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

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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 29 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.

Keywords: chronic musculoskeletal pain, psychologically based interventions, mediation analysis, moderation analysis, meta-analysis, systematic review.

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 et al., 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 et al., 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 established as benchmark for the management of people with chronic pain (de C Williams et al., 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 et al., 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 et al., 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 C Williams, et al., 2020; Hughes et al., 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 et al., 2013). Broadly, the mechanisms underlying treatment effects can be divided into specific and non-specific effects (Wampold et al., 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 et al., 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 et al. (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 et al., 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 et al., 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 et al., 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 et al., 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 et al., 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 et al., 2007; Preacher et al., 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 et al., 2020; VanderWeele, 2016). Structural equation modelling (derived from path analysis) is another possible approach to calculate indirect effect (De Stavola et al., 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., 2014a; Wertli et al., 2014b). 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 et al., 2017; Wertli, et al., 2014a; Wertli, et al., 2014b) 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 et al., 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 et al., 2014) and *medflex* (Steen et al., 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 22808 citations. We obtained 9941 potential citations after the removal of duplicate records, and 38 additional articles were identified through hand-searching. 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=4,652) (Cederberg et al., 2016; Chalder et al., 2015; Coronado et al., 2020; Durá-Ferrandis et al., 2017; Fordham et al., 2017; Garland et al., 2019;

Hedman-Lagerlof et al., 2019; Leeuw et al., 2008; Lin et al., 2018; Luciano et al., 2014; Mansell et al., 2016; Mansell et al., 2017a; Mansell et al., 2017b; Molinari et al., 2019; O'Neill et al., 2020; Pérez-Aranda et al., 2019; Simister et al., 2018; Smeets et al., 2006; Sodermark et al., 2020; Spinhoven et al., 2004; Taylor et al., 2018; Trompetter et al., 2015; Turner et al., 2007; van Koulil et al., 2011; Wetherell et al., 2011; Wiborg et al., 2012; Wicksell et al., 2013; Wicksell et al., 2010) and 11 moderation analyses (n=1,925) (Broderick et al., 2016; Buckelew et al., 1996; Day et al., 2019; Flink et al., 2010; Lawford et al., 2018; Leeuw, et al., 2008; Litt et al., 2010; Macedo et al., 2014; Probst et al., 2019; Turner, et al., 2007; Underwood et al., 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=3,655 and 1,685 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 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=1,518)(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., 2013; Wicksell, et al., 2010) 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 (**Fig. 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**.

5.4.1.1. 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, et al., 2017b; 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.

5.4.1.2. 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, et al., 2017a; 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, et al., 2017a) (**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).

5.4.1.3. 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 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).

5.4.1.4. 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., 2013; Wicksell, et al., 2010) 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., 2013; Wicksell, et al., 2010) 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.

5.4.1.5. 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 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. 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 summarised 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-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 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 et al., 2020a; Martinez-Calderon et al., 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 et al., 2014; Martinez-Calderon, et al., 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 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 et al., 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 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 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 et al., 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 et al., 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 et al., 2013; Linton & Bergbom, 2011). Among all included studies, only one intentionally targeted these constructs during treatment through specific techniques (Sodermark, et al., 2020).

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 et al., 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 et al., 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 et al., 2017; French et al., 2007; VanderWeele & Vansteelandt, 2014; VanderWeele, 2016). 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 et al., 2015; Cassidy et al., 2012; Gilliam et al., 2017; Greenberg et al., 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, et al., 2014a; Wertli, et al., 2014b). 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 et al., 2017; Gu et al., 2015; Parsons et al., 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

892 acknowledged is the between-trial heterogeneity in some meta-analysis due to the variety
893 across the studies in terms of interventions. This issue is particularly noticeable in the meta-
894 analyses for CBT as there is not one standardized protocol, and intervention delivery, duration
895 and components (ranging from very behaviorally focused such as exposure in vivo to very
896 cognitively focused such as cognitive restructuring) varied across interventions. Similarly,
897 slight variations with respect to the comparators was also observed, where for example, some
898 studies included some form of traditional (biomechanical) pain education in addition to
899 standard usual care.
900
901 **7. Conclusions**
902 The investigation of the mechanisms underlying the effects of psychologically based
903 interventions on pain and related disability is a complex yet crucial journey in order to refine
904 theoretical models, inform the direction of future research and ultimately improve outcomes.
905 The available evidence supports the idea that reductions in pain catastrophizing, pain-related
906 fear and avoidance as well as increases in self-efficacy mediate the effects of cognitive
907 behavioral therapy on pain-related disability, but not on pain intensity. Similarly, increases of
908 pain acceptance and psychological flexibility mediate the effects of acceptance and
909 commitment therapy on pain-related disability. Limitations notwithstanding, findings seem to
910 be consistent with the theoretical models and support targeting these constructs in treatment,
911 but further research is needed to understand the shared and specific mechanisms of these
912 interventions. Further examination is also needed to unravel whether or not pre-treatment status
913 of these constructs also acts as moderator of treatment.

