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How Do Hip Exercises Improve Pain in Individuals With Patellofemoral Pain? Secondary Mediation Analysis of Strength and Psychological Factors as Mechanisms

Understanding the underlying causal mechanisms that explain how interventions work is a critical step in process evaluation of complex interventions.³⁵ Process evaluation facilitates implementation of effective interventions.¹⁹ Mediation analysis is an approach to studying causal mechanisms. Mediation analysis of randomized clinical trial data can parse a treatment effect into

indirect and direct effects.⁴⁷ The indirect effect of an intervention is the effect on an outcome that is carried through a selected mediator; the direct effect is the remaining effect not explained by the selected mediator. Secondary mediation analyses can extend the value of resource-intensive randomized clinical trials.

Patellofemoral pain is one of the most common knee conditions. It affects 1 in 10 individuals⁴³ and often has a poor long-term prognosis, with a high propensity for long-term pain.^{7,39} Patellofemoral pain is characterized by diffuse pain around the patella that is aggravated by activities that load the patellofemoral joint (eg, squats).⁹ Lower-limb resistance exercises are supported by level I evidence⁴⁶ and recommended in guidelines for clinical practice,^{1,6,49} yet their mechanism of effect is unknown. Whether or not improvements in outcomes are mediated by improved strength (ie, the target of strength/resistance training interventions) or by other mechanisms is unclear. Apart from improving strength, exercise

● **OBJECTIVE:** To determine whether the effect of hip exercise on patellofemoral pain is mediated through changes in hip muscle strength or psychological factors.

● **DESIGN:** Secondary mediation analysis of a randomized clinical trial, in which 218 participants with patellofemoral pain were randomly assigned to receive foot orthoses or hip exercises.

● **METHODS:** Pain (Knee injury and Osteoarthritis Outcome Score pain subscale) and number of pain-free squats at 12 weeks were the outcomes for this mediation analysis, as they are pathogenic of patellofemoral pain. Hip strength dynamometry (abduction, adduction, and external rotation) and psychological characteristics (pain catastrophizing, kinesiophobia, and anxiety) measured at 6 weeks were considered as potential mediators. We used mediation analysis to decompose the total effect of treatment on the outcome

into (1) the “indirect effect” (ie, the portion acting through the mediator) and (2) the “direct effect.”

● **RESULTS:** The effect of hip exercise on pain and squats was not mediated by any of the strength or psychological mediators analyzed. All indirect effects were small and showed wide 95% confidence intervals (CIs) that contained zero (eg, for pain-free squats: abduction strength, -0.13; 95% CI: -0.49, 0.23; Tampa Scale of Kinesiophobia, -0.17; 95% CI: -0.64, 0.30).

● **CONCLUSION:** Hip strength improved after hip exercise, yet strength did not mediate improvements in pain and pain-free squats, and alternative psychological mediators were not implicated. *J Orthop Sports Phys Ther* 2021;51(12):602-610. doi:10.2519/jospt.2021.10674

● **KEY WORDS:** anterior knee pain, causal mechanism, exercise, muscle strength, resistance training

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may exert effects through psychological mediators,^{3,18,36,44} such as improving kinesiophobia,¹⁰ pain catastrophizing, pain self-efficacy, or anxiety.^{29,31}

We recently published the results of a randomized clinical trial that compared foot orthoses to hip exercises in 218 individuals with patellofemoral pain.^{32,33} We collected data on potential mediators, including hip muscle strength, anxiety, kinesiophobia, and pain catastrophizing, at 6 and 12 weeks. The primary hypothesis of this secondary mediation analysis was that hip exercises would improve pain (evaluated by the Knee injury and Osteoarthritis Outcome Score pain subscale [KOOS-P]) and number of pain-free squats performed at 12 weeks by improving hip strength. Our secondary hypothesis was that the effects would possibly also be explained by improvements in psychological factors.

METHODS

THIS IS A SECONDARY ANALYSIS OF data from a randomized clinical trial investigating the effect of hip exercises versus foot orthoses on patellofemoral pain³³ (the Foot Orthoses versus Hip eXercises [FOHX] trial³²). The trial was conducted in Brisbane, Australia and Aalborg, Denmark. The aims of the FOHX trial were to determine (1) whether patients with patellofemoral pain who had greater midfoot width mobility reported better outcomes from foot orthoses compared to hip exercises, and (2) whether hip exercises were superior to foot orthoses, irrespective of foot mobility. The detailed protocol³² and results of the trial are reported elsewhere.³³ This secondary analysis was intended to explore potential mechanisms of the treatment effect and was not prespecified in the protocol. The original study protocol was approved by the University of Queensland Medical Research Ethics Committee (2013000981) and the ethics committee in the North Denmark Region (N-20140022). The reporting of this secondary analysis follows the CON-

SORT checklist⁴¹ and its pain-specific supplement.¹⁷

Participants

Participants were recruited by advertisements and/or referral from health care practitioners. Participants were eligible for inclusion if they (1) were aged 18 to 40 years; (2) reported an insidious onset of anterior, retropatellar, or peripatellar pain of at least 6 weeks' duration that was aggravated by at least 2 of the following activities: climbing or descending stairs, crouching or squatting, running, or prolonged sitting; (3) reported their worst pain over the last 7 days to be 3 or greater on a numeric pain-rating scale (0-10, with 0 representing no pain and 10 representing the worst pain imaginable); (4) had tenderness on palpation of the patellar borders; and (5) had pain reproduced by a step-down or double-leg squat.

Participants were excluded if they reported traumatic onset of symptoms; concomitant injuries to or pain from the hip, lumbar spine, or other knee structures that manifested with similar symptoms; patellar dislocation or instability; previous knee surgery; evidence of knee joint effusion; foot conditions that precluded the use of foot orthoses; using anti-inflammatory drugs or corticosteroid medication; or previous treatment for patellofemoral pain that included foot orthoses or hip exercises. Eligible participants were also required to have a basic understanding of written and spoken English (Brisbane, Australia) or Danish (Aalborg, Denmark).³² All participants gave written informed consent prior to participation.

