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ORIGINAL RESEARCH

Mechanisms of action of therapeutic exercise for knee and hip OA remain a black box phenomenon: an individual patient data mediation study with the OA Trial Bank

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ABSTRACT

Objectives To evaluate mediating factors for the effect of therapeutic exercise on pain and physical function in people with knee/hip osteoarthritis (OA).

Methods For Subgrouping and TargetEd Exercise pRogrammes for knee and hip OsteoArthritis (STEER OA), individual participant data (IPD) were sought from all published randomised controlled trials (RCTs) comparing therapeutic exercise to non-exercise controls in people with knee/hip OA. Using the Counterfactual framework, the effect of the exercise intervention and the percentage mediated through each potential mediator (muscle strength, proprioception and range of motion (ROM)) for knee OA and muscle strength for hip OA were determined.

Results Data from 12 of 31 RCTs of STEER OA (1407 participants) were available. Within the IPD data sets, there were generally statistically significant effects from therapeutic exercise for pain and physical function in comparison to non-exercise controls. Of all potential mediators, only the change in knee extension strength was statistically and significantly associated with the change in pain in knee OA (β -0.03 (95% CI -0.05 to -0.01), 2.3% mediated) and with physical function in knee OA (β -0.02 (95% CI -0.04 to -0.00), 2.0% mediated) and hip OA (β -0.03 (95% CI -0.07 to -0.00), no mediation).

Conclusions This first IPD mediation analysis of this scale revealed that in people with knee OA, knee extension strength only mediated $\pm 2\%$ of the effect of therapeutic exercise on pain and physical function. ROM and proprioception did not mediate changes in outcomes, nor did knee extension strength in people with hip OA. As 98% of the effectiveness of therapeutic exercise compared with non-exercise controls remains unexplained, more needs to be done to understand the underlying mechanisms of actions.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Therapeutic exercise is consistently recommended for people with knee and/or hip osteoarthritis in all international guidelines. Nevertheless, the mechanisms of action for therapeutic exercise are largely unknown.

WHAT THIS STUDY ADDS

⇒ Despite indirect evidence for a mediating effect through lower limb muscle strength, proprioception and range of motion among people with knee osteoarthritis and through limb muscle strength among people with hip osteoarthritis, the current state-of-the-art mediation analyses on individual participant data from multiple randomised controlled trials showed only a small mediation effect through knee extension strength for therapeutic exercise for people with knee OA.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ A better understanding of the mechanisms of action of therapeutic exercise for people with knee and/or hip osteoarthritis is required, so that future interventions can be designed to better target these mechanisms and potentially improve patients' outcomes.

INTRODUCTION

Worldwide, over 250 million people (5%) suffer from symptomatic osteoarthritis (OA) of the hips and knees.^{1 2} Estimated annual total medical costs per patient are approximately \$8500 to \$10 000 in the US and €1000 to €2000 in Europe.^{3–5} Due to the ageing population and increase in obesity, OA has had one of the largest increases in years lived

with disability at the global population level over the past three decades.⁶

Currently, there is no cure for OA. Treatment is focused on improving physical function and managing pain. In this context, therapeutic exercise (ie, participation in physical activity that is planned, structured, repetitive and purposeful for the improvement or maintenance of OA symptoms, including general aerobic exercise, strengthening, flexibility, balance or body-region-specific exercises^{7,8}) is recommended in all international guidelines.^{9,10} However, randomised controlled trials (RCTs) investigating therapeutic exercise have demonstrated that effect sizes for improvements in pain and physical function are on average small-to-moderate can decline over time, and approximately only 50% of participants with knee OA and 30% of people with hip OA achieve a clinically important treatment response.¹¹⁻¹⁴

