

**Title:** How does pain lead to disability? A systematic review and meta-analysis of mediation studies in people with back and neck pain.

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## Abstract

Disability is an important outcome from a clinical and public health perspective. However, it is unclear how disability develops in people with low back pain or neck pain. More specifically, the mechanisms by which pain leads to disability are not well understood. Mediation analysis is a way of investigating these mechanisms by examining the extent to which an intermediate variable explains the effect of an exposure on an outcome. This systematic review and meta-analysis was aimed to identify and examine the extent to which putative mediators explain the effect of pain on disability in people with low back pain or neck pain. Five electronic databases were searched. We found 12 studies (N=2,961) that examined how pain leads to disability with mediation analysis. Standardized regression coefficients ( $\hat{a}$ ) of the indirect and total paths were pooled. We found evidence to show that self-efficacy ( $\hat{a} = 0.23$ , 95% CI = 0.10-0.34), psychological distress ( $\hat{a} = 0.10$ , 95% CI = 0.01-0.18), and fear ( $\hat{a} = 0.08$ , 95% CI = 0.01-0.14) mediated the relationship between pain and disability, but catastrophizing did not ( $\hat{a} = 0.07$ , 95% CI = -0.06-0.19). The methodological quality of these studies was low and we highlight potential areas for development. Nonetheless, the results suggest that there are significant mediating effects of self-efficacy, psychological distress, and fear, which underpins the direct targeting of these constructs in treatment.

**Keywords:** systematic review; Meta-Analysis; mediation analysis; low back pain; neck pain; musculoskeletal pain

## 1. Introduction

Low back pain (LBP) and neck pain are two of the most common musculoskeletal conditions [22,85]. Both conditions have high prevalence [36,38] and recurrence rates [14,39]. Globally, the annual incidence is approximately 36% for LBP [39], and 18% for neck pain [19]. LBP and neck pain are associated with significant disability. Compared with all health conditions, LBP is ranked as the number one cause of 'years lived with disability', and neck pain is ranked fourth [78]. From a public health perspective, disability adds to the rising economic [21,55] and societal [10,12] burden of LBP and neck pain. For the individual, LBP- and neck pain-related disability and comorbidities [30,48] can significantly impact quality of life [40,63]. Despite its importance however, it is unclear how disability develops in people with LBP and neck pain.

Pain intensity is often associated with disability [62,75]. However, the mechanisms underlying this association are not well understood. Pain is associated with a range of psychological, physical, and social factors [26,79], factors which are also associated with disability [1,41,67,80]. However, it is unknown whether specific biopsychosocial factors play an intermediate role that might explain how disability develops from pain [35,56]. That is, we do not know whether there are mediating variables that explain how pain leads to disability.

Mediation analysis examines the extent to which an intermediate variable (mediator) explains the effect of an exposure on an outcome [5,54] (Fig. 1). In mediation, alongside examining direct effects between an exposure and an outcome, indirect effects are quantified. That is, the effect of the exposure (e.g. pain) on the outcome (e.g. disability) via a mediator (e.g. physical activity). The overall objective of mediation analysis is to make causal inferences about mechanisms [42,54]. Investigating causal paths between pain and disability can provide a more complete understanding about the development of disability in patients with LBP and neck pain [57].

Mediation analysis can be applied to both experimental and observational data. However, the purpose and interpretation in these two designs are distinct [44,56]. Experimental mediation studies usually seek to understand the mechanisms of how a treatment works (if indeed it does) [43]. With random allocation to

intervention and control groups, mediation in experimental designs determines the extent to which the treatment exerts its effect on the outcome via the nominated mediator. In observational mediation studies, instead of treatment allocation, an observed variable (usually at baseline) acts as the exposure. This then allows the indirect path from the baseline variable to the outcome (via the mediator) to be quantified. Mediation analyses using observational data can provide empirical evidence for existing theories, and generate new hypotheses for potential treatment targets [56].

Theoretical models have been used to explain how pain leads to disability. The fear avoidance model, in its original formulation, posits that a painful stimulus may trigger a maladaptive cognitive process where catastrophic thinking and subsequent development of fear and disuse leads to disability [51,77]. A recent perspective has revised this model in light of the evidence to incorporate concepts of motivation, self-regulation, and goal-setting [20]. Social cognitive theory [4,24,84] describes the relationships between self-efficacy, outcome expectancies, intentions, and behaviour. Although there is no rigorous model in pain, pain related self-efficacy, defined as “the beliefs held by people with chronic pain that they can carry out certain activities, even when experiencing pain” [60] has been used to explain the association between pain and disability [18]. In response to criticisms of the lack of empirical support for the sequential pathways in these models [68,82], attempts have been made to test the mediating role of fear [45], catastrophizing [61], self-efficacy [18], and other variables such as psychological distress (depression and anxiety) [32]. Although these variables are included in conceptually distinct theoretical models, recent work has shown that they may overlap [13]. Physical and social factors such as leisure time activity, workplace loading, social networks, and cultural backgrounds may also be important mediators to consider within the biopsychosocial model [37,64]. Currently, despite the range of observational mediation studies, rigorous synthesis of these studies has not yet been performed, and therefore high quality evidence on putative mediators that may explain how pain leads to disability in people with LBP or neck pain is not available.

This systematic review and meta-analysis examined the evidence on how disability develops from pain in people with LBP or neck pain. The aim was to identify and quantify the extent to which putative psychological, social, and physical factors explain the effect of pain on disability in people with LBP and neck pain.

## **2. Methods**

### *2.1. Registration of systematic review*

The protocol for this review was registered with the PROSPERO international prospective register of systematic reviews (CRD42014013132) and can be accessed at

[http://www.crd.york.ac.uk/PROSPERO/display\\_record.asp?ID=CRD42014013132#.VGq3ovmUdXo](http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014013132#.VGq3ovmUdXo). This review is reported in accordance to the PRISMA statement [59].

### *2.2. Search strategy and study selection*

On the 1<sup>st</sup> of August 2014, an electronic search was conducted in the following databases: EMBASE (OvidSP), Medline (OvidSP), CINAHL (EBSCO host), PsycINFO (OvidSP), and Cochrane Central Register of Controlled Trials (OvidSP). All databases were searched since their inception. The reference lists of all included articles were hand searched to identify additional studies that were not identified by the electronic search. The search strategies outlined by the Cochrane Back Review Group ([http://back.cochrane.org/sites/back.cochrane.org/files/uploads/PDF/CBRG\\_searchstrat\\_Jun2011.pdf](http://back.cochrane.org/sites/back.cochrane.org/files/uploads/PDF/CBRG_searchstrat_Jun2011.pdf)) were used to identify studies including LBP and neck pain. To identify studies that conducted a mediation analysis, we used search terms such as: mediation analysis, structural equation modelling, product of coefficient, and indirect effect. Our search strategy was informed by previous systematic reviews that had specifically searched for studies that employed a mediation analysis [15,52,57,74]. The complete search strategy is provided in Appendix A.

