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# Do physical or imaging changes explain the effectiveness of progressive tendon loading exercises? A causal mediation analysis of athletes with patellar tendinopathy

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ABSTRACT

*Objectives:* To investigate whether the effectiveness of progressive tendon loading exercises (PTLE) on patellar tendinopathy is mediated through changes in physical or imaging properties.
*Design:* Mediation analyses based on a randomized clinical trial (n = 76) in patellar tendinopathy comparing PTLE with eccentric exercise therapy (EET).
*Methods:* Pain-related disability on Victorian Institute of Sports Assessment-Patella (VISA-P, 0 to 100) and pain (Visual Analogue Score) after single-leg decline squat (VAS-SLDS, 0 to 10) at 24 weeks were outcome measures. Selected mediators, including the physical (quadriceps muscle strength, ankle dorsiflexion range, jumping performance) and imaging domains (ultrasonographic tendon thickness and degree of neovascularization), were measured at 12 weeks. Directed acyclic graphs were performed to identify critical confounders. Causal mediation analysis was used to estimate natural indirect, natural direct and total effects by a simulation approach under the counterfactual framework.
*Results:* Complete data from 61 of 76 participants were included. There was no evidence showing that the beneficial effect of PTLE on VISA-P or VAS-SLDS outcomes was mediated by changes in any of the selected physical or imaging variables. The indirect effects for all mediators were unsubstantial (estimates ranging from −1.63 to 1.53 on VISA-P and −0.20 to 0.19 on VAS-SLDS), with all 95 % confidence intervals containing zero.
*Conclusions:* The beneficial effect of PTLE on patellar tendinopathy was not mediated by changes in physical properties, tendon thickness or degree of neovascularization. Healthcare professionals may consider exploring other potential factors when managing patients with patellar tendinopathy, but further large-scale research is needed to confirm these results and to identify alternative treatment targets.


## Practical implications

- The beneficial effect of PTLE over EET in pain is not mediated through the intermediate change in quadriceps muscle strength, ankle dorsiflexion range of motion, jumping performance, ultrasonographic tendon thickness and degree of neovascularization.
- The beneficial effect of PTLE over EET in pain-related disability is not mediated through the intermediate change in quadriceps muscle strength, ankle dorsiflexion range of motion, jumping performance, ultrasonographic tendon thickness and degree of neovascularization.
- We suggest that healthcare professionals should not rely on these physical and imaging factors as targets when managing patients with patellar tendinopathy.

## 1. Introduction

Patellar tendinopathy (PT) is a highly prevalent injury in jumping athletes,[1] leading to longstanding pain, decreased work productivity, and impaired sports performance.[2] Therapeutic exercises remain the cornerstone treatment for PT.[3,4] We recently found that a 4-stage progressive

*Abbreviations:* PTLE, progressive tendon loading exercises; EET, eccentric exercise therapy; PT, patellar tendinopathy; VISA-P, Victorian Institute of Sports Assessment-Patella; VAS-SLDS, pain after single-leg decline squat; DAGs, directed acyclic graphs; TE, total effect; NDE, natural direct effect; NIE, natural indirect effect.

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tendon loading exercise therapy (PTLE) over 24 weeks leads to more improved symptom severity when compared to eccentric exercise therapy (EET).[5]

Causal mediation analyses can offer a robust methodological framework to elucidate how an intervention works by identifying potential targets or mediators for an intervention that could affect the outcome.[6,7] Applying this approach for our trial can help advance theoretical understanding and optimize PTLE to improve effectiveness. PTLE, which incorporates isometric, isotonic, energy storage and sport-specific exercises, was designed to gradually load the patellar tendon, theoretically allowing tendons to increase tolerance to load.[8] However, it still needs to be determined whether the effects of this treatment are mediated by the improvement in physical properties (e.g., muscle strength). Additionally, from a clinical perspective, structural normalization, such as reduction in tendon thickening[9] and intratendinous neovascularization,[10] is thought to be one of the main reasons for the effectiveness of exercise therapy. Nevertheless, evidence on this underlying mechanism by which the PTLE may exert its effects also remains scarce.

This study aimed to determine whether the effects of PTLE compared to EET on disability and pain at 24 weeks were mediated by changes in physical or ultrasound-based imaging properties at 12 weeks. We hypothesized that PTLE effects may be mediated through changes in quadriceps muscle strength, ankle dorsiflexion range, jumping performance, tendon thickness, and degree of neovascularization.

