Reductions in kinesiophobia and distress after pain neuroscience education and exercise lead to favourable outcomes : a secondary mediation analysis of a randomized controlled trial in primary care

1. Introduction

Non-specific chronic spinal pain is an increasingly common condition and a leading cause of long-term disability and reduced health-related quality of life worldwide.[29] chronic spinal pain represents a considerable burden in primary care which is partly attributable to poor quality care and medication overuse.[4] Management of chronic spinal pain is difficult, and many established physiotherapy interventions have limited efficacy.[35; 44] Exercise therapy is considered the cornerstone for the management of chronic spinal pain in current clinical practice guidelines;[62] but yet only small to moderate short-term benefits have been shown at best.[35; 74]

Pain-related fears, cognitions and avoidance behaviours have a negative impact in chronic spinal pain and impede a favourable outcome from exercise therapy.[27; 49] In the last decades, exercise has been combined with psychological strategies in primary care (i.e., psychologically informed physiotherapy) to improve treatment outcomes.[78] Yet despite some promising results, only small superior effects on disability and quality of life have been reported when compared to standard physiotherapy.[12; 82] Recent advances on the understanding of pain mechanisms seem to indicate that central sensitisation (CS), and it's related distress, can also contribute to chronic spinal pain.[58] Some evidence suggests that the response to exercise is moderated by augmented central pain processing, motivating the need to address CS in patients with chronic spinal pain.[32; 60] Modern education-based interventions, such as pain neuroscience education (PNE), target patient pain perceptions and beliefs to reduce maladaptive cognitions and fear-avoidance behaviours, attenuate CS and its related distress, and ultimately improve patients' function.[54; 61] To date, though growing evidence supports the effectiveness of combining PNE with exercise;[77] little is known about its underlying therapeutic mechanisms.

Lately, pain rehabilitation research has started to move beyond examining the average treatment effects toward investigating the causal pathways and underlying therapeutic mechanisms.[47] Hence, mediation analysis has become progressively popular since it offers a method for examining whether an intermediate variable (i.e., a mediator) partially or fully accounts for the causal effect of an intervention on an outcome (i.e., indirect effect).[6] Most of the mediation analyses in chronic musculoskeletal pain have been mainly restricted to (pure) psychologically based interventions (e.g., cognitive behavioural therapy)[56] or psychologically informed physiotherapy[13; 19; 46]. Few studies have recently the underlying

therapeutic mechanisms of PNE through mediation analysis; [8; 38; 48] but still no research in this vein has been conducted when PNE is combined with exercise (PNE+Exercise).

Consequently, the aim of this study is to provide with new insights into the causal pathways of PNE+Exercise in chronic spinal pain by performing a mediation analysis in a previously published RCT[21] in primary care. We will do so by applying the recently proposed interventional effects approach for mediation analysis, which allows for disentangling indirect effects through multiple mediators without assuming a specific causal structure.

2. Methods

This is a secondary analysis of a previously published RCT[21] in patients chronic spinal pain in primary care. This mediation analysis was conducted and reported following the AGReMA[36] guidelines and recent recommendations for causal inference of mediation analysis with multiple mediators.[41; 56]

2.1. Study design and source data

The primary trial was a pragmatic multicentric RCT (registration number NTC03654235) conducted in primary care setting (Valladolid, Spain); where PNE+Exercise was compared to standard physiotherapy as the control group.[21] For further details on the results of the average treatment effect we refer to the primary trial[21].

At baseline, 170 patients with chronic spinal pain were included, of which 89 were randomized to the PNE+Exercise (73.03% females, 53.02±10.70 years old) and 81 to physiotherapy (87.65% females, 49.14±12.14 years old). The sample size calculation was not conducted for this secondary mediation analysis. Information on the trial eligibility and randomization process can be found in the study protocol[22]. The primary trial was approved by the Ethical Committee at the Valladolid-East and Valladolid-West Health Area (CASVE-NM_16-252 and 26/17).

2.2.Effects of interest and justification of the interventional effects approach for mediation analysis

PNE+Exercise, like other psychologically based interventions for pain, is designed to reduce disability and improve health-related quality of life by targeting multiple conceptually distinct therapeutic constructs (mediators) such as kinesiophobia and catastrophizing.

