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Effectiveness of adjunctive treatment combined with exercise therapy for patellofemoral pain: a protocol for a systematic review with meta-analysis of randomised controlled trials

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ABSTRACT

Introduction: Patellofemoral pain (PFP) is a chronic condition that affects up to 25% of the general population and has a negative impact on functionality and quality of life due to the high levels of pain experienced by these patients. In order to improve pain and function, rehabilitation programmes that combine adjunctive treatments with exercise therapy are often used in research and clinical settings. However, despite the variety of adjunctive treatments available, their effectiveness when compared to exercise therapy alone has yet to be elucidated. Thus, the aim of this systematic review is to evaluate whether adjunctive treatment combined with exercise therapy is more effective at improving pain and function in people with PFP than placebo adjunctive treatment plus exercise therapy or exercise therapy alone.

Methods and analysis: A systematic review will be conducted based on the Cochrane Collaboration recommendations and reported in line with Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol guidelines. Electronic searches will be performed in seven databases: Embase, PubMed (MEDLINE), CENTRAL, CINAHL, PEDro, SPORTDiscus and Web of Science. The inclusion criterion will be randomised controlled trials (RCTs) that compare adjunctive treatment combined with exercise therapy to placebo adjunctive treatment plus exercise therapy or exercise therapy alone. The outcomes of interest will be pain and function, with no restrictions on language, setting or year of publication. Study selection will be performed by two independent reviewers, based on the eligibility criteria. Methodological quality will be assessed using the PEDro scale and the evidence summarised via the GRADE approach.

Ethics and dissemination: No ethical statement will be required for this systematic review and meta-analysis. The findings will be published in a relevant international peer-reviewed journal and presented at conferences.

PROSPERO registration number CRD42020197081.

Keywords: PAIN MANAGEMENT, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, REHABILITATION MEDICINE, SPORTS MEDICINE

Article Summary

Strengths and limitations of this study

- This systematic review will include any adjunctive treatment and exercise therapy programme available that assessed outcome measures of pain and/or function;
- Randomised controlled trials (RCTs) with no restrictions on setting or year and language of publication will be included;
- This protocol will reduce the possibility of duplication and is written and reported in line with PRISMA guidelines;
- The PEDro scale and GRADE approach will be used to evaluate methodological quality and quality of evidence for the outcomes reported, respectively;
- The feasibility of this systematic review depends on the availability and homogeneity of trials and access to the data reported in the studies assessed.

INTRODUCTION

Patellofemoral pain (PFP) is a common chronic musculoskeletal condition characterised by pain around or behind the patella during activities that overload the patellofemoral joint, such as squatting, stair ambulation and running[1]. It affects both the general and athletic population, with an annual prevalence of approximately 23% of adults and 29% of adolescents in the general population, and 5.1-14.9% in adolescent amateur athletes over 1 season[2].

According to the literature, 57% of this population may experience persistent symptoms and unfavourable outcomes in 5-8 years[3,4]. The severity of pain and symptoms associated with this musculoskeletal disorder negatively affect quality of life by limiting the ability to perform activities of daily living and occupational tasks and reducing participation in physical activity[5,6]. Additionally, research suggests that PFP may precede the onset of patellofemoral osteoarthritis[7,8], which has no cure and causes significant socioeconomic impacts due to the high treatment costs and its limiting effect on patients' ability to be productive[9].

In regard to treatment modalities, the 2019 Clinical Practice Guidelines[10] cite combined interventions – exercise therapy plus adjunctive treatment – as strong evidence for the treatment of PFP. However, the best combination of exercise therapy and adjunctive treatment remains unclear. In a systematic review, Swart et al.[11] evaluated the additional effect of orthotic devices (patellar bracing, patellar taping and foot orthotics) on exercise therapy for pain and function. The authors concluded that additional studies with high methodological quality are needed to draw definitive conclusions.

Thus, taking into account the strong evidence for combined interventions as a treatment for PFP and the wide range of exercise programmes and adjunctive therapies available in both clinical and research settings, it is pertinent to summarise the findings of randomised controlled trials (RCTs) that evaluated the effects of combined interventions on pain and function, regardless of the modality assessed. Additionally, it is important to assess whether including adjunctive treatments in exercise programmes is effective in clinical settings, since their implementation may be costly, due to the expertise and materials needed, and require prolonged application times during the session.

Thus, the aim of this systematic review is to evaluate whether adjunctive treatment combined with exercise therapy is more effective at improving pain and function in

people with PFP than placebo adjunctive treatment plus exercise therapy or exercise therapy alone.

METHODS

The protocol was developed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA-P)[12] and the Cochrane Handbook guidelines for Systematic Reviews of Interventions[13], and registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42020197081).

Eligibility criteria

Inclusion criterion

Type of studies

Studies will be considered eligible for inclusion if they are RCTs that compare an intervention group (adjunctive treatment plus exercise therapy) to a control group (placebo adjunctive treatment plus exercise therapy or exercise therapy alone). The grey literature will not be assessed, meaning that publications such as reports, conference proceedings and theses or dissertations will not be considered for analysis[14].

Type of population

All patients with a clinical diagnosis of PFP with a non-traumatic onset will be included. Studies that use synonyms for PFP, such as patellofemoral pain syndrome; chondromalacia patella; anterior knee pain and/or syndrome; and runner's knee will also be included.

Type of intervention

Primary studies that assessed the effects of PFP treatment involving adjunctive treatment combined with any modality of exercise therapy and compared to placebo adjunctive treatment plus exercise therapy or exercise therapy alone will be included. The exercise therapy used in controls must be the same as that applied to the intervention group.

With respect to adjunctive treatment, the following will be considered:

- Non-pharmacological interventions such as knee braces, acupuncture, dry needling, behavioural/psychological therapy, weight loss intervention, visual biofeedback, kinesio taping, cryotherapy and any other complementary therapies;
- Patient education;
- Manual therapy: mobilisation or manipulation;
- Electrophysical therapy: shortwave, ultrasound or laser therapy, transcutaneous electrical nerve stimulation, electromyographic biofeedback, phonophoresis, iontophoresis and any other available electrophysical therapies.

Outcome measures

Studies that assess pain and function as outcomes measures will be included. Since the purpose of this systematic review is to assesses the effectiveness of adjunctive treatment over exercise therapy, the outcome measures should be assessed immediately post-treatment. Should the duration of treatment differ from that of adjunctive and exercise therapy, adjunctive treatment time will be considered. Whenever possible, outcomes will be assessed in the short (≤3 months), medium (3-12 months) and long term (≥12 months), as described by Lack *et al.*[15] and the 2019 Clinical Practice Guidelines[10]. Adverse events will be collected.

Exclusion criteria

Studies that examine other conditions (e.g., patellar dislocation, patellar subluxation, patellofemoral osteoarthritis, patellar tendinopathy, Osgood-Schlatter disease, iliotibial band syndrome, Sinding-Larsen-Johansson syndrome or clinical evidence of meniscal injury, ligament instability or joint effusion) or assess participants who have undergone surgery, have reported pain from the lumbar spine, hips, ankles or feet, and those with symptomatic osteoarthritis in any lower limb joint will be excluded.

Search strategy

Electronic searches will be carried out on the PubMed (including MEDLINE), Cochrane Central Register of Controlled Trials (CENTRAL), Embase (via Elsevier), Physiotherapy Evidence Database (PEDro), CINAHL, SPORTDiscus (both via EBSCO) and Web of Science (via Clarivate Analytics) databases. The PICO[13] framework was used to formulate the research question for this study: 'Is adjunctive treatment combined with exercise therapy more effective at improving pain and function in people with PFP

than placebo adjunctive treatment plus exercise therapy or exercise therapy alone?' The search strategy for each of the data sources was developed by two researchers (L.R.S., R.F.C.M.P.) and can be viewed in online supplementary appendix 1. There will be no restrictions on the setting, language or year of publication. The electronic searches will be complemented by manual searches through the lists of references of the articles included.

Data management

The search results will be entered into State of the Art through Systematic Review (START) reference management software, in order to identify and eliminate duplicates.