## 2. Methods

### 2.1. Design and participants

This mediation analysis is reported following the AGReMA Statement,[7] and is a secondary analysis from a previous published randomized control trial (JUMPER study) comparing the effectiveness between PTLE and EET in athletes with PT.[5] This RCT showed that PTLE resulted in a significantly larger improvement in disability over 24 weeks when compared to EET.[5] From January 2017 to July 2019, participants were eligible if they were aged between 18 and 35 years, participated in sports at least three times a week, and reported <80 of 100 points of the Victorian Institute of Sports Assessment-Patella (VISA-P) questionnaire. The diagnosis of PT was established based on clinical examination by a sports physician, and was confirmed on ultrasound performed by a radiologist. Further details on diagnostic criteria, inclusion and exclusion criteria have been reported elsewhere.[5] This trial was designed (ClinicalTrials.gov; NCT02938143) and conducted at Erasmus MC University Medical Center. The institutional review board approved the study (MEC-2016-500), and all participants provided written informed consent.

### 2.2. Interventions

#### 2.2.1. PTLE

The program of PTLE incorporated isometric, isotonic, energy storage, and sport-specific exercises, monitored by regular assessment of pain response (Visual Analogue Score, VAS) after single-leg decline squat test (VAS-SLDS ≤3 points on a scale of 0 to 10). Participants initially performed daily single-leg isometric exercises in 60° knee flexion. A 70 % maximal voluntary contraction load (5 repetitions of a 45-second hold) was recommended. As pain permitted, single-leg isotonic loading was performed every second day, initially within 10 to 60° of knee flexion and progressed to full knee extension, resistance corresponding from 15 repetitions maximum (RM) to 6 RM. Energy-storage loading and sport-specific exercises were progressed and customized according to the individual's sport among our study population, mainly focusing on jumping and landing training.

#### 2.2.2. EET

The control group comprised patients undergoing the EET program, and this program consisted of 2 stages: a pain-provoking single-leg squat on a decline board with a 25° slope (VAS ≥ 5/10) and sport-specific exercises.

These two unsupervised exercise therapies were delivered over 24 weeks. Details about the exercise protocols, education, and load management advice can be found in the previously published work.[5]

### 2.3. Measurements

#### 2.3.1. Outcome measures

The outcomes of interest in this mediation analysis were pain-related disability assessed with the VISA-P questionnaire (0 to 100 points) and pain intensity after single-leg decline squat, rated on a VAS (VAS-SLDS) at 24 weeks. These outcome measures are in line with the core domains for tendinopathy.[11]

#### 2.3.2. Proposed mediators

Potential mediators were collected at baseline and at 12 weeks after randomization. We pre-specified mediators using scientific evidence and clinical-perspective knowledge to avoid data dredging. The following mediators were selected: maximal isometric quadriceps muscle strength (N/kg); active ankle dorsiflexion range (degrees); jumping performance (cm); ultrasonographic tendon thickness (mm) and tendon neovascularization (low/high) using power Doppler. Details of measurement for each mediator can be found in Table 1 and Appendix A.

#### 2.3.3. Confounders

It is reasonable to assume that no confounders between exposure (intervention)-mediator and intervention-outcome effects were present due to the randomization process.[6,7] For mediator-outcome effects, we composed directed acyclic graphs (DAGs) to identify potential confounders (Appendix A). This was modified based on previous literature[12] and peer feedback. Based on these DAGs, we utilized the online tool 'DAGitty' (https://dagitty.net/) to identify the minimal set of confounders that should be adjusted for the mediator-outcome relationship, which included age, sex, physical activity level, as well as respective baseline values for the mediators studied (Fig. 1).

### 2.4. Statistical analysis

We conducted causal mediation analyses using the simulation-based approach under the counterfactual framework.[6] All analyses were conducted using R studio version 2023.12.0 with 'mediation' package. All codes relevant to this study can be found in the Appendix B Complete case analyses (participants with complete data on outcomes, mediators and confounders) were conducted.

In the primary assessment, we evaluated the strength of selected mediators for each outcome (VISA-P score and VAS-SLDS at 24 weeks), using single mediator models (Fig. 1). For each model, we fitted two regression models: linear regression was used for the models on the outcomes, adjusted for treatment group, mediator at 12 weeks, and set of confounders mentioned above. The mediator model for neovascularization was logistic, while the models for physical variables and tendon thickness were linear. All models were adjusted for the treatment group and baseline mediator values. Assumptions for linear regression models (homogeneity of variance, normality of residuals and linearity) were checked using graphic methods. Linearity was not checked in the logistic regression analysis because there were no quantitative predictors. We assumed no interaction term between the exposure and mediator.