In order to test these theoretical hypotheses, the main interest when examining mediation lies in disentangling the indirect effect for each mediator separately.[47] To date, the majority of the mediation analyses conducted in pain rehabilitation adopt parallel mediation models where mediators are presumed to be causally independent (**Fig. 1.A**).[56] However, causal independence among mediators is often unrealistic in pain research, as there may be unknown causal pathways flowing among them (i.e., mediators affect each other).[40; 88; 91]

Serial mediation analysis has been proposed for analysing path-specific effects when causal effects among mediators are assumed (**Fig. 1.B**).[15; 85; 86] However, causal inference of mediated effects under serial mediation models is linked to strong assumptions. First, when the directions of the causal effects among the mediators are unknown or cannot be accurately presumed (either **Fig. 1.B** and **Fig. 1.C** can depict the true causal structure among mediators), serial mediation analysis is inappropriate.[40; 88] Second, even when the causal structure among the mediators is correctly specified, path-specific effects with causally sequential mediators cannot be safely identified when there is unmeasured or hidden confounding among the mediators (i.e., mediator-mediator confounding; **Fig. 1.D**).[15; 85; 86] When this assumption cannot be met, misleading conclusions about the IEs can arise.

To overcome the beforementioned shortcomings, interventional (in)direct effects[40; 88] for mediation analysis with multiple mediators have been proposed within the counterfactual-based framework[65; 69]. Interventional effects permit valid inferences about causal pathways without necessitating assuming a (correct) causal structure among the mediators or eliminating all unmeasured confounding among the mediators. The estimation procedure has been described in detailed elsewhere[40] and can be also found in **Appendix 1**.

2.3.Causal assumptions underlying mediation analysis

Fig. 2 shows a causal directed acyclic graph representing the causal assumptions of the mediation analysis. We justify treatment-mediator, mediator-outcome and mediator-mediator causal assumptions depicted in the directed acyclic graph with theoretical and empirical-based rationale in **Table 1**.[41; 87]

2.4.Intervention

In short, PNE+Exercise consisted of 4 initial group sessions of PNE[5] (1.5h each), 18 sessions of time-contingent exercise[59] (1h each, 3 sessions per week) and one final PNE booster session (2h) to reinforce the main educational contents (**Table A.1 in Appendix 2**). On the other hand, the control intervention consisted of 15 (1h each, 3 sessions per week)

sessions of standard physiotherapy that included aerobic exercise and analgesic thermotherapy and electrotherapy.

2.5.Measurement

Outcome and mediator measures were all assessed at baseline (T0), immediately post-intervention (T1; week 11 after randomization), and at 6-month follow-up (T2; week 26 after randomization). For the mediation analyses, we used the 6-month follow-up outcome measure and the post-intervention mediator measure to ensure that the mediators temporally precede the outcome.[18; 31] The post-intervention measure of the outcome was also introduced as a competing candidate mediator in each respective mediation analysis.[51]

Outcomes

- **Disability**: pain-related disability was assessed with the Roland-Morris disability questionnaire (RMDQ).[34] The RMDQ ranges from 0 to 24, where higher scores indicate more disability. The RMDQ has shown good internal consistency (α=0.84) and test-retest reliability (ICC=0.87).[34]
- **Medication intake:** pain medication intake was quantified with the Medication Quantification Scale III (MQS)[26]. The composite MQS score was obtained by first multiplying a score for the dosage by the detriment weight for its given pharmacological class, and then calculating the sum across classes.[23]
- **Health-related quality of life:** health-related quality of life was assessed with the 36-Item Short Form Health Survey (SF-36).[90] This scale ranges from 0 to 100, where higher scores indicate a greater quality of life. The SF-36 has shown good internal consistency (α>0.80) and test-retest reliability (ICC>0.80).[90]

Candidate mediators

- **Pain catastrophizing**: The pain catastrophizing scale (PCS) was used to assess patients' pain experience and their tendency to magnify its threat value. The PCS ranges from 0 to 52, where higher scores indicate catastrophic thinking. The PCS has shown good internal consistency (α=0.79) and test-retest reliability (ICC=0.84).[70]
- **CS-related distress:** The central sensitisation inventory (CSI) was used to assess psychosocial distress related to CS. The CSI was originally proposed to indirectly measure hyperexcitability of the central nervous system and CS-related symptoms.[72]

However, it has been recently suggested that CSI measures psychosocial distress related to CS rather than central nervous system adaptations since it is strongly related to psychological functioning (e.g., anxiety, distress or somatization).[1] The CSI ranges from 0 to 100, where higher scores indicate greater distress. The CSI has shown good internal consistency (α=0.87) and test-retest reliability (ICC=0.91).[14]