Study selection and data extraction

Study selection

The selection process will be performed by two independent reviewers (L.R.S., M.S.S.) who will screen the titles and abstracts. Once a consensus has been reached, both researchers will independently apply the inclusion and exclusion criteria after reading the selected studies in full. In the event of disagreements, consensus will be sought; however, if disagreement persists, a third reviewer (A.M.M.) will be consulted. Should the complete article be unavailable, the reviewer (L.R.S.) will contact the study authors. If the authors are unable to provide the full article or fail to reply to the request after 3 attempts, the study will be excluded. The reasons for excluding trials will be recorded. The reviewers will not be blind to the journal titles, study authors or institutions. The study selection process is shown in a PRISMA flow diagram (figure 1)[16].

Data extraction

After the final consensus and selection of the primary studies, the two reviewers (L.R.S., M.S.S.) will work independently. Disagreements will be resolved by consensus and, should they persist, a third reviewer (A.M.M.) will be consulted. The following study characteristics will be extracted: publication details (author and year), participant characteristics (size and type of population, age, sex, pain intensity, severity of the functional disability and disease duration in months), number of individuals and men and women in each group, outcome measures and assessment tools used, treatment applied in the intervention and control groups (type of placebo, adjunctive and exercise therapies, treatment duration, number and frequency of sessions, follow-ups) and a summary of the

main findings. For the meta-analysis and effect size calculation, post-treatment means and standard deviations will be sourced from the original papers when available, or by contacting the authors via email in the event of missing data. Should the authors be unable to provide the missing data or fail to reply to the request after 3 attempts, the study will be excluded from further statistical analysis[17].

Risk of bias and clinical relevance

The PEDro scale will be used to assess the methodological quality of the studies included in this systematic review. The reliability of this tool is fair to good[18].

Although the scale contains 11 items, specification of eligibility criteria will not be included in the final score, which will therefore range from 0 – 10. Each affirmative answer will receive one point and all these points will then be added to obtain the final score[19]. The rating of studies indexed in the PEDro database will be maintained and the non-indexed studies will be independently evaluated by two reviewers (L.R.S., M.S.S.). In case of disagreement, a third reviewer (A.M.M.) will be consulted. Studies will be rated as high-quality (≥7/10), moderate-quality (4-6/10) and low-quality (≤3/10)[20] based on this scale. Methodological quality will not be an inclusion criterion. The criteria recommended by Higgins and Green[13] will be used to assess clinical relevance.

Quality of intervention descriptions

The Template for Intervention Description and Replication (TIDieR)[21] checklist and guideline will be applied to evaluate how well the interventions are described in the RCTs. This tool was developed to improve the reporting of interventions across different study designs, such as trials, case-control and cohort studies[21]. In order to adapt the instrument to the study purpose and create a score, a template similar to the PEDro scale was created[22], whereby the scores for each TIDieR item for the intervention and control groups were summed with each item assessed on a 3-point Likert scale, with the following categories: not reported (0), partially reported (1) and adequately reported (2). The summary score will be calculated by adding the score (0, 1 or 2) for the 12 items, with summary scores ranging from 0 to 24 points[22]. Based on these scores, the studies included in this systematic review will be rated as having good (≥21/24), moderate (18–20/24) or poor intervention descriptions (≤17/24), based on the scores reported by Briani *et al.* [23]. It is important to note that this is a customised rating

classification because there is currently no rating classification available in the literature. The TIDieR checklist will be completed and scored by two independent reviewers (L.R.S., M.S.S.). Any discrepancies will be resolved during a consensus meeting, and a third reviewer (A.M.M) will be available to resolve any disagreements if needed.

Data synthesis and statistical analysis

Data synthesis

The Review Manager Software Package RevMan (V.5.3.) will be used for the meta-analysis[24]. For data synthesis, studies will be assigned to a class in accordance with the type of adjunctive treatment applied, i.e., knee braces, laser therapy, dry needling etc. Meta-analysis will be performed only in the event of clinical and methodological homogeneity. Data will be pooled when studies are sufficiently homogenous in terms of the population studied, intervention applied and comparisons performed (outcome measured and assessment times). The mean difference or standardised mean differences with 95% CIs will be used to calculate the continuous variables.

Assessment of heterogeneity

Two reviewers (L.R.S., R.F.C.M.P.) will evaluate clinical, methodological and statistical heterogeneity. The I^2 statistic will be used to assess statistical heterogeneity, while methodological heterogeneity will be based on study biases and clinical heterogeneity on population characteristics[13].

Subgroup analysis

In the event of high heterogeneity within each class of adjunctive treatment in the included studies, subgroup analyses will be performed according to age group, type of exercise programme (i.e. strengthening, stretching) and clinical diagnosis of PFP (i.e. clinical diagnosis in accordance with the 2016 patellofemoral pain consensus statement[1], or clinical diagnosis based on physical impairment measures such as patellar apprehension tests), whenever possible.

Meta-biases

In order to determine whether reporting bias exists, the protocols of the studies included in this systematic review (when available) will be assessed to determine whether

they were published before patient recruitment began. The presence of selective reporting of outcomes (outcome reporting bias) will also be evaluated.

Qualitative data synthesis

A qualitative data synthesis will be presented, even if the meta-analysis is not performed, including study characteristics such as year of publication, country of origin, sample size, type of intervention, outcomes and assessment tools used.

Certainty of the evidence (Grading of Recommendation, Assessment, Development and Evaluation (GRADE) approach)

Two reviewers (L.R.S. and M.S.S.) will independently evaluate the overall confidence in the evidence and strength of the recommendation using the GRADE approach, which analyses the following domains: trial design limitations due to risk of bias, inconsistency of results, indirectness in assessing the quality of a body of evidence, imprecision of results, and publication bias[25]. The strength of the evidence will be presented according to a rating system with four categories: high, moderate, low, or very low, in line with the GRADE approach[25].

Dealing with missing data

Whenever possible, we will contact authors to request any missing data, especially for information that is needed to complete the meta-analysis. Should the authors be unable to provide the missing data or fail to reply after 3 attempts, the study will be excluded from further statistical analysis[17].

Plans for documenting important protocol amendments

Should an event of any protocol amendments occur, the date of each amendment will be accompanied by a description of the change and rationale in this section. Changes will not be incorporated into the protocol.

Patient and public involvement

No patient involved.

Data sharing statement

Not applicable once this study is a protocol.

PERSPECTIVES

PFP is a chronic condition that significantly affects the quality of life of this population and may precede PFOA[7,8], which results in greater functional disability and reduced quality of life. Thus, determining which treatment is most effective at improving pain and physical function in this population is highly relevant. In this respect, systematic reviews are important because they provide clinical evidence to guide clinical practice and scientific evidence for future studies, based on the gaps identified in the available literature. As such, we believe that this systematic review is important because it will make it possible to determine whether adjunctive treatment is relevant in a conventional exercise programme and, if so, which adjunctive treatment is more effective at improving pain and physical function when compared with a control group.

The results of this systematic review could contribute to justifying the necessity or not of the high costs and prolonged treatment times involved in implementing adjunctive therapy in clinical practice.

Acknowledgements

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Competing interests

The authors declare no competing interests.

Funding statement

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Ethics and dissemination

No ethical statement will be required for this systematic review and meta-analysis. The findings will be published in a relevant international peer-reviewed journal and

presented at conferences. The results will also contribute to improving therapeutic strategies for patients with PFP.

Author Contributions

LRS is the guarantor. LRS and FVS came up with the study idea. LRS, FVS, RFCMP, MSS and AMM designed the study. LRS and RFCMP designed the strategy search and the risk of bias. LRS, FVS and RFCMP designed the statistical analysis plan. LRS, FVS and RFCMP draft the manuscript. All authors provided feedback and gave important intellectual input. All authors read and consented to the content of the article.