Randomization

Randomization was stratified by site (Brisbane or Aalborg) and midfoot width mobility. Further details are reported elsewhere.^{32,33}

Interventions

Full details on the interventions can be found in the trial protocol and the main trial publication.^{32,33} Both interventions

were delivered by registered physical therapists.

Foot Orthoses Prescription of foot orthoses followed the protocol outlined in a previous randomized clinical trial.⁵ Physical therapists fitted commercially available prefabricated foot orthoses (Vionic Group LLC, San Rafael, CA) and a pair of orthosis-like contoured sandals.¹³ Participants performed a home exercise program of calf stretches and antipronation foot exercises twice per day, as described in the trial protocol.³² Over 6 weeks, participants attended 6 sessions to fit and revise orthoses and ensure home exercise adherence. No information was given regarding continuing or discontinuing foot orthoses after the 6 sessions.

Hip Exercises The hip exercises replicated those from a previous randomized clinical trial,¹⁶ and their efficacy has been supported in a subsequent trial.^{14,16} Hip exercises were delivered in physical therapist-supervised one-on-one exercise sessions, 3 times per week for 4 weeks (12 sessions total). In the exercise sessions, progressive, resisted hip exercises were performed bilaterally and focused on the hip abductor, external rotator, and hip extensor muscle groups in sidelying, supine, and standing. Resistance for each exercise was delivered via elastic exercise bands, at an intensity that allowed a maximum of 10 repetitions and a perceived exertion rating of 5 to 7 (hard to very hard) out of 10. No instructions were given regarding continuing or discontinuing hip exercises after the 12 sessions.

Baseline Measures

Baseline assessment included demographic and pain characteristics of the participants, as well as baseline evaluation of outcomes, mediators, and potential confounders of the mediator-outcome relationship (outlined below).

Outcome Measures

Our research question related to the mechanisms of interventions on pain in patients with patellofemoral pain. The outcomes selected for this causal medi-

ation analysis were the KOOS-P⁴⁰ and number of pain-free squats, both measured at 12-week follow-up. These outcomes were selected because they are pathognomonic of patellofemoral pain and specific to pain, our domain of interest. This contrasts with the global rating of change that was reported as the primary outcome in the FOHX trial, which is not specific to pain. The KOOS-P and pain-free squats indicated superiority of hip exercise compared to foot orthoses in the trial (coefficient, 4.1; 95% confidence interval [CI]: 0.6, 7.6; $P = .02$ and 2.9; 95% CI: 0.6, 5.1; $P = .01$, respectively).³³

The KOOS-P is a subscale of the KOOS and was administered at baseline and at 6 and 12 weeks.³² The KOOS-P is scored and converted to a 100-point scale, with 0 representing extreme problems and 100 representing no problems. Number of pain-free squats was determined by having participants stand with their feet shoulder-width apart and squat until they could touch both lateral malleoli with their fingers. Participants performed squats in time with a metronome set to 96 beats per minute, squatting down in 2 beats and standing in 2 beats. Participants continued until the onset of symptoms, the worsening of symptoms, or until they reached 25 repetitions without pain. The outcome assessor was blinded to treatment allocation.

Mediators

TABLE 1 outlines the selected mediators and theoretical rationale underpinning our selection of potentially relevant mediators. These mediators were selected prior to undertaking the analysis. All mediators were measured at baseline and at 6 weeks and are described below.

Hip Strength at 6 Weeks (Hip Abductors, Adductors, and External Rotators) Hip strength was measured by a maximal voluntary isometric contraction (MVIC) measured with a handheld dynamometer (Lafayette Instrument Company, Lafayette, IN). For each strength test, participants completed 2 practice contractions at approximately 50% MVIC and 100%

MVIC, followed by 3 test MVICs. For the tests, participants were instructed to hold the MVIC for 5 seconds, with a 30-second rest between each attempt. For the hip abductor and adductor tests, participants were lying in supine, with the dynamometer placed 5 cm proximal to the lateral or medial malleolus, respectively. Participants' test legs were extended in 0° of abduction and 0° of flexion. Hip external rotation was measured in supine, with the dynamometer 5 cm proximal to the medial malleolus and participants' hips in 30° of flexion. The dynamometer was stabilized by a rigid belt for hip abduction and adduction, and by a solid bracket for hip external rotation (see protocol³²). The maximum force output during each contraction was multiplied by the lever arm to give peak torque and was normalized to body mass (Newtons per kilogram). The lever arm for hip abduction and adduction was measured as the distance from the anterior superior iliac spine to 5 cm proximal to the lateral or medial malleolus, respectively. Limb length for hip external rotation was measured as the distance from the medial joint line to 5 cm proximal to the medial malleolus.

Psychological Characteristics at 6 Weeks As part of the test battery completed by participants at each time point, pain catastrophizing was measured using the Pain Catastrophizing Scale,⁴⁵ kinesiophobia via the Tampa Scale of Kinesiophobia,³⁴ and anxiety via the Hospital Anxiety and Depression Scale anxiety subscale.^{2,4}

Potential Confounders

Selection of potential confounders of the relationship between mediators and outcomes was based on theoretical causal relationships with the mediator and outcome. Pain duration was a pretreatment confounder. Baseline levels of the mediator and the outcome, as well as the stratifying variables of midfoot width mobility and site, were also included to further adjust for confounding of the mediator-outcome relationship.

Time Points and End Points

All variables (outcomes and mediators) were measured at baseline and at 6 and 12 weeks. The mediators used for this mediation analysis were the data collected at 6 weeks, while the outcomes were from the 12-week follow-up. Six weeks was the intermediate time point for the mediators, due to the assumptions of temporal precedence for the mediators (ie, changes in mediators occur prior to changes in outcomes).