- **Kinesiophobia**: The Tampa Scale of Kinesiophobia (TSK)-11 was used to assess the patients' fear of (re)injury by physical movement or activity. The TSK-11 ranges from 11 to 44, where higher scores indicate more kinesiophobia. The TSK-11 has shown good internal consistency (α=0.79) and test-retest reliability (ICC=0.82).[24; 92]
- **Pain intensity:** The 100mm visual analogue scale (VAS) was used to assess the average pain intensity.[9] The VAS ranges from 0 to 100mm, where higher scores indicate higher pain intensity. The VAS has shown moderate to good test-retest reliability.[10]

Measured confounders

The confounding assumptions for mediation analysis are extremely important and their violations can bias the results of the (in)direct effects.[86] Potential mediator-outcome confounders were identified using background knowledge about the causal relationship between the variables (**Table 1**).[76] These included baseline patients' sociodemographic (i.e., age, gender, educational level and employment status) and symptoms' characteristics (i.e., pain duration and pain distribution measured with the McGill's pain maps). The baseline values of the outcome and mediators were also included as confounders.[42]

2.6.Data analysis

For each outcome of interest (RMDQ, MQS and SF-36 at 6-month follow-up), the following set of linear regression models were fitted: a model for each of the five mediators given treatment allocation and confounders; and an outcome model given treatment allocation, all the mediators and confounders. We first (i) assumed only main effects for all the models. The regression parameters were then combined to obtain estimators of the interventional (in)direct effects (see **Appendix 1**).[40] The models were fitted jointly using *Lavaan*[71] in R version 4.1.0. Nonparametric bootstrap 95% confidence intervals (CIs) were constructed using 1000 bootstrap samples that randomly resampled n observations with replacement and repeated the estimation procedures for each bootstrap sample.

Next, we repeated the analysis by (ii) adding all pairwise mediator-mediator interaction terms in the outcome model to allow the effect of each mediator to differ based on the levels of another mediator(s) (i.e., the effect of a mediator on the outcome could be moderated by another mediator). Because the decomposition of the mediators in the model can lead to different estimators of the indirect effect, a permutation-based sensitivity analysis was performed by considering all possible combinations among the 5 mediators.[40] We refer interested readers to **Appendix 1** for full details on this method. The minimum and maximum indirect effect estimates (and bounds of the 95% CIs) across all the permutations were reported. Indirect effect estimates under each permutation can be found at the end of **Appendix 1**. If the causal interpretation of the indirect effect varies across different permutations (95%CIs included zero and non-zero), that indirect effect is potentially moderated by other mediator(s) (i.e., there is an indirect effect via mediator-mediator interaction terms in the outcome model). In other words, that mediator may have a greater (and significant) effect on the outcome when other mediators are also changed by PNE+Exercise.

Complete-case analysis approach was followed (Total n=148; PNE+Exercise n = 80; physiotherapy n = 68). A post hoc sensitivity analysis was additionally performed to assess the possible impact of missing data at random (MAR) by estimating again interventional (in)direct effect with no mediator-mediator interactions using full information maximum-likelihood. The results of this sensitivity analysis did not differ greatly, suggesting serious biases due to missing data in the complete-case analysis might have been unlikely.

3. Results

The baseline characteristics of the patients included in the mediation analysis can be found in **Table 2** (see **Table A.2 in Appendix 2** for further information of the patients who were lost to follow-up). **Table A.3 in Appendix 2** presents the pain medication intake by pharmacological class in the randomised sample.

3.1.Interventional (in)direct effect with no mediator-mediator interactions

Mediation analysis disability (RMDQ) at 6-month follow-up: An average reduction in disability of -5.37 (95%CI: -6.40, -4.21) was observed at 6-month follow-up after PNE+Exercise (compared to physiotherapy). A strong indirect effect was identified for RMDQ at post-intervention (-3.34; 95%CI: -4.92, -2.06), followed by TSK (-1.20; 95% CI: -2.33, -0.21) and CSI (-1.35; 95%CI: -2.60, -0.01). This indicates that disability reduces by 1.20 and by 1.35 points via changes in kinesiophobia and CS-related distress respectively. The indirect effects through PCS (0.01; 95%CI: -0.81, 1.07) and VAS (0.27; 95% CI: -0.71, 1.27) were small and non-significant. The direct effect was non-significant (0.32; 95%CI: -1.24, 1.65) **(Table 3).**

