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Why and how back pain interventions work: What can we do to find out?

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A B S T R A C T

Mediation analysis is a useful research method that potentially allows identification of the mechanisms through which treatments affect patient outcomes. This chapter reviews the theoretical framework, research designs and statistical approaches used in mediation analysis. It describes what can be learnt from previous mediation research, much of which has investigated mediating factors of psychosocial interventions in other health conditions. It also summarises the few treatment-mediation studies of psychosocial interventions conducted in back pain.

This chapter shows that there is emerging evidence about the role of some psychological factors as potential treatment mediators, such as self-efficacy and catastrophising. Mediation analysis can equally be applied to non-psychological factors. Pre-planned and appropriately conducted mediation analysis in adequately powered clinical trials would be a step forward in understanding treatment effects in back pain and improving patient management.

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Introduction

A recurring conclusion of high-quality systematic reviews and randomised controlled trials (RCTs) in the field of back pain is that most treatments show modest effects compared to natural course and small or no differences between the effectiveness of different interventions [1–4]. This leads to equivocal and sometimes contradictory messages in clinical practice guidelines [5,6] and frustration in clinicians attempting to provide evidence-based care for their patients. In part, the underwhelming results reported by these studies are likely due to incomplete understanding of what factors might be necessary to be included in interventions to help influence outcome. Studies have examined the physical [7,8], psychological [9,10] and social [11,12] aspects of interventions to try to identify these factors. To date however, satisfying answers remain elusive.

Mediation analysis offers a method of testing theories regarding the causal links between a predictor and an outcome. The establishment of causal mechanisms as opposed to simply associative links is critical to the understanding of the processes of treatment effect. Mediation analysis can be applied to data from various types of study designs: cross-sectional surveys, clinical registries, longitudinal cohorts and randomised and non-randomised clinical trials. While different study designs impose different restrictions on the explanatory power of mediation analysis, this flexibility makes mediation analysis a useful supplement to other, more commonly used, methods of analysis.

Mediation analysis tests whether the influence of a predictor or treatment on an outcome occurs via change in a particular intermediate variable, the mediator. For example, a treatment could aim to influence fear-avoidant behaviours, which if successfully changed could be responsible for change in outcomes such as disability or pain intensity. Where the predictor variable is a 'clinical feature' associated with a condition, such as pain intensity or psychological distress, mediation analysis helps us understand the pathway between it and the outcome of interest. This information can be very useful in identifying factors that should be targeted in treatment. Where the predictor is a 'specific treatment', such as allocation to a particular treatment arm in an RCT, mediation analysis provides insight into whether the effectiveness or ineffectiveness of a treatment is consistent with theories regarding its mechanism.

Currently in the management of back pain, many interventions are based on imprecise theoretical rationales, rather than empirically derived hypotheses. It is potentially very useful to disentangle factors merely associated with outcome from those that could potentially help to explain treatment effects. Making distinctions between causes, consequences and epiphenomena is vital, as treatments that target factors that are not modifiable or influential are unlikely to be successful. For example, anxiety has been shown to be predictive of poor recovery from low back pain (LBP) [13] and is commonly associated with pain. However, a recent mediation study [14] showed that the relationship between pain and disability in patients with LBP is not mediated by anxiety. This suggests that a treatment designed to only target anxiety in LBP patients would be unlikely to have an important effect on pain-related disability.

Identifying the mechanism of action of a particular treatment offers the opportunity to optimise its effectiveness. Investigation of the relationship between an intervention and its effect via mediation analysis can provide information as to whether and to what extent the hypothesised action is real. This information can be used to modify the intervention in order to target the appropriate mediating factor more directly and enhance the capacity of the treatment to reach its full potential effect.

To date, relatively few mediation analyses have been conducted in back pain research despite such studies being potentially capable of providing important insight into questions relevant to the field. The aim of this article is to introduce the theory and practice of mediation analysis and discuss some of the issues involved with study design, conduct and interpretation.

What is a mediator?

It is important to define what we mean by the term 'mediator' along with some other, related terms, as these terms can have slightly different meanings in different fields [15,16] and this can be a source of confusion.

