-analysis of mediation studies in people with back and neck pain. *Pain, 156*, 988–997. https://doi.org/10.1097/j.pain.0000000000000146

Lee, H., McAuley, J. H., Hübscher, M., Kamper, S. J., Traeger, A. C., & Moseley, G. L. (2016). Does changing pain-related knowledge reduce pain and improve function through changes in catastrophizing? *Pain, 157*, 922–930. https://doi.org/10.1097/j.pain.0000000000000472

Leeuw, M., Goossens, M. E., van Breukelen, G. J., de Jong, J. R., Heuts, P. H., Smeets, R. J., … Vlaeyen, J. W. (2008). Exposure in vivo versus operant graded activity in chronic low back pain patients: Results of a randomized controlled trial. *Pain, 138*, 192–207. https://doi.org/10.1016/j.pain.2007.12.009

Lefebvre, C., Glanville, J., Briscoe, S., Littlewood, A., Marshall, C., Metzendorf, M. I., … Thomas, J. (2019). Searching for and selecting studies. In *Cochrane Handbook for Systematic Reviews of Interventions* (pp. 67–107). https://doi.org/10.1002/9781119536604.ch4

Lewis, J., & O'Sullivan, P. (2018). *Is it time to reframe how we care for people with non-traumatic musculoskeletal pain?* BMJ Publishing Group Ltd and British Association of Sport and Exercise Medicine. https://doi.org/10.1136/bjsports-2018-099198

Lin, J., Klatt, L. I., McCracken, L. M., & Baumeister, H. (2018). Psychological flexibility mediates the effect of an online-based acceptance and commitment therapy for chronic pain: An investigation of change processes. *Pain, 159*, 663–672. https://doi.org/10.1097/j.pain.0000000000001134

Linton, S. J., & Bergbom, S. (2011). Understanding the link between depression and pain. *Scandinavian Journal of Pain, 2*, 47–54. https://doi.org/10.1016/j.sjpain.2011.01.005

Litt, M. D., Shafer, D. M., & Kreutzer, D. L. (2010). Brief cognitive-behavioral treatment for TMD pain: Long-term outcomes and moderators of treatment. *Pain, 151*, 110–116. https://doi.org/10.1016/j.pain.2010.06.030

Luciano, J. V., Guallar, J. A., Aguado, J., López-Del-Hoyo, Y., Olivan, B., Magallón, R., … Garcia-Campayo, J. (2014). Effectiveness of group acceptance and commitment therapy for fibromyalgia: A 6-month randomized controlled trial (EFFIGACT study). *Pain, 155*, 693–702. https://doi.org/10.1016/j.pain.2013.12.029

Macedo, L. G., Maher, C. G., Hancock, M. J., Kamper, S. J., McAuley, J. H., Stanton, T. R., … Hodges, P. W. (2014). Predicting response to motor control exercises and graded activity for patients with low back pain: Preplanned secondary analysis of a randomized controlled trial. *Physical Therapy, 94*, 1543–1554. https://doi.org/10.2522/ptj.20140014

MacKinnon, D. P., Fairchild, A. J., & Fritz, M. S. (2007). Mediation analysis. *Annual Review of Psychology, 58*, 593–614.

MacKinnon, D. P., Valente, M. J., & Gonzalez, O. (2020). The correspondence between causal and traditional mediation analysis: The link is the mediator by treatment interaction. *Prevention Science, 21*, 147–157. https://doi.org/10.1007/s11121-019-01076-4

Mansell, G., Hill, J. C., Main, C., Vowles, K. E., & van der Windt, D. (2016). Exploring what factors mediate treatment effect: Example of the STarT Back study high-risk intervention. *The Journal of Pain, 17*, 1237–1245. https://doi.org/10.1016/j.jpain.2016.08.005

Mansell, G., Hill, J. C., Main, C. J., Von Korff, M., & Van Der Windt, D. (2017). Mediators of treatment effect in the back in action trial: Using latent growth modeling to take change over time into account. *The Clinical Journal of Pain, 33*, 811. https://doi.org/10.1097/AJP.0000000000000463

Mansell, G., Kamper, S. J., & Kent, P. (2013). Why and how back pain interventions work: What can we do to find out? *Best Practice & Research. Clinical Rheumatology, 27*, 685–697. https://doi.org/10.1016/j.berh.2013.10.001

Mansell, G., Storheim, K., Løchting, I., Werner, E. L., & Grotle, M. (2017). Identification of indirect effects in a cognitive patient education (COPE) intervention for low Back pain. *Physical Therapy, 97*, 1138–1146. https://doi.org/10.1093/ptj/pzx091

