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Mediators of the effects of exercise and manual therapy for people with knee and hip osteoarthritis: A secondary, exploratory analysis of the MOA trial

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ABSTRACT

Objective: To explore whether pain beliefs and functional strength mediate the treatment effect of manual therapy (MT) and exercise therapy (ET) on the Western Ontario and McMaster Osteoarthritis Index (WOMAC) composite scores and its subscales in individuals with hip and/or knee osteoarthritis in the MOA trial.
Design: Secondary analysis of a randomised controlled trial that compared the incremental effects of supervised MT and ET in addition to usual care in patients with osteoarthritis of the hip or knee. 206 participants enrolled in the MOA trial were analysed. The primary outcome measure was the WOMAC composite score after 1 year.
Results: Pain belief mediated the effect of MT (b: −10.7, 95 % CI: −22.3, −0.9), ET (b: −14.5 95%CI: −26.0, −4.4). Functional strength did not mediate the effect of MT, ET, or MT + ET. Mediation sensitivity analyses suggest findings are likely to change if small confounding between those mediators and WOMAC composite score is present.
Conclusions: We identified possible mediators of MT and ET. Future confirmatory studies could be designed to assess the mechanisms through which manual therapy and exercise cause improvements in pain and function scores in patients with hip or knee osteoarthritis.

1. Introduction

Non-surgical interventions such as exercise therapy (including strengthening and aerobic exercises) are recommended when managing people with hip and knee osteoarthritis [1]. Meta-analysis of randomized controlled trials (RCTs) has shown exercise therapy to have a small-to-moderate effect on pain and function scores when compared to non-exercise interventions [2]. Despite those findings, there is limited evidence supporting how these interventions achieve their expected outcomes [3] Mediation analyses inform the mechanisms of action of an intervention [4]. The clinical guidelines from the European League Against Rheumatism recommended identifying mediators of treatment effects as a research priority [5].

The mechanisms of action through which exercise and manual therapy may cause improvement in pain and function are unknown. Theoretically, those intervention may improve other variables (i.e., mediators), which in turn, cause improvement in pain and function. Previous research has revealed some possible mediators of treatment effect in patients with hip or knee osteoarthritis, including lower limb muscle strength [6], self-efficacy [7], pain beliefs and pain catastrophizing thoughts [8]. Better understanding of the mechanisms through which these interventions act may inform ways of enhancing the effect of interventions.

We previously reported a randomized controlled trial [9] that compared manual physiotherapy and/or exercise physiotherapy in addition to usual care for patients with osteoarthritis of the hip or knee and found that exercise or manual therapy were more effective than usual care at 12 months of follow-up. The MOA trial also reported no added benefit when combining exercise and manual therapy compared to usual care. So far, little research has explored the mediators of exercise and manual therapy interventions for patients with hip or knee osteoarthritis. The aims of this study were to explore whether pain beliefs and functional strength mediate the treatment effect of manual and exercise therapy on WOMAC composite scores, WOMAC pain and WOMAC function scores in individuals with hip and/or knee osteoarthritis in the MOA trial.

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2. Methods

2.1. Design

This is a secondary analysis of data from the MOA trial that compared the clinical effectiveness of manual therapy and/or exercise therapy in addition to usual care for patients with hip and/or knee osteoarthritis [9].

2.2. Study population

A total of 206 participants with hip and/or knee osteoarthritis took part in the original trial [9]. To be included, participants had to meet the American College of Rheumatology clinical criteria (i.e., without radiography) for hip or knee osteoarthritis and were randomly allocated to receive manual physiotherapy (n = 54), multi-modal exercise physiotherapy (n = 51), combined exercise and manual physiotherapy (n = 50), or no trial physiotherapy (n = 51). During the trial, 44 (21 %) participants had arthroplasty of the index hip or knee. The number of participants receiving arthroplasty in each group were as follows: manual physiotherapy (n = 12), multi-modal exercise physiotherapy (n = 11), combined exercise and manual physiotherapy (n = 13), or no trial physiotherapy (n = 8).