REFERENCES

1 Crossley KM, van Middelkoop M, Callaghan MJ, et al. 2016 Patellofemoral pain consensus statement from the 4th International Patellofemoral Pain Research Retreat, Manchester. Part 2: recommended physical interventions (exercise, taping, bracing, foot orthoses and combined interventions). *Br J Sports Med* 2016;50:844–52. doi:10.1136/bjsports-2016-096268

2 Smith BE, Selfe J, Thacker D, et al. Incidence and prevalence of patellofemoral pain: a systematic review and meta-analysis. *PLoS One* 2018;13:e0190892. doi:10.1371/journal.pone.0190892

3 Vicenzino B, Collins N, Crossley K, et al. Foot orthoses and physiotherapy in the treatment of patellofemoral pain syndrome: a randomised clinical trial. *BMC Musculoskelet Disord* 2008;27;9:27. doi:10.1186/1471-2474-9-27

4 Lankhorst NE, Bierma-Zeinstra SMA, Van Middelkoop M. Risk factors for patellofemoral pain syndrome: a systematic review. *J Orthop Sports Phys Ther* 2012;42:81–94. doi:10.2519/jospt.2012.3803

5 Rathleff MS, Rathleff CR, Olesen JL, et al. Is knee pain during adolescence a self-limiting condition? prognosis of patellofemoral pain and other types of knee pain. *Am J Sports Med* 2016;44:1165–71. doi:10.1177/0363546515622456

6 Hall R, Foss KB, Hewett TE, et al. Sport specialization's association with an increased risk of developing anterior knee pain in adolescent female athletes. *J Sport Rehabil* 2015;24:31–5. doi:10.1123/jsr.2013-0101

7 Thomas MJ, Wood L, Selfe J, et al. Anterior knee pain in younger adults as a precursor to subsequent patellofemoral osteoarthritis: a systematic review. *BMC Musculoskelet Disord* 2010;11:201. doi:10.1186/1471-2474-11-201

8 Crossley KM. Is patellofemoral osteoarthritis a common sequela of patellofemoral pain? *Br J Sports Med* 2014;48:409–10. doi:10.1136/bjsports-2014-093445

9 Hunter DJ, Arden N, Conaghan PG, et al. Definition of osteoarthritis on MRI: results of a Delphi exercise. *Osteoarthritis Cartilage* 2011;19:963–9. doi:10.1016/j.joca.2011.04.017

10 Willy RW, Hoglund LT, Barton CJ, et al. Patellofemoral pain. *J Orthop Sports Phys Ther* 2019;49:CPG1–95. doi:10.2519/jospt.2019.0302

11 Swart NM, van Linschoten R, Bierma-Zeinstra SMA, et al. The additional effect of orthotic devices on exercise therapy for patients with patellofemoral pain syndrome: a systematic review. *Br J Sports Med* 2012;46:570–7. doi:10.1136/bjsm.2010.080218

12 Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647–g7647. doi:10.1136/bmj.g7647

13 The Cochrane Collaboration. *Cochrane Handbook for systematic reviews of interventions* version 6.2 (update February 2021). Cochrane, 2021. Available from (http://www.training.cochrane.org/handbook) accessed May 2021.

14 Lefebvre C, Glanville J, Briscoe S, et al. Chapter 4: Searching for and selecting studies. In: The Cochrane Collaboration. *Cochrane Handbook for systematic reviews of intervention* version 6.2 (update February 2021). Cochrane, 2021. Available from (http://www.training.cochrane.org/handbook) accessed May 2021.

15 Lack S, Barton C, Sohan O, et al. Proximal muscle rehabilitation is effective for patellofemoral pain: a systematic review with meta-analysis. *Br J Sports Med* 2015;49:1365-76. doi: 10.1136/bjsports-2015-094723.

16 Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009;6:e1000100. doi:10.1371/journal.pmed.1000100

17 de Oliveira Silva D, Pazzinatto M., Rathleff MS, et al. Patient education for patellofemoral pain: a systematic review. *J Orthop Sports Phys Ther* 2020;50:388–96. doi:10.2519/jospt.2020.9400

18 Maher CG, Sherrington C, Herbert RD, et al. Reliability of the PEDro scale for rating quality of randomized controlled trials. *Phys Ther* 2003;83:713–21.

19 Foley NC, Bhogal SK, Teasell RW, et al. Estimates of quality and reliability with the physiotherapy evidence-based database scale to assess the methodology of

randomized controlled trials of pharmacological and nonpharmacological interventions. *Phys Ther* 2006;86:817–24.

20 de Morton NA. The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. *Aust J Physiother* 2009;55:129–33. doi:10.1016/s0004-9514(09)70043-1

21 Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ* 2014;348:g1687. doi:10.1136/bmj.g1687

22 Yamato TP, Maher CG, Saragiotto BT, et al. Rasch analysis suggested that items from the template for intervention description and replication (TIDieR) checklist can be summed to create a score. *J Clin Epidemiol* 2018;101:28–34. doi:10.1016/j.jclinepi.2018.05.014

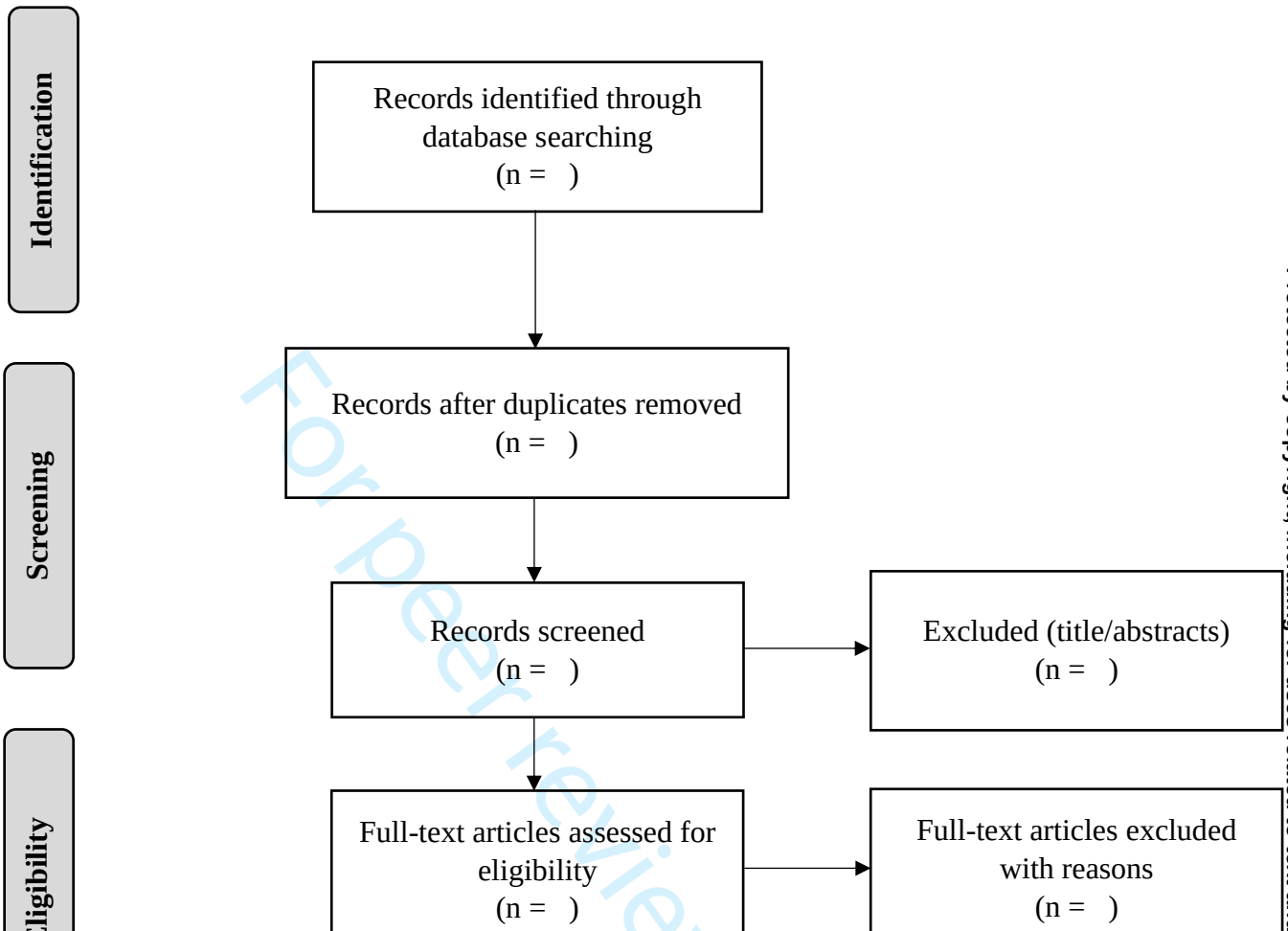
23 Briani RV, Ferreira AS, Pazzinatto MF, et al. What interventions can improve quality of life or psychosocial factors of individuals with knee osteoarthritis? a systematic review with meta-analysis of primary outcomes from randomised controlled trials. *Br J Sports Med* 2018;52:1031–8. doi:10.1136/bjsports-2017-098099

24 The Cochrane Collaboration. RevMan5, 2017. Available: http://community.cochrane.org/tools/review-production-tools/revman-5 accessed May 2021.