Knowledge about which mechanisms explain the effect of therapeutic exercise on pain and physical function in OA could help to better target future exercise programmes and potentially lead to improvements in patient outcomes. A systematic review of possible biomechanical and physiological mechanisms suggested increased muscle strength could be a potential mediator of the treatment effect (ie, pathway through which the treatment affects the outcome) of therapeutic exercise for people with knee OA and hip OA, while improved proprioception and reduction of knee joint extension deficits were suggested as potential mechanisms of therapeutic exercise only for knee OA.¹⁵ Unfortunately, all available studies used simple, unadjusted correlation analyses, inadequate for the investigation of presumed causal pathways.¹⁵ Additionally, meta-analyses at the study level (using aggregated study results) have been prone to aggregation (ecological) bias and study-level confounding, potentially providing misleading estimates of individual-level effects.¹⁶

The optimal meta-analysis approach to examine effects at the individual level is the synthesis of individual participant data (IPD). IPD provides participant-level information about the characteristics and outcomes of each individual, and so it allows the relationship between participant-level factors and outcomes to be modelled directly. Furthermore, compared with a meta-analysis of published results, IPD meta-analysis facilitates standardisation across studies, allows direct derivation of desired information independent of significance or reporting and may provide longer follow-up, more participants and more outcomes than were considered in original publications.^{16,17} Therefore, our objectives were to evaluate the mediating effects of (1) lower limb muscle strength, knee joint proprioception and knee joint range of motion (ROM) among people with knee OA and (2) lower limb muscle strength among those with hip OA.

METHODS

This mediation analysis is reported according to the Guideline for Reporting Mediation Analyses of Randomized Trials and Observational Studies¹⁸ and is part of the Subgrouping and TargetEd Exercise pROgrammes for knee and hip OsteoArthritis (STEER OA) project in collaboration with the OA Trial Bank, for which a detailed protocol has been published.^{8,19} In short, after an updated systematic search of the literature (eight electronic databases, searched up to February 2019) for RCTs comparing therapeutic exercise to a non-exercise control for the outcomes of pain and/or physical function among people with knee and/or hip OA, all leads of eligible RCTs were contacted to request the sharing of IPD. After signing a data sharing agreement, IPD were securely transferred to the STEER OA project team. Next, transferred data were assessed for integrity and published results were reproduced. Discrepancies in results or missing information were discussed and clarified with RCT leads. If discrepancies could not be resolved, the RCT data were disregarded.

RCTs shared as part of the STEER OA project were eligible for the mediation analyses on knee OA if they included IPD of individuals with knee OA and if pre-exercise and postexercise intervention measures of lower limb muscle strength, knee joint proprioception and/or ROM were available. For the mediation analyses on hip OA, RCTs needed to include people with hip OA and preintervention and postintervention measures of lower limb muscle strength.

Changes in self-reported pain and physical function from preintervention to immediately postintervention served as the primary outcomes in the current analyses. If more than one measure of self-reported pain and physical function were included in an RCT, we choose the highest in the hierarchy of outcome measures, as recommended by the Cochrane Musculoskeletal Review Group^{8,20}.

Data management

For each eligible RCT that shared IPD, preintervention and postintervention pain and physical function scores (measure closest to the end of the intervention period) were rescaled to a scale from 0 to 100, where higher scores represented more pain/functional limitations, by dividing the score for each individual by the maximal score of the scale and multiplying it by 100. The rescaled outcome measures were used to calculate the absolute change over the intervention period by deducting the rescaled preintervention scores from the rescaled postintervention scores.

For each RCT, the relative change of each potential mediator was calculated. For this, the absolute change in the mediator was divided over the baseline score and multiplied by 100. When available, the measurement of the mediator prior to the establishment of the outcome measurement was used to calculate its change (because of causality principles). If not available, the change from

baseline to the end of the exercise intervention period was used.

Data analyses

Data were extracted into tables to provide an overview of eligible RCTs, including a short description of exercise intervention group(s), description of control group, number of participants per group, duration of the exercise intervention, timing of the outcome measures and availability, timing and measurement method of all potential mediator variables (lower limb muscle strength, knee joint proprioception and knee joint ROM).

Normal distribution was assessed and confirmed for all mediators and outcome measures. Available IPD were first analysed for each individual mediator separately, for both pain and physical function outcomes. After that, a multimediator model was developed combining all potential mediators for the effect of exercise therapy on pain and physical function among people with knee OA. A multimediator model was not developed for hip OA as only a single potential mediator was evaluated.