Mediation analysis for pain medication intake (MQS) at 6-month follow-up: An average reduction in pain medication of -11.25 (95%CI: -14.00, -8.46) was observed at 6-month follow-up following PNE+Exercise. A significant indirect effect for changes at post-intervention MQS (-6.32; 95%CI: -9.00, -3.94), TSK (-3.63; 95%CI: -7.14, -0.99) and CSI (-3.68; 95%CI: -7.25, -0.25) was observed. This suggests that pain medication intake decreases by 3.63 and by 3.68 points via reductions in kinesiophobia and CS-related distress respectively. The indirect effects through PCS (0.68; 95% CI: -1.59, 3.45) and VAS (0.38; 95%CI: -1.98, 2.86) were again small and non-significant. The direct effect was non-significant (1.36; 95%CI: -2.45, 5.38) **(Table 3).**

Mediation analysis for health-related quality of life (SF-36) at 6-month follow-up: An average increase in health-related quality of life of 18.55 (95% CI: 13.95, 23.30) was observed at 6-month follow-up after PNE+Exercise. A strong indirect effect via gains in SF-36 at post-intervention was observed (16.96; 95%CI: 11.15, 22.05). A significant indirect effect was also observed through reductions in TSK (5.80; 95%CI: 1.42, 10.13). Neither post-intervention changes in PCS (-0.44; 95%CI: -4.97, 3.62), VAS (-0.98; 95%CI: -5.19, 3.78) nor CSI (0.55; 95%CI: -4.65, 6.33) were found to mediate health-related quality of life gains at follow-up. The direct effect was non-significant (-3.43; 95%CI: -8.63, 3.10) (**Table 3**).

Information on the point and uncertainty estimates for the treatment-mediator and mediator-outcome relationships in each mediation analysis can be found in **Table A.4 of Appendix 2**.

3.2.Interventional indirect effect with mediator-mediator interactions

No evidence for a significant indirect effect through post-intervention PCS or VAS was found across all permutation in any of the 3 mediation analyses (**Table 3**). In the *mediation*

analysis for disability at 6-month follow-up, conclusions on the (significant) IEs through post-intervention RMDQ remained unchanged across all permutations. By contrast, causal interpretation for the IEs through TSK and CSI varied across the different decompositions (95%CIs include zero and non-zero). Causal interpretation also varied across permutations for the IEs through post-intervention TSK, CSI and MQS in the *mediation analysis for pain medication intake at 6-month follow-up*. Conflicting interpretations for the IEs through post-intervention changes in TSK and SF-36 were also observed in the *mediation analysis for health-related quality of life at 6-month follow-up* (**Table 3**). These results, therefore, highlight an effect modification among the mediators (indirect effect via a particular mediator depend on the values of other mediators) rather than causal independence. In this manner, TSK and CSI may have, for example, a greater (and significant) effect on disability and medication intake when other mediators are also modified by PNE+Exercise. For interested readers, we provide a comprehensive description of the results from the analysis of interventional indirect effect with mediator-mediator interactions in **Appendix 1**.

4. Discussion

The latest advances in the understanding of pain mechanisms and the CS phenomenon have contributed to expanding the fear-avoidance model and shaping a new generation of education-based physiotherapy interventions. This original study provides the first insights into the causal pathways of PNE combined with exercise in chronic spinal pain by disentangling the indirect effects of key therapeutic constructs through the recently proposed interventional indirect effects approach for mediation analysis.[40; 88] Immediate post-intervention improvements in disability, pain medication intake and health-related quality of life strongly mediated PNE+Exercise effects on each of these outcomes at 6-month follow-up respectively. Post-intervention reductions in kinesiophobia also mediated PNE+Exercise effects on all outcomes, while reductions in CS-related distress mediated changes in disability and medication intake. Neither pain catastrophizing nor pain intensity contribute to improvements in any outcome. We also uncovered, in a novel manner, that the effects on the outcome of those therapeutic constructs are not independent, suggesting interdependencies among mediators.

In line with previous studies examining the mechanisms of psychologically informed physiotherapy, disability at follow-up was strongly mediated by reductions in kinesiophobia following PNE+Exercise.[19; 46] Kinesiophobia is suggested to be reduced in the PNE sessions where, by improving knowledge about pain, patients question their misconceptions

regarding the relationship between movement, pain and harm.[54; 61] Afterwards, patients have the opportunity to challenge their maladaptive assumptions by direct experiences within the time-contingent exercise program (i.e., kinesiophobia is decreased when movement is no longer associated with a harmful consequence).[28; 59] On the other hand, the current study also revealed a causal path toward decreasing disability via reductions in CS-related distress. This novel finding is consistent with one of the most differential theoretical foundations of PNE.[60] PNE aims to reconceptualize pain beliefs to convince the patients that CS, rather than local tissue damage, might be the cause of their long-lasting pain. Thus, the reduction of the threat value of pain and its associated fearful state results in an attenuation of the CS phenomenon (and its related psychological distress), which in turn can lead to reductions in disability.[3; 59] Importantly, we also uncovered that both of these PNE+Exercise-related mechanisms do not occur independently from changes in other mediators (i.e., mediator-mediator interactions). The study design does not allow to clarify which mediator moderates the other's indirect effect. Rather, it highlights the interrelationship of these processes during treatment and provides a more comprehensive picture of how disability is reduced after PNE+Exercise.