2.3. Interventions

The MOA trial was a 2 × 2 factorial trial with a 1-year follow-up. The trial was prospectively registered (ANZ Clinical Trial Registry – ACTRN12608000130369) and approved by the Lower South Regional Ethics Committee (New Zealand Ministry of Health, reference: LRS/07/11/044). The protocol [10] and the outcome evaluation study have already been published [9]. After baseline assessment, participants were randomly allocated to one of the four intervention groups: usual care, usual care plus manual therapy, usual care plus exercise therapy, usual care plus combined manual and exercise therapy. Participants allocated to usual care received routine care offered by their general practitioner or other healthcare providers. The manual therapy interventions were prescribed and tailored to individuals' clinical presentation, as per protocol, and were also prescribed home-based reinforcing activities (3× per week) to improve range of motion. Exercise therapy consisted of a multi-modal, supervised exercise programme that included warm-up and aerobic, strengthening, stretching, and neuromuscular control exercises. Clinicians could prescribe additional exercises from a limited list of interventions based on findings from clinical assessment. Participants allocated to usual care plus combined manual and exercise therapy received a combination of interventions as described for the manual therapy and exercise groups. None of the four groups received an education package as part of the intervention. The interventions are fully described in a freely available protocol [11].

2.4. Outcome measures

The primary outcome measure outcome in the trial was change in the Western Ontario and McMaster osteoarthritis index (WOMAC) composite score after 1 year. Participants completed the questionnaire at baseline, 9-week, 6-month and 12-month follow-up. We calculated the 12-month change. The MOA trial was powered to detect a minimum clinically important difference in the WOMAC score of 28 units (0–240 scale) [10].

Given the limited research in this field, we also explored the effect of putative mediators on the secondary outcome measures, i.e., WOMAC pain and WOMAC function scores at 12-month follow-up.

2.5. Putative mediators

We assessed the following variables as putative mediators: pain beliefs and functional strength. These variables were measured at baseline and 6-month follow-up. These mediators were selected based on data available from the original trial and findings from the literature [6–8]. Pain belief was assessed using the total score from the pain belief screening instrument [12]. This instrument has 7 items covering the following constructs: pain intensity (1 question), disability (1 question), self-efficacy (2 questions), fear (1 question), avoidance (1 question) and catastrophizing thinking (1 question) [12,13]. Scores for each question range from 0 to 10 (supplementary material – Section I). Sit-to-stand was assessed using the 30 s sit-to-stand test, which assesses functional strength [14]. Given the exploratory nature of this study, we analysed each putative mediator separately. The putative causal mechanism for each mediator is presented in Table 1.

Table 1
Description of putative mediators and its respective theoretical causal mechanism.

Mediator	Theoretical causal mechanism
Pain belief	Exercise therapy exposes patients to performing exercises that do not worsen symptoms, which change their beliefs about their pain. Manual therapy exposes patients to brief pain relief, which change their beliefs about their pain. Improved pain belief may cause improvements in WOMAC composite, pain or function scores.
Functional strength	Exercise therapy strengthens lower limb muscles, improve their function. Manual therapy has neuromuscular effects which facilitates recruitment of motor units, increasing neuromuscular control and muscle force generated. Higher functional strength may cause improvements in WOMAC composite, pain or function scores.

The directed acyclic graph for the mediation models is presented in Fig. 1.

2.6. Sample size estimation

Given this is a *post-hoc* secondary analysis of the MOA trial [9], we estimated the required sample size under two different scenarios, assuming: (1) a large treatment-mediator and mediator-outcome effect (r = 0.6); and (2) a moderate treatment-mediator and mediator-outcome effect (i.e. r = 0.3). In addition to those, we assumed there was: (3) no exposure-mediator confounding, given this is a randomized trial; (4) a moderate confounding for the mediator-outcome (r = 0.3) as suggested by Vittinghoff and Neilands [15]. For all analyses, power set at 0.8.

The sample size calculations suggested that: a minimum of 80 participants (40 per group) were required if there were large treatment-mediator and mediator-outcome effects; or a minimum of 342 participants were required if there were moderate treatment-mediator and mediator-outcome effects. Those analyses suggest our present study was powered for detecting a large mediating effect but lacked power for detecting a moderate mediating effect.