Statistical Analysis

All analyses were conducted in Stata Version 15 (StataCorp LLC, College Station, TX). Differences in potential mediators between randomized treatment groups

TABLE 1

DESCRIPTION OF SELECTED MEDIATORS, MEASUREMENTS, AND THEORETICAL RATIONALES

Construct/Measure	Theoretical Rationale
Strength	
Isometric abduction, adduction, and external rotation	Hip exercise increases hip strength, but it is unclear whether this improvement drives the effect of hip exercise on clinical outcomes
Psychological characteristics	
Hospital Anxiety and Depression Scale anxiety subscale	Anxiety decreases with treatment. Decreased anxiety is associated with decreased knee pain severity and knee-related disability ⁴⁰
Pain Catastrophizing Scale	Catastrophizing is associated with increased pain severity and increased knee-related disability. ⁴¹ Decreased catastrophizing could positively influence pain and disability
Tampa Scale of Kinesiophobia	Increased kinesiophobia is associated with increased disability. ^{42,43} Exposure to exercise may positively challenge maladaptive beliefs/associations

were first investigated by fitting a linear regression model for each mediator, including terms for randomized treatment group, the baseline value of the mediator, and the stratifying variables of site and midfoot width mobility. The mediation analysis was conducted using the “paramed” command in Stata,¹² which decomposes the total effect of the randomized treatment group on the outcome by fitting 2 linear regression models: one for the mediator and the other for the outcome. The model for the mediator at week 6 adjusted for baseline levels of the mediator and the outcome, treatment group, and stratifying variables. The model for the outcome adjusted for baseline levels of the mediator and the outcome, the value of the mediator recorded at week 6, randomized treatment group, pain duration, and stratifying variables.

The total effect of the treatment on the outcome is decomposed into an “indirect effect” that changes the outcome by first changing the mediator and a “direct effect” that describes the change in the outcome that is not brought about by a change in the mediator⁴⁷ (ie, total effect

= direct effect + indirect effect). Similarly, the indirect effect can then be quantified as the difference between the total effect and the direct effect (ie, indirect effect = total effect – direct effect) (FIGURE). Separate models were run for each mediator. The assumptions of linearity, normality, and homoscedasticity of residuals were assessed graphically and found to be valid for linear regression models for each outcome, adjusting for each mediator separately. We also estimated the proportion of the effect mediated, using the “mediation” package in Stata.²³ This proportion was only calculated in those situations where the indirect effect and total effect had the same sign.²⁴

The validity of 4 assumptions is required to obtain unbiased estimates of the indirect and direct effects. The first 2 of these are that all confounders of the relationship between the treatment group and the outcome and all confounders of the relationship between the treatment group and the mediator are included in the regression models. The third assumption is that all confounders of the mediator-outcome relationship are adjusted for. The fourth is that there are no effects

of treatment that confound the mediator-outcome relationship. The first 2 of these assumptions are satisfied by the random allocation of participants to treatment groups. That is, if successful, randomization produces treatment groups that are comparable with respect to both known and unknown confounders. As treatment allocation is the exposure, this means that potential confounding of the exposure-outcome and exposure-mediator relationships would be minimal. The second 2 assumptions cannot be verified statistically. We conducted sensitivity analyses to examine the robustness of unmeasured confounding. Sensitivity analyses were conducted using the “medsens” user-written Stata command.^{23,25}

RESULTS

OF THE 220 PARTICIPANTS RECRUITED and enrolled into the study between June 2014 and April 2017, 218 participants were randomized and included in the original trial (2 were excluded due to errors with randomization). Of these, 109 were randomized to wear foot orthoses and 109 were randomized to perform hip exercises (baseline characteristics are shown in TABLE 2; the inclusion flow chart is shown in the supplemental file, available at www.jospt.org). The participants allocated to hip exercises attended, on average, 10.1 of 12 (84%; range, 1-12) of their sessions; those allocated to foot orthoses attended, on average, 5.5 of 6 (92%; range, 1-6) of their sessions and reported that they wore their foot orthoses for 74% of waking hours.

Mediation Analyses

The means and standard deviations of the potential mediators at baseline and week 6 by treatment group are displayed in the supplemental file. TABLE 3 displays the effect of the independent variable on potential mediators. Path A indicates the effect of the independent variable on potential mediators. Path B indicates the effect of mediators on outcomes (KOOS-P and number of pain-free squats). Paths A and B represent indirect effects. Path C indicates the direct effect of the randomized treatment on outcomes. Abbreviation: KOOS-P, Knee injury and Osteoarthritis Outcome Score pain subscale.

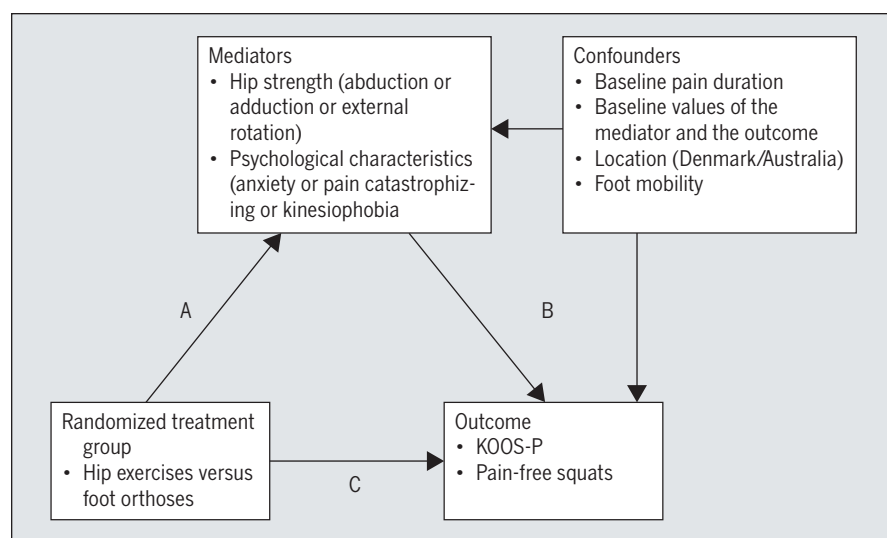


FIGURE. Model for the mediation analysis. This model was used to analyze potential mediation of the relationship between randomized treatment group (hip exercises versus foot orthoses) and outcomes (KOOS-P or number of pain-free squats) by selected mediator variables (hip strength or psychological characteristics). Path A indicates the effect of the independent variable on potential mediators. Path B indicates the effect of mediators on outcomes (KOOS-P and number of pain-free squats). Paths A and B represent indirect effects. Path C indicates the direct effect of the randomized treatment on outcomes. Abbreviation: KOOS-P, Knee injury and Osteoarthritis Outcome Score pain subscale.