Medication intake is a common concern among patients with chronic spinal pain. Though not primarily aimed, reductions in pain medication are often observed in patients with chronic spinal pain following exercise therapy.[43] This study provides the first evidence on how pain medication is unintentionally reduced during PNE+Exercise by revealing that decreases in intake 6-month after were mediated by reductions in CS-related distress and kinesiophobia. Pain intensity, psychological distress and catastrophic thinking are associated with medication intake.[30] Current research also suggests that chronic spinal pain patients with greater CS-related distress and somatization tend to consume more pain medication while evidence is still conflicting on the role of kinesiophobia.[30] Pain medication use is associated with low self-efficacy, which in turn is related to kinesiophobia.[57; 93] Patients with high kinesiophobia and avoidance beliefs have a lower sense of self-efficacy and are more likely to utilize passive coping strategies such as medication to control for pain. Interestingly, we also found that the indirect effect through post-intervention changes in mediation intake was also moderated by changes in other mediators rather than occurring independently. This breakthrough aligns with the PNE's postulates by supporting the idea that pain-negative cognitions and emotions need to be reshaped to shift away from maladaptive coping strategies towards activity engagement.[28; 54; 61]

On the other hand, only post-intervention gains in health-related quality of life and reductions in kinesiophobia were found to mediate PNE effects on health-related quality of life at follow-up. The current findings could be explained because, in addition to kinesiophobia, other factors (e.g., self-efficacy, anxiety or depression) rather than those examined account to a greater extent for improvements in health-related quality of life in patients with chronic spinal pain.[49]

Also, in line with previous mediation studies in psychologically informed physiotherapy, no evidence was found that reductions in pain catastrophizing led to positive outcomes.[13; 48] Several reasons could explain why the role of pain catastrophizing remains unclear despite being an important fear-avoidance model's construct. First, high levels of pre-treatment pain catastrophizing might be required in order that changes in this construct can mediate PNE effects on disability.[8] Second, changes in pain catastrophizing could occur early in the intervention and not be relevant to explain the causal pathways between post-intervention and follow-up.[55] Future research should address these two complex hypotheses by testing moderated mediation and time-varying mediation respectively.

This study has several strengths compared to the previous mediation literature in pain rehabilitation. It followed an appropriate reporting guideline[36] and recent recommendations[41; 56] to reduce the risk of bias specific to mediation analysis with multiple mediators. In contrast to previous studies,[56] the post-intervention outcome value was also included as another competing mediator as its omission can result in an overestimation of the indirect effect through other mediators.[51] The counterfactual-based framework[65; 69], which circumvents the limitations linked to the traditional mediation approaches (e.g., product-of-coefficients), was adopted in the current study. Some of the strengths of this framework are the definition of the (in)direct effects with causal interpretation, clarification of the assumptions required for their identification (in particular in terms of confounding control) and formulation of appropriate methods for their estimation.[86] The interventional effects approach applied in the present study permits valid causal inferences of the (in)direct effects in the presence of mediator-mediator interactions, even when the causal structure among the mediators is unknown and mediator-mediator unmeasured confounding is present.[40]

On the other hand, some limitations should also be acknowledged. This is a secondary analysis of a previously published RCT. Despite this being a common practice in mediation literature, a priori planning can help to improve the validity of the results by increasing statistical power and reducing potential bias (e.g., omission of important confounders).[7; 89] We did not perform sensitivity analyses for unmeasured (pre-treatment) mediator-outcome

confounding because these procedures have just recently been extended to the interventional effects approach.[64] Also, it should be pointed out that a proportion of the treatment effect can also be potentially explained by contextual effects (e.g., therapeutic alliance or satisfaction), which were not measured in the current study. Finally, we adopted a complete-cases approach because our analytic approach (interventional (in)direct effects with mediator-mediator interactions) doesn't allow for handling missing data by making assumptions about their relationships with the available data. Our sensitivity analysis suggested that the results from the complete-case analysis were also plausible under MAR assumption. However, it is possible that data were not missing at random.