2.7. Missing data

We used the mi function in the statistical software package Stata (StataCorp) for replacing missing data through multiple imputation. Prior to performing multiple imputation, we assessed whether missing data met assumptions of 'missing completely at random'. We assessed missing data patterns to determine the appropriate strategies for imputation of each variable. We generated 36 imputations of missing values

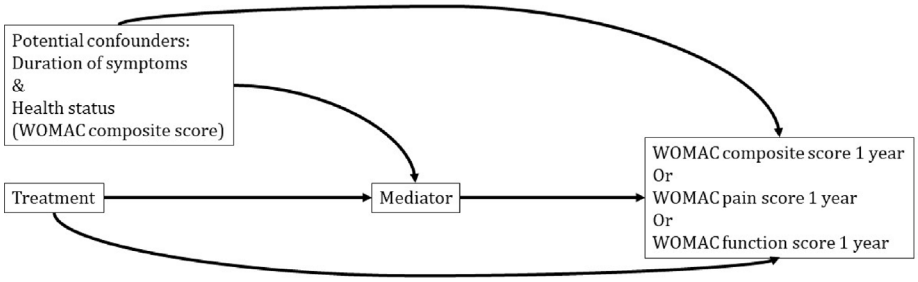

Fig. 1. Directed acyclic graph representing the causal model with mediator of treatment effect on clinical outcomes (WOMAC composite, pain or function score at 1 year follow-up).

for each of variable with missing data. We checked estimates to confirm imputed values did not deviate significantly from observed data by using in mean value, SD, minimum and maximum values.

2.8. Statistical analysis

Arthroplasty was an unplanned, non-randomised co-intervention, that is highly effective and very likely has different causal pathways between the interventions of interest, the mediator, and the outcome. Surgery is a post-randomization event and likely a consequence of the exposure, prognostic factors measured at baseline as well as other post-randomization factors (which may be unmeasured) [16–18]. Given the effect of hip or knee arthroplasty on pain and function, we excluded participants who underwent surgery (i.e., who did not adhere to their allocated intervention).

By restricting the analyses on a post-randomization event (i.e., surgery), the exchangeability between arms of the trial no longer holds, and there is a risk of selection bias (Figure S1 – supplementary material, Section II) [17,19]. We used inverse probability weighting to adjust for prognostic factors that are associated with adherence [16–18,20]. Inverse probability weights create a *pseudo-population* where everyone adheres to the allocated treatment, and through that, we adjust treatment estimates to selection bias [16–18,21].

2.9. Adherence adjustment using inverse probability weighting

We used stabilized IP weights to adjust for selection bias. When adjusting for adherence using inverse probability weighting we adopted the following steps [16–18]: (1) we estimated the inverse probability of adherence weights (i.e., the probability of not receiving surgery) using the complete dataset ($n = 206$), for each arm of the trial separately. This was done given the reasons for non-adherence are likely to be different between intervention arms (i.e., usual care, manual therapy, exercise therapy, or manual and exercise therapy) [16]. We used logistic regression model to estimate the probability of adherence weights. We included the following parameters (measured at baseline) in the model: age, WOMAC composite score, quadriceps muscle strength, body mass index and duration of symptoms. (2) We, then, estimated the outcome and mediator models using a weighted linear regression model with weights estimated during step 1. We present details for the outcome and mediator models below.

2.10. Mediation analysis

We performed mediation analyses within the counterfactual framework [22,23]. When performing mediation analyses, we assumed there was: (1) no unmeasured confounding between the intervention-mediator relationship; (2) no unmeasured confounding between intervention-outcome relationship; (3) no unmeasured confounding between mediator and outcome; and (4) no mediator-outcome confounder that is affected by the intervention. In addition, we assumed the presence of temporal sequence from exposure (i.e., intervention) to mediator and outcome, and mediator to outcome.

Assumptions #1 and #2 would be satisfied given participants were randomly allocated to interventions tested within the trial. Because we restricted our analyses to those participants who did not receive surgery, there is the risk of selection bias [16–18]. To remove this bias, we used inverse probability weighting in our regression models (details above). Given mediators were not randomized, we considered this path to be potentially confounded. We considered the following variables as confounders and included them as covariates in the regression models: stratification variable (hip or knee condition), age, sex, body mass index, duration of symptoms, quadriceps muscle strength and mental health. We also included in the regression models the baseline measures of putative mediators (i.e., pain beliefs or functional strength) and baseline measures of the outcome measure (i.e., composite WOMAC score) and included those as covariates in the regression models.

We performed mediation analysis using structural equation modelling (SEM) to estimate the average causal mediation effect, average direct effect, average total effect, and proportion mediated [23]. Such analyses were implemented for "inside the table" analyses, in which we compared: usual care vs usual care + manual therapy, usual care vs usual care + exercise therapy, usual care vs usual care + manual and exercise therapy.