For each model, we estimated total effect (TE), natural direct effect (NDE), natural indirect effect (NIE), and proportion of effect mediated. The TE is the average effect of treatment on the outcome; the NIE is the average effect of treatment on the outcome through the selected mediating path. The NDE is the average effect of treatment on the outcome through other pathways. The proportion mediated is the ratio of

**Table 1**
The description of the rationale and measurement for mediators within assumed causal relationships.

| Mediators | Rationale | Measurement[a] |
|---|---|---|
| Knee muscle strength | Individuals with patellar tendinopathy have significantly lower isometric and concentric knee extensor strength than those with asymptomatic controls.[25] PTLE was targeted to improve knee muscle strength by gradually increasing the load on the patellar tendon over time, allowing the tendon to adapt in response to the increasing demands. Together, this could improve the load tolerance assessed by VAS-SLDS. Increased knee function can also contribute to an improved VISA-P score. | Isometric quadriceps muscle strength by a handheld dynamometer. |
| Ankle dorsiflexion range | Lower ankle dorsiflexion during landing has been found to be associated with patellar tendinopathy.[26] The PTLE protocol was developed to augment the capacity for active ankle dorsiflexion range of motion during jump-landing maneuvers, such as drop landings, with the goal of enhancing athletic performance, which could improve load tolerance. Furthermore, the ability to optimize ankle movement could be important for lower limb control, which could positively influence perceived symptoms and function. | The ankle dorsiflexion range (or flexibility of the soleus muscle) was tested by using a weight-bearing dorsiflexion lunge test. |
| Jumping performance | PTLE, especially its energy-storage stage, aimed to increase jumping performance through gradual jumping training. This is likely to improve patients' performance. In addition, improved jumping ability is highly associated with increased load tolerance,[8] which may also affect the overall knee symptoms and function. | Vertical jump height was measured in centimeters using a digital vertical jump meter. |
| Tendon thickness | Increased tendon thickness or thickening is a morphological feature of patellar tendinopathy. This alteration may be predictive of symptom development[27] and could potentially be associated with less favorable outcomes by conservative treatment[28] in patellar tendinopathy. A reduction in thickness after a 12-week heavy slow resistance training has been observed.[9] This adaption seems to be correlated with positive treatment outcomes in patellar tendinopathy.[9,29] We hypothesized that decreased thickness in response to PTLE may partially explain the improvement in clinical outcomes. | The patellar tendon anteroposterior (AP) thickness was measured in the transverse plane at the thickest point within 1 cm distal to the inferior pole of the patella, using a built-in software involving caliper. |
| Degree of neovascularization | Increased Doppler flow (frequently referred to as 'neovascularization') is a common ultrasonographic finding in tendinopathy. The vascular theory suggested that increased blood flow within the tendon may be associated with the persistence of symptoms in tendinopathy.[30] Research has shown that, after a heavy slow resistance in patellar tendinopathy, there are an improved VISA-P score and pain, and a concomitant reduction in neovascularization.[9] Based on this, we speculated that PTLE would induce a reduction in neovascularization that could partially explain the improvement in clinical outcomes. | Power Doppler was assessed by the modified Ohberg score (MOS), ranging from 0 to 4+ (0 = no vessels; 1+ = one vessel posterior to the patella tendon; 2+ to 4+ = 1, 2, 3, 4 or more vessels throughout the tendon). We dichotomized this data into "no to low Doppler flow" (from 0 to 2+) and "moderate to high Doppler flow (from 3+ to 4+)". |

Abbreviations: PTLE, progressive tendon loading exercises; EET, eccentric exercise therapy; VISA-P, Victorian Institute of Sports Assessment-Patella (VISA-P).
[a] Other details in each measurement are reported in the Appendix A.

NIE to TE. 95 % confidence intervals for these causal effects were generated by bootstrapped samples with 2000 simulations.