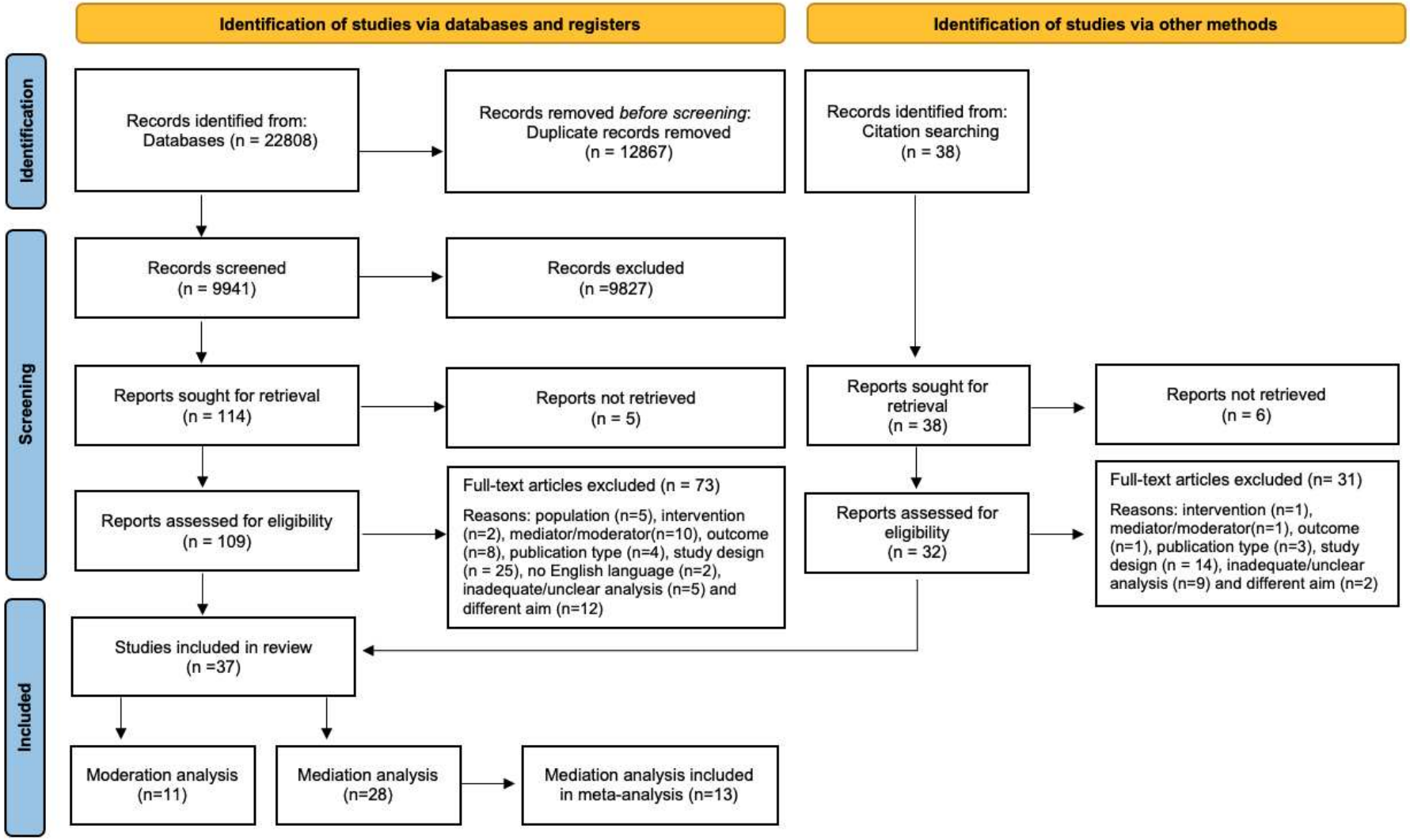


Figure 1. Flow chart of screening process

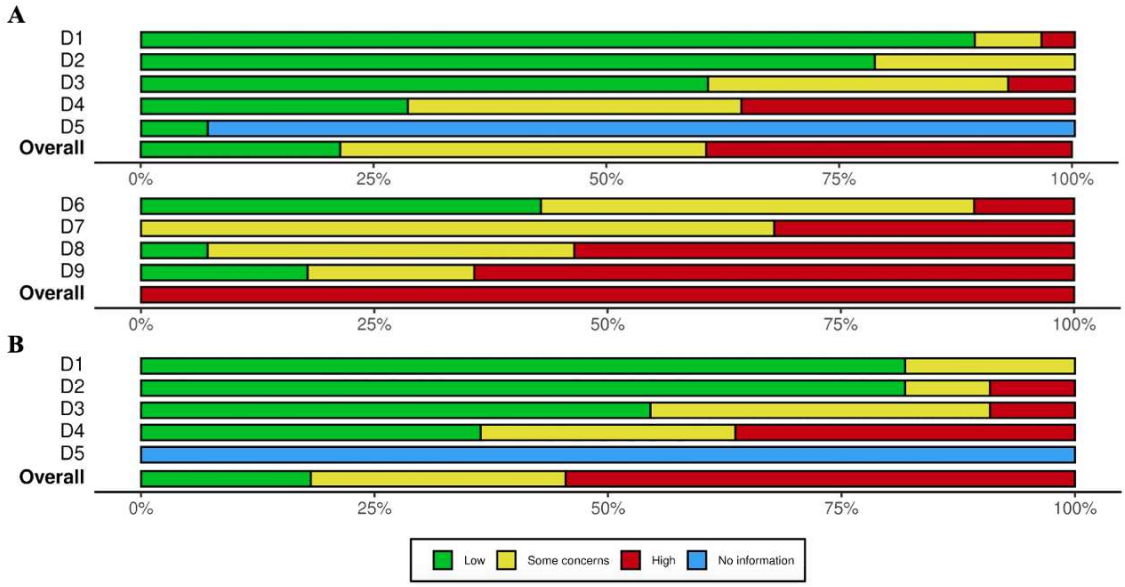


Figure 2. Summary of the results of risk of bias assessment for (A) mediation and (B) moderation studies. **Domain 1 (D1)**: Risk of bias arising from the randomization process; **Domain 2 (D2)**: Risk of bias due to deviations from the intended interventions; **Domain 3 (D3)**: Risk of bias due to missing 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 modelling bias.