Single mediator models

In the presence of a significant intervention effect on pain/physical function beyond a minimal clinical important difference, mediation analyses can provide

insight into the extent to which this effect is explained by changes in the potential mediator. In the absence of such clinically relevant intervention effects on pain/physical function, the evaluation of the intervention effect on changes in the potential mediator may provide insight into the potential reasons for the absence of effect. See [figure 1A](#) for the directed acyclic graph²¹ of the proposed analyses.

The effect of the exercise intervention (a) on the absolute change in outcome (Y) was determined, controlling for the relative change in mediator (m) under investigation and potential mediator-outcome confounders (c), using the ‘counterfactual framework’²²:

$$(1) E[Y|a,m,c] = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 a m + \theta_4 c$$

As only RCTs evaluating therapeutic exercise therapy versus non-exercise controls were included, interaction between the intervention and mediator was ignored. Hence, $\theta_3=0$.

Next, the effect of the exercise intervention on the relative change in the mediator was determined:

$$(2) E[M|a,c] = \beta_0 + \beta_1 a + \beta_2 c$$

A single covariate was added to both regression models to indicate each RCT, to adjust for possible residual confounding by RCT differences. Separate models were run for the outcomes of pain and physical function.

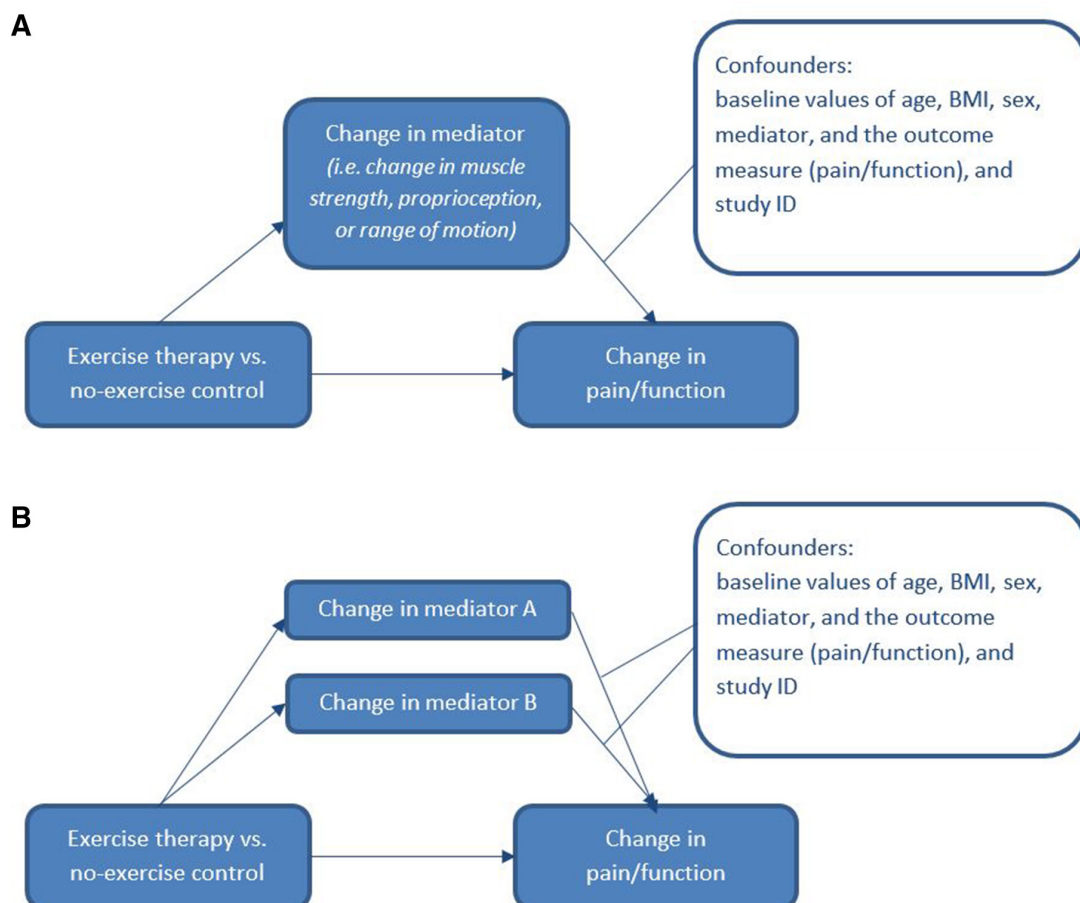


Figure 1 (A) Directed acyclic graph²¹ for the proposed single mediator models. (B) Directed acyclic graph²¹ for the proposed multimediator models. BMI, body mass index.