Maric, M., Wiers, R. W., & Prins, P. J. (2012). Ten ways to improve the use of statistical mediation analysis in the practice of child and adolescent treatment research. *Clinical Child and Family Psychology Review, 15*, 177–191. https://doi.org/10.1007/s10567-012-0114-y

Martinez-Calderon, J., Flores-Cortes, M., Morales-Asencio, J. M., Fernandez-Sanchez, M., & Luque-Suarez, A. (2020). Which interventions enhance pain self-efficacy in people with chronic musculoskeletal pain? A systematic review with meta-analysis of randomized controlled trials, including over 12 000 participants. *Journal of Orthopaedic & Sports Physical Therapy, 50*, 418–430. https://doi.org/10.2519/jospt.2020.9319

Martinez-Calderon, J., Flores-Cortes, M., Morales-Asencio, J. M., & Luque-Suarez, A. (2020b). Conservative interventions reduce fear in individuals with chronic low back pain: A systematic review. *Archives of Physical Medicine and Rehabilitation, 101*, 329–358. https://doi.org/10.1016/j.apmr.2019.08.470

Martinez-Calderon, J., Flores-Cortes, M., Morales-Asencio, J. M., & Luque-Suarez, A. (2020c). Which psychological factors are involved in the onset and/or persistence of musculoskeletal pain? An umbrella review of systematic reviews and meta-analyses of prospective cohort studies. *The Clinical Journal of Pain, 36*, 626–637. https://doi.org/10.1097/AJP.0000000000000838

McCracken, L. M., & Morley, S. (2014). The psychological flexibility model: A basis for integration and progress in psychological approaches to chronic pain management. *The Journal of Pain, 15*, 221–234. https://doi.org/10.1016/j.jpain.2013.10.014

McCracken, L. M., & Vowles, K. E. (2008). A prospective analysis of acceptance of pain and values-based action in patients with chronic pain. *Health Psychology, 27*, 215. https://doi.org/10.1037/0278-6133.27.2.215

McCracken, L. M., & Vowles, K. E. (2014). Acceptance and commitment therapy and mindfulness for chronic pain: Model, process, and progress. *American Psychologist, 69*, 178. https://doi.org/10.1037/a0035623

McKenzie, J. E., & Brennan, S. E. (2019). Synthesizing and presenting findings using other methods. In *Cochrane Handbook for Systematic Reviews of Interventions* (pp. 321–347). https://doi.org/10.1002/9781119536604.ch12

Miles, C. L., Pincus, T., Carnes, D., Homer, K. E., Taylor, S. J., Bremner, S. A., … Underwood, M. (2011). Can we identify how programmes aimed at promoting self-management in musculoskeletal pain work and who benefits? A systematic review of sub-group analysis within RCTs. *European Journal of Pain, 15*. https://doi.org/10.1016/j.ejpain.2011.01.016, 775. e1-75. e11.

Miller, C. T., Owen, P. J., Than, C. A., Ball, J., Sadler, K., Piedimonte, A., … Belavy, D. L. (2021). Attempting to separate placebo effects from exercise in chronic pain: a systematic review and meta-analysis. *Sports Medicine, 1-27*. https://doi.org/10.1007/s40279-021-01526-6

Molinari, G., Miragall, M., Enrique, A., Botella, C., Banos, R., & Garcia-Palacios, A. (2019). How and for whom does a positive affect intervention work in fibromyalgia: An analysis of mediators and moderators. *European Journal of Pain (London, England)*. https://doi.org/10.1002/ejp.1481

Moore, R., Derry, S., McQuay, H., Straube, S., Aldington, D., Wiffen, P., … for the ACTINPAIN writing group of the IASP Special Interest Group (SIG) on Systematic Reviews in Pain Relief. (2010). Clinical effectiveness: An approach to clinical trial design more relevant to clinical practice, acknowledging the importance of individual differences. *Pain, 149*, 173–176. https://doi.org/10.1016/j.pain.2009.08.007

Morley, S. (2011). Efficacy and effectiveness of cognitive behaviour therapy for chronic pain: Progress and some challenges. *Pain, 152*, S99–S106. https://doi.org/10.1016/j.pain.2010.10.042

Morley, S., Williams, A., & Eccleston, C. (2013). Examining the evidence about psychological treatments for chronic pain: Time for a paradigm shift? *Pain, 154*, 1929–1931. https://doi.org/10.1016/j.pain.2013.05.049