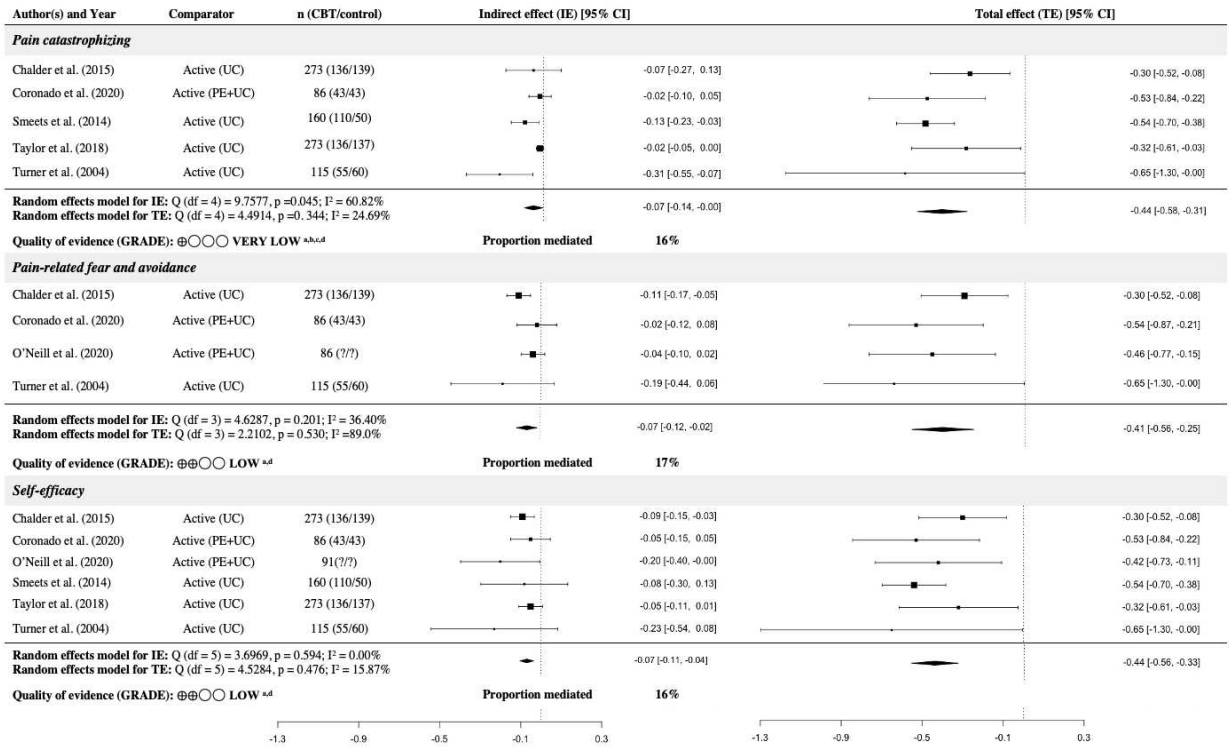


Figure 3. Meta-analysis on the indirect and total effects of CBT care on disability. Between-trial heterogeneity Cochran Q heterogeneity test and I^2 statistic are reported.

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.

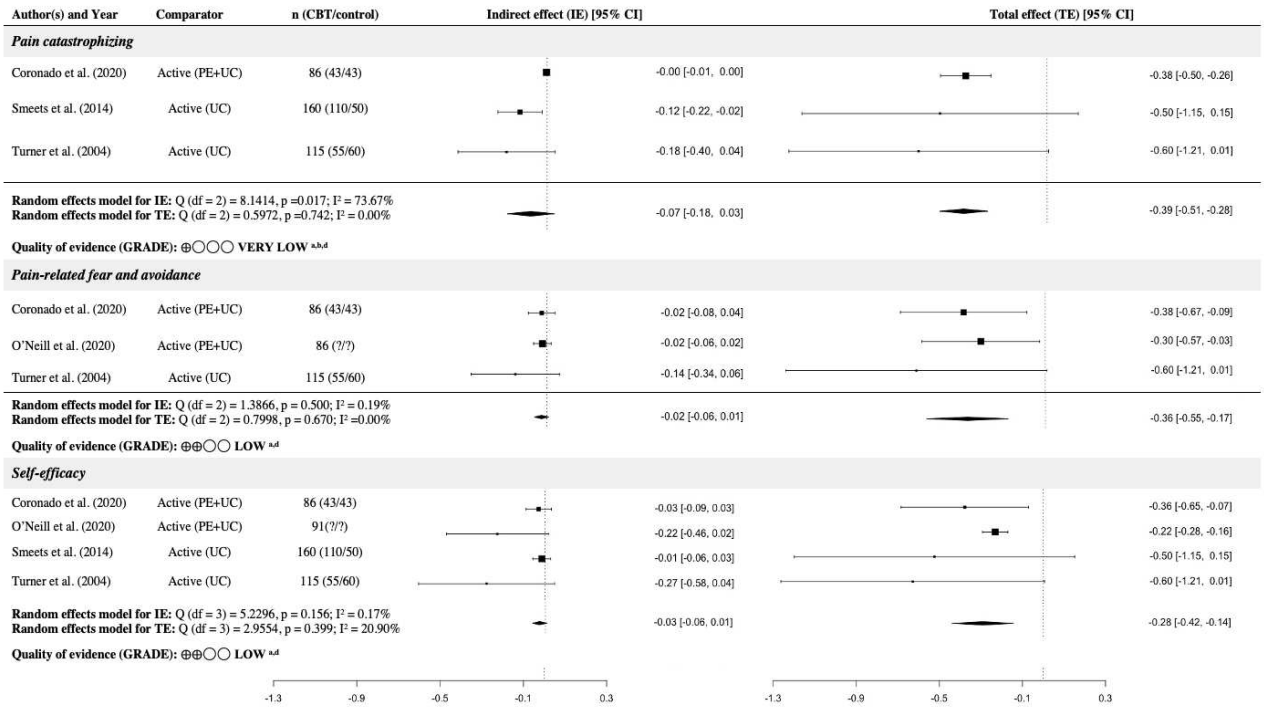


Figure 4. Meta-analysis on the indirect and total effects of CBT on pain intensity. Between-trial heterogeneity Cochran Q heterogeneity test and I^2 statistic are reported.
GRADE: [a] downgraded due to risk of bias, [b] downgraded due to inconsistency, [c] downgraded due to imprecision, [d] downgraded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