Potential mediator-outcome confounders were defined as baseline values of age, body mass index (BMI), sex, radiographic OA (Kellgren and Lawrence (KL) grade ≥ 2), the potential mediator, and pain/physical function scores.

Using models defined above, the natural direct effect (NDE) and natural indirect effect (NIE) were defined as:

(3) $NDE = (\theta_1 + \theta_3(\beta_0 + \beta_1 a + \beta_2 c))$; as $\theta_3 = 0$, this becomes:

(4) $NDE = \theta_1$

(5) $NIE = (\theta_2 \beta_1 + \theta_3 \beta_1 a)$; as $\theta_3 = 0$, this becomes: (6) $NIE = \theta_2 \beta_1$

and the total effect (TE) was equal to the sum of NDE and NIE. The percentage mediated was calculated by dividing NIE by TE and then multiplying this by 100%.

Multiple mediator models

Based on the availability within the RCT data obtained, any combination of two or more potential mediators was evaluated (see figure 1B). For each combination of mediators, a linear regression model was calculated for the effect of the exercise intervention and each mediator on the primary outcomes, assuming no interaction between the intervention and the potential mediators:

(7) $E[Y|a, m_i, c] = \theta_0 + \theta_1 a + \theta_2 m_i + \theta_3 c$

As for the single mediator models, all analyses were adjusted for the same potential mediator-outcome confounders and possible residual confounding by RCT differences. All analyses were conducted using IBM SPSS V.25, using $p < 0.05$ to determine statistical significance. Percentages mediated and accompanying CIs were calculated using *mediation* software in R Studio²³ in case of statistically significant exposure-mediator and mediator-outcome associations.

RESULTS

The systematic search of the literature conducted as part of the STEER OA project yielded 91 unique and eligible RCTs that compared therapeutic exercise to non-exercise controls among people with knee and/or hip OA.¹⁹ Of these, usable IPD were obtained from 31 RCTs. Of these, 19 were ineligible as they did not measure any of the selected potential mediators and 12 were eligible for one or more mediation analyses. In summary, eight RCTs included people with knee OA only,^{24–31} one included people with hip OA only³² and three RCTs included people with knee and/or hip OA.^{33–35} One RCT had an exercise intervention duration of 52 weeks, while all other RCTs had interventions lasting between 8 and 20 weeks. Among the RCTs including people with knee OA (1113 individuals from 11 RCTs), all had a measure of lower limb muscle strength, three RCTs had a measure of knee joint proprioception,^{24 27 28} and one RCT measured knee joint ROM.³⁵ Within the RCTs including people with hip OA (294 individuals from four RCTs), all had

a measure of lower limb muscle strength. See table 1 for more details.

Single mediator models

Lower limb muscle strength in knee OA

Only knee extension strength was available in all eligible RCTs and was, therefore, used as the measure of lower limb muscle strength. To minimise heterogeneity between RCTs, where possible, knee extension strength was obtained in Nm/kg or converted to Nm/kg, using strength (Nm) and body weight (kg) measures within the IPD.

Among the eligible RCTs on knee OA that measured knee extension strength, 70% of participants were women, mean age was 66.5 ± 7.7 years, mean BMI was 30.1 ± 5.8 kg/m² and baseline scores of the primary outcomes were 39.5 ± 21.4 for pain (N=1113) and 38.6 ± 22.0 for physical function (N=1062, see table 1), respectively. In 9 out of these 11 trials ($\pm 90\%$ of randomised participants), knee muscle strengthening was part of the intervention protocol. Radiographic OA was not available or missing for 72% of cases and, therefore, omitted as a confounder.