Mediators, also known as intermediate variables [17] or indirect effects [18], are variables that help explain how a treatment might work [15,19] and are by definition on the pathway between predictor

and outcome [19]. As illustrated in Fig. 1, the total effect of treatment on outcome can be separated into the direct effect and indirect (mediated) effect. Mediated effects differ from the direct effect of treatment in that the mediated effect combines the paths from the treatment to the mediator and from the mediator to the outcome. Mediators are modifiable and change during the course of, or in response to, treatment. For example, Fig. 1 shows that an intervention designed to reduce disability in back pain patients may work by reducing their levels of fear avoidance. The intervention causes fear avoidance to reduce, which results in improved function.

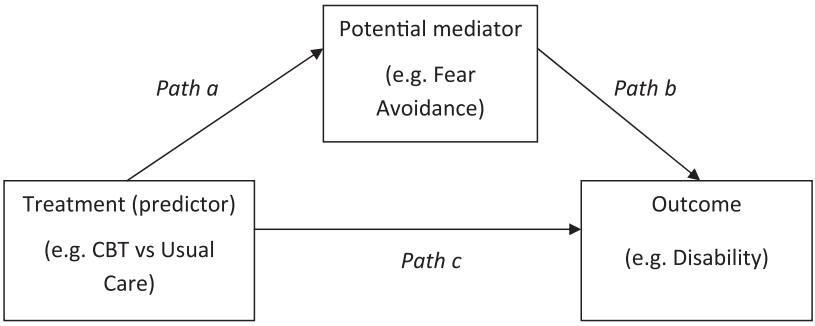
It is important to note the distinction between a mediator and a confounder. Confounders may explain the relationship between two variables but are not on a supposed causal pathway between them [20,21]. For example, in an observational study including different treatment options, patients referred for an exercise programme may be younger whereas those offered pain relief may be older. Functional outcome may turn out to be better in those offered the exercise programme. However, age is not a mediator of treatment effect as it cannot be changed by treatment, even though it may be causally associated with function. In this case, age is a confounder due to the unequal distribution of age between the two groups.

It is equally important to distinguish between a mediator and a treatment-effect modifier or moderator variable. A moderator is a baseline characteristic that stratifies treatment effect (i.e., identifies for whom a treatment is likely to have the most effect) but is not on a supposed causal pathway. For example, status on a prediction rule [22] at baseline has been reported to predict outcome in response to manual therapy. This does not necessarily mean that the features measured by the rule (e.g., hip range of motion, fear–avoidance beliefs and duration of symptoms) 'cause' the person's disability or are all addressed by the treatment.

It is important to note that while Fig. 1 denotes a single-mediator model, this is unlikely to be the case in reality. It is much more likely that several mediators exist on a pathway between the predictor or treatment and the outcome (e.g., confidence in their clinician or the prescription of pain medication might help to reduce the patient's fear avoidance, leading to an improvement in functioning). However, for simplicity, we only discuss examples of single-mediator models in this chapter.

Mediation across different study designs

Regardless of the way mediation is defined or how it is statistically analysed, it is described using causal language [17,23]. The concept of causality has a number of facets, but in mediation analysis, those most commonly discussed are temporality, consistency and dose–response [24]. It should be



Direct effect of treatment on outcome = path c

Mediating effect = ab (combination of paths a and b)

Total effect = ab + c

Fig. 1. Treatment mediation.

noted, however, that although addressing these facets allows us to be more confident that a causal association is present, this can never be fully established [25,26].

Temporality is the sequence in which variables change. In order for one variable to be potentially causing another, it must precede the proposed outcome in time [27]. It has been suggested that establishing temporality is less complicated in the context of an RCT compared to observational study designs. This is because an RCT has a clear 'start' and 'end' point to the intervention and any given variable that changes during or in response to treatment, and is associated with that treatment, is a potential mediator [17]. However, in order to truly establish a mediating pathway, we also need to consider how many assessments are required to establish temporality and when these assessments should take place. For example, we might expect an intervention to have an effect on patients very quickly so that we need to assess them early on to pick up any change, or perhaps we expect the intervention will take some time to have an impact so that we need to carry out assessments over a longer period of time. The more assessments that are included, the more confident we can be about the order in which variables change [28], although this does require the use of increasingly complex modelling procedures. It also increases patient burden as they will have to complete a larger number of questionnaires, examination procedures and/or biomedical tests.

Consistency is the observation of similar findings across multiple studies [27]. As with other study designs, the replication of findings from mediation studies in different settings and samples increases confidence in their accuracy. Dose–response is the observation of increasing or decreasing effect on outcome depending upon the level of (change in) the mediator [24]. These two aspects indicate that establishing mediating effects in different study designs, in different contexts and in different populations provides more convincing evidence for specific mediating factors.