In conclusion, the current results support, to some extent, the theoretical foundations of the PNE framework and highlight the importance of reducing kinesiophobia and CS-related distress when treating patients with chronic spinal pain. This study also provided the first insights into how these processes might interact which each other, emphasizing the need for implementing methods that allow to accommodate dependencies between mediators with unknown causal structure.

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Conflict of interest

The authors report no competing interests.

Data availability

The description of the estimation method as well as the related R code can be found in https://github.com/wwloh/disentangle-multiple-mediators

Table 1. Treatment-mediator, mediator-outcome and mediator-mediator causal assumptions

Causal path	Justification	Details
Treatment → Mediator(s)		
PNE+Exercise → catastrophizing, kinesiophobia, CS-related distress and pain intensity	Intervention theoretical rationale and existing literature	In short, Pain Neuroscience Education (PNE) based interventions aim to improve patients' knowledge on pain neurophysiology to reconceptualize maladaptive pain cognitions and emotions (i.e., **catastrophizing and kinesiophobia**) and attenuate the central sensitisation (CS) phenomenon (and **its related distress**).[54; 61] By reducing the threat value of pain and is associated fearful state, patients can shift away from pain control towards activity engagement through time-contingent exercise, breaking the cycle of catastrophizing-fear-distress-avoidance-disability.[39] Exercise alone decreases pain intensity, pain catastrophizing and kinesiophobia.[25; 68; 73; 81] Evidence supports that PNE is effective in reducing catastrophizing and kinesiophobia either, alone[52; 83] or in combination with exercise[77]. To date, promising but limited evidence seems to suggest that PNE and exercise therapy can also successfully reduce CS and its related distress alone[79; 83] or in combination.[45]
	Temporal precedence	Mediators are measured at post-intervention (T1). We included the post-intervention value of the outcome as competing mediator.
	Possible confounders	None due to randomization
Treatment → Outcome Average (Total) treatment effect		
PNE+Exercise → Disability, medication intake and health-related quality of life	Existing literature	No significant average treatment effect is required to test interventional indirect and direct effects.
	Temporal precedence	Outcomes are measured at 6-month follow-up (T2)
	Possible confounders	None due to randomization
Mediator(s) → Outcome		
Catastrophizing, kinesiophobia, CS-related distress and pain intensity → Disability, medication intake and health-related quality of life	Theoretical rationale and existing literature	Pain intensity is associated with disability[37]. There is consistent evidence that supports that maladaptive cognitions and behaviours contribute to long-term **disability.**[37; 49] In the last decade, advances on the understanding of pain mechanisms have provided supporting evidence to integrate the CS and its related distress into the fear avoidance model to explain chronic pain and related disability.[66; 80; 91] Similarly, lower **health-related quality of life** is associated with greater kinesiophobia, while there is no evidence on the relationship with pain intensity, catastrophizing and CS-related distress.[49] Finally, research has consistently reported that **pain medication intake** is not only related to pain intensity[2; 63], but also to pain catastrophizing and kinesiophobia.[30; 50] In addition, some recent evidence seems to suggest that patients with chronic spinal pain with greater CS-related distress tend to consume more pain medication.[11]
	Temporal precedence	Mediators' measures at post-intervention (T1) and outcomes measures at 6-month follow-up (T2) were taken for the analysis to allow for temporal Mediator-outcome precedence.
	Possible Mediator → Outcome confounders	Evidence has shown that **widespread pain** is associated with pain intensity, CS-related distress, pain catastrophizing, kinesiophobia, disability and pain medication in people with chronic spinal pain;[67; 75; 84] suggesting that it can be a common cause of the mediators and outcomes. Similarly, some evidence suggests that duration of the pain complaints can affect pain-related psychological variables, disability, medication intake and health-related quality of life.[16; 17; 53] Demographic factors such as **age, gender, education level** and **employment status** have often been reported to be determinants of disability, medication intake , quality of life, and pain-related psychological constructs; and therefore, could introduce spurious association between the mediator-outcome relationship.[33]
Mediator → Mediator		
Catastrophizing, kinesiophobia, CS-related distress and pain intensity	Existing literature	Though associations between pain intensity, pain catastrophizing, kinesiophobia and CS-distress have been consistently reported,[20; 84] no definitive causal effects between the mediators can be presumed.