25 Furlan AD, Malmivaara A, Chou R, et al. 2015 Updated Method Guideline for Systematic Reviews in the Cochrane Back and Neck Group. *Spine (Phila Pa 1976)* 2015;40:1660–73. doi:10.1097/BRS.0000000000001061

Figure legends

Figure 1. Flow chart and descriptions of study selection.



Supplementary Table 1. Search strategy

PubMed (including MEDLINE)
1. “Patellofemoral pain syndrome” [Mesh] OR “Patellofemoral Pain” OR “Anterior Knee Pain” OR “Patellofemoral Dysfunction”
2. “Exercise Therapy”[Mesh] OR “Exercise”[Mesh] OR “Resistance Training”[Mesh] OR “Kinesiotherapy” OR “Physical Therapy Modalities”[Mesh] OR “exercise intervention” OR “therapeutic exercise” OR “exercise therapeutic” OR “physical therapy” OR “physiotherapy”
3. 1 AND 2
Embase (via Elsevier)
1. ‘Patellofemoral pain syndrome’ OR ‘Patellofemoral Syndrome’ OR ‘Anterior Knee Pain Syndrome’ ‘Patellofemoral Pain’ OR ‘Anterior Knee Pain’ OR ‘Patellofemoral Dysfunction’
2. ‘Exercise Therapy’ OR Exercise OR ‘Resistance Training’ OR ‘Strength Training’ OR Kinesiotherapy OR ‘Physical therapy’ OR physiotherapy OR ‘exercise intervention’ OR ‘therapeutic exercise’ OR ‘exercise therapeutic’ OR ‘physical therapy modalities’
3. 1 AND 2
Cochrane Central Register of Controlled Trials (CENTRAL)
1. patellofemoral pain OR MeSH descriptor: [Patellofemoral Pain Syndrome] explode all trees OR anterior knee pain OR patellofemoral dysfunction
2. MeSH descriptor: [Exercise Therapy] explode all trees OR MeSH descriptor: [Exercise] explode all trees OR MeSH descriptor: [Resistance Training] explode all trees OR Kinesiotherapy OR MeSH descriptor: [Physical Therapy Modalities] explode all trees OR exercise intervention OR therapeutic exercise OR exercise therapeutic
3. 1 AND 2

PEDro

1. **Abstract & Title:** Patellofemoral pain; **Body Part:** lower leg or knee; **Method:** clinical trial.
2. **Abstract & Title:** Patellofemoral pain syndrome; **Body Part:** lower leg or knee; **Method:** clinical trial.
3. **Abstract & Title:** Patellofemoral syndrome; **Body Part:** lower leg or knee; **Method:** clinical trial.
4. **Abstract & Title:** Anterior knee pain syndrome; **Body Part:** lower leg or knee; **Method:** clinical trial.
5. **Abstract & Title:** Anterior knee pain; **Body Part:** lower leg or knee; **Method:** clinical trial.
6. **Abstract & Title:** Patellofemoral dysfunction; **Body Part:** lower leg or knee; **Method:** clinical trial.

SPORTDiscus (via EBSCO)

1. patellofemoral pain syndrome OR patellofemoral syndrome OR anterior knee pain syndrome OR patellofemoral pain OR anterior knee pain OR patellofemoral dysfunction
2. exercise therapy OR exercise OR resistance training OR strength training OR kinesiotherapy OR physical therapy OR physiotherapy OR exercise intervention OR therapeutic exercise OR exercise therapeutic OR physical therapy modalities
3. 1 AND 2

CINAHL (via EBSCO)

1. patellofemoral pain syndrome OR patellofemoral syndrome OR anterior knee pain syndrome OR patellofemoral pain OR anterior knee pain OR patellofemoral dysfunction
2. exercise therapy OR exercise OR resistance training OR strength training OR kinesiotherapy OR physical therapy OR physiotherapy OR exercise intervention OR therapeutic exercise OR exercise therapeutic OR physical therapy modalities
3. 1 AND 2

Web of Science (via Clarivate Analytics)

1. TI=(Patellofemoral pain syndrome OR Patellofemoral Syndrome OR Anterior Knee Pain Syndrome OR Patellofemoral Pain OR Anterior Knee Pain OR Patellofemoral Dysfunction)

2. AB=(Patellofemoral pain syndrome OR Patellofemoral Syndrome OR Anterior Knee Pain Syndrome OR Patellofemoral Pain OR Anterior Knee Pain OR Patellofemoral Dysfunction)

3. TI=(Exercise Therapy OR Exercise OR Resistance Training OR Strength Training OR Kinesiotherapy OR Physical therapy OR physiotherapy OR exercise intervention OR therapeutic exercise OR exercise therapeutic OR physical therapy modalities)

4. AB=(Exercise Therapy OR Exercise OR Resistance Training OR Strength Training OR Kinesiotherapy OR Physical therapy OR physiotherapy OR exercise intervention OR therapeutic exercise OR exercise therapeutic OR physical therapy modalities)

5. 1 OR 2

6. 3 OR 4

7. 5 AND 6

MeSH: Medical Subject Headings; TI: title; AB: abstract

Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	2
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a (the protocol is not an update of a previous

		systematic review)	
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3,6
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	2
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	13
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	11
Support			
Sources	#5a	Indicate sources of financial or other support for the review	12
Sponsor	#5b	Provide name for the review funder and / or sponsor	12
Role of sponsor	#5c	Describe roles of funder(s), sponsor(s), and / or	12

or funder		institution(s), if any, in developing the protocol	
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5-8
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6,7
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6-9
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7,8 (Supplementary appendix 1)
Study records - data	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8

management			
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8,9
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8,9
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8,9
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	9
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	10

Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	10
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	11
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10,11
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

Notes:

- 1b: n/a (the protocol is not an update of a previous systematic review)
- 10: 7,8 (Supplementary appendix 1) The PRISMA-P elaboration and explanation paper is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 04. June 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Effectiveness of adjunctive treatment combined with exercise therapy for patellofemoral pain: a protocol for a systematic review with network meta-analysis of randomised controlled trials

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Effectiveness of adjunctive treatment combined with exercise therapy for patellofemoral pain: a protocol for a systematic review with network meta-analysis of randomised controlled trials

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ABSTRACT

Introduction: Patellofemoral pain (PFP) is a chronic condition that affects up to 25% of the general population and has a negative impact on functionality and quality of life due to the high levels of pain experienced by these patients. In order to improve pain and function, rehabilitation programmes that combine adjunctive treatments with exercise therapy are often used in research and clinical settings. However, despite the variety of adjunctive treatments available, their effectiveness when compared to exercise therapy has yet to be elucidated. Thus, the aim of this study is to evaluate the effectiveness of adjunctive treatments plus exercise therapy versus exercise therapy alone, and determine the relative efficacy of different types of adjunctive treatments plus exercise therapy for individuals with PFP.

Methods and analysis: A systematic review and network meta-analysis will be conducted based on the Cochrane Collaboration recommendations and reported in line with PRISMA guidelines. We will search Embase, PubMed (MEDLINE), CENTRAL, CINAHL, PEDro, SPORTDiscus, Web of Science and OpenGrey. It will be included randomised controlled trials that compared adjunctive treatment plus exercise therapy to placebo adjunctive treatment plus exercise therapy or exercise therapy. The outcomes of interest will be pain and function, with no restrictions on language, setting or year of publication. Study selection will be performed by two independent reviewers, based on the eligibility criteria. Methodological quality will be assessed using the PEDro scale and the evidence summarised via the GRADE approach. A Bayesian network meta-analysis will be performed to compare the efficacy of different adjunctive treatments plus exercise therapy. Consistency between direct and indirect comparisons will be assessed.

Ethics and dissemination: No ethical statement will be required for this systematic review and meta-analysis. The findings will be published in a relevant international peer-reviewed journal and presented at conferences.

PROSPERO registration number CRD42020197081.

Keywords: PAIN MANAGEMENT, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, REHABILITATION MEDICINE, SPORTS MEDICINE

Article Summary

Strengths and limitations of this study

- This systematic review will include any adjunctive treatment and exercise therapy programme available that assessed outcome measures of pain and/or function;
- Randomised controlled trials (RCTs) with no restrictions on setting or year and language of publication will be included;
- This protocol will reduce the possibility of duplication and is written and reported in line with PRISMA guidelines;
- The PEDro scale and GRADE approach will be used to evaluate methodological quality and quality of evidence for the outcomes reported, respectively;
- The feasibility of this systematic review depends on the availability and homogeneity of trials and access to the data reported in the studies assessed.