Most research examining mediation has been performed in cross-sectional studies and therefore is of limited usefulness because temporal precedence cannot be established [29]. However, finding an association between the potential mediator and the outcome might be an important first step in establishing consistency. Studies that include longitudinal analyses are much more useful from a mediation perspective [30] as they allow the investigation of associations between variables over time, helping to establish temporality. Longitudinal designs can also provide some information on dose–response by investigating whether there is an association between the magnitude of change in the potential mediator and magnitude of change in the outcome. However, neither design allows causal mechanisms to be established. Clinical trial designs have several advantages over observational study methods for providing evidence for causality and reducing bias [31–34], such as active manipulation of the potential mediator, which lends more credence to any mediating effects found in the treatment arm (yet not in a control arm) and also helps to best establish dose–response. These factors help bring us closer to our goal in mediation: that of finding a causal pathway that explains the link between the predictor (independent) variable (in this case, the intervention) and the outcome (dependent) variable.

In summary, while mediating factors can be explored using a variety of study designs, RCTs have the potential to provide the most robust answers about how treatments work. However, observational studies and other research designs may be useful in developing testable and empirically based hypotheses about treatment mediation. Identification of causal mechanisms is strengthened by the plausibility of mechanisms based on previous evidence, consistency of findings with those from preceding studies and the demonstration of dose–response.

Action Theory and Conceptual Theory

Action Theory and Conceptual Theory provide a framework for understanding and interpreting mediation analyses in controlled trials. Action Theory refers to whether the intervention potentially causes significant change in the mediator, and Conceptual Theory refers to whether the outcome of interest is affected by change in the mediator (see Fig. 1) [35]. Action Theory addresses the question of whether the intervention is actually effective according to its theorised mechanism [36]. Conceptual Theory provides information regarding whether the rationale upon which the treatment is based is valid. Chen [37] explains that a weak (or absent) relationship between the intervention and the mediator would suggest that the intervention is not being implemented in the optimum way (Action Theory), whereas if the relationship between the mediator and outcome was weak or non-existent, this

would suggest the theory or concept underlying the intervention is the problem (Conceptual Theory). Thus, the relationships (or lack thereof) observed in both parts of the model provide useful and interpretable information.

Mediation analysis: how is it done?

Review of statistical approaches to mediation analysis

A number of different approaches to conducting mediation analysis have been proposed. MacKinnon et al. [18] identified 14 different methods, which they grouped into three different approaches: causal steps, difference in coefficients and product of coefficients.

1. Causal steps' approach

These methods seek to test different links in a chain of variables in which the order is assumed to be causal [18,38]. They involve using multiple regression analysis to test each of the paths illustrated in Fig. 1, and each path must be statistically significant. In the context of an RCT, the test of mediation occurs when the potential mediating factor is included in the model with the independent (treatment) and dependent (outcome) variables. If the relationship between treatment and outcome is no longer significant or is substantially reduced when the potential mediator is included, a mediation effect is identified [15,18]. The contribution of the mediating variable to the relationship between the treatment and outcome is sometimes estimated by the proportional change that occurs in the relationship between treatment and outcome when the mediator is introduced to the model [39].

However, these approaches are criticised in the literature [18,40,41]. The requirement for the treatment-outcome path to be statistically significant has been contested by a number of authors as it reduces the approach's power to detect mediating effects [18] and is highly dependent on sample size; hence, larger studies are more likely to show significant results [17]. Further, only performing mediation analysis in studies where there is a treatment effect precludes research into why treatments 'do not' work.

Overall, the review by MacKinnon et al. [18] of all 14 methods concluded that the causal steps' approach was the least optimal test of mediation. Although some researchers still advocate their use in certain contexts (e.g., Ref. [42]), they appear to have been superseded by more sophisticated methods.

2. Difference in coefficients' approach

This approach examines the difference between regression coefficients before and after the inclusion of a potential mediating variable [18]. Conceptually, this is similar to the causal steps' approach but the statistical equations used are different (see MacKinnon et al. [18] or Hayes [40] for a detailed discussion). This approach has been found to have more power but MacKinnon's review found the method to be still susceptible to Type II errors (a true mediation effect is missed) and useful only when testing a single mediating factor. As a single-mediator model is often too simplistic to suitably account for real-world situations, the usefulness of this approach is limited.