anxiety subscale score and external rotation strength, there did not appear to be evidence for a difference between groups with respect to other potential mediators. Nevertheless, we considered all potential mediators for the full mediation analysis. **TABLE 4** demonstrates the effect of mediators on outcomes (path B).

Indirect, direct, and total effects, adjusted for trial site, foot mobility (the original trial's primary aim), and symptom duration, are presented in **TABLE 5**. There was evidence of a difference in KOOS-P score and pain-free squats between the hip exercise and foot orthosis groups. There did not appear to be evidence of the mediation of the effects (indirect effects) by any of the potential mediators considered.

Sensitivity Analyses

The results of the sensitivity analysis for the KOOS-P indicated that the indirect effects of the treatment that acted through the Hospital Anxiety and Depression Scale anxiety subscale and through external hip rotation strength were sensitive to the degree of residual confounding. This means that relatively small amounts of residual confounding may lead to indications of indirect effects on the KOOS-P (supplemental file). The sensitivity analysis for pain-free squats indicated that the indirect treatment effect on the Hospital Anxiety and Depression Scale anxiety subscale and on external hip rotation strength was also sensitive to the degree of residual confounding (supplemental file).

DISCUSSION

PREVIOUS STUDIES DEMONSTRATED the efficacy of hip exercises on pain and clinical outcomes. Our secondary mediation analysis of the FOHX trial data formally assesses some of the plausible mechanisms of the treatment effect of hip exercises. We found no evidence that changes in hip strength, anxiety, kinesiophobia, or pain catastrophizing mediated the effect of hip exercises on

pain and number of pain-free squats in patients with patellofemoral pain. Therefore, we question prevailing assumptions regarding the mechanisms underpinning how hip exercises help in managing patellofemoral pain.

How Do Hip Exercises Affect Outcomes in People With Patellofemoral Pain?

Clinicians recommend hip muscle strength exercises for patients who have patellofemoral pain because people with patellofemoral pain have weak hip muscles.³⁸ Despite prospective studies showing that weakness of the hips is a result of patellofemoral pain and not a risk factor,^{15,38} hip muscle-strengthening exercises are advocated in guidelines for managing patellofemoral pain.¹⁶ The rationale was that exercise strengthens weakened muscles, which influences pa-

tellofemoral stress and thus pain. This has never been tested, nor have nonspecific mechanisms been identified.

We did not find any mediating effect of hip strength. One reason for this may be the effect of hip exercises on strength. Treatment effects on hip strength were not large, and only hip external rotation had relatively narrow CIs that did not contain the null value (zero). The magnitude of these improvements in hip strength was similar to that of such improvements in a previous study using the same hip-strengthening protocol.¹⁶ None of the strength mediators were associated with outcomes. Hypothetically, strengthening interventions may exert their effect either through other measures of muscle performance or through nonspecific contextual effects. Exercises might influence pain-induced muscle inhibition, as seen

TABLE 2

BASILINE CHARACTERISTICS FOR THE HIP EXERCISE AND FOOT ORTHOSIS GROUPS^a

	Hip Exercises	Foot Orthoses
Age, y	28.3 ± 6.0	27.9 ± 6.0
Body mass index, kg/m ²	25.5 ± 4.9	24.7 ± 4.8
Sex (women), n (%)	70 (64.2)	81 (74.3)
Participants with bilateral symptoms, n (%)	69 (63.3)	77 (70.6)
Pain duration, mo	52.3 ± 61.9	55.4 ± 60.8

^aValues are mean ± SD unless otherwise indicated.

TABLE 3

PATH A: EFFECT OF RANDOMIZED TREATMENT GROUP ON POTENTIAL MEDIATORS AT 6 WEEKS^a

Potential Mediator	n ^b	Foot Orthosis – Hip Exercise	
		Mean Difference ^c	P Value
Abduction strength, Nm/kg	189	-0.04 (-0.10, 0.01)	.15
Adduction strength, Nm/kg	189	-0.04 (-0.10, 0.02)	.20
External rotation strength, Nm/kg	188	-0.04 (-0.07, -0.02)	<.01
HADS anxiety subscale	191	-0.88 (-1.55, -0.21)	.01
Pain Catastrophizing Scale	191	0.47 (-1.44, 2.38)	.63
Tampa Scale of Kinesiophobia	192	0.77 (-0.74, 2.28)	.32

Abbreviation: HADS, Hospital Anxiety and Depression Scale.

^aAdjusted for the baseline measure of the potential mediator and for the stratifying variables of site and midfoot width mobility.

^bThe sample size indicates the number of participants who had complete data for the mediator and all other variables included in the models.

^cValues in parentheses are 95% confidence interval.

in individuals with anterior knee pain,²² or influence lower-limb kinematics/kinetics and patellofemoral joint stress²² as a mechanism of action. These possible mechanisms of effect (and others) requires systematic evaluation in future research.