INTRODUCTION

Patellofemoral pain (PFP) is a common chronic musculoskeletal condition characterised by pain around or behind the patella during activities that load the patellofemoral joint, such as squatting, stair ambulation and running[1]. It affects both the general and athletic population, with an annual prevalence of approximately 23% of adults and 29% of adolescents in the general population, and 5.1-14.9% in adolescent amateur athletes over 1 season[2].

According to the literature, 57% of this population may experience persistent symptoms and unfavourable outcomes in 5-8 years[3,4]. The severity of pain and symptoms associated with this musculoskeletal disorder negatively affect quality of life by limiting the ability to perform activities of daily living and occupational tasks and reducing participation in physical activity[5,6].

Focusing on the rehabilitation of this population, some systematic reviews have evaluated the effectiveness of several adjunctive treatments combined with exercise therapy [7–20] and/or multimodal physiotherapy programmes [7–12,14–16,20]. These adjunctive treatments include patellar taping [7–12,14], knee [10,12,14] and foot [8,10,14–16] orthoses, electromyography biofeedback [8,14,17], dry needling [19] and neuromuscular electrical stimulation [8,14,20]. In general, there is limited and inconclusive evidence to draw conclusions regarding the effectiveness of these adjunctive treatment modalities for pain and function outcomes.

Although systematic reviews have investigated the effectiveness of including different adjunctive treatments in multimodal physiotherapy and/or exercise programmes, we feel it is relevant to synthesize the evidence based on an analysis of primary studies that evaluate the effectiveness of combining only one adjunctive treatment with exercise programmes, that is, not concomitantly including other treatment modalities, in order to assess the real effect of adding an adjunctive treatment in clinical practice. Another noteworthy point is that the comparative effectiveness of all the adjunctive treatments available combined with exercise programmes has never been studied. As such, conducting a network meta-analysis (NMA) provides an opportunity to combine direct and indirect evidence on treatment comparisons in a single analysis. Additionally, NMA can provide an estimate of the treatment most and least likely to be effective for a given outcome.

Thus, given the wide range of exercise programmes and adjunctive therapies available in both clinical and research settings, it is pertinent to summarise the findings of randomised controlled trials (RCTs) that evaluated the effects of combined

interventions on pain and function, regardless of modality, using NMA. It is also important to assess whether including adjunctive treatment in exercise programmes is effective in a clinical setting, since its implementation requires the availability of material and therapist training to ensure the technique is correctly applied.

As such, the aim of this systematic review is to evaluate the effectiveness of adjunctive treatments combined with exercise therapy versus exercise therapy alone, and determine the relative efficacy of different types of adjunctive treatments plus exercise therapy for individuals with PFP using a Bayesian NMA.

METHODS

The protocol was developed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA-P)[21] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for NMA (PRISMA-NMA)[22]. The protocol followed the Cochrane Handbook guidelines for Systematic Reviews of Interventions[23], and it was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42020197081).

Eligibility criteria

Inclusion criterion

Type of studies

Studies will be considered eligible for inclusion if they are RCTs that compare an intervention group (adjunctive treatment plus exercise therapy) to a control group (placebo adjunctive treatment plus exercise therapy or exercise therapy alone).

Type of population

Participants must have been diagnosed with PFP in line with the current recommendations for PFP diagnosis, whose core criterion is pain around or behind the patella, aggravated by at least one activity that load the patellofemoral joint during weight bearing on a flexed knee (e.g., squatting, stair ambulation, jogging/running, hopping/jumping).[1]

Type of intervention

The aim of the RCTs included in this review should be to assess the potential additional effect of the adjunctive treatment on exercise therapy. To that end, it is vital that both the intervention and control groups be submitted to the same exercise programme, with the adjunctive therapy being the only difference between them. Strength, stretching, endurance, power and proprioception exercises will be considered for the exercise programme.

With respect to adjunctive treatment, the following will be considered:

- Non-pharmacological interventions such as patellofemoral knee orthoses (bracing), visual and EMG biofeedback, patellar taping, foot orthoses, manual therapy (mobilisation/manipulation), needling therapies (acupuncture and dry needling), patient education, behavioural/psychological therapy, weight loss intervention and any other complementary therapies;
- Biophysical agents: shortwave, ultrasound, cryotherapy, phonophoresis, iontophoresis, electrical stimulation and laser therapy and any other complementary therapies.

Comparison of interest

Placebo adjunctive treatment plus exercise therapy or exercise therapy alone.

Outcome measures

Studies that assess pain and function through validate measures within PFP population will be included. Whenever possible, outcomes will be assessed in the short (≤3 months), medium (3-12 months) and long term (≥12 months), as described by Lack et al.[24] and the '2019 Patellofemoral Pain Clinical Practice Guideline'[25].

Exclusion criteria

Studies that examine other conditions (e.g., patellar dislocation, patellar subluxation, patellofemoral osteoarthritis, patellar tendinopathy, Osgood-Schlatter disease, iliotibial band syndrome, Sinding-Larsen-Johansson syndrome or clinical evidence of meniscal injury, ligament instability or joint effusion) or assess participants who have undergone surgery, have reported pain from the lumbar spine, hips, ankles or feet, and those with symptomatic osteoarthritis in any lower limb joint will be excluded.

Search strategy

Electronic searches will be carried out on the PubMed (including MEDLINE), Cochrane Central Register of Controlled Trials (CENTRAL), Embase (via Elsevier), Physiotherapy Evidence Database (PEDro), CINAHL, SPORTDiscus (both via EBSCO) and Web of Science (via Clarivate Analytics) databases. In regard to grey literature, OpenGrey.eu will be searched to identify unpublished studies. The PICO [25] framework was used to formulate the research question for this study: 'Is adjunctive treatment combined with exercise therapy more effective at improving pain and function in people with PFP than placebo adjunctive treatment plus exercise therapy or exercise therapy alone?' The search strategy for each of the data sources was developed by two researchers (L.R.S., R.F.C.M.P.) and can be viewed in online supplementary appendix 1. There will be no restrictions on the setting, language or year of publication. The electronic searches will be complemented by manual searches through the lists of references of the articles included.

Data management

The search results will be entered into State of the Art through Systematic Review (START) reference management software, in order to identify and eliminate duplicates.

Study selection and data extraction

Study selection

The selection process will be performed by two independent reviewers (L.R.S., M.S.B.) who will screen the titles and abstracts. Once a consensus has been reached, both researchers will independently apply the inclusion and exclusion criteria after reading the selected studies in full. In the event of disagreements, consensus will be sought; however, if disagreement persists, a third reviewer (A.M.M.) will be consulted. Should the complete article be unavailable, the reviewer (L.R.S.) will contact the study authors. If the authors are unable to provide the full article or fail to reply to the request after 3 attempts, the study will be excluded. The reasons for excluding trials will be recorded. The reviewers will not be blind to the journal titles, study authors or institutions. The study selection process is shown in a PRISMA flow diagram (figure 1)[26].

Data extraction

After the final consensus and selection of the primary studies, the two reviewers (L.R.S., M.S.B.) will work independently. Disagreements will be resolved by consensus and, should they persist, a third reviewer (A.M.M.) will be consulted. The following study characteristics will be extracted: publication details (author and year), participant characteristics (size and type of population, age, sex, pain intensity, severity of the functional disability and disease duration in months), number of individuals and men and women in each group, outcome measures and assessment tools used, treatment applied in the intervention and control groups (type of placebo, adjunctive and exercise therapies, treatment duration, number and frequency of sessions, follow-ups), adverse events and a summary of the main findings. For the meta-analysis and effect size calculation, post-treatment means and standard deviations will be sourced from the original papers when available, or by contacting the authors via email in the event of missing data. Should the authors be unable to provide the missing data or fail to reply to the request after 3 attempts, the study will be excluded from further statistical analysis[27].

Risk of bias and clinical relevance

The PEDro scale will be used to assess the methodological quality of the studies included in this systematic review. The reliability of this tool is fair to good[28].

Although the scale contains 11 items, specification of eligibility criteria will not be included in the final score, which will therefore range from 0 – 10. Each affirmative answer will receive one point and all these points will then be added to obtain the final score[29]. The rating of studies indexed in the PEDro database will be maintained and the non-indexed studies will be independently evaluated by two reviewers (L.R.S, M.S.B.). In case of disagreement, a third reviewer (A.M.M.) will be consulted. Studies will be rated as high-quality (≥7/10), moderate-quality (4-6/10) and low-quality (≤3/10)[30] based on this scale. Methodological quality will not be an inclusion criterion. The criteria recommended by Higgins and Green[23] will be used to assess clinical relevance.