Using the available IPD, there was a statistically significant effect of therapeutic exercise on pain ($\beta -9.0$ (95% CI -10.8 to -7.1)) and physical function ($\beta -6.7$ (95% CI -8.2 to -5.1)) compared with non-exercise controls, as measured directly after the exercise intervention (on a 0–100 scale). There was a statistically significant association between the change in knee extension strength and changes in pain ($\beta -0.03$ (95% CI -0.05 to -0.01)) and physical function ($\beta -0.02$ (95% CI -0.04 to -0.00)). In both models, there was a statistically significant effect of therapeutic exercise on the change in knee extension strength ($\beta 8.0$ (95% CI 2.8 to 13.1) for pain and $\beta 8.0$ (95% CI 2.7 to 13.3) for physical function). The percentages of the effects of therapeutic exercise on pain and physical function mediated through knee extension strength were, however, small, at only 2.3% (95% CI 0.4% to 6.0%) and 2.0% (95% CI 0.0% to 5.0%), respectively.

Proprioception in knee OA

Among the three RCTs that measured knee joint proprioception (N=163), 74% of participants were women, mean age was 65.1 ± 7.9 years, mean BMI was 33.3 ± 7.4 kg/m², 61% of the knees had KL-grade ≥ 2 and baseline scores of the primary outcomes were 52.5 ± 22.8 and 39.7 ± 21.9 for pain and physical function, respectively (see table 1).

There was a statistically significant effect of therapeutic exercise on pain ($\beta -17.3$ (95% CI -23.3 to -11.4)) and physical function ($\beta -14.1$ (95% CI -18.8 to -9.4)) compared with non-exercise controls, as measured directly after the intervention. There was no statistically significant association between the change in knee joint proprioception and changes in pain ($\beta 0.00$ (95% CI -0.06 to 0.06)) or physical function ($\beta -0.01$ (95% CI -0.06 to 0.04)). In both models, there was no statistically significant effect of therapeutic exercise on the change in knee joint proprioception ($\beta 3.4$ (95%

Table 1 Summary table of included RCTs

RCT author	OA joint	Group A	Group B	Intervention duration	Timing pain	Timing function	Muscle strength	Proprioception	Timing ROM	Timing	Confounders
Bennell <i>et al</i> ³⁰	Knee	Hip strengthening (N=45)	No exercise control (N=44)	12 weeks	BL, 3M	BL, 3M	Maximal isometric strength	-	-	BL, 3M	Age, BMI, sex
Cochrane & Davey ³³	Hip and knee	Aquatic lower limb and exercise therapy (N=153)	No exercise control (N=159)	52 weeks	BL, 12M	BL, 12M	Maximal isometric strength	-	-	BL, 12M	Age, BMI, sex
De Rooij <i>et al</i> ²⁴	Knee	Exercise therapy (N=63)	No exercise control (N=63)	20 weeks	BL, 6M	BL, 6M	Mean isokinetic muscle strength	Proprioceptive accuracy	-	BL, 3M	Age, BMI, sex, ROA
Fernandes <i>et al</i> ³²	Hip	Education+exercise (N=55)	Education (N=54)	12 weeks	BL, 3M	BL, 3M	Muscle strength	-	-	BL, 3M	Age, BMI, sex
Hinman <i>et al</i> ³⁴	Hip and knee	Aquatic exercise (N=36)	No exercise control (N=35)	6 weeks	BL, 3M	BL, 3M	Maximal isometric muscle strength	-	-	BL, 6W	Age, BMI, sex
Hopman-Rock <i>et al</i> ³⁵	Hip and knee	Education+exercise (N=60)	No exercise control (N=60)	6 weeks	BL, 3M	BL, 3M	Mean isometric muscle strength	-	Active ROM	BL, 3M	Age, BMI, sex
Hurley <i>et al</i> ²⁵	Knee	UC+exercise (N=278)	UC (N=140)	6 weeks	BL, 3M	BL, 3M	Maximal muscle strength	-	-	BL, 3M	Age, BMI, sex
Lim <i>et al</i> ³¹	Knee	Strength training (N=53)	No exercise control (N=54)	12 weeks	BL, 3M	BL, 3M	Maximal isometric muscle strength	-	-	BL, 3M	Age, BMI, sex, ROA
Munukka <i>et al</i> ²⁶ 2016	Knee	Aquatic resistance training (N=43)	No exercise control (N=44)	16 weeks	BL, 3M	BL, 3M	Isometric muscle strength	-	-	BL, 3M	Age, BMI, sex, ROA
Levinger ²⁷	Knee	UC+exercise therapy (N=20)	No exercise control (N=10)	8 weeks	BL, 3M	BL, 3M	3RM	Proprioception test	-	BL, 3M	Age, BMI, sex