We conducted 2 sensitivity analyses:

1. Strong assumptions are required to obtain valid estimated NIE and NDE. Specifically, there are no unmeasured confounders in exposure–mediator, exposure–outcome, and mediator–outcome relationships[6,7] in mediation analyses. Thus, we employed the mediational E-value[13] to assess the robustness of these observed effects to potential unmeasured confounding. A large E-value suggests that only strong unmeasured confounding could nullify the observed association, while a small E-value indicates that even weak confounding could do so. Details in calculations can be found in Appendix A.
2. To assess the robustness of the influence of the missing data, we reanalyzed the data using 20 imputed datasets by multiple

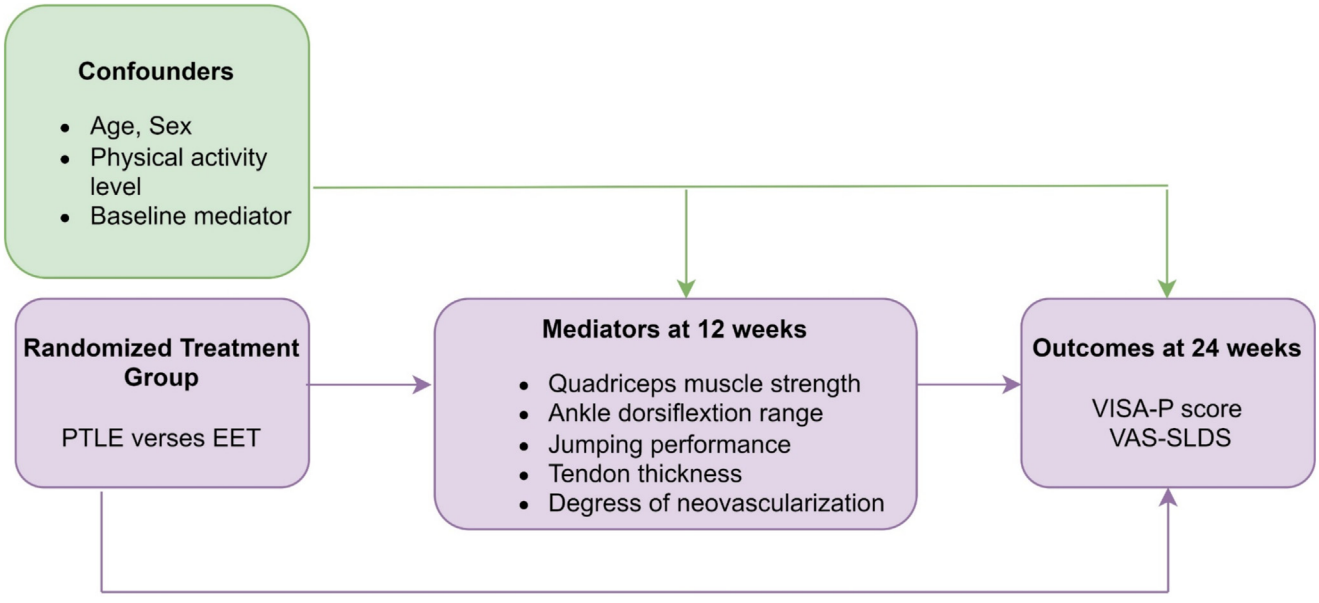


**Fig. 1.** Single mediator model for VISA-P score and VAS-SLDS at 24 weeks. Confounders (age, sex, physical activity level, mediator at baseline) which could distort the mediator–outcome relationship were adjusted. Abbreviations: VISA-P, Victorian Institute of Sports Assessment-Patella (VISA-P); VAS-SLDS, Visual Analogue Score after single-leg decline squat.

**Table 2**
The description of baseline characteristics for included and original datasets.[a]

| Baseline characteristics | Included dataset (n = 61) | Original dataset (n = 76) |
|---|---|---|
| Age, y | 24 (4) | 25 (4) |
| Male, n (%) | 44 (72) | 58 (76) |
| BMI, kg/m$^2$ | 24.1 (3.0) | 23.9 (2.9) |
| Physical activity[b], n (%) | | |
| Level 1: 4 to 7 d/wk | 13 (21) | 17 (22) |
| Level 2: 1 to 3 d/wk | 48 (79) | 59 (78) |
| Symptom duration, wk | 104 [52 to 260] | 104 [49 to 208] |
| VAS-SLDS (0 to 10 points) | 5 (2) | 5 (2) |
| VISA-P score (0 to 100 points) | 55 (13) | 55 (13) |
| Treatment group, n (%) | | |
| PTLE | 34 (56) | 38 (50) |
| EET | 27 (44) | 38 (50) |
| EQ-5D-3L index[c] | 0.84 [0.80 to 0.84] | 0.84 [0.81 to 0.84] |
| Quadriceps muscle strength, N/kg | 4.6 (1.0) | 4.7 (1.0) |
| Active ankle dorsiflexion range, (°) | 42 (6) | 41 (7) |
| Jumping performance, cm | 49 (10) | 50 (10) |
| Tendon AP thickness, mm | 8.2 (2.2) | 8.4 (2.3) |
| Neovascularization[d], n (%) | | |
| No to low Doppler flow | 21 (34) | 25 (33) |
| Moderate to high Doppler flow | 40 (66) | 51 (67) |

Abbreviations: BMI, body mass index; VAS-SLDS, Visual Analog Scale after single-leg decline squat test; VISA-P, Victorian Institute of Sports Assessment-Patella; PTLE, progressive tendon loading exercises; EET, eccentric exercise therapy; EQ-5D-3L, a standardized measure of health status developed by the EuroQol Group with three-level version; AP, anterior–posterior; wk, weeks.

[a] Values are mean (SD) if continuous data with normal distribution; otherwise, for continuous data with non-normal distribution, median [interquartile range, IQR] is used.

[b] Physical activity is semi-quantified by Cincinnati Sports Activity Scale (CSAS).[31]

[c] EQ-5D-3L index is calculated using a set of weights on Dutch population.[32] Values are anchored at 1 (full health) and 0 (a state as bad as being dead).

[d] No to low Doppler flow: from score 0 to score 2+, using modified Ohberg score [MOS]. Moderate to high Doppler flow: from score 3+ to score 4+.

imputation given that the missing mechanism is missing at random (MAR). For the imputation model, we included confounders described above as well as auxiliary variables (baseline BMI, quality of life [the EuroQol Group with three-level index, EQ-5D-3L index], VAS-SLDS and VISA-P score at 12 weeks). We applied the simulation approach for each imputed dataset to compute NIE and NDE, and subsequently combined them to obtain pooled point estimates and confidence intervals (CIs).

We had planned to apply multiple mediator models, but due to the absence of significant mediators in the single mediator models, this approach was not performed.

## 3. Results

Of the enrolled 76 participants in the original RCT, 9 (12 %) were lost to follow-up at 24 weeks; 1 in the PTLE group and 8 in the EET group. Most of the participants (n = 61, 80 %) were included in the mediation analysis, contributing complete data on the treatment, mediator, outcome and confounders. The baseline characteristics for included and original participants can be found in Table 2.

The percentages of missing values per variable during follow-up were reported (Appendix A).

### 3.1. Mediation analysis

Table 3 displays the indirect, direct, and total effects for selected mediators on VISA-P score and VAS-SLDS at 24 weeks. Compared with EET, PTLE showed a superior mean improvement in VISA-P and reduction in VAS-SLDS at 24 weeks, which was supported by statistically significant NDE and TE. However, the selected mediators did not account for these beneficial outcomes, as indicated by the negligible indirect effects.

### 3.2. Sensitivity analysis

Estimates of NDE and TE exhibited moderate robustness to unmeasured confounding in the exposure–outcome association, with E-values ranging from 2.74 to 3.75 for all estimates. The estimates of NIE were found to be robust to unmeasured confounding, with non-null E-values ranging from 1.24 to 1.93. Details of interpretation for these E-values can be found in Appendix A.

Fig. 2 presents the sensitivity analysis comparing datasets with complete cases to dataset with imputation. The magnitude of NDE in the imputed dataset was slightly smaller than that in the complete-case dataset. However, the positive effects on VISA-P score and VAS-SLDS at 24 weeks were still not mediated through these selected mediators in the imputed dataset. This implied our findings performed robustness to missing data.

## 4. Discussion

This study is the first to use causal mediation analysis to investigate the potential underlying mechanisms behind the beneficial effect of PTLE in improving patellar tendinopathy. We aimed to examine whether the improvement in clinical outcomes at 24 weeks after PTLE compared with EET was through the change in physical and ultrasound-based imaging properties at 12 weeks. Our findings do not

**Table 3**
Estimates of total, natural direct and indirect effects of treatment on VISA-P score and VAS-SLDS at 24 weeks for 5 potential mediators at 12 weeks.[a]

| | TE | | NDE | | NIE | | Proportion mediated (95 % CI) |
|---|---|---|---|---|---|---|---|
| | Effect (95 % CI) | p value | Effect (95 % CI) | p value | Effect (95 % CI) | p value | |
| VISA-P score (0 to 100 points) | | | | | | | |
| Quadriceps muscle strength | 11.75 (3.54 to 20.47) | 0.005 | 11.18 (0.97 to 22.22) | 0.032 | 0.57 (−4.45 to 4.84) | 0.796 | 0.05 (−0.38 to 0.76) |
| Ankle dorsiflexion angle | 12.14 (4.12 to 21.38) | 0.004 | 12.30 (4.23 to 21.75) | 0.004 | −0.16 (−2.29 to 1.14) | 0.797 | NA[b] |
| Jumping performance | 13.31 (5.04 to 21.93) | 0.002 | 11.78 (3.83 to 20.43) | 0.008 | 1.53 (−0.23 to 4.39) | 0.100 | 0.12 (−0.02 to 0.39) |
| Patellar tendon thickness | 12.30 (3.77 to 21.45) | 0.002 | 12.82 (3.83 to 21.89) | 0.005 | −0.52 (−2.98 to 1.23) | 0.599 | NA[b] |
| Degree of neovascularization[c] | 11.96 (3.98 to 22.19) | 0.004 | 13.59 (3.67 to 23.32) | 0.007 | −1.63 (−4.18 to 1.48) | 0.455 | NA[b] |
| VAS-SLDS (0 to 10 points) | | | | | | | |
| Quadriceps muscle strength | −1.28 (−2.39 to −0.27) | 0.018 | −1.27 (−2.53 to −0.08) | 0.034 | −0.01 (−0.59 to 0.56) | 0.955 | 0.01 (−0.66 to 0.72) |
| Ankle dorsiflexion angle | −1.35 (−2.41 to −0.31) | 0.013 | −1.42 (−2.49 to −0.40) | 0.070 | 0.07 (−0.16 to 0.44) | 0.611 | NA[b] |
| Jumping performance | −1.36 (−2.44 to −0.35) | 0.010 | −1.17 (−2.30 to −0.11) | 0.033 | −0.20 (−0.51 to 0.05) | 0.108 | 0.14 (−0.05 to 0.68) |
| Patellar tendon thickness | −1.19 (−2.24 to −0.15) | 0.024 | −1.24 (−2.33 to −0.12) | 0.027 | 0.05 (−0.15 to 0.30) | 0.705 | NA[b] |
| Degree of neovascularization[c] | −1.14 (−2.38 to −0.11) | 0.031 | −1.33 (−2.52 to −0.11) | 0.031 | 0.19 (−0.28 to 0.49) | 0.565 | NA[b] |

Abbreviations: TE, total effect; NDE, natural direct effect; NIE, natural indirect effect; VISA-P, Victorian Institute of Sports Assessment-Patella (VISA-P); VAS-SLDS, Visual Analogue Score after single-leg decline; NA, not applicable.

[a] The point estimates and uncertainty estimates were measured as mean differences and 95 % confidence intervals (CIs) with bootstrap samples. We used seed (set.seed) before running the mediation analysis to make results reproducible during simulation approach.

[b] The proportion mediated is only calculated when the TE and NIE have the same sign.

[c] The effect is denoted as log odds using logistic regression.