Improvements in isometric knee extension strength mediated improvements in pain and symptoms (versus a no-intervention control) in patients who had knee osteoarthritis.^{21,28} Does the mechanism of effect of exercise differ under different musculoskeletal conditions or with differences in genesis and pathophysiology? Larger treatment effects on strength in the osteoarthritis study are likely related to comparison with a no-intervention control rather than with another intervention, rather than with another intervention, which was the case in our trial. These findings also reiterate the importance of understanding the causal mechanisms of how an intervention works, in addition to estimating its treatment effects in randomized parallel-group study designs.¹⁹ Understanding how interventions work is key to delivering effective interventions, achieving successful outcomes, and implementing research into clinical practice.⁸

Is There Potential for Psychological Mediators of the Effect of Hip Exercises?

In addition to improving the force-generating capacity of muscles, resistance exercises are associated with psychological benefits.^{3,18,36,44} Individuals with patellofemoral pain have higher levels of anxiety, kinesiophobia, and pain catastrophizing^{29,31} than individuals who do not have patellofemoral pain, which is important for treating patellofemoral pain.^{10,26,29,30,37,42} Our mediation analysis did not detect any mediation of these psychological features. We hypothesized that exposure to exercise in a safe environment would influence these characteristics and may explain some of the benefits of exercise. This was not the case: there was little impact of hip exercises relative to the foot orthosis intervention on any of the psychological characteristics.

Estimates of path B (FIGURE) indicated that both pain catastrophizing and kinesiophobia at 6 weeks were associated with outcomes at 12 weeks (TABLE 4). It is tempting to speculate that interventions specifically targeting these characteristics may have more potential, but this requires investigation due to the potential for type I error. Taking a broader perspective on persistent pain, pain catastrophizing and kinesiophobia are components of the fear-avoidance model of persistent pain,⁴⁸ and have been implicated in the causal effects of treatments for persistent low back pain.^{20,27}

Strengths and Weaknesses

The FOHX trial was designed to evaluate hip exercises versus foot orthoses for patellofemoral pain, with midfoot width mobility as an effect modifier. The strengths were that the trial (1) randomly assigned participants to interventions, (2) had high adherence to exercise (and foot orthoses), and (3) collected the potential mediators at an intermediate time

point before the end point of interest. It is possible that further changes in the mediators could have occurred prior to outcome measurement.

Our mediation analysis is an exploratory analysis designed to generate new hypotheses about mechanisms, and we were limited by the data collected in the original trial. We did not assess some of the other plausible mediators (eg, lower-limb kinematics, muscle function other than strength/force output, patellofemoral joint stress, pain self-efficacy, or psychophysical pain assessment). Some of the selected measures may not be ideal for capturing the selected constructs (eg, strength was measured isometrically rather than dynamically, and the psychological questionnaires were not developed specifically for this population). Thus, we caution against categorically ruling out hip strength or the psychological factors that we studied as potential mechanisms.

Our results are sensitive to the degree of residual confounding. Better control

TABLE 4

PATH B: EFFECT OF MEDIATORS ON OUTCOMES, FROM LINEAR REGRESSION MODELS^a

Outcome/Mediator	n ^b	Coefficient ^c	P Value
KOOS pain subscale			
HADS anxiety subscale	179	-0.60 (-1.43, 0.23)	.16
Pain Catastrophizing Scale	180	-0.73 (-1.00, -0.46)	<.01
Tampa Scale of Kinesiophobia	179	-0.77 (-1.11, -0.42)	<.01
Abduction strength ^d	177	2.71 (-7.35, 12.77)	.60
Adduction strength ^d	177	2.93 (-6.43, 12.29)	.54
External rotation strength ^d	175	2.70 (-20.15, 25.55)	.82
Pain-free squats			
HADS anxiety subscale	165	-0.47 (-0.99, 0.05)	.08
Pain Catastrophizing Scale	166	-0.11 (-0.29, 0.07)	.22
Tampa Scale of Kinesiophobia	165	-0.25 (-0.48, -0.02)	.03
Abduction strength ^d	167	3.20 (-2.80, 9.21)	.30
Adduction strength ^d	167	4.02 (-1.33, 9.36)	.14
External rotation strength ^d	165	9.47 (-3.90, 22.84)	.16

Abbreviations: HADS, Hospital Anxiety and Depression Scale; KOOS, Knee injury and Osteoarthritis Outcome Score.

^aAdjusted for baseline levels of the outcome and potential mediator, the stratifying variables of site and midfoot width mobility, and duration of symptoms.

^bThe sample size indicates the number of participants who had complete data for the outcome, mediator, and all other variables included in the models.

^cValues in parentheses are 95% confidence interval.

^dStudy knee, normalized.

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for the confounding of the mediator-outcome relationship might have provided stronger estimates of indirect effects. For example, other psychological characteristics such as self-efficacy or treatment expectations could be considered as potential unmeasured confounders. We had a high response rate at follow-ups. However, given our completed case analysis, the small amount of missing data could potentially have influenced the results. This is the first study to use a mediation analysis in an attempt to elucidate mechanisms of an exercise treatment effect in patellofemoral pain—there is a need for a priori studies designed to further evaluate potential mechanisms.

CONCLUSION

THE EFFECT OF HIP-STRENGTHENING exercises compared to that of foot orthoses on pain or pain-related

function in patients with patellofemoral pain was not mediated by changes in isometric hip strength, pain catastrophizing, anxiety, or kinesiophobia. ●

KEY POINTS

FINDINGS: The effect of hip strengthening on improvements in pain and number of pain-free squats in patients with patellofemoral pain was not mediated by increased hip strength. Psychological mediators such as kinesiophobia, pain catastrophizing, and anxiety were not implicated in the causal pathway.

IMPLICATIONS: Clinicians may wish to reconsider targeting improvements in hip strength as the main way to improve outcomes for patients with patellofemoral pain.

CAUTION: This trial was not designed to evaluate all potential mediators, and we were limited to the data available. We did not capture all theoretically plausi-

ble mediators in the domains of strength and psychological factors.