We performed mediation analysis by fitting two linear models: the mediator model and the outcome model. The mediator model considered the putative mediator (i.e., pain beliefs or functional strength) as the dependent variable and treatment allocation as the independent variable. The outcome model considered composite WOMAC score at 1-year follow-up as the dependent variable and treatment allocation as the independent variable. We used the *mediate* function (mediation package) [24] to compute the average causal mediation effect, average direct effect, average total effect, and proportion mediated, with bootstrap simulations ($n = 1000$) to compute 95 % confidence intervals [24].

The first regression model included the mediator (i.e., pain beliefs or functional strength) as dependent variable; treatment as the independent variable, and the following variables as covariates: stratification variable (hip or knee condition), age, body mass index, number of years since symptom onset, quadriceps muscle strength and mental health.

The second regression model included the composite WOMAC score at 1-year follow-up as dependent variable, and treatment and the following variables as covariates: stratification variable (hip or knee condition), age, body mass index, number of years since symptom onset, quadriceps muscle strength and mental health.

It is possible that indirect and direct effects are dependent on treatment allocation. For that reason, we included an interaction term (treatment x mediator) in the outcome model. We calculated two separate average causal mediation effects, each conditional on treatment exposure ($x = 1$ and $x = 0$) and their respective marginal effects. This is important as interaction effects can lead to significant bias on indirect and direct estimates of treatment effect [25,26]. We used the function "mediate" in R to estimate the total, direct, indirect effects and the proportion mediated [27].

We performed sensitivity analyses to assess the robustness of our mediation analyses to the no unmeasured confounding assumption [28].

Table 2
Participants' demographics and clinical characteristics.

	Usual care ($n = 51$)	Usual care plus manual therapy ($n = 54$)	Usual care plus exercise therapy ($n = 51$)	Usual care plus combined manual and exercise therapy ($n = 50$)
Demographics				
Age	66.1 (10.4)	66.7 (11.1)	66.3 (7.6)	65.1 (9.3)
Female, *n* (%)	21 (49.0)	20 (47.6)	26 (65.0)	25 (67.5)
Mass (kg)	83.9 (17.9)	83.4 (17.6)	79.8 (16.3)	84.1 (16.8)
Body mass index (kg/m^2)	29.8 (5.6)	29.1 (6.0)	29.3 (6.2)	30.7 (6.0)
Clinical				
WOMAC score (0–240) *(lower scores represent less pain, stiffness and disability)*	86.1 (51.6)	104.0 (56.4)	85.3 (56.0)	95.9 (50.1)
WOMAC pain (0–20)	17.1 (10.8)	22.0 (11.9)	17.2 (11.0)	19.8 (9.7)
WOMAC function (0–68)	60.0 (38.5)	72.2 (41.9)	59.4 (41.3)	65.7 (37.3)
Quadriceps muscle strength (kg/kg body mass)	0.21 (0.11)	0.21 (0.10)	0.21 (0.09)	0.20 (0.08)
Mental health (0 score indicates low risk of depression, 1 and 2 indicating high risk), *n* (% of group)	25 (58.1)	23 (54.7)	22 (55)	22 (59.4)

Given treatment allocation was randomized, we meet the no unmeasured confounding assumption for treatment-mediator or treatment-outcome relationships, but we cannot rule out the possibility of confounding for the mediator-outcome relationship [25,29]. Hence, sensitivity analyses were performed using the *medsens* function (mediation package), for exploring how different levels of unmeasured confounding influence the average causal mediation effect [28].

When conducting the sensitivity analyses, the correlation between the residuals (error terms) from the mediator and outcome models represents the level of confounding due to unknown confounders. This correlation is denoted ρ (rho). If there is no correlation between residuals, then $\rho = 0$ and that can be interpreted as absence of unmeasured confounding. The *medsens* function explores how varying levels of ρ (ranging from -1 and $+1$) impact on the average causal mediation effect (ACME). The output of this function informs how large the unmeasured confounding would need to be to invalidate the estimated ACME.

We used descriptive statistics for summarizing participants' characteristics: with mean and standard deviations used for describing continuous variables, or number and percentage for describing categorical variables. We used R Software [30] for conducting all analyses and set alpha at 0.05.