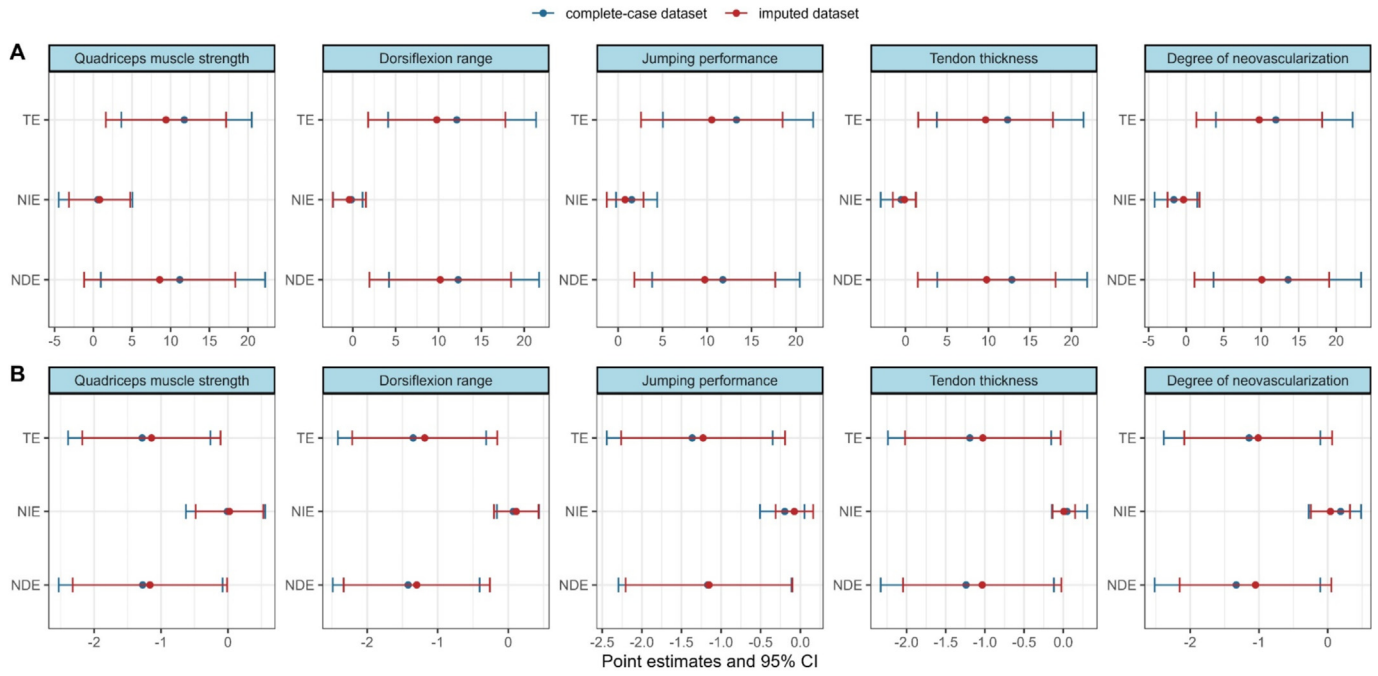


**Fig. 2.** Panels A and B show sensitivity analysis for causal effects on 24-week VISA-P, and VAS-SLDS respectively, comparing complete-case dataset (n = 61) with imputed datasets (n = 76). Dots represent point estimates. I bars indicate 95 % confidence intervals by bootstrapped samples.

support our hypothesis that the improvement in disability and pain following PTLE is mediated through changes in quadriceps muscle strength, ankle dorsiflexion range, jumping performance, tendon thickness, or degree of neovascularization.

To date, PTLE shows promise as the initial conservative treatment for PT.[5] It is critical to understand how this intervention exerts its effect, which can advance and refine the theory to improve the effectiveness in clinical practice. Identifying mediators by conducting a mediation analysis from a trial is particularly relevant to answering this question.[6]

### 4.1. Physical mediators

Physical properties remain pivotal in understanding the response to exercise treatment in musculoskeletal conditions.[14,15] Previous mediation analyses were performed in an exercise-based trial for gluteal tendinopathy,[14] and patellofemoral pain.[15] Align with our findings, these authors also reported that improvements in pain and function, or the global rate of change were not explained by changes in muscle strength or joint movement. There is one study[16] suggesting that muscle strength acts as a weak mediating effect in knee osteoarthritis following exercise treatment, with around 2 % of the effect mediated. Caution should be taken when comparing these results, considering that variables (intervention, mediator, and outcome) were diverse across these studies.

One possibility for the absence of a mediating effect is that both exercise therapies were performed in a home-based and unsupervised way, which may have led to less significant changes in these selected physical variables at 12 weeks between PTLE and EET (Appendix A). Another explanation could be that, compared to these easy-to-perform measurement, there are other physical variables that might be more sensitive and better at explaining changes in pain and function following PTLE. Several studies have reported altered muscle activation resulting from changes in the neuromuscular pathways in PT.[17,18] A study with a small sample size indicated that immediate isometric contraction could reduce pain in patients with PT, parallel with a reduction in cortical inhibition.[17] These findings may provide new insight into neurophysiological mechanisms by which PTLE may work, as tolerable exercise-induced pain experience is the keystone for this specific loading program. This may be an area for future study.