ACKNOWLEDGMENTS: *We would like to thank all the participants who volunteered for this research as well as the physical therapists who delivered the interventions.*

STUDY DETAILS

AUTHOR CONTRIBUTIONS: The data used in this secondary analysis were originally collected as part of the FOHX trial by Drs Matthews, Vicenzino, and Rathleff. All authors contributed to the concept and design of this secondary mediation analysis. Drs Holden, Rathleff, Matthews, and Vicenzino developed the initial theoretical framework, including selection of relevant mediators (and their theoretical mechanism), potential confounders, and outcomes of interest, on which Dr Kasza provided critical intellectual input. Dr Kasza conducted the

TABLE 5

TOTAL, DIRECT, AND INDIRECT EFFECT ESTIMATES OF RANDOMIZED TREATMENT GROUP ON THE OUTCOMES, WITH BOOTSTRAPPED STANDARD ERRORS^a

Outcome/Mediator	Total Effect		Direct Effect		Indirect Effect		Proportion of Effect Mediated ^{b,c}
	Effect ^b	P Value	Effect ^b	P Value	Effect ^b	P Value	
KOOS pain subscale							
Abduction strength (n = 187)	-5.00 (-8.69, -1.31)	.008	-4.89 (-8.58, -1.20)	.009	-0.11 (-0.52, 0.30)	.61	0.02 (0.01, 0.07)
Adduction strength (n = 187)	-4.99 (-8.82, -1.16)	.011	-4.87 (-8.71, -1.03)	.013	-0.12 (-0.54, 0.30)	.57	0.02 (0.01, 0.08)
External rotation strength (n = 185)	-4.92 (-8.81, -1.02)	.013	-4.80 (-8.76, -0.85)	.017	-0.11 (-1.11, 0.89)	.83	0.02 (0.01, 0.09)
HADS anxiety subscale (n = 189)	-4.07 (-7.95, -0.20)	.039	-4.55 (-8.28, -0.82)	.017	0.48 (-0.42, 1.37)	.29	NA ^d
PCS (n = 189)	-4.06 (-7.74, -0.38)	.031	-3.69 (-7.21, -0.17)	.040	-0.37 (-1.86, 1.13)	.63	0.08 (0.04, 0.43)
TSK (n = 189)	-4.49 (-8.33, -0.64)	.022	-3.88 (-7.57, -0.18)	.040	-0.61 (-1.92, 0.70)	.36	0.14 (0.07, 0.75)
Pain-free squats							
Abduction strength (n = 188)	-2.39 (-4.60, -0.18)	.034	-2.26 (-4.48, -0.04)	.046	-0.13 (-0.49, 0.23)	.48	0.05 (0.02, 0.28)
Adduction strength (n = 188)	-2.50 (-4.82, -0.17)	.035	-2.33 (-4.66, 0.01)	.051	-0.17 (-0.54, 0.20)	.37	0.06 (0.03, 0.38)
External rotation strength (n = 186)	-2.66 (-5.01, -0.30)	.027	-2.26 (-4.68, 0.16)	.067	-0.39 (-0.96, 0.17)	.17	0.13 (0.07, 0.73)
HADS anxiety subscale (n = 190)	-3.28 (-5.72, -0.84)	.008	-3.68 (-6.15, -1.20)	.004	0.39 (-0.32, 1.11)	.28	NA ^d
PCS (n = 190)	-3.14 (-5.39, -0.90)	.006	-3.09 (-5.34, -0.83)	.007	-0.06 (-0.36, 0.25)	.72	0.01 (0.01, 0.04)
TSK (n = 190)	-3.17 (-5.44, -0.90)	.006	-3.00 (-5.25, -0.75)	.009	-0.17 (-0.64, 0.30)	.49	0.04 (0.02, 0.15)

Abbreviations: HADS, Hospital Anxiety and Depression Scale; KOOS, Knee injury and Osteoarthritis Outcome Score; NA, not applicable; PCS, Pain Catastrophizing Scale; TSK, Tampa Scale of Kinesiophobia.

^aAll models include the baseline levels of the outcome and potential mediator, the stratifying variables of site and midfoot width mobility, and duration of symptoms.

^bValues in parentheses are 95% confidence interval.

^cThe proportion of the effect mediated was calculated using the “mediation” Stata package, while the direct and indirect effects are calculated using the “paramed” command. The supplemental file includes all results from the “mediation” Stata package.

^dThe proportion of the effect mediated is only calculated when the total and indirect effects have the same sign. Therefore, this was not calculated for the HADS anxiety subscale mediator.

statistical analysis. All authors provided feedback and gave important intellectual input to the draft manuscript written by Dr Holden. All authors agreed to publish the final manuscript.

DATA SHARING: Data are available on reasonable request to the corresponding author.

PATIENT AND PUBLIC INVOLVEMENT: Patients were not involved in this secondary mediation analysis.