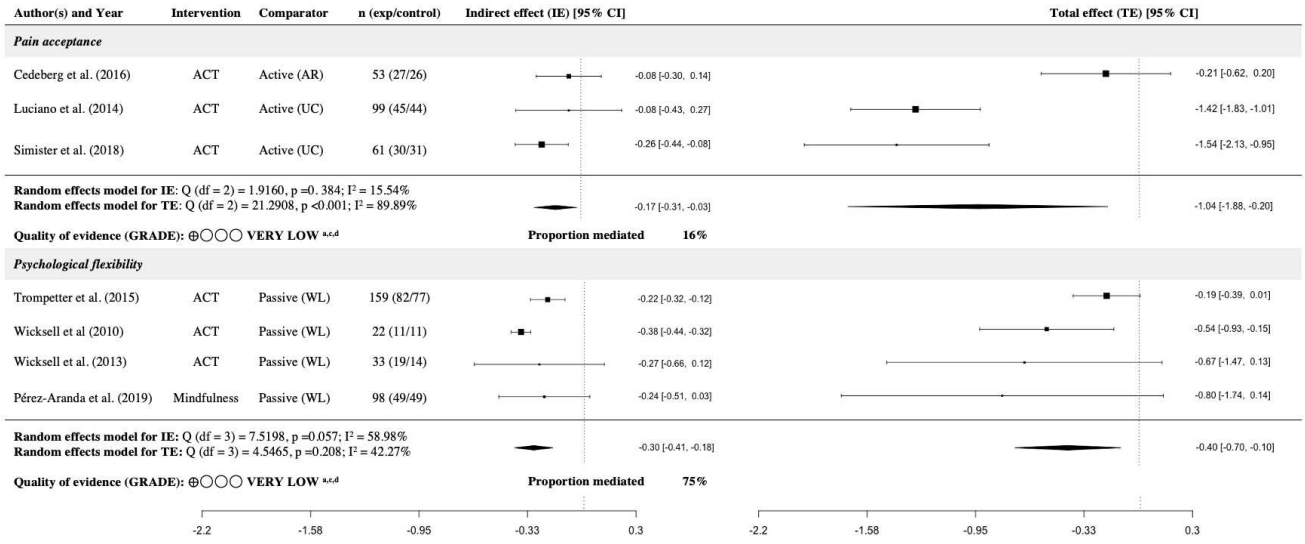


Figure 5. Meta-analysis on the indirect and total effects of ACT on disability. Between-trial heterogeneity Cochran Q heterogeneity test and I^2 statistic are reported.
GRADE: [a] downgraded due to risk of bias, [b] downgraded due to inconsistency, [c] downgraded due to imprecision, [d] downgraded due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