Studies that included individuals who were 18 years or older with complaints of acute and/or chronic neck pain and/or LBP were eligible. Studies that included patients with specific spinal pathology (for example, fracture, cauda-equina syndrome, inflammatory arthritis, malignancy, or spinal stenosis) were excluded. In

studies where mixed populations were sampled, we included only those studies in which patients with LBP and/or neck pain represented more than 75% of the sample. We included cross-sectional and longitudinal mediation analyses from observational cohort studies and randomized controlled trials. We included studies that used mediation analysis to investigate the relationship between pain and physical disability. Disease specific (e.g. Neck disability index [76]) and generic measures (e.g. SF-36 physical function subscale [7]) of physical disability were included. We did not limit the inclusion of studies based on the mediator. We also included studies that investigated core elements of the fear avoidance model with mediation analysis. Two sequential paths of the fear avoidance model that explicitly describe the development of disability from pain were included: pain and fear mediated by catastrophizing, catastrophizing and disability mediated by fear. We included only those studies that had formally conducted a mediation analysis (for example, product of coefficient test, difference in coefficient test, Baron and Kenny's causal steps of mediation, structural equation modelling) and/or significance tests of mediation (for example, Sobel's first-order test or bootstrapped confidence intervals). We excluded studies published in languages for which we could not find a translator, and also excluded non-original research, conference proceedings, and dissertations. Two independent reviewers used the above inclusion criteria to screen the titles and abstracts of the identified studies. Full texts were retrieved for studies that were potentially relevant, or where exclusion could not be determined from the study title or abstract. Disagreements between reviewers were resolved by discussion and consensus. Any remaining disagreements were resolved by consulting a third reviewer.

### *2.3. Data extraction*

Data were extracted by one reviewer using a data extraction form, and the extracted data were verified independently by a second reviewer. Study and participant characteristics including, study design, setting, length of follow-up, number of participants, age, gender, location of pain, and pain duration were extracted. Data were extracted for the exposure, mediator, and outcome variables (construct, measurement tool, time of measurement), methodological approach taken for mediation analysis, significance test(s) of mediation, measures taken to control for confounders, and standardized regression coefficients ( $\beta$ ) for the indirect and total effects. Any disagreements between the reviewers on the extracted data were resolved by discussion and by revisiting the original study. If the required information was not in the published article, up to three emails

were sent to the corresponding author to request the data. If the corresponding author did not respond, we attempted to contact the co-authors. If we still failed to contact the co-authors, we ceased attempts to obtain unreported data.

#### *2.4. Data synthesis and analysis*

Prior to pooling, we categorized the data by study design (cross-sectional and longitudinal), and classified all mediators by construct. For each analysis, we used standardized regression coefficients ( $\beta$ ) [11,66] and sample sizes to calculate a pooled effect size for the indirect (product of path a and path b) [47], and total effects (path c) (Fig. 1). To provide a summary of each mediation model, we calculated the ratio of the pooled indirect effect and the pooled total effect [71]. We assessed heterogeneity using the  $I^2$  statistic, and assigned thresholds of 25%, 50%, and 75% to signify low, moderate, and high heterogeneity, respectively [34]. In cases where heterogeneity was above moderate (>50%), we used a random effects model.

Subgroup analysis was planned to evaluate whether the location of pain (LBP, neck pain) and duration of pain (*acute/sub-acute VS chronic*) affected the indirect and total effects. This was only carried out when more than one study was available for each subgroup. Acute/sub-acute pain was defined as pain duration of less than three months, and chronic pain was defined as pain duration of three months or longer. When a study reported multiple outcomes for a single mediation model (for example, Gheldof et al. [29] reported 2 outcomes for disability), we computed a 'synthetic' effect size (average effect size with adjusted variance) [9] and used this in the meta-analysis. Thus, only one effect size was used to represent a study. All analyses were conducted using Comprehensive Meta-Analysis (Version 2.2).

#### *2.5. Study quality assessment*

The criteria used in this review for the assessment of methodological quality are modified from the critical appraisal tool developed by Mansell et al. [57]. Two independent reviewers (HL, GM) applied the 7 criteria and provided a score of 1 (yes), or 0 (no) to each item. The sum of these scores was computed to provide the total quality score for each study. Disagreements between reviewers were resolved by discussion. The quality assessment items are outlined in Appendix B.

### 3. Results

#### 3.1. Study selection

The search strategy identified 7818 records for consideration, of which 151 potential relevant full-text articles were retrieved and screened to determine eligibility. Finally, 12 articles met the inclusion criteria and were included for review (Fig. 2).

#### 3.2. Description of studies

From 12 included studies, 9 studies, comprising 2539 participants, tested 34 models to evaluate the relationship between pain and disability [18,27–29,32,45,46,70,73]; and 3 studies, comprising 422 participants, tested 3 models to evaluate the path from catastrophizing to disability (via fear) as part of the fear avoidance model [50,61,62]. Overall, 5 studies tested 9 longitudinal models [32,46,50,61,70], 4 studies tested 9 cross-sectional models [27,29,62,73], and 3 studies tested 6 longitudinal and 13 cross-sectional models [18,28,45]. Eight studies (20 models) included patients with LBP [18,27–29,32,46,50,70], and 4 studies (17 models) included patients with whiplash-associated neck pain [45,61,62,73]. The mean age of the participants in the included studies ranged from 31 to 51 years, and 63% of the total sample were male. A description of the each study characteristic is provided in Table 1.

All of the identified mediators were psychological constructs and no study tested the mediating role of physical or social constructs. Specifically, 7 studies (19 models) tested the mediating effect of fear [18,27–29,45,46,73]; 3 studies (6 models) tested the mediating effect of catastrophizing [27,45,73]; 2 studies (3 models) tested the mediating effect of self-efficacy [18,73]; and 2 studies (6 models) tested the mediating effect of psychological distress (depression and anxiety) [32,70]. With regard to the fear avoidance model, 3 studies (3 models) tested the relationship between catastrophizing and disability with fear as the mediator [50,61,62]; no study tested the relationship between pain and fear with catastrophizing as the mediator.

#### 3.3. Meta-analysis

The pooled correlation coefficients for path a, path b, indirect effect, and total effect, with their confidence intervals are presented in Table 2.