REFERENCES

- Barton CJ, Lack S, Hemmings S, Tufail S, Morrissey D. The 'Best Practice Guide to Conservative Management of Patellofemoral Pain': incorporating level 1 evidence with expert clinical reasoning. *Br J Sports Med.* 2015;49:923-934. <https://doi.org/10.1136/bjsports-2014-093637>
- Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale: an updated literature review. *J Psychosom Res.* 2002;52:69-77. [https://doi.org/10.1016/s0022-3999\(01\)00296-3](https://doi.org/10.1016/s0022-3999(01)00296-3)
- Cavarretta DJ, Hall EE, Bixby WR. The acute effects of resistance exercise on affect, anxiety, and mood – practical implications for designing resistance training programs. *Int Rev Sport Exerc Psychol.* 2019;12:295-324. <https://doi.org/10.1080/1750984X.2018.1474941>
- Chan YF, Leung DY, Fong DY, Leung CM, Lee AM. Psychometric evaluation of the Hospital Anxiety and Depression Scale in a large community sample of adolescents in Hong Kong. *Qual Life Res.* 2010;19:865-873. <https://doi.org/10.1007/s11136-010-9645-1>
- Collins N, Crossley K, Beller E, Darnell R, McPoil T, Vicenzino B. Foot orthoses and physiotherapy in the treatment of patellofemoral pain syndrome: randomised clinical trial. *BMJ.* 2008;337:a1735. <https://doi.org/10.1136/bmj.a1735>
- Collins NJ, Barton CJ, van Middelkoop M, et al. 2018 consensus statement on exercise therapy and physical interventions (orthoses, taping and manual therapy) to treat patellofemoral pain: recommendations from the 5th International Patellofemoral Pain Research Retreat, Gold Coast, Australia, 2017. *Br J Sports Med.* 2018;52:1170-1178. <https://doi.org/10.1136/bjsports-2018-099397>
- Collins NJ, Bierma-Zeinstra SM, Crossley KM, van Linschoten RL, Vicenzino B, van Middelkoop M. Prognostic factors for patellofemoral pain: a multicentre observational analysis. *Br J Sports Med.* 2013;47:227-233. <https://doi.org/10.1136/bjsports-2012-091696>
- Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ.* 2008;337:a1655. <https://doi.org/10.1136/bmj.a1655>
- Crossley KM, Stefanik JJ, Selfe J, et al. 2016 patellofemoral pain consensus statement from the 4th International Patellofemoral Pain Research Retreat, Manchester. Part 1: terminology, definitions, clinical examination, natural history, patellofemoral osteoarthritis and patient-reported outcome measures. *Br J Sports Med.* 2016;50:839-843. <https://doi.org/10.1136/bjsports-2016-096384>
- Doménech J, Sanchis-Alfonso V, Espejo B. Changes in catastrophizing and kinesiophobia are predictive of changes in disability and pain after treatment in patients with anterior knee pain. *Knee Surg Sports Traumatol Arthrosc.* 2014;22:2295-2300. <https://doi.org/10.1007/s00167-014-2968-7>
- Doménech J, Sanchis-Alfonso V, López L, Espejo B. Influence of kinesiophobia and catastrophizing on pain and disability in anterior knee pain patients. *Knee Surg Sports Traumatol Arthrosc.* 2013;21:1562-1568. <https://doi.org/10.1007/s00167-012-2238-5>
- Emsley R, Liu H. PARAMED: Stata module to perform causal mediation analysis using parametric regression models. Available at: <https://ideas.repec.org/c/boc/bocode/s457581.html>. Accessed November 8, 2021.
- Escalona-Marfil C, McPoil TG, Mellor R, Vicenzino B. A radiographic and anthropometric study of the effect of a contoured sandal and foot orthosis on supporting the medial longitudinal arch. *J Foot Ankle Res.* 2014;7:38. <https://doi.org/10.1186/s13047-014-0038-5>
- Ferber R, Bolgia L, Earl-Boehm JE, Emery C, Hamstra-Wright K. Strengthening of the hip and core versus knee muscles for the treatment of patellofemoral pain: a multicenter randomized controlled trial. *J Athl Train.* 2015;50:366-377. <https://doi.org/10.4085/1062-6050-49.3.70>
- Finnoff JT, Hall MM, Kyle K, Krause DA, Lai J, Smith J. Hip strength and knee pain in high school runners: a prospective study. *PM R.* 2011;3:792-801. <https://doi.org/10.1016/j.pmrj.2011.04.007>
- Fukuda TY, Melo WP, Zaffalon BM, et al. Hip posterolateral musculature strengthening in sedentary women with patellofemoral pain syndrome: a randomized controlled clinical trial with 1-year follow-up. *J Orthop Sports Phys Ther.* 2012;42:823-830. <https://doi.org/10.2519/jospt.2012.4184>
- Gewandter JS, Eisenach JC, Gross RA, et al. Checklist for the preparation and review of pain clinical trial publications: a pain-specific supplement to CONSORT. *Pain Rep.* 2019;4:e621. <https://doi.org/10.1097/PR9.0000000000000621>
- Gordon BR, McDowell CP, Hallgren M, Meyer JD, Lyons M, Herring MP. Association of efficacy of resistance exercise training with depressive symptoms: meta-analysis and meta-regression analysis of randomized clinical trials. *JAMA Psychiatry.* 2018;75:566-576. <https://doi.org/10.1001/jamapsychiatry.2018.0572>
- Gottfredson DC, Cook TD, Gardner FE, et al. Standards of evidence for efficacy, effectiveness, and scale-up research in prevention science: next generation. *Prev Sci.* 2015;16:893-926. <https://doi.org/10.1007/s1121-015-0555-x>
- Hall AM, Kamper SJ, Emsley R, Maher CG. Does pain-catastrophising mediate the effect of tai chi on treatment outcomes for people with low back pain? *Complement Ther Med.* 2016;25:61-66. <https://doi.org/10.1016/j.ctim.2015.12.013>
- Hall M, Hinman RS, Wrigley TV, Kasza J, Lim BW, Bennell KL. Knee extensor strength gains mediate symptom improvement in knee osteoarthritis: secondary analysis of a randomised controlled trial. *Osteoarthritis Cartilage.* 2018;26:495-500. <https://doi.org/10.1016/j.joca.2018.01.018>
- Hart JM, Pietrosimone B, Hertel J, Ingersoll CD. Quadriceps activation following knee injuries: a systematic review. *J Athl Train.* 2010;45:87-97. <https://doi.org/10.4085/1062-6050-45.1.87>
- Hicks R, Tingley D. Causal mediation analysis. *Stata J.* 2011;11:605-619.
- Imai K, Keele L, Tingley D. A general approach to causal mediation analysis. *Psychol Methods.* 2010;15:309-334. <https://doi.org/10.1037/a0020761>
- Imai K, Keele L, Yamamoto T. Identification, inference and sensitivity analysis for causal mediation effects. *Stat Sci.* 2010;25:51-71. <https://doi.org/10.1214/10-STS321>
- Jensen R, Hystad T, Baerheim A. Knee function and pain related to psychological variables in patients with long-term patellofemoral pain syndrome. *J Orthop Sports Phys Ther.* 2005;35:594-600. <https://doi.org/10.2519/jospt.2005.35.9.594>
- Lee H, Mansell G, McAuley JH, et al. Causal mechanisms in the clinical course and treatment of back pain. *Best Pract Res Clin Rheumatol.* 2016;30:1074-1083. <https://doi.org/10.1016/j.berh.2017.04.001>
- Lim BW, Hinman RS, Wrigley TV, Sharma L, Bennell KL. Does knee malalignment mediate the effects of quadriceps strengthening on knee adduction moment, pain, and function in medial knee osteoarthritis? A randomized controlled trial. *Arthritis Rheum.* 2008;59:943-951. <https://doi.org/10.1002/art.23823>
- Maclachlan LR, Collins NJ, Hodges PW, Vicenzino B. Psychological and pain profiles in persons with patellofemoral pain as the primary symptom. *Eur J Pain.* 2020;24:1182-1196. <https://doi.org/10.1002/ejp.1563>
- Maclachlan LR, Collins NJ, Matthews MLG, Hodges PW, Vicenzino B. The psychological features of patellofemoral pain: a systematic review. *Br J Sports Med.* 2017;51:732-742. <https://doi.org/10.1136/bjsports-2016-096705>
- Maclachlan LR, Matthews M, Hodges PW, Collins NJ, Vicenzino B. The psychological features of patellofemoral pain: a cross-sectional study.