3. Results

3.1. Sample characteristics

A total of 206 participants were enrolled in the trial, with 193 participants (93.2 %) completing the 1-year follow-up. Participants' demographics are presented in Table 2. Participants' mean age was 66.5 years (SD = 9.5) and mean WOMAC composite score was 101 (SD = 54.2) at baseline. Overall, the sample consisted of middle-aged and overweight adults.

3.2. Mediation analysis

Our findings suggest that: pain belief mediated the effect of manual therapy (b: −10.7, 95 % CI: −22.3 to −0.9) and exercise therapy (b: −14.5 95%CI: −26.0 to −4.4) (Table 3). We did not observe a mediation effect for functional strength, when considering WOMAC composite scores as the outcome (Table 3).

We present findings for exploratory mediation analyses on the secondary outcomes (WOMAC pain or WOMAC function scores) in the supplementary material (Section III).

The sensitivity analyses suggest the estimated mediation effect of those interventions are not robust (supplementary material Section IV). Small violations of the no unmeasured confounding assumption (e.g., $r \geq 0.1$) would change our estimate of mediation effect (supplementary material Section IV). Figures on the supplementary material illustrate how the magnitude of unmeasured confounding impact on the average mediation effect. The solid line represents the estimated indirect effect for the putative mediator as a function of the sensitivity parameter ρ (i.e., the magnitude of confounding between mediator and the outcome). The grey area represents the 95 % confidence interval for the indirect effect at a given value of ρ. The horizontal dashed line represents the point estimate of the indirect effect under the assumption of no unmeasured confounding. We did not observe significant exposure-mediator interactions in mediation for most of analyses performed.

4. Discussion

We explored potential mediators of the effect of manual and exercise therapy in pain and function scores in individuals with hip and/knee osteoarthritis by conducting a secondary analysis of the MOA Trial. We found that pain beliefs may mediate treatment effect of manual therapy and exercise therapy and that functional strength did not mediate the effect of manual therapy, exercise therapy, or manual and exercise therapy combined.

Our findings provide preliminary evidence of mechanisms through which manual therapy, exercise therapy or manual and exercise therapy combined cause improvements in pain or function scores in patients with hip or knee osteoarthritis. In interpreting these findings, the strengths and limitations of our study should be considered. The strengths include: (1) a thorough secondary analyses to explore the mechanisms of action of interventions tested in the MOA trial; (2) we followed best practices for reporting mediation and moderation analyses [31]. The limitations are: (1) none of the analyses performed in our study were planned *a priori*. Hence, we are underpowered for identifying moderate treatment-mediator and mediator-outcome effects; (2) we performed few exploratory analyses, which presents risk of type I error. However, the goal of those exploratory analyses was to identify potential mechanisms of action of interventions tested, to inform independent validation studies and improve the design of future interventions; (3) when estimating the inverse probability weights, we adjusted for variables we considered prognostic factors for adhering to the allocated intervention and not receiving surgery. It is possible that other unmeasured prognostic factors caused patients to undertake surgery. On the other hand, we followed best practices for adjusting for selection bias given the data available. Despite those limitations, our exploratory analyses provide valuable insight into how putative mediators caused changes in clinical outcomes during the MOA trial.

Table 3
Pain beliefs and functional strength as mediators of treatment effect, considering WOMAC composite scores at 1-year follow-up.

Analysis	Total effect estimate	Average direct effect estimate	Indirect effect estimate	Exposure-mediator effect (Path a)	Mediator-outcome effect (Path b)	Proportion mediated (0–1)
WOMAC Composite Score						
Pain belief						
Usual care vs Usual care + Manual Therapy	−24.5 (−43.8 to −3.8)	−14.4 (−31.4 to 2.9)	−10.1 (−22.3 to −0.9)	−4.6 (−8.9 to −0.3)	8 (−26.9 to 42.9)	0.4 (0–1.2)
Usual care vs Usual care + Exercise Therapy	−15.8 (−34.5 to 3.2)	−1.3 (−18.3 to 16.3)	−14.5 (−26 to −4.4)	−6 (−10.1 to −1.9)	−8.4 (−45.1 to 28.3)	0.9 (−2 to 7)
Usual care vs Usual care + Manual and exercise Therapy	−14.7 (−29.1 to 0)	−9.7 (−23.5 to 4.6)	−4.9 (−11.6 to 1.1)	−3.3 (−7.4 to 0.9)	11.9 (−17.6 to 41.5)	0.3 (−0.5 to 1.7)
Functional strength						
Usual care vs Usual care + Manual Therapy	−22 (−40.4 to −2.3)	−21.7 (−39.3 to −3.4)	−0.3 (−6.7 to 5.9)	0.1 (−1 to 1.2)	−11.1 (−53.3 to 31)	0.0 (−0.5 to 0.4)
Usual care vs Usual care + Exercise Therapy	−17.9 (−36.4 to 1)	−15.3 (−33.6 to 3.9)	−2.6 (−8.8 to 1.5)	1.3 (0.1–2.4)	2 (−51.6 to 55.5)	0.1 (−0.2 to 0.9)
Usual care vs Usual care + Manual and Exercise Therapy	−17.5 (−32.5 to −1.9)	−14.3 (−30 to 1.1)	−3.1 (−9.4 to 2)	1.4 (0.5–2.4)	−2.4 (−43.9 to 39.1)	0.2 (−0.2 to 0.9)