### *3.3.1. Fear as a mediator for the relationship between pain and disability*

The pooled estimates of the indirect effect of fear were significant in longitudinal (N=906, 4 studies, 5 models) and cross-sectional (N=1827, 6 studies, 14 models) designs. The percentage of the total effect that was explained by the indirect effect was 20% in longitudinal designs; heterogeneity was low-moderate for the indirect effect ( $p = .48$ ,  $I^2 = 0\%$ ), and moderate-high for the total effect ( $p = .01$ ,  $I^2 = 72\%$ ). The percentage of the total effect that was explained by the indirect effect was 26% in cross-sectional designs; heterogeneity was low-moderate for the indirect effect ( $p = .24$ ,  $I^2 = 26\%$ ), and high for the total effect ( $p < .01$ ,  $I^2 = 84\%$ ).

### *3.3.2. Catastrophizing as a mediator for the relationship between pain and disability*

One longitudinal study (N=103) found that catastrophizing did not significantly mediate the relationship between pain and disability. The pooled estimate of the indirect effect of catastrophizing was not significant in cross-sectional designs (N=234, 3 studies, 5 models); heterogeneity was low for the indirect effect ( $p = .80$ ,  $I^2 = 0\%$ ) and low-moderate for the total effect ( $p = .18$ ,  $I^2 = 42\%$ ).

### *3.3.3. Self-efficacy as a mediator for the relationship between pain and disability*

One longitudinal study (N=172) found that self-efficacy significantly mediated the relationship between pain and disability. The pooled estimate for the indirect effect of self-efficacy was significant in cross-sectional designs (N=236, 2 studies, 2 models). The percentage of the total effect that was explained by the indirect effect was 38%; heterogeneity was low for the indirect effect ( $p = .73$ ,  $I^2 = 0\%$ ), and high for the total effect ( $p = .01$ ,  $I^2 = 86\%$ ).

### *3.3.4. Psychological distress as a mediator for the relationship between pain and disability*

The pooled estimate for the indirect effect of distress was significant in longitudinal designs (N=502, 2 studies, 5 models). The percentage of the total effect that was explained by the indirect effect was 31%; heterogeneity was low for the indirect effect ( $p = .30$ ,  $I^2 = 8\%$ ) and moderate-high for the total effect ( $p = .13$ ,  $I^2 = 55\%$ ). No study evaluated this model in a cross-sectional design.

### *3.3.5. Fear as a mediator for the relationship between catastrophizing and disability*

The pooled estimate for the indirect effect of fear was not significant in longitudinal designs (N=275, 2 studies, 2 models); heterogeneity was low for the indirect effect ( $p = .28$ ,  $I^2 = 13\%$ ) and the total effect ( $p = .41$ ,  $I^2 = 0\%$ ). One cross-sectional study (N=147) found that fear significantly mediated the relationship between catastrophizing and disability.

### *3.4. Sub-group analysis*

#### *3.4.1. By area (LBP, neck pain)*

Sub-group analysis was only performed for the studies that tested fear as a mediator for the relationship between pain and disability in cross-sectional designs. The pooled correlation coefficients for the indirect effect of fear were similar for LBP (pooled  $\beta = 0.16$ , 95% CI = 0.11 – 0.21,  $p < 0.01$ ) and neck pain (pooled  $\beta = 0.15$ , 95% CI = 0.03 – 0.26,  $p = 0.02$ ). The pooled estimates for the total effect (path c) was weaker for LBP (pooled  $\beta = 0.57$ , 95% CI = 0.43 – 0.67,  $p < 0.01$ ) compared to neck pain (pooled  $\beta = 0.69$ , 95% CI = 0.62 – 0.75,  $p < 0.01$ ). For all other mediators, we were unable to conduct sub-group analyses for the area of pain because of the limited number of studies per subgroup.

#### *3.4.2. By duration of pain (acute/sub-acute VS chronic)*

For all mediators, we were not able to conduct sub-group analyses for the duration of pain because of the limited number of studies per subgroup.

### *3.5. Quality assessment*

Most of the studies cited a theoretical framework (11/12) and reported psychometric properties of the mediator and outcome variables (9/12). No study reported a power calculation, and only a small number of studies employed appropriate statistical methods (3/12) and controlled for confounding variables (3/12). None of the 12 studies established whether changes in the predictor preceded changes in the mediator, nor whether changes in the mediator preceded changes in the outcome. The individual study quality assessment is presented in Table 3.

## **4. Discussion**

Our aim was to identify and quantify the extent to which putative mediators explain the development of disability in people with LBP and neck pain. We found evidence that self-efficacy, distress, and fear, but not catastrophizing, significantly mediated the effect of pain on disability. Longitudinal studies showed that the magnitude of the indirect effect appears to be strongest for self-efficacy, followed by distress, then fear. Similarly, cross-sectional studies showed that self-efficacy was the strongest mediator, followed by fear. With regards to the fear-avoidance model, fear did not mediate the relationship between catastrophizing and disability in longitudinal designs; however, one cross-sectional study found that fear was a significant mediator for this relationship. Our subgroup analyses showed that the area of pain (LBP or neck pain) did not influence the indirect effect of fear for the relationship between pain and disability. We were unable to conduct subgroup analyses for the duration of pain due to insufficient data.

The methodological flaws in the included studies were similar to those found in mediation studies from other areas of healthcare [15,52,74]. Although we reviewed observational mediation studies, the adapted quality assessment criteria were comparable to those used in experimental mediation studies [15,57]. A range of statistical methods can be applied for testing mediation, but some are more efficient than others. In this group of studies, a combination of the early Baron and Kenny's causal steps approach [5] (8/12 studies) and Sobel's test of significance [72] (7/12 studies) were the most commonly used methods. Two studies [45,70] clearly stated the use of bootstrapped analysis, and two others [28,46] used structural equation modelling, which are considered to be more powerful and efficient than the causal steps approach [33,53]. As a general guide, it is recommended that samples between 150 and 200 participants are required to detect mediating effects in the absence of type-II errors [25,56]. From our 12 included studies, 6 studies sampled fewer than 150 participants, thus at least half of the included studies were likely to be underpowered, a problem that is also common in other fields [15,74].