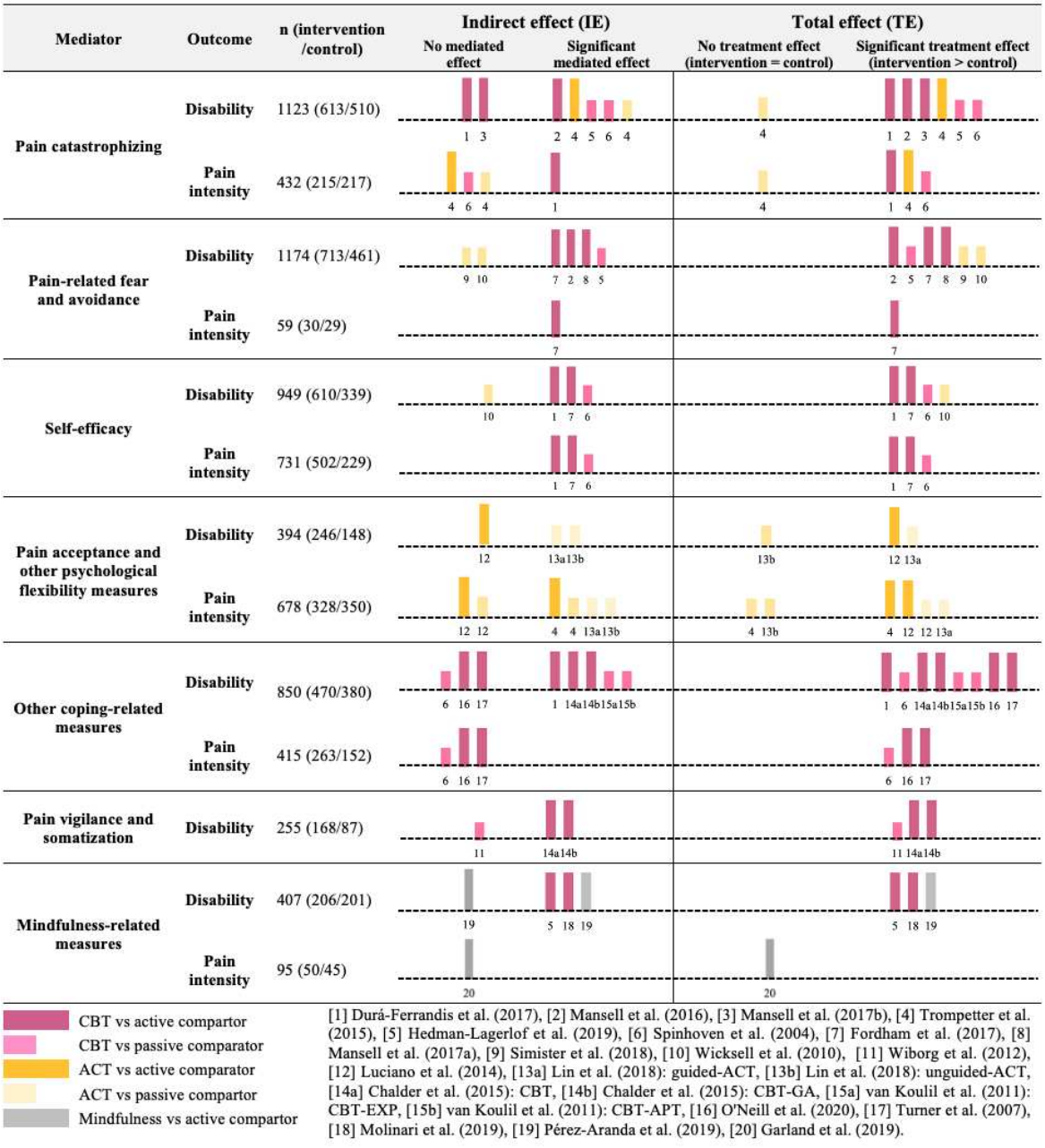