From a theoretical point of view, it is reasonable to expect that the trial interventions improve pain or function levels through changes in psychological variables (e.g., improving pain belief or catastrophic thinking). Our findings broadly support this but are exploratory in nature so should be interpreted only as an indication of possible causal relationships between the putative mediators and the WOMAC composite, pain, or function scores in that population. The point estimates for the indirect effect and their respective confidence intervals suggest uncertainties on the mechanism of action of those interventions. In addition, the sensitivity analyses suggest these estimates are not robust. Future confirmatory studies could be designed to assess the mechanisms through which manual therapy and exercise cause improvements in pain and function scores in patients with hip or knee osteoarthritis.

A recent scoping review [32] identified studies that performed mediation analyses in trials with patients with osteoarthritis [6,8,33–37]. Those studies focused on patients with knee osteoarthritis and explored the role of mediators such as body weight, knee muscle strength, and self-efficacy. Findings from that review suggest there is preliminary evidence to support knee muscle strength and self-efficacy as mediators for exercise therapy interventions in this population. Unfortunately, no trials of manual therapy were identified. Our findings do not support self-efficacy to significantly mediate either the exercise or manual therapy interventions tested in the MOA trial. As the original trial was not designed to test mediation effects, this exploratory study is underpowered to detect moderate treatment-mediator and mediator-outcome effects. Most trials report small to moderate treatment effects on outcome measures such as pain and function in patients with hip or knee osteoarthritis; the present results cannot rule out the role of self-efficacy as a mediator of manual or exercise therapy.

Hall et al. [6] found knee extensor muscle strength mediated treatment effect of a strength programme on pain and function scores in patients with knee osteoarthritis. Another trial [38] found that arthritis self-efficacy and perceived pain control mediated the effect of a multifaceted intervention (i.e., cognitive behavioural therapy and focused on physical activity, weight management and cognitive-behaviour pain management strategies) on WOMAC function scores, when compared to usual care [38]. That trial found catastrophizing did not mediate treatment effects [38]. Those previous studies [6,38] did not perform sensitivity analyses for their mediation analyses, which limits our interpretation of and comparisons between their and our findings in regard to how violations to the no unmeasured confounding assumption would influence their mediation effect estimates.

Future studies should be designed and explore whether pain belief and catastrophic thinking mediate the effect of manual therapy, exercise therapy or manual and exercise therapy combined on WOMAC scores. Researchers may use Bayesian networks to explore possible pathways within complex interventions through exploratory-hypothesis lenses [39]. Such pathways can inform the design of future trials that can be designed to assess causal relationships between exposure, putative mediators, and clinical outcomes.

This study explored potential mediators of treatment by conducting a secondary analysis of the MOA trial. Our results suggest pain beliefs may mediate treatment effect of manual therapy or exercise therapy. However, mediation sensitivity analyses suggest those findings are likely to change if even small confounding was present between those mediators and WOMAC composite score.

Author contributions

DCR and JHA were responsible for conceiving this study. JHA provided the dataset from the MOA trial. DCR conducted all analyses. All authors made substantial contributions to analysis and interpretation of data, revising it critically for important intellectual content and approved the version to be submitted for publication.

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Declaration of competing interest

At the end of the text, under a subheading "Conflict of interest statement" all authors must disclose any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and research grants or other funding.

Appendix A. Supplementary data

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