Continued

Table 1 Continued

RCT author	OA joint	Group A	Group B	Intervention duration	Timing pain	Timing function	Muscle strength	Timing Proprioception	Timing ROM	Timing Confounders
Takacs <i>et al</i> ²⁸	Knee	Exercise therapy (N=20)	No exercise control (N=20)	10 weeks	BL, 3M	BL, 3M	Maximal isokinetic muscle strength	Average joint position sense error	BL, 3M	Age, BMI, sex, ROA
Talbot <i>et al</i> ²⁹	Knee	Education+ walking exercise (N=17)	Education (N=17)	12 weeks	BL, 3M	BL, 3M	Maximal isometric muscle strength	BL, 3M	BL, 3M	Age, BMI, sex

Defined as KL-grade ≥ 2 .
BL, baseline; BMI, body mass index; 3M, 3 months; OA, osteoarthritis; RCT, randomised controlled trial; ROA, radiographic OA; ROM, range of motion.

CI -14.8 to 21.6) for pain and β 3.0 (95% CI -15.0 to 20.9) for physical function).

ROM in knee OA

Knee joint ROM was only measured in one eligible RCT that shared their IPD (with N=70 participants). In that RCT, 89% of participants were women, mean age was 65.1 \pm 5.7 years, mean BMI was 27.9 \pm 4.4 kg/m², and baseline scores of the primary outcomes were 46.7 \pm 20.7 and 68.1 \pm 23.7 for pain and physical function, respectively (see table 1). No measure of radiographic knee OA was available in this RCT.

There was no statistically significant effect of therapeutic exercise on pain (β -7.0 (95% CI -14.8 to 0.8)) or physical function (β 4.3 (95% CI -3.1 to 11.6)) compared with non-exercise controls, as measured directly after the intervention. There was no statistically significant association between the change in knee joint ROM and changes in pain (β -0.2 (95% CI -0.9 to 0.6)) or physical function (β -0.2 (95% CI -0.9 to 0.5)). Also, there was no statistically significant effect of therapeutic exercise on the change in knee joint ROM (β 0.7 (95% CI -2.1 to 3.5) for pain and β -1.0 (95% CI -3.9 to 1.9) for physical function).

Multiple mediator model for knee OA

Among all individuals in whom knee extension strength and knee joint proprioception were measured (N=153), 73% were women, mean age was 65.0 \pm 8.0 years, mean BMI was 33.5 \pm 7.4 kg/m², 59% of the knees had KL-grade ≥ 2 and baseline scores of the primary outcomes were 52.6 \pm 22.7 and 39.0 \pm 22.0 for pain and physical function, respectively.

There was a statistically significant effect of therapeutic exercise on pain (β -17.5 (95% CI -23.7 to -11.3)) and physical function (β -15.1 (95% CI -20.5 to -9.7)) compared with non-exercise controls, as measured directly after the intervention. All mediator-outcome and exposure-mediator associations were small and statistically non-significant (see online supplemental appendix table 1).

Lower limb muscle strength in hip OA

Knee extension strength was the only lower limb strength measure available in all four eligible RCTs that included people with hip OA (N=294). In total, 67% of participants were women, mean age was 65.3 \pm 9.0 years, mean BMI was 28.2 \pm 5.3 kg/m² and baseline scores were 39.9 \pm 19.5 for pain and 42.4 \pm 23.0 for physical function (see table 1). Radiographic hip OA scores were unavailable or missing for 72% of cases and, therefore omitted as a confounder.