Quality of intervention descriptions

The Template for Intervention Description and Replication (TIDieR)[31] checklist and guideline will be applied to evaluate how well the interventions are described in the RCTs. This tool was developed to improve the reporting of interventions across different study designs, such as trials, case-control and cohort studies[31]. In order

to adapt the instrument to the study purpose and create a score, a template similar to the PEDro scale was created[32], whereby the scores for each TIDieR item for the intervention and control groups were summed with each item assessed on a 3-point Likert scale, with the following categories: not reported (0), partially reported (1) and adequately reported (2). The summary score will be calculated by adding the score (0, 1 or 2) for the 12 items, with summary scores ranging from 0 to 24 points[32]. Based on these scores, the studies included in this systematic review will be rated as having good (≥21/24), moderate (18-20/24) or poor intervention descriptions (≤17/24), based on the scores reported by Briani et al.[33]. It is important to note that this is a customised rating classification because there is currently no rating classification available in the literature. The TIDieR checklist will be completed and scored by two independent reviewers (L.R.S., M.S.B.). Any discrepancies will be resolved during a consensus meeting, and a third reviewer (A.M.M) will be available to resolve any disagreements if needed.

Data synthesis and statistical analysis

Data synthesis

Pairwise meta-analysis

The Review Manager Software Package RevMan (V.5.3.) will be used for the pairwise meta-analysis[34]. For data synthesis, studies will be assigned by subgroup category considering the type of adjunctive treatment applied, i.e., knee braces, laser therapy, dry needling etc. Meta-analysis will be performed only in the event of clinical and methodological homogeneity. Data will be pooled when studies are sufficiently homogenous in terms of the population studied, intervention applied and comparisons performed (outcome measured and assessment times). The mean difference or standardised mean differences with 95% CIs will be used to calculate the continuous variables.

Network meta-analysis

Bayesian network meta-analysis will be conducted to compare the effects of different adjunctive treatments through direct and indirect comparisons. The Markov Chain Monte Carlo algorithm will be applied. All network meta-analyses will be carried out using WinBUGS software (V.1.4, Medical Research Council, UK, and Imperial College of Science, Technology and Medicine, University of Cambridge, UK).

Measure of the pain and function outcomes will be presented as mean difference or standardised mean difference, with their 95% credible intervals. Both fixed and random effects models will be fit and model fit compared using the deviance information criterion and posterior mean residual deviance.

Assessment of heterogeneity

Two reviewers (L.R.S., R.F.C.M.P.) will evaluate clinical, methodological and statistical heterogeneity. The I^2 statistic will be used to assess statistical heterogeneity, while methodological heterogeneity will be based on study biases and clinical heterogeneity on population characteristics[23].

Transitivity analysis

For transitivity analysis, participant setting, symptom duration, age and baseline outcome values will be considered modifiers of treatment effects. Exercise modality and dose/intensity as well as adjunctive treatments will also be considered effect modifiers.

Exploring inconsistency in the network

Inconsistency (agreement between direct and indirect evidence) for both the pain and knee function outcomes will be evaluated globally and locally for each treatment comparison using node-splitting [35] and by evaluating the statistical inconsistency of the network separately in every closed loop [36]. Local inconsistency will be deemed statistically significant if loop-specific 95% confidence intervals do not include zero.

Meta-biases

In order to determine whether reporting bias exists, the protocols of the studies included in this systematic review (when available) will be assessed to determine whether they were published before patient recruitment began. The presence of selective reporting of outcomes (outcome reporting bias) will also be evaluated.

Qualitative data synthesis

A qualitative data synthesis will be presented, even if the meta-analysis is not performed, including study characteristics such as year of publication, country of origin, sample size, type of intervention, outcomes and assessment tools used.

Certainty of the evidence (Grading of Recommendation, Assessment, Development and Evaluation (GRADE) approach)

Two reviewers (L.R.S. and M.S.B.) will independently evaluate the overall confidence in the evidence and strength of the recommendation using the GRADE approach, which analyses the following domains: trial design limitations due to risk of bias, inconsistency of results, indirectness in assessing the quality of a body of evidence, imprecision of results, and publication bias[37]. The strength of the evidence will be presented according to a rating system with four categories: high, moderate, low, or very low, in line with the GRADE approach[37].

Dealing with missing data

Whenever possible, we will contact authors to request any missing data, especially for information that is needed to complete the meta-analysis. Should the authors be unable to provide the missing data or fail to reply after 3 attempts, the study will be excluded from further statistical analysis[27].

Plans for documenting important protocol amendments

Should an event of any protocol amendments occur, the date of each amendment will be accompanied by a description of the change and rationale in this section. Changes will not be incorporated into the protocol.

Patient and public involvement

No patient involved.

Data sharing statement

Not applicable once this study is a protocol.

PERSPECTIVES

PFP is a chronic condition that significantly affects the quality of life of this population and may precede PFOA[38,39], which results in greater functional disability and reduced quality of life. Thus, determining which treatment is most effective at improving pain and physical function in this population is highly relevant. In this respect, systematic reviews are important because they provide clinical evidence to guide clinical practice and scientific evidence for future studies, based on the gaps identified in the

available literature. As such, we believe that this systematic review is important because it will make it possible to determine whether adjunctive treatment is relevant in a conventional exercise programme and, if so, which adjunctive treatment is more effective at improving pain and physical function when compared with a control group.

The results of this systematic review could contribute to justifying the need or not for costs related to the availability of material and therapist training when implementing adjunctive therapy in clinical practice.

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Competing interests

The authors declare no competing interests.

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Ethics and dissemination

No ethical statement will be required for this systematic review and meta-analysis. The findings will be published in a relevant international peer-reviewed journal and presented at conferences. The results will also contribute to improving therapeutic strategies for patients with PFP.

Author Contributions

LRS is the guarantor. LRS and FVS came up with the study idea. LRS, FVS, RFCMP, MSB and AMM designed the study. LRS and RFCMP designed the strategy search and the risk of bias. LRS, FVS and RFCMP designed the statistical analysis plan.

LRS, FVS and RFCMP draft the manuscript. All authors provided feedback and gave important intellectual input. All authors read and consented to the content of the article.

REFERENCES

1 Crossley KM, van Middelkoop M, Callaghan MJ, et al. 2016 Patellofemoral pain consensus statement from the 4th International Patellofemoral Pain Research Retreat, Manchester. Part 2: recommended physical interventions (exercise, taping, bracing, foot orthoses and combined interventions). *Br J Sports Med* 2016;50:844–52. doi:10.1136/bjsports-2016-096268

2 Smith BE, Selfe J, Thacker D, et al. Incidence and prevalence of patellofemoral pain: a systematic review and meta-analysis. *PLoS One* 2018;13:e0190892. doi:10.1371/journal.pone.0190892

3 Vicenzino B, Collins N, Crossley K, et al. Foot orthoses and physiotherapy in the treatment of patellofemoral pain syndrome: a randomised clinical trial. *BMC Musculoskelet Disord* 2008;27;9:27. doi:10.1186/1471-2474-9-27

4 Lankhorst NE, Bierma-Zeinstra SMA, Van Middelkoop M. Risk factors for patellofemoral pain syndrome: a systematic review. *J Orthop Sports Phys Ther* 2012;42:81–94. doi:10.2519/jospt.2012.3803

5 Rathleff MS, Rathleff CR, Olesen JL, et al. Is knee pain during adolescence a self-limiting condition? prognosis of patellofemoral pain and other types of knee pain. *Am J Sports Med* 2016;44:1165–71. doi:10.1177/0363546515622456

6 Hall R, Foss KB, Hewett TE, et al. Sport specialization's association with an increased risk of developing anterior knee pain in adolescent female athletes. *J Sport Rehabil* 2015;24:31–5. doi:10.1123/jsr.2013-0101

7 Barton C., Balachandar V., Lack S., *et al.* Patellar taping for patellofemoral pain: a systematic review and meta-analysis to evaluate clinical outcomes and biomechanical mechanisms. *Br J Sports Med* 2014;48:417–24 doi: 10.1136/bjsports-2013-092437