3. Product of coefficients' approach

This final approach involves multiplying the regression coefficients of the proposed mediating pathways (paths *a* and *b* in Fig. 1) to estimate the amount of variance in the outcome that is explained by the treatment through the mediator [18]. Sobel [43] extended this method to allow determination of its statistical significance, by dividing the product of coefficients by its standard error and comparing that value to a normal distribution.

However, the Sobel test assumes that the mediated effect is normally distributed [18,44], which often may not be the case. Several methods have been proposed to deal with this, (see Ref. [18]) the most promising of which is the statistical technique known as bootstrapping [29,44]. Bootstrapping does not assume normal distribution and allows the generation of bias-corrected confidence intervals (CIs) around the mediation effect. It can also be applied to smaller samples [45], which helps to

resolve the problem of inadequate power often encountered in mediation analysis studies. MacKinnon and colleagues argue that this approach should be the preferred method for investigating mediation effects.

Statistical methods for testing mediation

To perform the analyses described above, linear regression or structural equation modelling (SEM) techniques are most often used [16]. Linear regression is simple to use and perhaps more familiar to researchers but makes strong assumptions about the data that are not always satisfied. For example, the assumption of no measurement error in the tools used to assess the variables of interest [15] is difficult to sustain in the investigation of psychological factors where the variables being examined are latent and therefore not directly measurable. Measurement error is a particular problem when using regression analysis for mediation, as we are trying to establish whether change in a particular factor is responsible for change in the outcome. Measures need to be highly accurate when measuring change, as this involves at least two measurements, each with its own error [46].

Although more complex, SEM is viewed as a better choice of statistical technique for mediation analysis. SEM is a combination of regression analysis and factor analysis and, while making many of the same assumptions about the data, it handles the inclusion of several mediating factors more readily, it can include latent (unobserved) factors and it can account for measurement error [15,30,44]. SEM also provides goodness-of-fit statistics that allow comparisons between tested models [31]. This technique does however require larger sample sizes than traditional regression analysis [47,48].

More recent developments in mediation analysis methods include latent growth modelling (LGM), performed within SEM [38]. This method allows the inclusion of several time points for the mediator and the outcome variable and also allows the modelling of the change that occurs within an individual (within-subject effects) rather than only change between different people (between-subject effects) [49].

Overall, this literature suggests that a product of coefficients approach performed using SEM, with bootstrapped CIs, is currently the most effective method for addressing the assumptions made when performing mediation analysis. However, while these more complex statistical techniques are necessary in order for us to gauge more accurately the mediating effect of particular variables, the results may be more difficult to interpret and more difficult to implement in clinical settings. It is important that the right balance is struck between the integrity of the analysis performed and its practical application.

What evidence on treatment mediation does already exist?

Evidence from other fields

To date, research into treatment-mediating factors has mostly been undertaken in fields other than musculoskeletal health, particularly in the area of behavioural interventions. The results of this work have been synthesised in four systematic reviews for the outcomes of physical activity in children and adults [50], change in dietary behaviour in adolescents [35,51] and the physical and psychological health of cancer patients [36]. These reviews not only describe the evidence for factors mediating these outcomes but also report the methodological quality of the included studies and make recommendations on the design of future studies of mediation.

These reviews also report on the design [51] and adaptation [35] of a critical appraisal tool that can be used to assess aspects of study design, such as the properties of the measures used and whether the study was adequately powered (see Table 1). This tool was further adapted [50] to extend the appraisal of mediation methodology by including an assessment of temporality and a judgement of the appropriateness of the analysis used.

These systematic reviews identified a variety of potential psychosocial mediators, with self-efficacy being the one most tested and most often found to mediate outcomes. However, the reviews found considerable heterogeneity in their included studies (populations, factors investigated, methods and strength of findings) that precluded robust conclusions.

Table 1
Summary of the development of the critical appraisal tool.