Scand J Pain. 2018;18:261-271. <https://doi.org/10.1515/sjpain-2018-0025>

32. Matthews M, Rathleff MS, Claus A, et al. The Foot Orthoses versus Hip eXercises (FOHX) trial for patellofemoral pain: a protocol for a randomized clinical trial to determine if foot mobility is associated with better outcomes from foot orthoses. *J Foot Ankle Res.* 2017;10:5. <https://doi.org/10.1186/s13047-017-0186-5>
33. Matthews M, Rathleff MS, Claus A, et al. Does foot mobility affect the outcome in the management of patellofemoral pain with foot orthoses versus hip exercises? A randomised clinical trial. *Br J Sports Med.* 2020;54:1416-1422. <https://doi.org/10.1136/bjsports-2019-100935>
34. Miller RP, Kori SH, Todd DD. The Tampa scale: a measure of kinesiophobia [abstract]. *Clin J Pain.* 1991;7:51.
35. Moore GF, Audrey S, Barker M, et al. Process evaluation of complex interventions: Medical Research Council guidance. *BMJ.* 2015;350:h1258. <https://doi.org/10.1136/bmj.h1258>
36. O'Connor PJ, Herring MP, Carvalho A. Mental health benefits of strength training in adults. *Am J Lifestyle Med.* 2010;4:377-396. <https://doi.org/10.1177/1559827610368771>
37. Priore LB, Azevedo FM, Pazzinatto MF, et al. Influence of kinesiophobia and pain catastrophism on objective function in women with patellofemoral pain. *Phys Ther Sport.* 2019;35:116-121. <https://doi.org/10.1016/j.ptsp.2018.11.013>
38. Rathleff MS, Rathleff CR, Crossley KM, Barton CJ. Is hip strength a risk factor for patellofemoral pain? A systematic review and meta-analysis. *Br J Sports Med.* 2014;48:1088. <https://doi.org/10.1136/bjsports-2013-093305>
39. Rathleff MS, Rathleff CR, Olesen JL, Rasmussen S, Roos EM. Is knee pain during adolescence a self-limiting condition? Prognosis of patellofemoral pain and other types of knee pain. *Am J Sports Med.* 2016;44:1165-1171. <https://doi.org/10.1177/0363546515622456>
40. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)—development of a self-administered outcome measure. *J Orthop Sports Phys Ther.* 1998;28:88-96. <https://doi.org/10.2519/jospt.1998.28.2.88>
41. Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med.* 2010;152:726-732. <https://doi.org/10.7326/0003-4819-152-11-201006010-00232>
42. Smith BE, Moffatt F, Hendrick P, et al. The experience of living with patellofemoral pain—loss, confusion and fear-avoidance: a UK qualitative study. *BMJ Open.* 2018;8:e018624. <https://doi.org/10.1136/bmjopen-2017-018624>
43. Smith BE, Selve J, Thacker D, et al. Incidence and prevalence of patellofemoral pain: a systematic review and meta-analysis. *PLoS One.* 2018;13:e0190892. <https://doi.org/10.1371/journal.pone.0190892>
44. Strickland JC, Smith MA. The anxiolytic effects of resistance exercise. *Front Psychol.* 2014;5:753. <https://doi.org/10.3389/fpsyg.2014.00753>
45. Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: development and validation. *Psychol Assess.* 1995;7:524-532. <https://doi.org/10.1037/1040-3590.7.4.524>
46. van der Heijden RA, Lankhorst NE, van Linschoten R, Bierma-Zeinstra SM, van Middelkoop M. Exercise for treating patellofemoral pain syndrome. *Cochrane Database Syst Rev.* 2015;1:CD010387. <https://doi.org/10.1002/14651858.CD010387.pub2>
47. VanderWeele TJ. Mediation analysis: a practitioner's guide. *Annu Rev Public Health.* 2016;37:17-32. <https://doi.org/10.1146/annurev-publhealth-032315-021402>
48. Vlaeyen JWS, Linton SJ. Fear-avoidance model of chronic musculoskeletal pain: 12 years on. *Pain.* 2012;153:1144-1147. <https://doi.org/10.1016/j.pain.2011.12.009>
49. Willy RW, Högund LT, Barton CJ, et al. Patellofemoral pain. *J Orthop Sports Phys Ther.* 2019;49:CPG1-CPG95. <https://doi.org/10.2519/jospt.2019.0302>



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