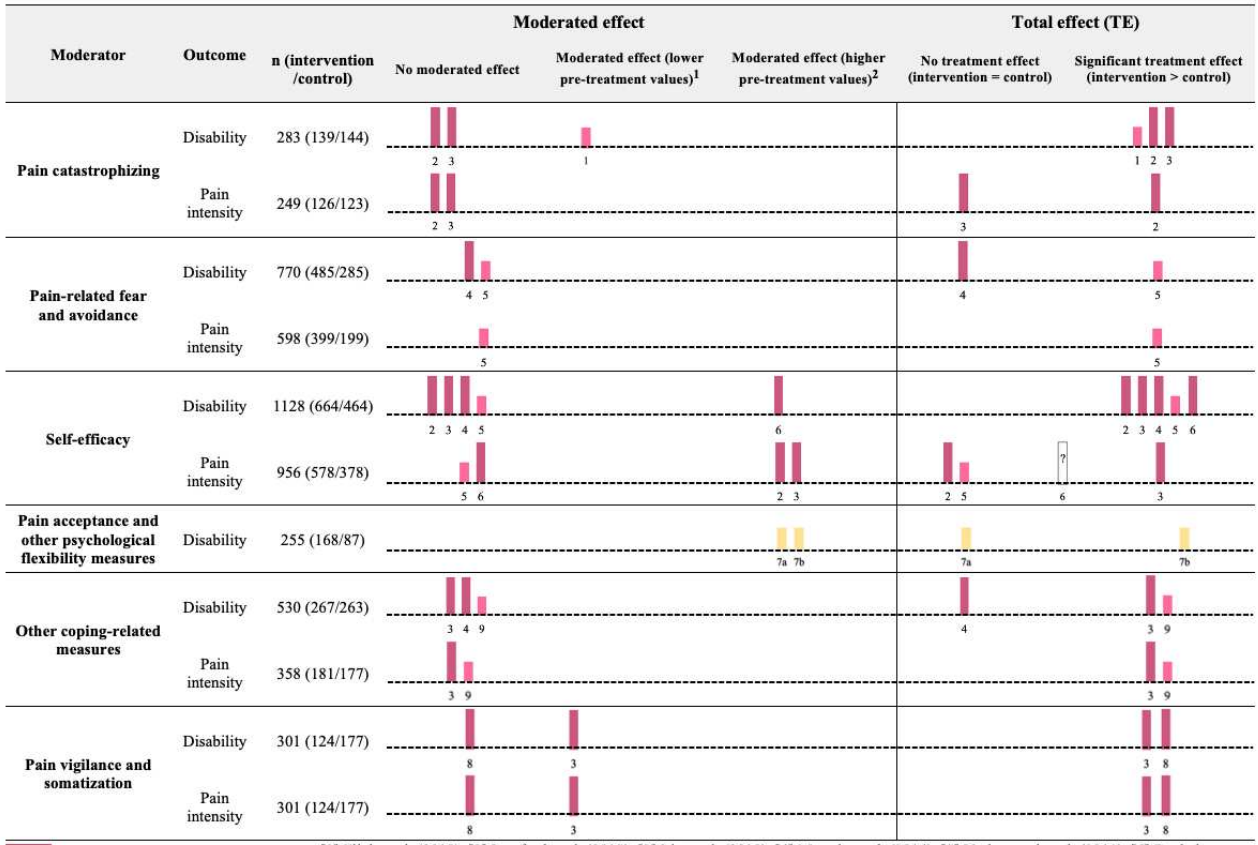