Lubans et al. [51]	Cerin et al. [35]	Mansell et al. [this review]
Did the study cite a theoretical framework?	√	√
Were the study measures/ procedures designed to influence mediating variables?	√	√
Were pilot studies conducted/ reported to test the effect of the intervention on mediators?	*X*	√
Was an objective measure of physical activity used?	*X*	*X*
Were the psychometric characteristics of mediator variables reported and were they within accepted ranges (Cronbach's alpha and test-retest reliability >.60)?	√	√
Did the study report a power calculation and was the study adequately powered to detect mediation?	√	√
Did the study use an experimental design?	√	√
Was post-intervention physical activity controlled for baseline physical activity?	*X*	*X*
	Were all 3 steps for testing validity of a theory of behaviour change performed?	*X*
	Were the psychometric characteristics of the outcome measure reported, and were they within acceptable ranges (i.e., test-retest or Cronbach's alpha>.60?)	√
	Were statistically appropriate/ acceptable methods of data analysis used?	√
	Did the study ascertain whether changes in the mediating variables preceded changes in the outcome variables?	√
		Did the study report a change between baseline and follow-up for each mediator tested/reported?
		Was the change in the potential mediator correlated with change in outcome?
		Did the study control for possible confounding factors, e.g., baseline values?

Collectively, these reviews recommended that future mediation studies should: state clear theoretical links between the variables of interest, use adequate measures of constructs, establish temporal precedence, use only appropriate tests of mediation, be adequately powered and report a power calculation and include more complex models that test multiple mediators reflective of the complex nature of the interventions. They also advocated the calculation of CIs of the mediated effect, which is possible using the bootstrapping method.

Systematic review of treatment-mediation research in musculoskeletal pain

In order to explore mediation research in the musculoskeletal field, a systematic review of mediators of psychological interventions for musculoskeletal pain was conducted by one of the authors (GM). The aim was to identify mediators of psychological musculoskeletal pain interventions and report the methodological quality of the studies investigating them.

This review included clinical trials of adults with non-traumatic, non-inflammatory musculoskeletal pain (including back pain) who had received a psychological intervention aimed at reducing their level of disability. A psychological intervention was defined as any intervention that specifically aimed to change psychological factors during treatment. Included studies needed to report results from some form of mediation analysis, measure functional disability as an outcome, be available in full-text English and have been peer-reviewed. Although some mediation methods appear superior, any method was deemed acceptable for inclusion in order to incorporate the maximum number of studies. Studies were identified via a detailed search (available from the first author) conducted in four electronic databases (PsycINFO from 1806, MEDLINE from 1950, AMED from 1985 and CINAHL from 1981) from their inception up until February 2012.

The critical appraisal tool used in the previous reviews was further adapted to our topic of interest and some new items, recommended in the above review of the methodological literature, were added. Table 1 describes the tool. Total score was not calculated, as current recommendations suggest that descriptive summaries of the various quality criteria are more interpretable and reliable than the use of quality sum scores [52].

The electronic search identified 7325 unique references. After scanning titles and abstracts, 93 full-text articles were retrieved for further inspection and seven papers were finally included. The main reasons for exclusion were: no mediation analysis performed, disability not measured as a study outcome, not a musculoskeletal pain population, not an intervention study and no control or comparison group. Similar to previous reviews, there was heterogeneity in the study populations, the method of mediation analysis performed and the intervention investigated. The seven included studies are summarised in Table 2.

Included studies

Four studies [53–56] were conducted in the USA, two in The Netherlands [57,58] and one in Sweden [59]. Two studies were conducted in primary care [57,58], one in secondary care [54] and the rest examined community populations or specific patient groups (e.g., Wicksell et al. [59] recruited patients through a patient organisation for sufferers of their condition of interest). A range of painful musculoskeletal conditions were investigated including fibromyalgia [53], whiplash associated disorder [59], temporomandibular disorder [54], knee or hip osteoarthritis [55,56] and LBP [57,58]. Sample sizes ranged from 21 [59] to 351 [56]. Several studies included more than one active intervention group [55,57,58], and all the interventions lasted for either 8 or 10 weeks, except in the case of Focht et al. [55], where the intervention lasted for 18 months. The length of follow-up varied between 4 [59], 6 [53,54,56] and 12 months [58], and two studies did not follow up patients up after the intervention had ended.

Mediators identified

Numerous different psychological mediators were tested in the included studies and a small number were found to mediate the outcome of the intervention (see Table 2). Reduced pain catastrophising [54,57,58] and increased self-efficacy [54–56] were the factors most often tested as mediators and pain catastrophising was found to mediate outcome in every study that tested it. Other factors that were found to mediate outcome in single studies were pain coping [54], reduced psychological inflexibility [59] and a reduction in negative pain beliefs [54].