Because mediation analysis is primarily aimed at identifying causal mechanisms, confounding must be carefully considered. Without controlling for potential confounders (variables that may causally affect the exposure, mediator, or outcome, but are not on the causal pathway), estimations of the mediating effect may be spuriously inflated [16,42]. Despite the importance of this, only 3 studies controlled for the effect of potential confounders. Recent developments in more sophisticated causal mediation methods have provided methods

for assessing the possible effect of unobserved confounders via sensitivity analysis [42]. No study in this review applied this technique. Another requirement for making causal inferences is to address the issue of temporality [16,58]. In this review, 59% of the models were cross-sectional; and even within the small proportion of available longitudinal models, it was difficult to ascertain whether the change in the exposure preceded the mediator, or whether the change in the mediator preceded the outcome. Temporal precedence and adjustment for confounding variables are critical methodological concepts for causal inference in mediation studies. Therefore, we suggest that the items for temporality (items 5 and 6) and confounding (item 7) are given more weight. In general, the findings of our quality assessment suggest that the application of mediation analysis in musculoskeletal pain research is still in its early stages. Future studies should apply careful consideration to the design and analysis of mediation studies to ensure they report unbiased estimates.

Our review suggests that catastrophizing may not explain the development of disability from LBP and neck pain. However, experimental mediation studies have suggested that catastrophizing mediates the effect of behavioural and physical treatments on disability. Mansell et al. [57] included 7 studies that applied mediation analysis to clinical trials of psychological interventions that aimed to reduce disability in patients with musculoskeletal pain. They found that catastrophizing significantly mediated treatment effects in all studies. Wertli et al. [81] reported mixed results for catastrophizing as a potential mediator of treatment effects on disability in people with LBP. This discrepancy between the findings from experimental and observational mediation studies reflects the difference in the relationship (path a) between the exposure (treatment allocation versus pain) and the mediator. Indeed experimental and observational mediation studies have distinct purposes. Although catastrophizing may mediate treatment effects, it seems that catastrophizing may not explain the development of disability in the context of the clinical course of LBP and neck pain.

In recent years, the fear avoidance model [51,77] has been criticised for the lack of empirical evidence to support the sequential paths outlined by the model [6,82]. Simply, the model posits a sequence of cognitive processes whereby pain triggers an early catastrophizing response that leads to an increase in fear, that then leads to depression and disability [51,77]. However, the time sequences between the key intermediate variables of the model are not well defined. From a reductionistic perspective, it is widely accepted that the evidence supports separated components of the model. For example, cross-sectional studies have shown

associations between catastrophizing, fear, and disability [17,31]; and prospective longitudinal studies have corroborated these findings [8,65]. However, whether or not the intermediate variables of the model change in a sequential manner on a causal pathway remains unknown. Wideman et al. [82] highlighted this shortcoming and used three waves of assessments to show that changes in catastrophizing did not precede changes in fear. The intermediate variables of the fear avoidance model have also been tested with longitudinal mediation analysis. Our pooled estimates do not support catastrophizing as a mediator, and found a weak mediating effect for fear. We did not find any mediation studies that examined the first two paths of the fear avoidance model (pain-catastrophizing-fear), and found that longitudinal mediation studies did not support the subsequent paths of the model (catastrophizing- fear- disability). It is important to note that these results are from mixed acute and chronic samples. Subgroup analysis was not possible due to a small number of studies, therefore these findings should be interpreted with this in mind; especially given the fact that the fear avoidance model is usually contextualized within chronic populations. These findings are consistent with recent developments of the fear avoidance model, and do not support the notion that intermediate variables are time-sequenced. Furthermore, in a recent topical review, Wideman et al. [83] called for a rejection of the 'simplistic pathway', and suggested that the lack of empirical data to support the order of intermediate variables could be fundamentally flawed by 'incorrect theoretical assumptions' of the fear avoidance model. Future mediation studies that can adequately address the issue of temporality might provide useful evidence for further development and refinement of the fear avoidance model.

In contrast to the fear avoidance model, social cognitive theory [4,24] has not received much attention in the musculoskeletal pain literature. Despite a small number of studies, evidence from this review supports self-efficacy as a mediator in explaining the development of disability from LBP and neck pain. This finding is consistent with the evidence from mixed chronic pain populations [2,3], which suggests that the mediating effect of self-efficacy may be generalizable to other painful conditions. It is notable that systematic reviews in other areas of healthcare consistently identify self-efficacy as a significant mediator for interventions aimed at behaviour change, for example, dietary behaviour change [15], physical activity promotion [52], and obesity prevention [74]. Our findings provide evidence to suggest that behavioural interventions for LBP and neck pain might also work by enhancing self-efficacy.

Limited evidence suggests that psychological distress might mediate the effect of pain on disability. This finding is new because previous research has identified distress as a prognostic factor for poor outcomes [23,67], but it has seldom been considered as a mediating variable. We defined distress as an overarching construct including depression, stress, and anxiety. We took this approach because of a recent finding that demonstrated that measures of anxiety and depression have conceptual overlap [13]. However, one study [32] showed that mediation effects were partial to each individual construct, concluding that depression and stress, but not anxiety, mediated the relationship between pain and disability. Due to a small number of available studies, and the lack of longitudinal data, there is preliminary evidence to support the role of distress as a mediating variable in the development of disability. Therefore, our findings are not conclusive and further work is required in this area.

This systematic review was prospectively registered and did not deviate from the original protocol. Although meta-analyses of mediation studies is new to the field of musculoskeletal pain, similar methods have been employed in other areas of healthcare research [49]. This approach has allowed us to quantitatively summarise the evidence for mediators that explain how disability develops. The results generated by the meta-analysis provide an objective comparison for future studies. We adapted the quality assessment tool from Mansell et al. [57] to assess observational mediation studies. In future, this tool will provide a useful framework to assess the methodological quality of observational mediation studies. This quantitative summary of the evidence for mechanisms and theoretical models that explain the development of disability provides a platform for future mediation studies in the field.

This review has some limitations. Due to the limited number of studies for specific mediators and the poor quality of these studies we cannot make definitive conclusions about the causal mechanisms that underlie the development of disability. We note that more than half of the studies used cross-sectional designs. This limits causal interpretation of the findings and reflects the need for future studies to implement longitudinal designs to examine sequential relationships between variables. We acknowledge that there were differences in the numbers of studies for each mediator tested, and that only one longitudinal study was found for catastrophizing and self-efficacy, so we could not pool the data. Thus, comparisons of the relative strength of the mediating effect between the identified mediators should be interpreted with caution. Subgroup analyses

were also limited, and we envisage that a larger number of studies conducted on different subgroups would be required to conduct meaningful analyses to investigate the differential mediating effects stratified by area and duration of pain. Surprisingly, there were a large proportion of males in this review. This was mainly due to two studies [28,29] that sampled a large number of males. It is unknown whether gender moderates the mediation effects found in this review. Future studies should investigate whether causal mechanisms differ for males and females through moderated mediation analysis [69].