Table 2. Baseline characteristics of patients included in the mediation analysis (complete-cases analysis)

	Physiotherapy (n=68)	PNE+Exercise (n=80)	Total (n=148)
Gender			
Female	61 (89.7%)	61 (76.3%)	122 (82.4%)
Male	7 (10.3%)	19 (23.8%)	26 (17.6%)
Age (years old) *	52.0 [24.0, 68.0]	55.0 [26.0, 69.0]	53.5 [24.0, 69.0]
Academic education			
Unfinished Primary education	5 (7.4%)	3 (3.8%)	8 (5.4%)
Primary education	25 (36.8%)	29 (36.3%)	54 (36.5%)
Secondary education	10 (14.7%)	13 (16.3%)	23 (15.5%)
Vocational Education and Training	11 (16.2%)	12 (15.0%)	23 (15.5%)
Higher Education certificate	6 (8.8%)	9 (11.3%)	15 (10.1%)
Bachelors' Degree	11 (16.2%)	14 (17.5%)	25 (16.9%)
Employment Status			
Student	1 (1.5%)	0 (0%)	1 (0.7%)
Unemployed	8 (11.8%)	17 (21.3%)	25 (16.9%)
Houseperson	15 (22.1%)	14 (17.5%)	29 (19.6%)
Employed	34 (50.0%)	31 (38.8%)	65 (43.9%)
Retired	10 (14.7%)	18 (22.5%)	28 (18.9%)
Duration of complaints (months)*	48.0 [6.00, 360]	65.0 [7.00, 540]	60.0 [6.00, 540]
Widespread (0-24)*	7.00 [2.00, 18.0]	8.00 [1.00, 24.0]	8.00 [1.00, 24.0]
RMDQ (0-24)*	8.00 [2.00, 19.0]	10.0 [2.00, 23.0]	8.00 [0, 23.0]
SF-36 Total score (0-100)	58.9 (14.7)	52.9 (13.7)	54.7 (15.0)
Medication intake (% consumers)	61 (89.7%)	75 (93.8%)	136 (91.9%)
MQS†	17.3 (10.4)	18.7 (10.7)	16.6 (11.3)
VAS (0-100mm)	66.9 (14.6)	75.0 (14.0)	71.3 (14.8)
PCS (0-52)	28.2 (9.42)	30.3 (8.75)	29.3 (9.09)
TSK (11-44)	27.9 (7.20)	29.3 (6.46)	28.7 (6.82)
CSI (0-100)	38.5 (11.9)	43.4 (12.2)	41.1 (12.3)

PT, Physiotherapy; PNE, Pain Neuroscience Education; FU, Follow-up; RMDQ, Roland-Morris Disability Questionnaire; SF-36, 36-Item Short Form Health Survey; MQS, Medication Quantification Scale; VAS, Visual Analogue Scale, PCS, Pain Catastrophizing Scale, TSK, Tampa Scale of Kinesiophobia; CSI, Central Sensitization Inventory.

Notes: *Median and IQR. † See further details on the pharmacological classes defined by MQS in **Table 3** of Appendix 2.

Table 3. Results of the interventional indirect effects with and without including mediator-mediator interactions in the outcome model.