Two studies focussed specifically on mediators of psychological interventions in chronic LBP. Smeets et al. [57] investigated the mediating effects of change in internal control and pain catastrophising. They found that only pain catastrophising mediated the outcome of disability for both cognitive–behavioural treatment and also active physical treatment, suggesting that treatment elements that do not deliberately target cognitive factors can still reduce pain catastrophising. Spinhoven et al. [58] examined whether changes in pain coping and cognition mediated the outcome of activity tolerance following cognitive–behavioural treatment. They found that changes in catastrophising partially mediated this particular outcome.

Table 2
Summary of papers included in the systematic review.

Reference	Study population, setting	Intervention(s) and control	Follow-up	Factors found to mediate functional disability
Focht et al., 2005 [55]	Patients with radiographic evidence of knee OA Community	Exercise ($n = 80$) Dietary weight loss ($n = 82$) Combination therapy ($n = 76$) Control: Healthy lifestyle ($n = 78$)	6 m, 18 m	Stair climbing self-efficacy
Nicassio et al., 1997 [53]	Patients with diagnosed fibromyalgia Community	Behavioural treatment ($n = 48$) Control: Education ($n = 38$)	Post-treatment (10weeks); 6 m	None
Seymour et al., 2009 [56]	Patients with hip/Knee OA Community	Fit & Strong! Programme (exercise therapy) delivered by physiotherapists Control: Fit and Strong! Programme delivered by certified exercise instructors	2 m, 6 m	Exercise adherence self-efficacy
Smeets et al., 2006 [57]	Participants with chronic non-specific low back pain Primary care	Cognitive–behavioural therapy ($n = 55$) Active Physical Therapy ($n = 52$) Combined Therapy ($n = 55$) Control: Waiting list ($n = 49$)	Post-treatment (10 weeks)	Pain catastrophising
Spinhoven et al., 2004 [58]	Patients with chronic low back pain Primary care	Operant Behavioural Treatment with Cognitive Coping Skills ($n = 59$) Operant Behavioural Treatment with Group Discussion ($n = 58$) Control: Waiting list ($n = 31$)	12 m	Catastrophising
Turner et al., 2007 [54]	Patients with diagnosed temporomandibular disorder (TMD) Secondary care	Cognitive–behavioural therapy ($n = 55$) Control: Education/ attention ($n = 60$)	Post-treatment (8 weeks), 6 m, 12 m	Pain beliefs, coping, catastrophising and self-efficacy
Wicksell et al., 2010 [59]	Patients diagnosed with whiplash-associated disorder (WAD) Community – WAD support group	Acceptance and Commitment Therapy ($n = 11$) Control: Treatment as usual ($n = 10$)	Post-treatment (8 weeks), 4 m	Psychological flexibility

The evidence for mediating factors in musculoskeletal pain populations is limited by the small number of studies featuring these analyses to date and by the methodological issues reported below.

Methodological issues

The critical appraisal of the seven mediation studies highlighted issues similar to those described in the reviews of other health conditions. Most of the interventions were based on aspects of cognitive–behavioural theory, but the techniques used to treat patients varied widely. For example, the trials of both Smeets et al. [57] and Spinhoven et al. [58] trials in back pain used operant behavioural techniques; but, while one of them [57] focussed on aspects of graded activity and problem solving, the other [58] only reported trying to increase 'healthy' behaviours without giving specific details as to how this was done. The variety of techniques and principles employed in the included studies, and the different variables investigated as potential mediators, highlights the potential difficulties in using

broad theoretical frameworks on which to base an intervention and not deciding *a priori* how the theory might work in an intervention context.

Closely related to theory is the choice of potential mediator variables. Just as theory might help in guiding how to perform an intervention, it might also help in choosing variables that are likely to change during treatment and how they are likely to be associated with outcome [60]. Where empirical evidence is not available, it is helpful to test these associations, which are prerequisites for mediation, through preliminary analysis before conducting mediation analysis. The presentation of results from preliminary analysis was included in the critical appraisal tool. All of the included studies reported that patient scores on the mediator measures changed between baseline and post-treatment/follow-up, but only three studies [53,58,59] reported the results of correlation analyses to show that this change was associated with change in the outcome measure. The fact that not all studies presented the results of such tests suggests that these criteria were not adequately assessed.