There was a statistically significant effect of therapeutic exercise on pain (β -4.8 (95% CI -8.0 to -1.6)) and physical function (β -3.1 (95% CI -6.1 to -0.2)) compared with non-exercise controls, as measured directly after the intervention. There was no statistically significant association between the change in knee extension strength and changes in pain (β -0.01 (95% CI -0.04 to 0.03)), but

change in knee extension strength was statistically significantly associated with changes in physical function (β -0.03 (95% CI -0.07 to -0.00)). There was no statistically significant effect of therapeutic exercise on the change in knee extension strength (β -6.4 (95% CI -17.5 to 4.8) for pain and β -5.7 (95% CI -17.1 to 5.7) for physical function).

DISCUSSION

In the first IPD mediation analysis of this scale, we evaluated to what extent the effects of therapeutic exercise on pain and physical function in knee and hip OA, compared with non-exercise controls, were mediated by factors previously identified as potential mediators based on published meta-data. We used IPD from between 1 and 11 RCTs, across 10 mediation analyses and results showed that most potential mediators were not significantly associated with changes in pain and physical function. Only the change in knee extension strength was statistically significantly associated with pain and physical function in knee OA and with physical function in hip OA. Of note, observed mediating effects were small, with a maximal percentage mediated of 2.3% for overall small-to-moderate effects of therapeutic exercise on pain and physical function. Therefore, the main working mechanisms that explain the effects of therapeutic exercise compared with non-exercise controls for OA remain unknown, and the challenge to optimise the effectiveness of exercise by focusing on key underlying mechanisms continues.

Within the available IPD, knee extension muscle strength was by far the most frequently measured potential mediator and has been suggested as an important mediator for the effect of therapeutic exercise.^{36–38} Nevertheless, to our knowledge, only a single RCT has used mediation analyses to evaluate the mediating effects of knee extension muscle strength in therapeutic exercise for knee OA.³⁹ Data from this one RCT showed a significant and large percentage of the effect on pain was mediated (38%) through the change in knee extension muscle strength. However, when these data were combined with 10 other knee OA RCTs in the current IPD analysis, the overall mediating effect of the change in knee extension muscle strength on OA symptoms reduced to only a small effect of 2.0%. Potentially, differences across the RCTs in measurement protocols (eg, isometric vs isokinetic muscle strength testing, differences in knee joint angles during testing, the use of warm-up protocols) and in strength definitions (eg, mean vs maximal strength over several RCTs, three-repetition maximum) introduced heterogeneity in the measurement and, therefore, reduced the association with outcomes. Moreover, poor reporting of measurement properties and procedures in many of the shared RCTs hampered strong conclusions on the role of knee extension muscle strength as a mediator of the effect of therapeutic exercise for knee OA. We were also unable to draw firm conclusions about the

role of lower limb muscle strength for hip OA, but in that case, due to a lack of RCTs.

The absence of a strong mediating effect through gains in knee extension muscle strength was indirectly supported by a recent and large RCT (N=377)⁴⁰; after an 18-month strength training intervention programme for people with knee OA, there were no significant differences in pain and function between the high-intensity strength training group and the attention control group, despite significant differences in quadriceps strength gains between the groups. Also a meta-regression analysis of RCTs concluded that therapeutic exercise would require considerably large gains in muscle strength (30%–40%) for only small benefits in OA symptoms, and, therefore, the authors deemed that a predominant focus on muscle strength as the mechanism through which to obtain improvements in pain and function from exercise therapy is likely ‘inappropriate in clinical practice’.⁴¹

Together with this knowledge, the current results add to the growing debate on the lack of specific effects of exercise therapy for OA and the increasing interest in contextual factors^{42,43}; in the absence of specific effects, it is perhaps unrealistic to find mediating effects of biomechanical and physiological factors. Other mediating factors, potentially related to contextual effects such as psychological or social factors, were not considered in the current analyses. Several previous studies have shown that the effects of therapeutic exercise on pain and physical function are (partly) mediated by factors like pain catastrophising, arthritis-related self-efficacy, fear of movement and pain control cognitions.^{44–49} As education is often part of intervention packages comprising therapeutic exercise, the effect of interventions that target these factors could be of interest for future research.