Figure 6. Harvest plot. Summary of the narrative synthesis of results from mediation studies not included in the meta-analysis



[1] Flink et al. (2010), [2] Lawford et al. (2018), [3] Litt et al. (2010), [4] Macedo et al. (2014), [5] Underwood et al. (2011), [6] Buckelew et al. (1996), [7] Broderick et al. (2016), [8] Turner, et al. (2007), [9] Probst et al. (2019)

Notes: 1) Superior treatment effect in the intervention group compared to control in patients with lower values of the moderator at baseline.
2) Superior treatment effect in the intervention group compared to control in patients with higher values of the moderator at baseline

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

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, et al. (2017a) †	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 modelling	CBT (21%) and WL (24.1%) Simple imputation
Mansell, et al. (2017b) †	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 question**) and stress (**DASS-stress**)	≈3-month	Outcome baseline value[3]	Disability (**ODI**) Pain intensity (**NRPS**)	≈9-month	Parallel (separate) MA Natural/indirect effect	CBT (31.1%) and UC (25%) 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=302, 84.1% ♀)	Mediators grouped in **[1]** latent variable Pain acceptance (**CPAQ-willingness and activity engagement** and **AAQ-II**).	No	Post-therapy	No	Disability (**MPI-interference, BPI-interference**) Pain intensity (**NRPS**)	≈4-month	Single MA Product-of-coefficient	Guided-ACT (46.0%), unguided-ACT (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.

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

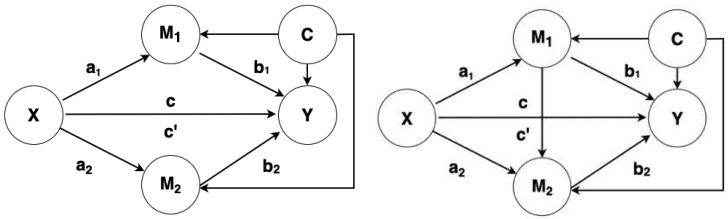
CBT, Cognitive behavioral therapy; FM; fibromyalgia; ASES, Arthritis Self-Efficacy Scale; AIMS, Arthritis Impact Measurement Scales; VAS, Visual Analogue Scale; OA, osteoarthrosis; MPI, Multidimensional Pain Inventory; CEQ, Credibility/Expectancy Questionnaire; BDI, Beck Depression Inventory; BPI, Brief 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.

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)

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