Muller, D., Judd, C. M., & Yzerbyt, V. Y. (2005). When moderation is mediated and mediation is moderated. *Journal of Personality and Social Psychology, 89*, 852. https://doi.org/10.1037/0022-3514.89.6.852

O'Neill, A., O'Sullivan, K., O'Sullivan, P., Purtill, H., & O'Keeffe, M. (2020). Examining what factors mediate treatment effect in chronic low back pain: A mediation analysis of a cognitive functional therapy clinical trial. *European Journal of Pain (United Kingdom)*.. https://doi.org/10.1002/ejp.1624

O'Rourke, H. P., & MacKinnon, D. P. (2018). Reasons for testing mediation in the absence of an intervention effect: A research imperative in prevention and intervention research. *Journal of Studies on Alcohol and Drugs, 79*, 171–181. https://doi.org/10.15288/jsad.2018.79.171

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., … Brennan, S. E. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *Bmj, 372*. https://doi.org/10.1136/bmj.n71

Parsons, C. E., Zachariae, R., Landberger, C., & Young, K. S. (2021). How does cognitive behavioural therapy for insomnia work? A systematic review and meta-analysis of mediators of change. *Clinical Psychology Review, 102027*. https://doi.org/10.1016/j.cpr.2021.102027

Pérez-Aranda, A., Feliu-Soler, A., Montero-Marín, J., García-Campayo, J., Andrés-Rodríguez, L., Borràs, X., … McCracken, L. M. (2019). A randomized controlled efficacy trial of mindfulness-based stress reduction compared with an active control group and usual care for fibromyalgia: The EUDAIMON study. *Pain, 160*, 2508–2523. https://doi.org/10.1097/j.pain.0000000000001655

Pincus, T., Miles, C., Froud, R., Underwood, M., Carnes, D., & Taylor, S. J. (2011). Methodological criteria for the assessment of moderators in systematic reviews of randomised controlled trials: A consensus study. *BMC Medical Research Methodology, 11*, 14. https://doi.org/10.1186/1471-2288-11-14

Preacher, K. J., & Kelley, K. (2011). Effect size measures for mediation models: Quantitative strategies for communicating indirect effects. *Psychological Methods, 16*, 93. https://doi.org/10.1037/a0022658

Preacher, K. J., Rucker, D. D., & Hayes, A. F. (2007). Addressing moderated mediation hypotheses: Theory, methods, and prescriptions. *Multivariate Behavioral Research, 42*, 185–227. https://doi.org/10.1080/00273170701341316

Probst, T., Baumeister, H., McCracken, L. M., & Lin, J. (2019). Baseline psychological inflexibility moderates the outcome pain interference in a randomized controlled trial on internet-based acceptance and commitment therapy for chronic pain. *Journal of Clinical Medicine, 8*. https://doi.org/10.3390/jcm8010024

Rossettini, G., Carlino, E., & Testa, M. (2018). Clinical relevance of contextual factors as triggers of placebo and nocebo effects in musculoskeletal pain. *BMC Musculoskeletal Disorders, 19*, 1–15. https://doi.org/10.1186/s12891-018-1943-8

Schutze, R., Rees, C., Smith, A., Slater, H., Campbell, J. M., & O'Sullivan, P. (2018). How can we best reduce pain catastrophizing in adults with chronic noncancer pain? A systematic review and meta-analysis. *The Journal of Pain, 19*, 233–256. https://doi.org/10.1016/j.jpain.2017.09.010

Sebbag, E., Felten, R., Sagez, F., Sibilia, J., Devilliers, H., & Arnaud, L. (2019). The world-wide burden of musculoskeletal diseases: A systematic analysis of the World Health Organization burden of diseases database. *Annals of the Rheumatic Diseases, 78*, 844–848. https://doi.org/10.1136/annrheumdis-2019-215142

Simister, H. D., Tkachuk, G. A., Shay, B. L., Vincent, N., Pear, J. J., & Skrabek, R. Q. (2018). Randomized controlled trial of online acceptance and commitment therapy for fibromyalgia. *The Journal of Pain, 19*, 741–753. https://doi.org/10.1016/j.jpain.2018.02.004

Smeets, R. J. E. M., Vlaeyen, J. W. S., Kester, A. D. M., & Knottnerus, J. A. (2006). Reduction of pain catastrophizing mediates the outcome of both physical and cognitive-behavioral treatment in chronic low Back pain. *The Journal of Pain, 7*, 261–271. https://doi.org/10.1016/j.jpain.2005.10.011