Our findings have important implications. We have shown that further work to untangle the complex interactions between mediating variables and the sequence of events within the fear avoidance model can be studied with mediation studies. While self-efficacy seems to be a promising mediator in the development of disability, more rigorously conducted studies are required to support its role in the clinical course of LBP and neck pain. It is worth highlighting that the current literature has only focused on psychological mediators. For instance, physical factors such as leisure time activity or physical loading [37], and social factors such as social isolation [64] could explain how pain leads to disability. It is important to investigate these variables as mediators because the development of disability cannot be entirely attributed to psychological factors. Understanding alternative causal pathways and their interrelationship could lead to the development of more comprehensive treatments under the biopsychosocial framework. We recommend that future studies investigate the role of physical and social factors using reliable and responsive measures of physical and social constructs, in order to understand their involvement in the development of LBP- or neck pain-related disability. We also recommend that future mediation studies should control for potential confounding variables and implement longitudinal designs with a time sequence between the predictor, mediator, and the outcome. Stronger evidence from future studies, especially in accordance with the initiative to develop a multi-dimensional framework for pain-related disability [83], will lead to important research findings.

The current findings are also relevant to the management of patients with LBP and neck pain. The significant mediating effects of self-efficacy, psychological distress, and fear, suggest that these factors are important targets for treatments. Regular monitoring of these mediators during treatment and targeting therapies to improve self-efficacy, minimise distress, and fear, may lead to lower levels of disability.

## 5. Conclusion

The aim of this systematic review and meta-analysis was to examine putative mediators that could explain the effect of pain on disability in people with LBP and neck pain. The available evidence shows that self-efficacy, psychological distress, and fear, mediate the relationship between pain and disability in people with LBP and neck pain, but catastrophizing does not. In addition, the sequential pathway of the fear avoidance model is not supported by longitudinal mediation studies.

ACCEPTED

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**Fig. 1.** Simple mediation model. The indirect effect is quantified by the product of paths a and b. The total effect (path c) is the sum of the indirect and direct effects.

**Fig. 2.** Study flow chart (adapted from PRISMA)

ACCEPTED

## Appendix A. Search strategy

	Spinal pain related terms	Mediation analysis related terms
<b>Keywords and Search terms</b>	<p>The updated search strategies of the Cochrane Back Review Group (<a href="http://back.cochrane.org/sites/back.cochrane.org/files/uploads/PDF/CBRG%20Search%20Strategies%20Jan%202013.pdf">http://back.cochrane.org/sites/back.cochrane.org/files/uploads/PDF/CBRG%20Search%20Strategies%20Jan%202013.pdf</a>) were used to identify studies of LBP and neck pain.</p> <p>Updated Search Strategies for CBG Jan 2013</p>	<p>mediat* OR indirect OR "structural equation modeling" OR "structural equation modelling" OR " path" OR (Baron and Kenny) OR "MacKinnon" OR "product of coefficient" OR "difference in coefficient" OR "process of change" OR "sobel*" OR "causal pathway" OR "intermediate" OR "indirect effect" OR "process variable" OR "treatment ADJ2 effect" OR "process ADJ2 evaluation" OR "mechanism" OR "SEM"</p>

Medline (OvidSP)

EMBASE (OvidSP)

PsycINFO (OvidSP)

Cochrane Central Register of Controlled Trials (OvidSP)

CINAHL (EBSCO host)

## Search Strategy for MEDLINE (OVID) (Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present:

Part B: Specific search for thoracic, low back, sacrum and coccyx problems

14. dorsalgia.ti,ab.
15. exp Back Pain/
16. backache.ti,ab.
17. exp Low Back Pain/
18. (lumbar adj pain).ti,ab.
19. coccyx.ti,ab.
20. coccydynia.ti,ab.
21. sciatica.ti,ab.
22. sciatic neuropathy/
23. spondylosis.ti,ab.
24. lumbago.ti,ab.
25. back disorder\$.ti,ab.
26. or/14-25

Part C: Specific search for neck problems

27. neck muscles.sh.
28. exp Neck/
29. exp neck pain/
30. whiplash injuries.sh.
31. neck.ti,ab.
32. or/27-31

Part D: Other spinal disorders

33. exp Spine/
34. discitis.ti,ab.
35. exp Spinal Diseases/
36. (disc adj degeneration).ti,ab.
37. (disc adj prolapse).ti,ab.
38. (disc adj herniation).ti,ab.
39. spinal fusion.sh.
40. spinal neoplasms.sh.
41. (facet adj joints).ti,ab.
42. intervertebral disc.sh.
43. Intervertebral Disc Displacement.sh.
44. postlaminectomy.ti,ab.
45. arachnoiditis.ti,ab.
46. (failed adj back).ti,ab.
47. or/33-46

PART: Mediation

mediat\$.mp

mediation analysis.mp

structural equation modeling.mp

structural equation modelling.mp

(Baron and Kenny).mp

product of coefficient.mp

difference in coefficient.mp

process of change.mp

sobel\$.mp

causal pathway.mp

intermediate.mp

indirect effect.mp

process variable.mp

process ADJ2 evaluation.mp

48. limit XX to human

49. limit XX to humans

ACCEPTED

## SEARCH STRATEGY FOR EMBASE (OVID)

Part B: Specific search for thoracic, low back, sacrum and coccyx problems

37 dorsalgia.mp.  
38 back pain.mp.  
39 exp LOW BACK PAIN/  
40 exp BACKACHE/  
41 (lumbar adj pain).mp.  
42 coccyx.mp.  
43 coccydynia.mp.  
44 sciatica.mp.  
45 exp ISCHIALGIA/  
46 spondylosis.mp.  
47 lumbago.mp.  
48 back disorder\$.ti,ab.  
49 or/37-48

Part C: Specific search for neck problems

50 neck muscles.mp.  
51 exp NECK/  
52 whiplash injuries.mp.  
53 neck.mp.  
54 exp neck pain/  
55 exp neck muscle/  
56 neck disorder\*.mp.  
57 or/50-56

Part D: Other spinal disorders

58 exp SPINE/  
59 discitis.mp.  
60 exp Spine Disease/  
61 (disc adj degeneration).mp.  
62 (disc adj prolapse).mp.  
63 (disc adj herniation).mp.  
64 spinal fusion.mp.  
65 spinal neoplasms.mp.  
66 (facet adj joints).mp.  
67 intervertebral disk.mp.  
68 postlaminectomy.mp.  
69 arachnoiditis.mp.  
70 (failed adj back).mp.  
71 or/58-70