Our results are consistent with conclusions of previous studies; which all forms of therapeutic exercise, at least those tested in the IPD available for the current analyses, lead to similar effects on OA symptoms.^{11,41} Therefore, other important aspects of therapeutic exercise, such as patients’ preferences,⁵⁰ adherence, patient–clinician therapeutic relationship⁵¹ and availability of resources, may need to be considered when deciding on therapeutic exercise for people with knee or hip OA.^{7,50,52}

Although anti-inflammatory effects were previously not identified as potential mediators of the effect of therapeutic exercise for people with OA,¹⁵ new evidence has emerged since that review. In a diet and exercise programme for people with knee OA who were overweight, changes in inflammatory factors (eg, interleukin-6, TNF- α , CRP) mediated 15% of the effect on pain and 29% of the effect on physical function, largely independent of changes in body weight.⁵³ To date, there is only indirect evidence for a mediating effect through anti-inflammatory effects available in the literature.^{54,55} Further mediation analyses on data from therapeutic exercise RCTs for people with knee OA that also measure inflammatory factors are warranted. Especially since the anti-inflammatory effect of exercise can be

optimised through, for example, choosing concentric over eccentric exercise, increasing the duration of exercise bouts, targeting large muscle groups and aiming for moderate rather than low or high intensities.^{56–58}

The current analyses have strengths and limitations. A major strength was the use of IPD, which greatly increased the potential for combining data from multiple studies and increased statistical power. Moreover, by using mediation analyses, including adjustments for mediator-outcome confounders, the chance of biased outcomes was reduced. Under the assumption that the selected mediator-outcome confounders appropriately represent all outcome and mediator predictors that are differentially distributed across RCTs, current analyses adequately address potential heterogeneity between included RCTs.¹⁷ The lack of a measure for radiographic OA in several RCTs could obviously challenge these assumptions.

Despite representing the most comprehensive pooling of RCT data to date investigating biomechanical and physiological mechanisms of therapeutic exercise for people with OA, only a small percentage of available RCTs shared their IPD and, as highlighted for the entire field of OA research,⁵⁹ RCTs with people with hip OA were underrepresented. Therefore, the size of IPD was limited and close to the required sample size for mediation analyses ($n \approx 74$ to 118 for 80% power and a medium effect size for the exposure-mediator and mediator-outcome associations) for some single mediator models.⁶⁰ Also, we were unable to study some intended combinations of potential mediators. Due to differences in the designs of RCTs that shared their IPD, we had to combine RCTs with varying length of follow-up, a mixture of exercise types, heterogeneous comparator groups and substantial variation in outcome measures and potential mediators. Sensitivity analyses only including RCTs directly targeting the mediator of study were disregarded due to limited statistical power. All but two RCTs evaluated the changes in the potential mediators at the time the outcome measures were assessed, rather than prior to the assessment of the outcome. This violates causality principles and, therefore, allows for potential effects of the changes in the outcome on the mediator, which were not taken into account in current analyses. The differences in study design between the two trials who did assess changes in the mediator prior to the assessment of the outcome^{24 34} hampered sensitivity analyses, including these trials only. Finally, current counterfactual approach only allowed for testing (combinations of) prior hypothesised mediators. Future research should also consider more data-driven modelling approaches for generating new hypothesis on working mechanisms of therapeutic exercise for OA.

In conclusion, increased knee extension strength only mediated approximately 2% of the effect of therapeutic exercise for pain and physical function in knee OA compared with non-exercise controls. We observed no such mediating effect of ROM or proprioception in people with knee OA, nor for knee extension strength in

people with hip OA. As 98% of the effectiveness of therapeutic exercise compared with non-exercise controls remains unexplained, more needs to be done to understand the underlying mechanisms of action of exercise among people with knee and hip OA.

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