Another issue, also reported by previous reviews, was the lack of information on the properties of the measures used. Only Smeets et al. [57] reported information on the measurement properties of both the potential mediator and the outcome measures. Focht et al. [55] and Wicksell et al. [59] reported characteristics only for their outcome measures and Spinhoven et al. [58] reported characteristics only for their mediator measures.

In terms of the type of mediation analysis conducted, only two studies [54,59] used an optimal mediation analysis method as recommended by the above literature (i.e., tested the mediated effect using non-parametric bootstrapping), and one of these [54] carried out analysis using SEM. No study reported a power calculation showing that the study was adequately powered to detect mediating effects. One study included a very small sample [59] and in all cases, the sample used to investigate mediation relationships was <100. This suggests that the samples may not have been large enough to adequately perform mediation analysis through the usual methods of multiple regression or SEM and raises the possibility of Type II errors.

Overall, this review of musculoskeletal treatment mediation reinforces the findings of systematic reviews on other health conditions: few mediation studies have been undertaken, few factors have been consistently investigated, studies are usually underpowered and methodological quality is often suboptimal. Collectively, these systematic reviews covering a variety of health conditions indicate that while there is a pool of applied mediation studies, greater methodological rigour would help move mediation research forward and potentially provide us with more definitive information regarding the factors that explain how treatments work. Despite this, the mediation literature reports some consistency in the type of psychological factors tested and those found to be mediators.

To date, very few mediation analyses have been conducted in the field of back pain, and only one [57] appears to have been planned at the time of data collection. We believe that incorporating mediation analyses into intervention studies presents an excellent opportunity to maximise the yield of clinical research. Due to the adaptability of the method to different types of studies, including mediation analyses is likely to require only minor adjustments to study design and conduct. Box 1 summarises the recommendations from the above literature.

Box 1 Points to consider when investigating mediation in back pain intervention studies.

- Think about how the intervention might work, using theory to guide what variables might be important and how these might lead to change in the outcome
- Ensure the trial is adequately powered to detect mediating effects
- Choose measures for the mediator and outcome variables that have good measurement properties (i.e., reliable and responsive)
- Ensure the trial is adequately powered to detect mediating effects

Summary

Mediation analysis has the potential to help identify why treatments do or do not work for back pain. There is clarity about current best practice in mediation study design, analysis and interpretation that is useful at an individual-study level, and at the condition-specific level there are theoretical and methodological frameworks within which mediation analysis studies can be planned, staged and evaluated. Preplanned and appropriately conducted mediation analysis in adequately powered clinical trials would be a step forward in understanding treatment effects.

There is emerging evidence about the role of some psychological factors as potential treatment mediators, such as self-efficacy and catastrophising (see chapter 5), but the evidence is inconsistent and few mediation studies have been conducted in back pain. Mediation analysis can also be applied to non-psychological factors, such as social factors in mediating the relationship between patient-centred interventions and return to work (see chapter 6 of this issue) and physical factors in mediating the relationship between exercise and activity limitation.

There is a clear need for further research that investigates plausible mediators. Convincing research will be based on strong theory and previous evidence, show consistency of findings across studies and hopefully demonstrate evidence of dose–response. This evidence would contribute to greater certainty about the role of mediators in the treatment of back pain and facilitate the refinement of interventions. This approach holds promise in disentangling some of the reasons why most back pain treatments show modest-sized effects and in optimising patient management.

Practice Points

- Mediation analysis is useful as it has the potential to help identify why treatments do or do not work for back pain.
- There is emerging evidence about the role of some psychological factors as treatment mediators, such as self-efficacy and catastrophising.
- Few mediation studies have been conducted in back pain-intervention studies.
- Mediation analysis can equally be applied to non-psychological, modifiable factors.

Research Agenda

- While there is a pool of applied mediation studies for musculoskeletal pain, greater methodological rigour would help move mediation research forward.
- Treatment-mediation research should ideally: state clear theoretical links between the variables of interest, be preplanned, use adequate measures of constructs, establish temporal precedence by including measurements during the intervention period, use only appropriate tests of mediation, be conducted in adequately powered randomised controlled trials and include models that test multiple mediators reflective of the complex nature of the interventions.
- Randomised controlled trials that incorporate the above-mentioned design aspects are required to add to the evidence base of those factors already identified as potential mediators. There is also scope to test specific theoretical hypotheses to enhance understanding of the mechanism of action of intervention regimens for back pain.

Conflict of interest statement

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