PART: Mediation

mediat\$.mp

mediation analysis.mp

structural equation modeling.mp

structural equation modelling.mp

(Baron and Kenny).mp

product of coefficient.mp

difference in coefficient.mp

process of change.mp

sobel\$.mp

causal pathway.mp

intermediate.mp

indirect effect.mp

process variable.mp

process ADJ2 evaluation.mp

48. limit XX to human

49. limit XX to humans

ACCEPTED

## SEARCH STRATEGY FOR PSYCINFO (OVID)

PART B, BACK PAIN, SPINAL DISORDERS OR NECK PAIN

20. BACK PAIN/
21. LUMBAR SPINAL CORD/
22. (LOW ADJ BACK ADJ PAIN).MP. [MP=TITLE, ABSTRACT, SUBJECT HEADINGS, HEADING WORD, DRUG TRADE NAME, ORIGINAL TITLE, DEVICE MANUFACTURER, DRUG MANUFACTURER, DEVICE TRADE NAME, KEYWORD]
23. (BACK ADJ PAIN).MP. [MP=TITLE, ABSTRACT, SUBJECT HEADINGS, HEADING WORD, DRUG TRADE NAME, ORIGINAL TITLE, DEVICE MANUFACTURER, DRUG MANUFACTURER, DEVICE TRADE NAME, KEYWORD]
24. SPINAL COLUMN/
25. (LUMBAR ADJ2 VERTEBRA\*).MP. [MP=TITLE, ABSTRACT, SUBJECT HEADINGS, HEADING WORD, DRUG TRADE NAME, ORIGINAL TITLE, DEVICE MANUFACTURER, DRUG MANUFACTURER, DEVICE TRADE NAME, KEYWORD]
26. COCCYX.MP.
27. SCIATICA.MP.
28. LUMBAGO.MP.
29. DORSALGIA.MP.
30. BACK DISORDER\*.MP.
31. ((DISC OR DISK) ADJ DEGENERAT\*).MP. [MP=TITLE, ABSTRACT, SUBJECT HEADINGS, HEADING WORD, DRUG TRADE NAME, ORIGINAL TITLE, DEVICE MANUFACTURER, DRUG MANUFACTURER, DEVICE TRADE NAME, KEYWORD]
32. ((DISC OR DISK) ADJ HERNIAT\*).MP.
33. ((DISC OR DISK) ADJ PROLAPSE\*).MP.
34. (FAILED ADJ BACK).MP.
35. NECK PAIN/
36. (NECK ADJ PAIN).MP. [MP=TITLE, ABSTRACT, SUBJECT HEADINGS, HEADING WORD, DRUG TRADE NAME, ORIGINAL TITLE, DEVICE MANUFACTURER, DRUG MANUFACTURER, DEVICE TRADE NAME, KEYWORD]
37. CERVICAL SPINE/
38. NECK DISORDER\*.MP.
39. WHIPLASH INJURY/
40. OR/20-39

PART: Mediation

mediat\$.mp

mediation analysis.mp

structural equation modeling.mp

structural equation modelling.mp

(Baron and Kenny).mp

product of coefficient.mp

difference in coefficient.mp

process of change.mp

sobel\$.mp

causal pathway.mp

intermediate.mp

indirect effect.mp

process variable.mp

- 48. limit XX to human
- 49. limit XX to humans

ACCEPTED

## SEARCH STRATEGY FOR CENTRAL register of Controlled trials – ONLINE (OVID)

Part A: Specific search for back pain and spinal disorders

- #1 MeSH descriptor Back Pain explode all trees
- #2 dorsalgia
- #3 backache
- #4 MeSH descriptor Low Back Pain explode all trees
- #5 (lumbar next pain) or (coccyx) or (coccydynia) or (sciatica) or (spondylosis)
- #6 MeSH descriptor Spine explode all trees
- #7 MeSH descriptor Spinal Diseases explode all trees
- #8 (lumbago) or (discitis) or (disc near degeneration) or (disc near prolapse) or (disc near herniation)
- #9 spinal fusion
- #10 spinal neoplasms
- #11 facet near joints
- #12 MeSH descriptor Intervertebral Disk explode all trees
- #13 postlaminectomy
- #14 arachnoiditis
- #15 failed near back
- #16 MeSH descriptor Cauda Equina explode all trees
- #17 lumbar near vertebra\*
- #18 spinal near stenosis
- #19 slipped near (disc\* or disk\*)
- #20 degenerat\* near (disc\* or disk\*)
- #21 stenosis near (spine or root or spinal)
- #22 displace\* near (disc\* or disk\*)
- #23 prolap\* near (disc\* or disk\*)
- #24 MeSH descriptor Sciatic Neuropathy explode all trees
- #25 sciatic\*
- #26 back disorder\*
- #27 back near pain
- #28 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27)

Part B: Specific search for neck pain

- #29 MeSH descriptor Neck, this term only
- #30 MeSH descriptor Neck Pain explode all trees
- #31 MeSH descriptor Neck Muscles explode all trees
- #32 MeSH descriptor Neck Injuries explode all trees
- #33 MeSH descriptor Whiplash Injuries explode all trees
- #34 whiplash
- #35 neck pain
- #36 neck disorder\*
- #37 cervical near vertebra\*
- #38 neck near pain
- #39 (#29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38)

PART: Mediation

mediat\$.mp

mediation analysis.mp

structural equation modeling.mp

structural equation modelling.mp

(Baron and Kenny).mp

product of coefficient.mp

difference in coefficient.mp

process of change.mp

sobel\$.mp

causal pathway.mp

intermediate.mp

indirect effect.mp

process variable.mp

process ADJ2 evaluation.mp

ACCEPTED

**SEARCH STRATEGY FOR CINAHL (EBSCO) Part B: Specific search for thoracic, low back, sacrum and coccyx problems**

S48 S35 or S43 or S47  
S47 S44 or S45 or S46  
S46 "lumbago"  
S45 (MH "Spondylolisthesis") OR (MH "Spondylolysis") Page 5 of 9  
S44 (MH "Thoracic Vertebrae")  
S43 S36 or S37 or S38 or S39 or S40 or S41 or S42  
S42 lumbar N2 vertebra  
S41 (MH "Lumbar Vertebrae")  
S40 "coccydynia" OR "back disorder\*"  
S39 "coccyx"  
S38 "sciatica"  
S37 (MH "Sciatica")  
S36 (MH "Coccyx")  
S35 S29 or S30 or S31 or S32 or S33 or S34  
S34 lumbar N5 pain  
S33 lumbar W1 pain  
S32 "backache"  
S31 (MH "Low Back Pain")  
S30 (MH "Back Pain+")  
S29 "dorsalgia"