Sodermark, M., Linton, S. J., Hesser, H., Flink, I., Gerdle, B., & Boersma, K. (2020). What works? Processes of change in a transdiagnostic exposure treatment for patients with chronic pain and emotional problems. *Clinical Journal of Pain, 36*, 648–657. https://doi.org/10.1097/AJP.0000000000000851

Spinhoven, P., Ter Kuile, M., Kole-Snijders, A. M., Hutten Mansfeld, M., Den Ouden, D. J., & Vlaeyen, J. W. (2004). Catastrophizing and internal pain control as mediators of outcome in the multidisciplinary treatment of chronic low back pain. *European Journal of Pain (London, England), 8*, 211–219. https://doi.org/10.1016/j.ejpain.2003.08.003

Steen, J., Loeys, T., Moerkerke, B., & Vansteelandt, S. (2017). Medflex: An R package for flexible mediation analysis using natural effect models. *Journal of Statistical Software, 76*.

Sterne, J. A., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., … Eldridge, S. M. (2019). RoB 2: A revised tool for assessing risk of bias in randomised trials. *Bmj, 366*. https://doi.org/10.1136/bmj.l4898

Sterne, J. A., Sutton, A. J., Ioannidis, J. P., Terrin, N., Jones, D. R., Lau, J., … Schmid, C. H. (2011). Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *Bmj, 343*. https://doi.org/10.1136/bmj.d4002

Taylor, S. S., Oddone, E. Z., Coffman, C. J., Jeffreys, A. S., Bosworth, H. B., & Allen, K. D. (2018). Cognitive mediators of change in physical functioning in response to a multifaceted intervention for managing osteoarthritis. *International Journal of Behavioral Medicine, 25*, 162–170. https://doi.org/10.1007/s12529-017-9689-5

Tingley, D., Yamamoto, T., Hirose, K., Keele, L., & Imai, K. (2014). Mediation: R package for causal mediation analysis. *Journal of Statistical Software, 59*, 1–38. https://doi.org/10.18637/jss.v059.i05

Trompetter, H. R., Bohlmeijer, E. T., Fox, J.-P., & Schreurs, K. M. G. (2015). Psychological flexibility and catastrophizing as associated change mechanisms during online Acceptance & Commitment Therapy for chronic pain. *Behaviour Research and Therapy, 74*, 50–59. https://doi.org/10.1016/j.brat.2015.09.001

Trompetter, H. R., Bohlmeijer, E. T., Van Baalen, B., Kleen, M., Köke, A., Reneman, M., & Schreurs, K. M. (2014). The psychological inflexibility in pain scale (PIPS). *European Journal of Psychological Assessment*. https://doi.org/10.1027/1015-5759/a000191

van Tulder, M. W., Ostelo, R., Vlaeyen, J. W., Linton, S. J., Morley, S. J., & Assendelft, W. J. (2000). Behavioral treatment for chronic low back pain: A systematic review within the framework of the Cochrane Back Review Group. *Spine, 25*, 2688–2699. https://doi.org/10.1097/00007632-200010150-00024

Turk, D. C., & Monarch, E. S. (2018). Biopsychosocial perspective on chronic pain. In D. C. Turk, & E. S. Monarch (Eds.), *Psychological approaches to pain management: A practitioner's handbook* (2nd ed., pp. 138–158). New York: Guilford publications.

Turner, J. A., Holtzman, S., & Mancl, L. (2007). Mediators, moderators, and predictors of therapeutic change in cognitive–behavioral therapy for chronic pain. *Pain, 127*, 276–286. https://doi.org/10.1016/j.pain.2006.09.005

Underwood, M., Mistry, D., Lall, R., & Lamb, S. (2011). Predicting response to a cognitive-behavioral approach to treating low back pain: Secondary analysis of the BeST data set. *Arthritis Care & Research, 63*, 1271–1279. https://doi.org/10.1002/acr.20518

VanderWeele, T., & Vansteelandt, S. (2014). Mediation analysis with multiple mediators. *Epidemiological Methods, 2*, 95–115. https://doi.org/10.1515/em-2012-0010

VanderWeele, T. J. (2016). Mediation analysis: A practitioner's guide. *Annual Review of Public Health, 37*, 17–32. https://doi.org/10.1146/annurev-publhealth-032315-021402

Vansteelandt, S., & Daniel, R. M. (2017). Interventional effects for mediation analysis with multiple mediators. *Epidemiology (Cambridge, Mass.), 28*, 258. https://doi.org/10.1097/EDE.0000000000000596

Veehof, M. M., Trompetter, H., Bohlmeijer, E. T., & Schreurs, K. M. G. (2016). Acceptance-and mindfulness-based interventions for the treatment of chronic pain: A

meta-analytic review. *Cognitive Behaviour Therapy, 45*, 5–31. https://doi.org/10.1080/16506073.2015.1098724

Viechtbauer, W. (2010). Conducting meta-analyses in R with the metafor package. *Journal of Statistical Software, 36*, 1–48.