8 Collins NJ, Bisset LM, Crossley KM, *et al.* Efficacy of nonsurgical interventions for anterior knee pain: systematic review and meta-analysis of randomized trials. *Sports Med* 2012;42:31–49. doi:10.2165/11594460-000000000-00000

9 Callaghan MJ, Selfe J. Patellar taping for patellofemoral pain syndrome in adults. *Cochrane Database Syst Rev* 2012;(4):CD006717. doi:10.1002/14651858.CD006717.pub2

10 Swart NM, van Linschoten R, Bierma-Zeinstra SMA, et al. The additional effect of orthotic devices on exercise therapy for patients with patellofemoral pain syndrome: a systematic review. *Br J Sports Med* 2012;46:570–7. doi:10.1136/bjsm.2010.080218

11 Logan C.A., Bhashyam A.R., Tisosky A.J., *et al.* Systematic Review of the Effect of Taping Techniques on Patellofemoral Pain Syndrome. *Sports Health* 2017;9:456–61. doi:10.1177/1941738117710938

12 Warden SJ, Hinman RS, Watson MAJ, *et al.* Patellar taping and bracing for the treatment of chronic knee pain: a systematic review and meta-analysis. *Arthritis Rheum* 2008;59:73–83. doi:10.1002/art.23242

13 Smith TO, Drew BT, Meek TH, *et al.* Knee orthoses for treating patellofemoral pain syndrome. *Cochrane Database Syst Rev* 2015;8;(12):CD010513. doi:10.1002/14651858.CD010513.pub2

14 Saltychev M, Dutton RA, Laimi K, *et al.* Effectiveness of conservative treatment for patellofemoral pain syndrome: A systematic review and meta-analysis. *J Rehabil Med* 2018;50:393–401. doi:10.2340/16501977-2295

15 Barton C.J., Munteanu S.E., Menz H.B., *et al.* The efficacy of foot orthoses in the treatment of individuals with patellofemoral pain syndrome: a systematic review. *Sports Med* 2010;40:377–95. doi:10.2165/11530780-000000000-00000

16 Hossain M, Alexander P, Burls A, *et al.* Foot orthoses for patellofemoral pain in adults. *Cochrane Database Syst Rev* 2011;19:CD008402. doi:10.1002/14651858.CD008402.pub2

17 Wasielewski NJ, Parker TM, Kotsko KM. Evaluation of electromyographic biofeedback for the quadriceps femoris: a systematic review. *J Athl Train* 2011;46:543–54. doi:10.4085/1062-6050-46.5.543

18 Lake DA, Wofford NH. Effect of therapeutic modalities on patients with patellofemoral pain syndrome: a systematic review. *Sports Health* 2011;3:182–9. doi:10.1177/1941738111398583

19 Rahou-El-Bachiri Y, Navarro-Santana MJ, Gómez-Chiguano GF, *et al.* Effects of Trigger Point Dry Needling for the Management of Knee Pain Syndromes: A Systematic Review and Meta-Analysis. *J Clin Med* 2020;9:2044 doi:10.3390/jcm9072044

20 Martimbianco A.L.C., Torloni M.R.R., Andriolo B.N., *et al.* Neuromuscular electrical stimulation (NMES) for patellofemoral pain syndrome. *Cochrane Database Syst Rev* 2017;12(12): CD011289 doi:10.1002/14651858.CD011289.pub2

21 Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647–g7647. doi:10.1136/bmj.g7647

22 Hutton B, Salanti G, Caldwell DM, *et al.* The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162:777–84. doi:10.7326/M14-2385

23 The Cochrane Collaboration. *Cochrane Handbook for systematic reviews of interventions* version 6.2 (update February 2021). Cochrane, 2021. Available from (http://www.training.cochrane.org/handbook) accessed May 2021.

24 Lack S, Barton C, Sohan O, et al. Proximal muscle rehabilitation is effective for patellofemoral pain: a systematic review with meta-analysis. *Br J Sports Med* 2015;49:1365-76. doi: 10.1136/bjsports-2015-094723.

25 Willy RW, Hoglund LT, Barton CJ, et al. Patellofemoral pain. *J Orthop Sports Phys Ther* 2019;49:CPG1–95. doi:10.2519/jospt.2019.0302

26 Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009;6:e1000100. doi:10.1371/journal.pmed.1000100

27 de Oliveira Silva D, Pazzinatto M., Rathleff MS, et al. Patient education for patellofemoral pain: a systematic review. *J Orthop Sports Phys Ther* 2020;50:388–96. doi:10.2519/jospt.2020.9400

28 Maher CG, Sherrington C, Herbert RD, et al. Reliability of the PEDro scale for rating quality of randomized controlled trials. *Phys Ther* 2003;83:713–21.

29 Foley NC, Bhogal SK, Teasell RW, et al. Estimates of quality and reliability with the physiotherapy evidence-based database scale to assess the methodology of randomized controlled trials of pharmacological and nonpharmacological interventions. *Phys Ther* 2006;86:817–24.

30 de Morton NA. The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. *Aust J Physiother* 2009;55:129–33. doi:10.1016/s0004-9514(09)70043-1

31 Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ* 2014;348:g1687. doi:10.1136/bmj.g1687

32 Yamato TP, Maher CG, Saragiotto BT, et al. Rasch analysis suggested that items from the template for intervention description and replication (TIDieR) checklist can be summed to create a score. *J Clin Epidemiol* 2018;101:28–34. doi:10.1016/j.jclinepi.2018.05.014

33 Briani RV, Ferreira AS, Pazzinatto MF, et al. What interventions can improve quality of life or psychosocial factors of individuals with knee osteoarthritis? a systematic review with meta-analysis of primary outcomes from randomised controlled trials. *Br J Sports Med* 2018;52:1031–8. doi:10.1136/bjsports-2017-098099

34 The Cochrane Collaboration. RevMan5, 2017. Available: http://community.cochrane.org/tools/review-production-tools/revman-5 accessed May 2021.

35 Dias S, Welton NJ, Caldwell DM, *et al.* Checking consistency in mixed treatment comparison meta-analysis. *Stat Med* 2010;29:932–44. doi:10.1002/sim.3767

36 Chaimani A, Salanti G. Visualizing Assumptions and Results in Network Meta-analysis: The Network Graphs Package. *Stata J* 2015;15:905–50. doi:10.1177/1536867X1501500402

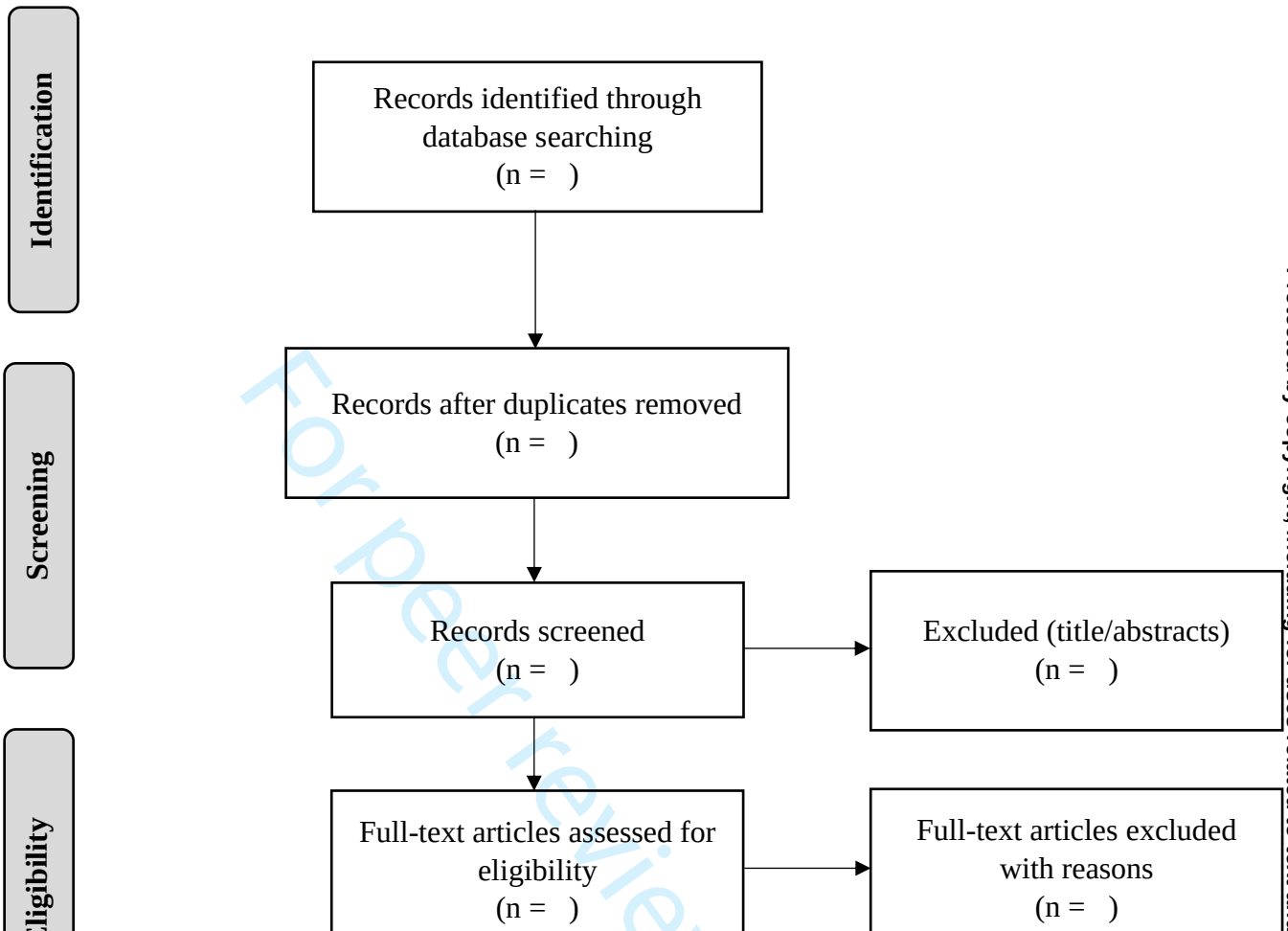
37 Furlan AD, Malmivaara A, Chou R, et al. 2015 Updated Method Guideline for Systematic Reviews in the Cochrane Back and Neck Group. *Spine (Phila Pa 1976)* 2015;40:1660–73. doi:10.1097/BRS.0000000000001061