Mediator	Interventional indirect effects with no M-M interactions		Interventional indirect effects with M-M interactions (120 permutations)					
	CCA	FIML	Estimate		Lower bound 95%CI		Upper bound 95%CI	
	Estimate & 95%CI	Estimate & 95%CI	min	max	min	max	min	max
Mediation analysis: disability (RMDQ) at 6-month follow-up (n = 148)								
ATE	**-5.37 (-6.40, -4.21)**	**-5.35 (-6.32, - 4.30)**						
DE	0.32 (-1.24, 1.65)	0.32 (-1.16, 1.63)						
IE PCS	0.01 (-0.81, 1.07)	0.01 (-0.79, 1.13)	-1.38	1.57	-2.97	-0.16	0.86	3.50
IE TSK	**-1.20 (-2.33, -0.21)**	**-1.32 (-2.50, -0.02)**	**-2.96**	**0.97**	**-5.08**	**-1.25**	**-0.95**	**2.78**
IE CSI	**-1.35 (-2.60, -0.01)**	**-1.18 (-2.24, -0.20)**	**-3.92**	**1.18**	**-6.29**	**-0.91**	**-1.78**	**3.31**
IE VAS	0.27 (-0.71, 1.27)	0.26 (-0.75, 1.29)	-2.15	3.00	-4.30	-0.15	0.31	5.59
IE RMDQ	**-3.34 (-4.92, -2.06)**	**-3.27 (-4.83, -2.00)**	**-4.23**	**-3.34**	**-6.57**	**-4.86**	**-2.61**	**-1.47**
Mediation analysis: pain medication intake (MQS) at 6-month follow-up (n = 148)								
ATE	**-11.25 (-14.00, -8.46)**	**-11.25 (-14.00, -8.43)**						
DE	1.36 (-2.45, 5.38)	1.49 (-2.59, 5.70)						
IE PCS	0.68 (-1.59, 3.45)	0.69 (-1.82, 3.43)	-3.33	6.50	-8.18	-1.68	0.67	12.41
IE TSK	**-3.63 (-7.54, -0.75)**	**-3.66 (-7.14, -0.99)**	**-8.61**	**2.89**	**-14.67**	**-2.57**	**-3.28**	**8.45**
IE CSI	**-3.68 (-7.25, -0.25)**	**-3.60 (-6.59, -0.57)**	**-6.44**	**0.06**	**-11.78**	**-3.99**	**-1.57**	**5.43**
IE VAS	0.38 (-1.98, 2.86)	0.34 (-2.28, 2.69)	-1.50	2.60	-6.87	-1.68	1.97	7.35
IE MQS	**-6.32 (-9.00, -3.94)**	**-6.19 (-8.67, -3.97)**	**-12.78**	**-1.41**	**-17.98**	**-4.97**	**-8.54**	**2.98**
Mediation analysis: health-related quality of life (SF-36) at 6-month follow-up (n = 148)								
ATE	**19.20 (14.30, 24.12)**	**18.55 (13.66, 23.20)**						
DE	-3.43 (-8.63, 3.10)	-3.50 (-8.80, 2.70)						
IE PCS	-0.44 (-4.97, 3.62)	-0.53 (-4.82, 3.50)	-2.89	2.86	-13.43	-5.03	5.01	14.17
IE TSK	**5.80 (1.42, 10.13)**	**5.69 (1.21, 10.37)**	**-1.61**	**10.48**	**-18.41**	**1.99**	**7.81**	**23.41**
IE CSI	0.55 (-4.65, 6.33)	0.54 (-5.43, 5.98)	-5.55	4.00	-19.68	-6.11	4.15	17.12
IE VAS	-0.98 (-5.19, 3.78)	-1.24 (-5.23, 3.22)	-7.94	5.73	-23.90	-2.34	1.23	22.55
IE SF-36	**16.98 (11.15, 22.05)**	**17.16 (11.49, 22.85)**	**9.01**	**26.20**	**-3.53**	**14.94**	**18.15**	**41.31**

ATE, Average Treatment Effect; DE, Direct effect; IE, indirect effect; M-M, mediator-mediator; CI, confidence interval; CCA, complete-case analysis; FIML, full information maximum likelihood; RMDQ, Roland-Morris Disability Questionnaire; SF-36, 36-Item Short Form Health Survey; MQS, Medication Quantification Scale; VAS, Visual Analogue Scale; PCS, Pain Catastrophizing Scale; TSK, Tampa Scale of Kinesiophobia; CSI, Central Sensitization Inventory.

Notes:

(1) All the results are unstandardized.

(2) **Interventional indirect effect with no mediator-mediator interactions**: significant interventional indirect effects (95% CIs exclude zero) are highlighted in bold.

(3) **Interventional indirect effect with mediator-mediator interactions:** interventional indirect effects which are significant across all the permutations are highlighted in blue (95% CIs always exclude zero). Those interventional indirect effects whose causal interpretation varied across different permutations, and were thus moderated by another mediator, are highlighted in red (95% CIs include zero and non-zero).

Figure 1. Diagrams for causal assumptions in settings with multiple mediators. (A) Mediators M_1 and M_2 are causally independent. **(B)** M_1 causally precedes M_2. **(C)** Inverse scenario, M_2 causally precedes M_1. **(D)** M_1 and M_2 do not affect each other but are correlated because they share an unobserved common cause (U), which induces mediator-mediator confounding.

Figure 2. Hypothesized directed acyclic graphs. Red arrows depict the indirect effect from PNE+Exercise to the outcome through the candidate mediators. Green dashed arrows depict possible unknown causal effects and correlations between the mediators (we are agnostic about the directionality of causal influences between the mediators). The back arrow depicts the total effect and the remaining (direct) effect from PNE+Exercise to the outcome. For visual simplicity, all baseline confounders are represented by a single node C, although their effects on each variable are permitted to differ. The baseline confounders were age, gender, educational level, employment status, pain duration, pain distribution as well as the baseline values of the outcome and mediators. The timepoints at which the variables are measured are stated below the figure (T0 Baseline; T1 Post-intervention; T2; 6-month Follow-up).
ATE, average treatment effect; IE, indirect effect; DE, direct effect

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