Vlaeyen, J. W., & Crombez, G. (2020). Behavioral conceptualization and treatment of chronic pain. *Annual Review of Clinical Psychology, 16*, 187–212. https://doi.org/10.1146/annurev-clinpsy-050718-095744

Vlaeyen, J. W., & Linton, S. J. (2012). Fear-avoidance model of chronic musculoskeletal pain: 12 years on. *Pain, 153*, 1144–1147. https://doi.org/10.1016/j.pain.2011.12.009

Vlaeyen, J. W., & Morley, S. (2005). *Cognitive-behavioral treatments for chronic pain: What works for whom?* LWW.

Vo, T.-T., Superchi, C., Boutron, I., & Vansteelandt, S. (2020). The conduct and reporting of mediation analysis in recently published randomized controlled trials: Results from a methodological systematic review. *Journal of Clinical Epidemiology, 117*, 78–88. https://doi.org/10.1016/j.jclinepi.2019.10.001

Wampold, B. E., Minami, T., Tierney, S. C., Baskin, T. W., & Bhati, K. S. (2005). The placebo is powerful: Estimating placebo effects in medicine and psychotherapy from randomized clinical trials. *Journal of Clinical Psychology, 61*, 835–854. https://doi.org/10.1002/jclp.20129

Wertli, M. M., Burgstaller, J. M., Weiser, S., Steurer, J., Kofmehl, R., & Held, U. (2014). Influence of catastrophizing on treatment outcome in patients with nonspecific low back pain: A systematic review. *Spine, 39*, 263–273. https://doi.org/10.1097/BRS.0000000000000110

Wertli, M. M., Rasmussen-Barr, E., Held, U., Weiser, S., Bachmann, L. M., & Brunner, F. (2014). Fear-avoidance beliefs—A moderator of treatment efficacy in patients with low back pain: A systematic review. *The Spine Journal, 14*, 2658–2678. https://doi.org/10.1016/j.spinee.2014.02.033

Wetherell, J. L., Afari, N., Rutledge, T., Sorrell, J. T., Stoddard, J. A., Petkus, A. J., … Lang, A. J. (2011). A randomized, controlled trial of acceptance and commitment therapy and cognitive-behavioral therapy for chronic pain. *Pain, 152*, 2098–2107. https://doi.org/10.1016/j.pain.2011.05.016

Wiborg, J. F., Knoop, H., Frank, L. E., & Bleijenberg, G. (2012). Towards an evidence-based treatment model for cognitive behavioral interventions focusing on chronic fatigue syndrome. *Journal of Psychosomatic Research, 72*, 399–404. https://doi.org/10.1016/j.jpsychores.2012.01.018

Wicksell, R. K., Kemani, M., Jensen, K., Kosek, E., Kadetoff, D., Sorjonen, K., … Olsson, G. L. (2013). Acceptance and commitment therapy for fibromyalgia: A randomized controlled trial. *European journal of pain (london, england), 17*, 599–611. https://doi.org/10.1002/j.1532-2149.2012.00224.x

Wicksell, R. K., Olsson, G. L., & Hayes, S. C. (2010). Psychological flexibility as a mediator of improvement in acceptance and commitment therapy for patients with chronic pain following whiplash. *European Journal of Pain, 14*. https://doi.org/10.1016/j.ejpain.2010.05.001, 1059. e1-59. e11.

Wicksell, R. K., Olsson, G. L., & Melin, L. (2009). The chronic pain acceptance questionnaire (CPAQ)-further validation including a confirmatory factor analysis and a comparison with the Tampa scale of Kinesiophobia. *European Journal of Pain, 13*, 760–768. https://doi.org/10.1016/j.ejpain.2008.09.003

Windgassen, S., Goldsmith, K., Moss-Morris, R., & Chalder, T. (2016). *Establishing how psychological therapies work: the importance of mediation analysis*. https://doi.org/10.3109/09638237.2015.1124400