**Part C: Specific search for neck problems**

S55 S54 or S53 or S52 or S51 or S50 or S49  
S54 (MH "Whiplash Injuries")  
S53 (MH "Cervical Vertebrae")  
S52 (MH "Neck Pain")  
S51 (MH "Neck")  
S50 "neck muscles"  
S49 (MH "Neck Muscles")  
**Part D: Other spinal disorders**  
S66 S65 or S64 or S63 or S62 or S61 or S60 or S59 or S58 or S57 or S56  
S65 failed W1 back  
S64 (MH "Laminectomy")  
S63 facet W1 joint  
S62 (MH "Spinal Fusion")  
S61 disc W5 herniation  
S60 disc W5 prolapse  
S59 disc W5 degeneration  
S58 (MH "Spinal Diseases+")  
S57 (MH "Intervertebral Disk")  
S56 (MH "Spine+")

**PART: Mediation**

mediat\$.mp

mediation analysis.mp

structural equation modeling.mp

structural equation modelling.mp

(Baron and Kenny).mp

product of coefficient.mp

difference in coefficient.mp

process of change.mp

sobel\$.mp

causal pathway.mp

intermediate.mp

indirect effect.mp

process variable.mp

process ADJ2 evaluation.mp

ACCEPTED

**Appendix B. Study quality assessment tool for observational mediation studies**

Items	Yes	No
1. Did the study cite a theoretical framework?		
2. Were the psychometric characteristics of the mediator and outcome variables reported? (Computed from the present study or a reference provided)		
3. Did the study report a power calculation? If so, was the study adequately powered to detect mediation?		
4. Were statistically appropriate/ acceptable methods of data analysis used? (This includes the product of coefficient approach with bootstrapped confidence intervals, structural equation modelling, latent growth modelling, and causal mediation analysis)		
5. Did the study ascertain whether changes in the mediating variable preceded changes in the outcome variable?		
6. Did the study ascertain whether changes in the predictor variable preceded changes in the mediator variable?		
7. Did the study control for possible confounding factors (e.g., baseline values)?		

This is an adapted version of a quality assessment tool that was designed for treatment mediation studies [57]. We consulted the original authors of this tool to identify items that were most relevant to observational mediation studies. Item 6 was added to account for the temporal precedence of the predictor and mediator variables.

**Table 1**  
Study characteristics.

Study	N at baseline (N analysed); N of Females; Mean age (years) ± SD	Setting	Spine area	Stage of condition (baseline)	Predictor (measure)	Mediator (measure)	Outcome (measure)	Design and follow-up time-points	Analysis method; significance test; single/multiple mediator model; confounders
Costa et al. 2011	- 184 (172) - 88 - 43.9±14.0	Primary care	LBP	Chronic	Pain (SF-36-pain scale)	-Fear (TSK) -Self-efficacy (PSEQ)	Disability (RMDQ)	- CS - 3m - LO (change) - 3m to 12m	Baron and Kenny; Sobel; Single; Uncontrolled
Gay et al. 2014	- 67 - 47 - 31.4±12.1	General community	LBP	Chronic	Pain (NRS)	-Catastrophizing (PCS) -Fear (FABQ, FDAQ)	Disability (ODI-modified)	- CS - BL	PROCESS macro; Sobel; Single; Uncontrolled
Gheldof et al. 2006	- 890 - 111 - 39.5±8.4	Working employees	LBP	Mixed	Pain (NRS)	-Fear (TSK-adapted)	Disability (PDI, QBPDS)	- CS - BL - CS - BL	Baron and Kenny; Sobel; Single; Controlled
Gheldof et al. 2010	- 527 (429) - 47 - 40.3±7.8	Companies	LBP	Mixed	Pain (NRS)	-Fear (TSK-adapted)	Disability (PDI)	- CS - BL - CS - 18m - LO - BL/18m/18m	SEM; Nil; Single; Uncontrolled
Hall et al. 2011	- 259 - 124 - 49.9±15.8	Hospital and community	LBP	Sub-acute	Pain (NRS)	-Distress (DASS)	Disability (RMDQ)	- LO - BL/BL/12w - LO - BL/6w/12w - LO (change) - BL to 6w - LO (change) - BL to 12w	Baron and Kenny; Nil; Single; Uncontrolled
Kamper et al. 2012	- 205 (103) - 137/69 - 38.6±NR	Primary care	NP	Acute	Pain (VAS)	-Catastrophizing (CSQ- subscale) - Fear (PFAcTS, TSK)	Disability (NDI)	- CS - BL - CS - 3m - CS - 6m - LO - BL/BL/3m	INDIRECT macro; Bootstrapped Cis; Single; Uncontrolled
Karoly et al. 2008	- 100 - 56 - 26% between 25–44; 41% between 45–64; and 33% between 65–80	General community	LBP	Chronic	Pain (PCP:S-pain severity scale)	-Fear (PCP:EA-fear scale)	Disability (PDI)	- LO - BL/BL/3m	SEM; Sobel; Single; Uncontrolled

Leeuw et al. 2007	- 152 - 94 - 47.3±10.7	General community	LBP	Chronic	Catastrophizing (PCS)	-Fear (TSK)	Disability (QBPDS)	- LO - BL/6m/6m	Baron and Kenny; Sobel; Single; Controlled
Neito et al. 2009	- 147 - 105 - 34.4±10.4	Rehabilitation services	NP	Sub-acute	Catastrophizing (PCS)	-Fear (TSK)	Disability (NDI)	- CS - BL	Baron and Kenny; Sobel; Single; Controlled
Neito et al. 2013	- 123 - 93 - 34.8±10.2	Rehabilitation services	NP	Acute	Catastrophizing (PCS)	-Fear (TSK)	Disability (NDI)	- LO - BL/BL/6m	Baron and Kenny; Nil; Single; Controlled
Seekatz et al. 2013	- 243 - 150 - 50.6±7.2	Inpatient rehabilitation centre	LBP	Chronic	Pain (NRS)	-Distress (PHQ-depression scale)	Disability (SF-36 physical function subscale)	- LO - BL/6m/12m	Baron and Kenny; Bootstrapped Cis; Single; Uncontrolled
Sodulund et al. 2010	- 64 - 39 - 36.0±12.9	Primary care	NP	Acute	Pain (NRS)	-Catastrophizing (CSQ-subscale) -Fear (TSK) -Self-efficacy (SES)	Disability (PDI)	- CS - BL	Baron and Kenny; Sobel; Multiple; Controlled

*Abbreviations:* BL=baseline; CI=confidence interval; CS=cross-sectional; CSQ=Coping Strategies Questionnaire; DASS=Depression Anxiety and Stress Scale; FABQ=fear-avoidance beliefs questionnaire; FDAQ=fear of daily activities questionnaire; LBP=low back pain; LO=longitudinal; m=months; NDI=Neck disability index; NP=neck pain; NRS=numeric rating scale; ODI=Oswestry Disability Index; PCP:EA=Profile of Chronic Pain: Extended Assessment battery; PCP:S=profile of chronic pain:screen; PCS=pain catastrophizing scale; PDI=Pain disability index; PFAcTS= Pictorial Fear of Activity Scale; PHQ=Patient health questionnaire; PSEQ=pain self-efficacy questionnaire; QBPDS=Quebec Back Pain Disability Scale; MDQ=Roland Morris Disability Questionnaire; SF-36=short-form health survey 36; SEM=structural equation modelling; SES=Self-efficacy Scale; TSK=Tampa scale for kinesiophobia; VAS=visual analogue scale

**Table 2**

Pooled correlation coefficients for path a, path b, indirect effect, and total effect.

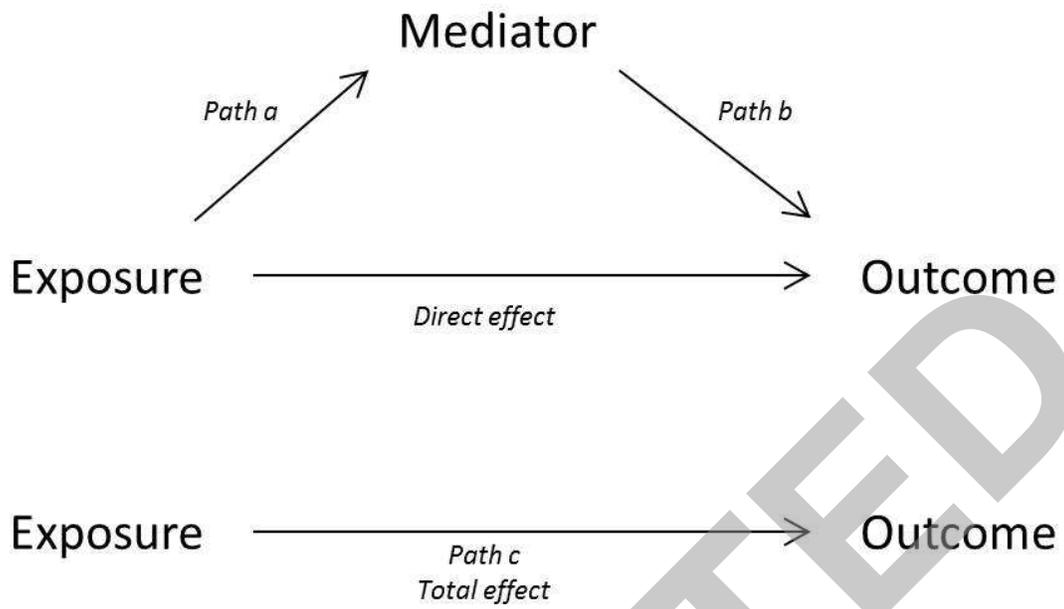
	Design	No. of studies	No. of models	N	path a			path b			Indirect effect (path ab)			Total effect (path c)		
					pooled $\beta$	Lower limit	Upper limit	pooled $\beta$	Lower limit	Upper limit	pooled $\beta$	Lower limit	Upper limit	pooled $\beta$	Lower limit	Upper limit
Fear	CS	6	14	1827	0.37*	0.28	0.45	0.38*	0.25	0.50	0.16*	0.11	0.20	0.61*	0.52	0.69
	LO	4	5	906	0.25*	0.09	0.39	0.32*	0.22	0.42	0.08*	0.01	0.14	0.40*	0.28	0.50
Catastrophizing	CS	3	5	234	0.33*	0.12	0.50	0.22*	0.09	0.34	0.07	-0.06	0.19	0.60*	0.51	0.67
	LO	1 <sup>†</sup>	1	103	-0.03	-	-	0.30*	-	-	-0.01	-	-	0.40*	-	-
Self-efficacy	CS	2	2	236	-0.41*	-0.51	-0.29	-0.54*	-0.69	-0.33	0.23*	0.10	0.34	0.60*	0.30	0.79
	LO	1 <sup>†</sup>	1	172	-0.32*	-	-	-0.43*	-	-	0.14*	-	-	0.43*	-	-
Distress	CS	0	0	-	-	-	-	-	-	-	-	-	-	-	-	-
	LO	2	5	502	0.25*	0.10	0.39	0.39*	0.25	0.52	0.10*	0.01	0.18	0.32*	0.19	0.43
FAM	CS	1 <sup>†</sup>	1	147	0.65*	-	-	0.34*	-	-	0.22*	-	-	0.33*	-	-
	LO	2	2	275	0.41	-0.02	0.71	0.24*	0.13	0.35	0.10	-0.02	0.22	0.04	-0.09	0.15

\* =  $P < 0.05$ ; <sup>†</sup> = result from one study; lower limit and upper limits refer to 95% confidence intervals; CS=cross-sectional; FAM = fear avoidance model (catastrophizing-fear-disability); LO=longitudinal

**Table 3**

Quality assessment.

	Kamper et al. 2012	Gheldof et al. 2006	Leeuw et al. 2007	Neito et al. 2013	Costa et al. 2011	Hall et al. 2011	Neito et al. 2009	Karoly et al. 2008	Sodulund et al. 2010	Gay et al. 2014	Gheldof et al. 2010	Seekatz et al. 2013
1. Did the study cite a theoretical framework?	1	1	1	1	1	1	1	1	0	1	1	1
2. Were the psychometric characteristics of the mediator and outcome variables reported? (Computed from the present study or a reference provided).	1	1	1	1	0	0	1	0	1	1	1	1
3. Did the study report a power calculation? If so, was the study adequately powered to detect mediation?	0	0	0	0	0	0	0	0	0	0	0	0
4. Were statistically appropriate/ acceptable methods of data analysis used? This includes the product of coefficient approach with bootstrapped confidence intervals, structural equation modelling, latent growth modelling, and causal mediation analysis.	1	0	0	0	0	0	0	0	0	1	0	1
5. Did the study ascertain whether changes in the predictor variable preceded changes in the mediator variable?	0	0	0	0	0	0	0	0	0	0	0	0
6. Did the study ascertain whether changes in the mediating variables preceded changes in the outcome variables?	0	0	0	0	0	0	0	0	0	0	0	0
7. Did the study control for possible confounding factors, e.g., baseline values?	0	0	1	1	0	0	1	0	0	0	0	0



ACCEPTED