### 4.2. Imaging mediators

Tendon thickening and neovascularization, as observed via ultrasound (US), are common features in PT.[19] These ultrasonographic findings substantiate the underlying pathological changes occurring in tendinopathy, such as increased water content, collagen disorganization as well as vascular and nerve ingrowth.[20] It is well established that healthy tendons respond favorably to mechanical loading or exercise, attributed to structural remodeling.[20] This adaptive capability underpins the hypothesis that the effectiveness of therapeutic exercises in PT may be achieved by targeting structural normalization, as observed in Achilles tendinopathy.[21]

A systematic review by Drew et al.[22] reported no association between improvement in pain and function and change in tendon thickness and neovascularization in tendinopathy. In contrast, another systematic review,[10] specifically in PT and Achilles tendinopathy, implied a positive link. Nevertheless, it is crucial to emphasize that both studies only addressed associations rather than causal relationships due to the absence of mediation analysis in their methodologies. Our study addresses this gap in the field of PT.

We did not find any significant mediating effect in tendon thickness or the degree of neovascularization. The reason for this could be that the absolute between-group difference in these ultrasonographic findings is too subtle (e.g. $<1$ mm in tendon thickness) (Appendix A). A similar small effect on these conventional ultrasound findings was reported in patients with PT performing heavy slow resistance training (HSR) over EET.[9] These findings highlight the need for future research to explore other precise imaging variables that could accurately elucidate the mechanisms underlying the effectiveness of exercise. Advanced imaging techniques such as share-wave electrography (SWE),[23] ultrashort echo time (UTE) MRI[24] hold promise in this regard by offering more insights into the mechanical and material components. However, the practical application of these technologies in a clinical setting remains challenging due to their complexity and resource requirements.

### 4.3. Strengths and limitations

This study was based on the largest RCT in the field of PT to date with longitudinal data, enabling a clear chronological order between

exposure, mediator, and outcome, which is the premise for the direction of the causal relationship.[7] We further corroborated our findings through two sensitivity analyses by assessing the robustness of causal assumptions and the influence of missing data, which are crucial components in mediation analysis for validity. Measurement error was reduced as the same individual conducted all assessments, and the methods used for measurement demonstrated relatively high reliability.

One of the most important limitations of our study is that we did not collect psychological variables, such as pain catastrophizing, and pain self-efficacy. These factors could be potential mediators for PTLE over EET, as they appear to mediate the effectiveness of exercise therapy in other musculoskeletal conditions such as gluteal tendinopathy.[14] Since PTLE was designed to alleviate exercise-induced pain, investigating these pain-related psychological mechanisms would be plausible. Another limitation of this study is the small sample size (n = 61), which may have limited power to detect stable indirect effects. This may also limit our ability to explore the interaction between a potential mediator and exposure or non-linear relationships in this analysis, given the speculation that the physical and structural response to exercise intervention could vary by patients. Future large-scale studies are needed to improve the stability of the mediation effects and to unravel these complex relationships.

### *4.4. Recommendation for future research*

Future studies should consider investigating other potential mediators, such as neuromuscular adaptations or tendon stiffness, which may be potential targets for optimized interventions in patellar tendinopathy. Additionally, studies with sufficient sample size are essential to confirm our findings and to explore complex relationship between exercise effects and change in physical or imaging properties. Investigating long-term outcomes may also help to better understand the mechanisms of interventions.

## 5. Conclusion

The beneficial effect of progressive tendon loading exercises over eccentric exercise therapy in pain and pain-related disability for patellar tendinopathy is not mediated by changes in physical factors (quadriceps muscle strength, ankle dorsiflexion range, and jumping performance) or imaging factors (tendon thickness and degree of neovascularization). However, these findings should be confirmed in studies with larger sample size. We also emphasize the need to evaluate alternative mechanisms, as they may be important for clinicians to use as treatment targets.

## CRediT authorship contribution statement

JD, RJDV and JR were involved in the design of this study. SJB performed data acquisition. JD performed data analysis. All authors contributed to the interpretation of the data and drafted manuscript. All authors gave their final approval to this version of the manuscript and agree to be accountable for all aspects of this work.

## Confirmation of ethical compliance

The original trial received ethical approval from the Erasmus MC University Medical Center Ethics Committee (MEC-2016-500).

## Funding information

The initial trial was sponsored by National Basketball Association (NBA) and GE Healthcare Orthopedics and Sports Medicine Collaboration. The current study was performed without support from additional funding agencies in the public, commercial, or not-for-profit sectors.

## Declaration of interest statement

EHGO and R-JdV had financial support from the National Basketball Association (NBA) and GE Healthcare Orthopedics and Sports Medicine Collaboration for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jsams.2024.12.006.

## Data availability

All data relevant to the study are available as supplementary files.

## References

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