38 Thomas MJ, Wood L, Selfe J, et al. Anterior knee pain in younger adults as a precursor to subsequent patellofemoral osteoarthritis: a systematic review. *BMC Musculoskelet Disord* 2010;11:201. doi:10.1186/1471-2474-11-201

39 Crossley KM. Is patellofemoral osteoarthritis a common sequela of patellofemoral pain? *Br J Sports Med* 2014;48:409–10. doi:10.1136/bjsports-2014-093445

Figure legends

Figure 1. Flow chart and descriptions of study selection.



Supplementary Table 1. Search strategy

PubMed (including MEDLINE)
1. “Patellofemoral pain syndrome” [Mesh] OR “Patellofemoral Pain” OR “Anterior Knee Pain” OR “Patellofemoral Dysfunction”
2. “Exercise Therapy”[Mesh] OR “Exercise”[Mesh] OR “Resistance Training”[Mesh] OR “Kinesiotherapy” OR “Physical Therapy Modalities”[Mesh] OR “exercise intervention” OR “therapeutic exercise” OR “exercise therapeutic” OR “physical therapy” OR “physiotherapy”
3. 1 AND 2
Embase (via Elsevier)
1. ‘Patellofemoral pain syndrome’ OR ‘Patellofemoral Syndrome’ OR ‘Anterior Knee Pain Syndrome’ ‘Patellofemoral Pain’ OR ‘Anterior Knee Pain’ OR ‘Patellofemoral Dysfunction’
2. ‘Exercise Therapy’ OR Exercise OR ‘Resistance Training’ OR ‘Strength Training’ OR Kinesiotherapy OR ‘Physical therapy’ OR physiotherapy OR ‘exercise intervention’ OR ‘therapeutic exercise’ OR ‘exercise therapeutic’ OR ‘physical therapy modalities’
3. 1 AND 2
Cochrane Central Register of Controlled Trials (CENTRAL)
1. patellofemoral pain OR MeSH descriptor: [Patellofemoral Pain Syndrome] explode all trees OR anterior knee pain OR patellofemoral dysfunction
2. MeSH descriptor: [Exercise Therapy] explode all trees OR MeSH descriptor: [Exercise] explode all trees OR MeSH descriptor: [Resistance Training] explode all trees OR Kinesiotherapy OR MeSH descriptor: [Physical Therapy Modalities] explode all trees OR exercise intervention OR therapeutic exercise OR exercise therapeutic
3. 1 AND 2

PEDro

1. **Abstract & Title:** Patellofemoral pain; **Body Part:** lower leg or knee; **Method:** clinical trial.
2. **Abstract & Title:** Patellofemoral pain syndrome; **Body Part:** lower leg or knee; **Method:** clinical trial.
3. **Abstract & Title:** Patellofemoral syndrome; **Body Part:** lower leg or knee; **Method:** clinical trial.
4. **Abstract & Title:** Anterior knee pain syndrome; **Body Part:** lower leg or knee; **Method:** clinical trial.
5. **Abstract & Title:** Anterior knee pain; **Body Part:** lower leg or knee; **Method:** clinical trial.
6. **Abstract & Title:** Patellofemoral dysfunction; **Body Part:** lower leg or knee; **Method:** clinical trial.

SPORTDiscus (via EBSCO)

1. patellofemoral pain syndrome OR patellofemoral syndrome OR anterior knee pain syndrome OR patellofemoral pain OR anterior knee pain OR patellofemoral dysfunction
2. exercise therapy OR exercise OR resistance training OR strength training OR kinesiotherapy OR physical therapy OR physiotherapy OR exercise intervention OR therapeutic exercise OR exercise therapeutic OR physical therapy modalities
3. 1 AND 2

CINAHL (via EBSCO)

1. patellofemoral pain syndrome OR patellofemoral syndrome OR anterior knee pain syndrome OR patellofemoral pain OR anterior knee pain OR patellofemoral dysfunction
2. exercise therapy OR exercise OR resistance training OR strength training OR kinesiotherapy OR physical therapy OR physiotherapy OR exercise intervention OR therapeutic exercise OR exercise therapeutic OR physical therapy modalities
3. 1 AND 2

Web of Science (via Clarivate Analytics)
1. TI=(Patellofemoral pain syndrome OR Patellofemoral Syndrome OR Anterior Knee Pain Syndrome OR Patellofemoral Pain OR Anterior Knee Pain OR Patellofemoral Dysfunction)
2. AB=(Patellofemoral pain syndrome OR Patellofemoral Syndrome OR Anterior Knee Pain Syndrome OR Patellofemoral Pain OR Anterior Knee Pain OR Patellofemoral Dysfunction)
3. TI=(Exercise Therapy OR Exercise OR Resistance Training OR Strength Training OR Kinesiotherapy OR Physical therapy OR physiotherapy OR exercise intervention OR therapeutic exercise OR exercise therapeutic OR physical therapy modalities)
4. AB=(Exercise Therapy OR Exercise OR Resistance Training OR Strength Training OR Kinesiotherapy OR Physical therapy OR physiotherapy OR exercise intervention OR therapeutic exercise OR exercise therapeutic OR physical therapy modalities)
5. 1 OR 2
6. 3 OR 4
7. 5 AND 6
OpenGrey
1. (“Patellofemoral pain syndrome” OR “Patellofemoral Syndrome” OR “Anterior Knee Pain Syndrome” OR “Patellofemoral Pain” OR “Anterior Knee Pain” OR “Patellofemoral Dysfunction”)
2. (“Exercise Therapy” OR Exercise OR “Resistance Training” OR “Strength Training” OR Kinesiotherapy OR “Physical therapy” OR physiotherapy OR “exercise intervention” OR “therapeutic exercise” OR “exercise therapeutic” OR “physical therapy modalities”)
3. 1 AND 2

MeSH: Medical Subject Headings; TI: title; AB: abstract

Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a (the protocol is not an update of a

		previous systematic review)	
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2,5
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	12,13
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	11
Support			
Sources	#5a	Indicate sources of financial or other support for the review	12
Sponsor	#5b	Provide name for the review funder and / or sponsor	12

Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	12
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	4,5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5,6
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5,6
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7,8
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7 (Supplementary appendix 1)

Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7-9
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or	8

		study level, or both; state how this information will be used in data synthesis	
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	9
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	9,10
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

Notes:

- 1b: n/a (the protocol is not an update of a previous systematic review)

- 10: 7 (Supplementary appendix 1) The PRISMA-P elaboration and explanation paper is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 04. June 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai