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Six Treatments Have Positive Effects at 3 Months for People With Patellofemoral Pain: A Systematic Review With Meta-analysis

OBJECTIVE: To determine the effects of nonsurgical treatments on pain and function in people with patellofemoral pain (PFP).

DESIGN: Systematic review with meta-analysis.

LITERATURE SEARCH: We searched MEDLINE, Web of Science, and Scopus databases from their inception until May 2022 for interventional randomized controlled trials (RCTs) in people with PFP.

STUDY SELECTION CRITERIA: We included RCTs that were scored ≥7 on the PEDro scale.

DATA SYNTHESIS: We extracted homogenous pain and function data at short- (≤3 months), medium- (>3 to ≤12 months) and long-term (>12 months) follow-up. Interventions demonstrated *primary efficacy* if outcomes were superior to sham, placebo, or wait-and-see control. Interventions demonstrated *secondary efficacy* if outcomes were superior to an intervention with primary efficacy.

RESULTS: We included 65 RCTs. Four interventions demonstrated short-term *primary efficacy*: knee-targeted exercise therapy for pain (standardized mean difference [SMD], 1.16; 95% CI: 0.66, 1.66) and function (SMD, 1.19; 95% CI: 0.51, 1.88), combined interventions for pain (SMD, 0.79; 95% CI: 0.26, 1.29) and function (SMD, 0.98; 95% CI: 0.47, 1.49), foot orthoses for global rating of change (OR = 4.31; 95% CI: 1.48, 12.56), and lower-quadrant manual therapy for function (SMD, 2.30; 95% CI: 1.60, 3.00). Two interventions demonstrated short-term *secondary efficacy* compared to knee-targeted exercise therapy: hip-and-knee-targeted exercise therapy for pain (SMD, 1.02; 95% CI: 0.58, 1.46) and function (SMD, 1.03; 95% CI: 0.61, 1.45), and knee-targeted exercise therapy and perineural dextrose injection for pain (SMD, 1.34; 95% CI: 0.72, 1.95) and function (SMD, 1.21; 95% CI: 0.60, 1.82).

CONCLUSIONS: Six interventions had positive effects at 3 months for people with PFP, with no intervention adequately tested beyond this time point. *J Orthop Sports Phys Ther 2022;52(11):750-768. Epub: 8 September 2022. doi:10.2519/jospt.2022.11359*

KEY WORDS: *knee, patellofemoral joint, systematic review/meta-analysis*

Patellofemoral pain (PFP) affects up to 29% of active adolescents and 23% of both active and sedentary adults in the general population.[97] People with PFP have a poorer health-related quality of life[68] and lower physical activity levels than their peers,[45] and may be on a trajectory to patellofemoral osteoarthritis.[23,102] Patellofemoral pain has a poor prognosis, with over 50% of people reporting persistent pain more than 5 years posttreatment.[65] Clinicians and researchers need to do more to understand how PFP is best managed.

Consensus statements[21,27] and clinical practice guidelines[12,107,109] have summarized the evidence for nonsurgical treatment of PFP, but it remains unclear which nonsurgical interventions demonstrate primary efficacy (ie, superior to placebo, sham, or wait-and-see) or secondary efficacy (ie, superior to an intervention with established efficacy).[75] Winters et al[110] recently developed and published a living systematic review with network meta-analysis. Findings broadly agreed with recommendations in previous consensus statements[21,27] and guideline documents,[12,107,109] with all treatments (education, exercise, education and foot orthoses, education and exercise, and patellar taping/mobilisation) reported as superior to wait-and-see control at 3-months follow-up.

Despite the strength of network meta-analysis methods, the narrow inclusion criteria of RCTs reporting only global rating of change (GROC) or worst pain scores in the past week meant that only 22 trials were included.[110] These methodological decisions limit the certainty, completeness, and generalizability of the findings. Potentially relevant RCTs using valid outcome measures, including the

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anterior knee pain (Kujala) scale[24] and the knee injury and osteoarthritis outcome score PFP subscale (KOOS-PF)[26] were excluded. An aggregate meta-analysis with broader eligibility criteria is warranted and may provide greater insight for clinical practice.

This systematic review with meta-analysis aimed to determine which nonsurgical treatments have primary or secondary efficacy for pain and function outcomes in people with PFP, by synthesizing data from all available high-quality RCTs at short-, medium-, and long-term follow-up.

METHODS

We preregistered this systematic review with PROSPERO (CRD42019152252). It was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.[73] There was 1 deviation from the registered protocol in line with our grant application: To align with the methods of Morrissey et al,[75] we decided to include and synthesize data only from RCTs with adequate methodological quality.

Search Strategy

We used the following search terms, duplicated from the work of Barton et al[12]: (patell* OR femoropat* OR anterior knee pain) AND (pain OR syndrome OR dysfunction) AND (clinical trial OR controlled trial OR random*). We searched MEDLINE, Web of Science, and Scopus from their inception until May 2022, with the English language and human participants as limitations. A single investigator (C.B.) completed an additional citing reference search in Google Scholar and hand searched the reference lists of subsequent included studies.

Inclusion Criteria

One investigator (B.S.N.) exported all identified studies into EndNote X7 (Thompson Reuters, Philadelphia, PA). We used the following eligibility criteria, again duplicated from the work of Barton et al[12]: (1) RCTs involving participants with PFP and (2) RCTs investigating nonsurgical interventions. Two independent investigators (B.S.N. and C.B.) reviewed all titles and abstracts to determine eligibility, with full texts reviewed if necessary. A third investigator (S.D.L.) was available, but not required, to resolve discrepancies.

Methodological Quality Assessment (PEDro) and Risk of Bias (RoB2)

We used the PEDro scale[69] to determine *methodological* quality given its strong convergent validity and correlation with the Cochrane Risk of Bias II (RoB2) tool.[114] Two independent investigators (B.S.N. and C.B.) applied the PEDro scale to all eligible studies, with a third investigator (S.D.L.) available, but not required, to resolve discrepancies. Scores of ≥7 were considered to reflect high quality,[76] and these trials were included in quantitative synthesis. A single author (B.S.N.) applied the Cochrane RoB2 tool[99] to retained studies and risk of bias (RoB) was classified as being high, low, or of some concern.

Diagnostic Criteria

We applied the PFP diagnostic checklist as described by Barton et al,[13] a 7-item checklist that identifies the key criteria for diagnosing PFP, to all retained high-quality RCTs. This was completed by 2 independent investigators (B.S.N. and C.B.) with a third investigator (S.D.L.) available, but not required, to resolve discrepancies. A higher score indicates a more comprehensive diagnostic process with a greater number of criteria reported.

Data Extraction

Data pertaining to study characteristics were extracted from all retained RCTs by a single investigator (C.B.) and the accuracy reviewed by a second investigator (B.N.). These included the primary intervention, sample size, participant age, body mass index (BMI), symptom duration, and study duration (**APPENDIX A**, available at www.jospt.org). We then extracted within-group mean change and associated standard deviation (SD) for outcomes pertaining to pain (eg, numerical pain-rating scale) and function (eg, the Kujala scale), with a maximum of 2 outcomes per retained RCT. Where RCTs presented more than one pain or function outcome, we extracted the smallest within-group effect to minimize the potential for type I error. Ordinal data (eg, GROC) were extracted if presented in the absence of nominal data. Authors who did not report data in these forms were contacted up to 3 times. Follow-up was defined from commencement of treatment as short- (≤3 months), medium- (>3 but <12 months), and long-term (≥12 months).[32] When RCTs provided multiple data points within 1 follow-up period (eg, 4 and 8 weeks), the latest data point was extracted.[75]

Statistical Methods

We performed statistical analyses using Review Manager 5.4 (The Cochrane Collaboration, Copenhagen, Denmark). Analyses were conducted by a single investigator (B.S.N.), and the accuracy of data entry was reviewed by a second investigator (S.D.L.). If the variance of a reported mean change was reflected by either a 95% confidence interval (CI) or standard error (SE) instead of SD, these were converted as per the Cochrane guidelines.[56] Within-group mean change and SD were used to calculate standardized mean differences (SMDs) with 95% CIs and were classified as small (≤0.59), large (0.60-1.19), and very large (≥1.20).[39] Nominal data were used to calculate odds ratios (ORs) with 95% CIs and were interpreted as small (1.0-1.99), large (2.0-4.99), and very large (≥5.0).[41] Data were pooled and meta-analysis conducted where studies were deemed to be methodologically homogeneous and treatment modalities comparable, using a random-effects model.[17] Statistical homogeneity for pooled data was determined using I^2 statistics, with heterogeneity defined as $I^2>50\%$, $P<.05$.[57]

Evaluating Efficacy

We adapted and extended the approach defined by Morrissey et al,[75] where interventions are explored by an adequately

powered RCT or data pooling, demonstrated the following:

- **Primary proof of efficacy**: a significant difference compared with sham, placebo, or a true wait-and-see control
- **Secondary proof of efficacy**: a significant difference between an intervention or combined interventions where at least one has primary efficacy at the defined time point
- **Superiority**: a significant difference between 2 interventions with proven efficacy at the defined time point
- **Equivalence**: no significant difference between 2 interventions where at least one has proven efficacy at the defined time point
- **No additional benefit**: no significant difference between interventions with proven efficacy at the defined time point, with an additional intervention in 1 treatment arm (ie, an A+B versus A design)
- **No indication of efficacy**: equivalent or inferior to sham, placebo, or a true wait-and-see control
- **Inadequately tested**: a comparison of interventions where efficacy is obscured by inadequate trial power or a comparison between interventions without primary efficacy

We determined adequate sample size using G*Power (version 3.1.9.6, Heinrich-Heine University, Germany), with 23 participants per group required to identify the minimum detectable change score of 2 points for numerical pain-rating scale and 10 points for the Kujala Scale[24] with $\alpha = 5\%$ and $\beta = 0.90$. Data from single inadequately powered RCTs or pooled data failing to achieve adequate power were considered inadequately tested and were not included in formulating efficacy recommendations.

Certainty of Evidence

Two authors (B.S.N. and S.D.L.) independently determined certainty of evidence to be high, moderate, low, or very low for each outcome using the GRADE approach.[49] Certainty of evidence started as high and was then adjusted according to specific criteria,[33,52] with a ceiling of moderate certainty applied to outcomes from single studies. *Risk of bias* was used to rate down 1 level if serious (>50% and ≤75% of pooled data coming from studies with high or some concern of RoB, or a single study with some concern of RoB) or 2 levels if very serious (>75% of pooled data coming from studies with high or some concern of RoB, or a single study with a high concern of RoB). *Inconsistency* was used to rate down 1 level if $I^2 > 50\%$ or where data pooling was not possible.[51] *Imprecision* was used to rate down 1 or 2 levels if either 95% CI crossed 1 or 2 effect size thresholds, respectively.[50] *Effect size* was used to rate up 1 level if large, or 2 levels if very large.[49] *Publication bias* could not be considered as no outcome involved data pooling from >10 RCTs.[61]

RESULTS

The systematic search identified 5740 titles and abstracts for screening. After removing duplicates and studies that failed to meet the inclusion criteria, and adding 30 eligible studies identified following cited reference searching, 170 RCTs were eligible for quality appraisal (**FIGURE 1**).

Quality Screening and Eligibility

After applying the PEDro scale to all eligible RCTs, 105 trials were rated as low quality and excluded (**APPENDIX B**, available at www.jospt.org), and 65 trials were rated as high quality and retained for data synthesis (**TABLE**).[1–3,6–9,14–16,18–20,22,25,29–31,35–38,41–44,46,47,53–55,59,60,62,66,67,71,72,74,77–79,83,85–91,93–96,98,100,101,103,105,108,111–113,115–117] Extracted data pertaining to study characteristics for retained trials are found in **APPENDIX A** (available at www.jospt.org), including 3796 participants with a median symptom duration of 43 months (range 6-114). The retained trials investigated exercise therapies (n = 30), electrotherapies (n = 9), manual therapies (n = 6), foot orthoses (n = 4), dry needling/acupuncture (n = 4), injection therapies (n = 3), taping techniques (n = 3), gait retraining (n = 2), combined interventions (encompassing hip-and-knee-targeted exercise therapy, vastus medialis oblique biofeedback, soft tissue stretching, and patellar taping; n = 2), blood flow restriction training (n = 1), and psychological therapies (n = 1). Fifteen RCTs did not present data in a manner allowing for meta-analysis, and these authors did not respond to requests or could not provide raw data upon contact.[7,19,30,44,53,59,60,67,90,93–95,101,111,112]

Diagnostic Criteria

After applying the PFP diagnostic validity scale to all high-quality studies retained for data synthesis, scores ranged from 0 to 7 with a mean (SD) of 4.7 (±1.8). A retropatellar or prepatellar pain location was the least frequently reported domain (30/65 trials), and symptoms consistent with PFP were the most frequently reported domain (54/61 trials). Only 2 high-quality trials reported no domains at all, and nine reported all described domains (**APPENDIX C**, available at www.jospt.org).

Risk of Bias

Of the 65 high quality RCTs retained for meta-analysis, 23 were at high RoB,[1,6,9,14,15,18–20,30,31,36,47,53,87,89,91,95,96,105,111,112,115] 20 had some concerns,[3,8,16,29,37,43,59,60,62,67,72,77,78,83,86,90,94,100,108,117] and 22 were at low RoB,[2,7,22,25,35,38,41,42,44,46,55,66,71,74,85,88,93,98,101,103,113,116] (**APPENDIX D**, available at www.jospt.org).

Efficacy Estimations

A summary of all efficacy estimations is detailed in an evidence gap map (**FIGURE 2**).

Primary Proof of Efficacy (FIGURE 3)

Knee-Targeted Exercise Therapy Versus Wait-and-See Control Based on data from 2 RCTs,[42,98] there was high-certainty evidence of large effect that knee-targeted exercise therapy is efficacious at short-term follow-up, improving pain (SMD, 1.16; 95% CI: 0.66, 1.66, $I^2 = 0\%$) compared to a wait-and-see control.

Based on data from 2 RCTs,[42,98] there was moderate-certainty evidence of large effect that knee-targeted exercise therapy is efficacious at short-term follow-up,

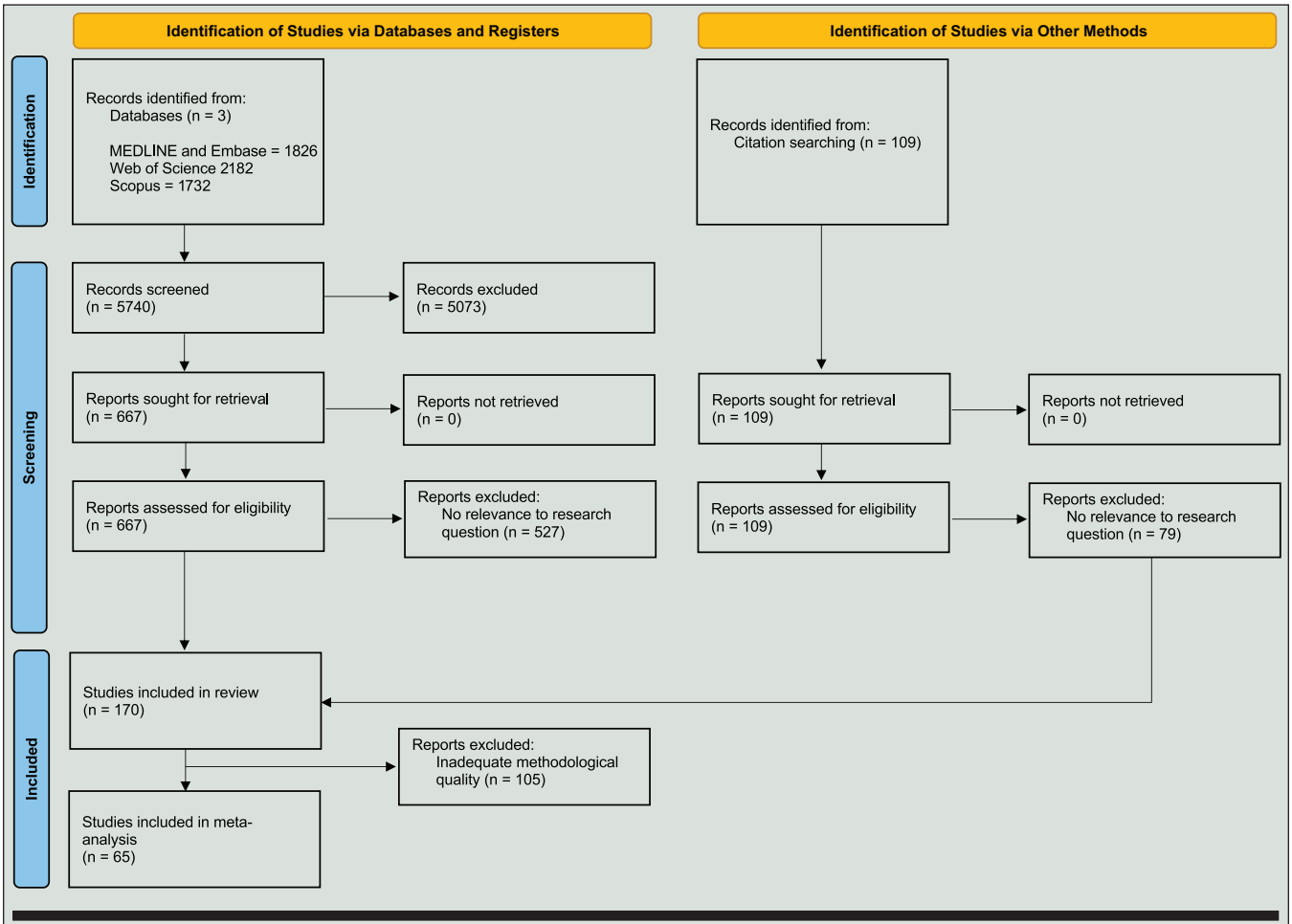


FIGURE 1. The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram.

improving function (SMD, 1.19; 95% CI: 0.51, 1.88; I^2 = 45%) compared to a wait-and-see control.

Combined Interventions Versus Wait-and-See Control Based on data from 1 adequately powered RCT,[25] there was low certainty of evidence of large effect that combined interventions are efficacious at short-term follow-up, improving pain (SMD, 0.79; 95% CI: 0.29, 1.29) and function (SMD, 0.98; 95% CI: 0.47, 1.49) compared to a wait-and-see control.

Foot Orthoses Versus Sham Orthoses Based on data from 1 adequately powered RCT,[22] there was low certainty of evidence of large effect that foot orthoses are efficacious at short-term follow-up and are associated with a positive GROC score (OR = 4.31; 95% CI: 1.48, 12.56) when compared to sham orthoses.

Lower-Quadrant Manual Therapy Versus Wait-and-See Control Based on data from 1 adequately powered RCT,[116] there was moderate-certainty evidence of very large effect that lower-quadrant manual therapy is efficacious at short-term follow-up, improving function (SMD, 2.30; 95% CI: 1.60, 3.00) compared to a wait-and-see control.

Secondary Proof of Efficacy (FIGURE 4A)

Hip-and-Knee-Targeted Exercise Therapy Versus Knee-Targeted Exercise Therapy Based on data from 2 adequately and 4 inadequately powered RCTs,[31,41,62,77,79,91] there was very low certainty of evidence of large effect that hip-and-knee-targeted exercise therapy is efficacious at short-term follow-up, improving pain (SMD, 1.02; 95% CI: 0.58, 1.46; I^2 = 51%) compared to knee-targeted exercise therapy.

Based on data from 2 adequately and 3 inadequately powered RCTs,[31,41,62,77,91] there was very low certainty of evidence of large effect that hip-and-knee-targeted exercise therapy is efficacious at short-term follow-up, improving function (SMD, 1.03; 95% CI: 0.61, 1.45; I^2 = 65%) compared to knee-targeted exercise therapy.

Knee-Targeted Exercise Therapy and Perineural Dextrose Injection Versus Knee-Targeted Exercise Therapy Based on data from 1 adequately powered RCT,[43] there was moderate-certainty evidence of large effect that perineural dextrose injection

TABLE PEDro Scores for the Retained High-Quality Randomized Controlled Trials

Study	A	B	C	D	E	F	G	H	I	J	Total
Azab[7]	1	1	1	0	0	1	1	1	1	1	8
Aghakeshizadeh[1]	1	1	1	1	0	1	1	0	1	1	8
Albornoz-Cabello[2]	1	1	1	0	0	1	1	1	1	1	8
Almeida[3]	1	1	0	0	0	1	1	1	1	1	7
Arrebola[6]	1	1	1	0	1	1	0	0	1	1	7
Bagheri[8]	1	1	1	0	0	1	1	0	1	1	7
Bakhitary[9]	1	1	1	0	0	0	1	1	1	1	7
Baldon[31]	1	1	0	1	0	0	1	1	1	1	7
Behrangrad[14]	1	1	1	1	1	0	1	0	1	1	8
Boitrago[29]	1	1	1	0	0	1	1	0	1	1	8
Bolgla[15]	1	0	1	0	0	1	1	1	1	1	7
Bonacci[16]	1	1	1	0	0	1	1	0	1	1	7
Callaghan[18]	1	1	1	1	0	1	1	0	1	1	8
Celik[19]	1	0	1	1	0	0	1	1	1	1	7
Clark[20]	1	0	1	0	0	1	1	1	1	1	7
Coelho[66]	1	1	1	0	0	1	1	1	1	1	8
Collins[22]	1	1	1	0	0	1	1	1	1	1	8
Crossley[25]	1	1	1	1	0	1	1	1	1	1	9
Das[30]	1	0	1	1	0	1	1	0	1	1	7
Emamvirdi[36]	1	1	1	1	0	0	1	0	1	1	7
Esculier[37]	1	1	0	0	0	1	1	1	1	1	7
Espi-Lopez[38]	1	1	1	0	0	1	1	1	1	1	8
Fukuda[42]	1	1	1	0	0	1	1	1	1	1	8
Fukuda[41]	1	1	1	0	0	1	1	1	1	1	8
Garcia-Triana[43]	1	1	1	0	0	1	1	0	1	1	7
Giles[44]	1	1	1	1	0	1	1	1	1	1	9
Glaviano[46]	1	1	1	0	0	1	1	1	1	1	9
Gobbi[47]	1	1	1	1	0	0	1	0	1	1	7
Hains[53]	1	1	1	1	0	0	1	1	1	1	8
Halabchi[54]	1	1	1	0	0	0	1	1	1	1	7
Hart[55]	1	1	1	1	0	1	1	1	1	0	8
Hott[60]	1	1	0	0	0	1	1	1	1	1	7
Hott[59]	1	1	0	0	0	1	1	1	1	1	7
Iammarrone[94]	1	1	1	0	0	1	1	0	1	1	7
Ismail[62]	1	1	1	0	0	1	1	0	1	1	7
Ma[67]	1	1	1	0	0	1	1	0	1	1	7
Matthews[71]	1	1	0	1	1	1	1	1	1	1	9
Mills[72]	1	1	1	1	0	1	1	0	1	1	8
Molgaard[74]	1	1	1	0	0	1	0	1	1	1	7
Motealleh[77]	1	1	1	0	0	1	1	0	1	1	7
Nakagawa[78]	1	1	1	1	0	1	1	0	1	1	8
Osteras[83]	1	1	1	0	0	1	1	0	1	1	7
Priore[84]	1	1	1	0	0	1	1	1	1	1	8
Rabelo[35]	1	1	1	0	0	1	1	1	1	1	8
Rasti[86]	1	1	1	1	0	1	1	0	1	1	8

Table continues on next page.

and knee-targeted exercise therapy is efficacious at short-term follow-up, improving pain (SMD, 1.34; 95% CI: 0.72, 1.95) and function (SMD, 1.21; 95% CI: 0.60, 1.82) compared to knee-targeted exercise therapy.

Superiority (FIGURE 4B)

Combined Interventions Versus Knee-Targeted Exercise Therapy Based on data from 1 adequately powered RCT,[54] there was very low certainty of evidence of large effect that combined interventions are superior to knee-targeted exercise therapy at short-term follow-up, improving pain (SMD, 1.03; 95% CI: 0.45, 1.60) and function (SMD, 1.05; 95% CI: 0.47, 1.62).

Equivalence (FIGURE 4C)

Hip-Targeted Exercise Therapy Versus Knee-Targeted Exercise Therapy Based on data from 1 adequately powered RCT,[15] there was very low certainty of evidence that hip-targeted exercise therapy is equivalent to knee-targeted exercise therapy at short-term follow-up, with no significant differences identified for pain (SMD, 0.06; 95% CI: −0.22, 0.34) or function (SMD, −0.03; 95% CI: −0.30, 0.25) outcomes.

Foot Orthoses Versus Hip-Targeted Exercise Therapy Based on data from 1 adequately powered RCT,[71] there was low-certainty evidence that foot orthoses are equivalent to hip-targeted exercise therapy at short-term follow-up, with neither intervention associated with a positive GROC score (OR = 0.92; 95% CI: 0.52, 1.63).

No Additional Benefit (FIGURE 5A)

Combined Interventions and Foot Orthoses Versus Combined Interventions Based on data from 1 adequately powered RCT,[22] there was very low certainty of evidence that combined interventions and foot orthoses provided no additional benefit to combined interventions alone at short-term follow-up (OR = 0.75; 95% CI: 0.16, 3.58).

Hip-and-Knee-Targeted Exercise Therapy and Dry Needling Versus Hip-and-Knee-Targeted Exercise Therapy Alone Based on pooling data from 1 adequately and 1 inadequately powered RCT,[38,117] there

TABLE PEDro Scores for the Retained High-Quality Randomized Controlled Trials (continued)

Study	A	B	C	D	E	F	G	H	I	J	Total
Rathleff[87]	1	0	1	0	0	1	1	1	1	1	7
Riel[88]	1	1	1	1	0	0	1	1	1	1	8
Rogvi-Hansen[89]	1	0	1	1	1	1	1	0	1	0	7
Saad[90]	1	1	0	0	0	1	1	1	1	1	7
Sahin[91]	1	1	1	0	0	1	1	0	1	1	7
Selhorst[93]	1	1	1	1	1	1	1	1	1	1	10
Shah[95]	1	1	1	1	0	1	1	0	1	1	8
Singer[96]	1	0	1	1	1	1	1	1	1	0	8
Song[98]	1	1	1	0	0	1	1	1	1	1	8
Sutlive[100]	1	1	0	1	0	1	1	1	1	1	8
Syme[101]	1	1	1	0	0	1	1	1	1	1	8
van den Dolder[103]	1	1	1	0	0	1	1	1	1	1	8
Van Linschoten[104]	1	1	1	0	0	0	1	1	1	1	7
Whittingham[108]	1	1	1	0	0	1	1	0	1	1	7
Witvrouw[112]	1	1	1	0	0	1	1	0	1	1	7
Witvrouw[111]	1	1	1	0	0	1	1	0	1	1	7
Yanez-Alvarez[115]	1	0	1	0	0	1	1	1	1	1	7
Zago[116]	1	1	1	0	0	1	1	1	1	1	8
Zarei[117]	1	1	0	0	0	1	1	1	1	1	7
Wu[113]	1	1	1	0	0	1	1	1	1	1	8
	100%	88%	86%	32%	9%	85%	97%	62%	100%	95%	

Abbreviations: A, random allocation; B, concealed allocation; C, comparable groups at baseline; D, participant blinding; E, clinician blinding; F, outcome assessor blinding; G, >85% data collection; H, intention-to-treat analyses; I, between-group statistical comparisons; J, variability reported.

was low-certainty evidence that hip-and-knee-targeted exercise therapy and dry needling provided no additional benefit to hip-and-knee-targeted exercise therapy alone at short-term follow-up for pain (SMD, −0.95; 95% CI: −2.68, 0.78; I^2 = 93%) or function.

Based on pooling data from 1 adequately and 1 inadequately powered RCT,[38,117] there was moderate-certainty evidence that hip-and-knee-targeted exercise therapy and dry needling provided no additional benefit to hip-and-knee-targeted exercise therapy alone at short-term follow-up for function (SMD, −1.26; 95% CI: −3.38, 0.85; I^2 95%).

Hip-and-Knee-Targeted Exercise Therapy and Vibration Therapy Versus Hip-and-Knee-Targeted Exercise Therapy Alone Based on data from 2 adequately and 1 inadequately powered RCTs,[86,113,115] there was very low certainty of evidence that hip-and-knee-targeted exercise therapy and vibration therapy provided no additional benefit to hip-and-knee-targeted exercise therapy alone at short-term follow-up for pain (SMD, −0.07; 95% CI: −0.42, 0.28; I^2 = 0%).

Based on data from 2 adequately powered RCTs,[113,115] there was very low certainty of evidence that hip-and-knee-targeted exercise therapy and vibration therapy provided no additional benefit to hip-and-knee-targeted exercise therapy alone at short-term follow-up for function (SMD, 0.76; 95% CI: −0.85, 2.37; I^2 = 93%).

No Indication of Efficacy (FIGURE 5B)

Hip-and-Knee-Targeted Exercise Therapy and Hyaluronic Acid Injection Versus Hip-and-Knee-Targeted Exercise Therapy and Sham Injection (Saline) Based on data from 1 adequately powered RCT,[55] there was very low certainty of evidence that hip-and-knee-targeted exercise therapy and hyaluronic acid injection had no indication of efficacy compared to hip-and-knee-targeted exercise therapy and sham injection at short-term follow-up for pain (SMD, −0.21; 95% CI: −0.64, 0.21).

Based on data from 1 adequately powered RCT,[55] there was low-certainty evidence that hip-and-knee-targeted exercise therapy and hyaluronic acid injection had no indication of efficacy compared to hip-and-knee-targeted exercise therapy and sham injection at short-term follow-up, with a superior change in function in the sham group (SMD, −0.57; 95% CI: −1.00, −0.13).

Based on data from 1 adequately powered RCT,[55] there was low-certainty evidence that hip-and-knee-targeted exercise therapy and hyaluronic acid injection had no indication of efficacy compared to hip-and-knee-targeted exercise therapy and sham injection at medium-term follow-up for pain (SMD, 0.00; 95% CI: −0.42, 0.43).

Based on data from 1 adequately powered RCT,[55] there was very low certainty of evidence that hip-and-knee-targeted exercise therapy and hyaluronic acid injection had no indication of efficacy compared to hip-and-knee-targeted exercise therapy and sham injection at medium-term follow-up for function (SMD, −0.39; 95% CI: −0.81, 0.04).

Foot Orthoses Versus Sham Orthoses Based on data from 1 adequately powered RCT,[22] there was very low certainty of evidence that foot orthoses had no indication of efficacy when compared to sham orthoses at medium-term follow-up and are not associated with a positive GROC score (OR = 1.13; 95% CI: 0.38, 3.39).

Based on data from 1 adequately powered RCT,[22] there was very low certainty of evidence that foot orthoses had no indication of efficacy when compared to sham orthoses at long-term follow-up and are not associated with a positive

Intervention	Control	Outcome Measure	Short Term	Medium Term	Long Term
Interventions with primary proof of efficacy					
Knee-targeted exercise therapy	Wait and see	Pain (2 studies)	Positive, high certainty, 1.16 (0.66, 1.66)$^{+}$		
		Function (2 studies)	Positive, moderate certainty, 1.19 (0.51, 1.88)$^{+}$		
Combined interventions	Wait and see	Pain (1 study)	Positive, low certainty, 0.79 (0.26, 1.29)$^{+}$		
		Function (1 study)	Positive, low certainty, 0.98 (0.47, 1.49)$^{+}$		
Foot orthoses	Sham foot orthoses	Outcome (1 study)	Positive, low certainty, OR 4.31 (1.48, 12.56)$^{+}$	Neutral, very low certainty, OR 1.13 (0.38, 3.39)	Neutral, very low certainty, OR 1.99 (0.69, 5.75)
Lower-quadrant manual therapy	Wait and see	Pain (2 studies)	Neutral, moderate certainty, 2.19 (−1.02, 5.41)		
		Function (1 study)	Positive, moderate certainty, 2.30 (1.60, 3.00)$^{+}$		
Interventions with secondary proof of efficacy					
Hip-and-knee-targeted exercise therapy	Knee-targeted exercise therapy	Pain (6 studies)	Positive, very low certainty, 1.02 (0.58, 1.46)$^{+}$		
		Function (5 studies)	Positive, low certainty, 1.03 (0.61, 1.45)$^{+}$		
Knee-targeted exercise therapy and perineural dextrose injection	Knee-targeted exercise therapy	Pain (1 study)	Positive, moderate certainty, 1.34 (0.72, 1.95)$^{+}$		
		Function (1 study)	Positive, moderate certainty, 1.21 (0.60, 1.82)$^{+}$		
Interventions with superiority					
Combined interventions	Knee-targeted exercise therapy	Pain (1 study)	Positive, very low certainty, 1.03 (0.45, 1.60)$^{+}$		
		Function (1 study)	Positive, very low certainty, 1.05 (0.47, 1.62)$^{+}$		
Interventions with equivalence					
Hip-targeted exercise therapy	Knee-targeted exercise therapy	Pain (1 study)	Neutral, very low certainty, 0.06 (−0.22, 0.34)		
		Function (1 study)	Neutral, very low certainty, −0.11 (−0.65, 0.44)		
Foot orthoses	Hip-targeted exercise therapy	Outcome (1 study)	Neutral, low certainty, OR 0.92 (0.52, 1.63)		
Interventions with no additional benefit					
Combined interventions and foot orthoses	Combined interventions	Outcome (1 study)	Neutral, vey low certainty, OR 0.75 (0.16, 3.58)		
Hip-and-knee-targeted exercise therapy and dry needling	Hip-and-knee-targeted exercise therapy	Pain (2 studies)	Neutral, low certainty, −0.95 (−2.68, 0.78)		
		Function (2 studies)	Neutral, moderate certainty, −1.26 (−3.38, 0.85)		
Hip-and-knee-targeted exercise therapy and vibration	Hip-and-knee-targeted exercise therapy	Pain (3 studies)	Neutral, very low certainty, −0.07 (−0.42, 0.28)		
		Function (2 studies)	Neutral, very low certainty, 0.76 (−0.85, 2.37)		
Interventions with no indication of efficacy					
Hip-and-knee-targeted exercise therapy and hyaluronic acid injection	Hip-and-knee-targeted exercise therapy and sham injection	Pain (1 study)	Neutral, very low certainty, −0.21 (−0.64, 0.21)	Neutral, low certainty, 0.00 (−0.42, 0.43)	
		Function (1 study)	Negative, low certainty, −0.57 (−1.00, −0.13)	Neutral, very low certainty, −0.39 (−0.81, 0.04)	
Dry needling	Sham needling	Pain (1 study)	Neutral, very low certainty, −0.19 (−0.73, 0.35)		
		Function (1 study)	Neutral, very low certainty, 0.02 (−0.51, 0.55)		

Key		
Positive	Neutral	Negative
High	High	High
Moderate	Moderate	Moderate
Low	Low	Low
Very low	Very low	Very low

FIGURE 2. Evidence gap map.

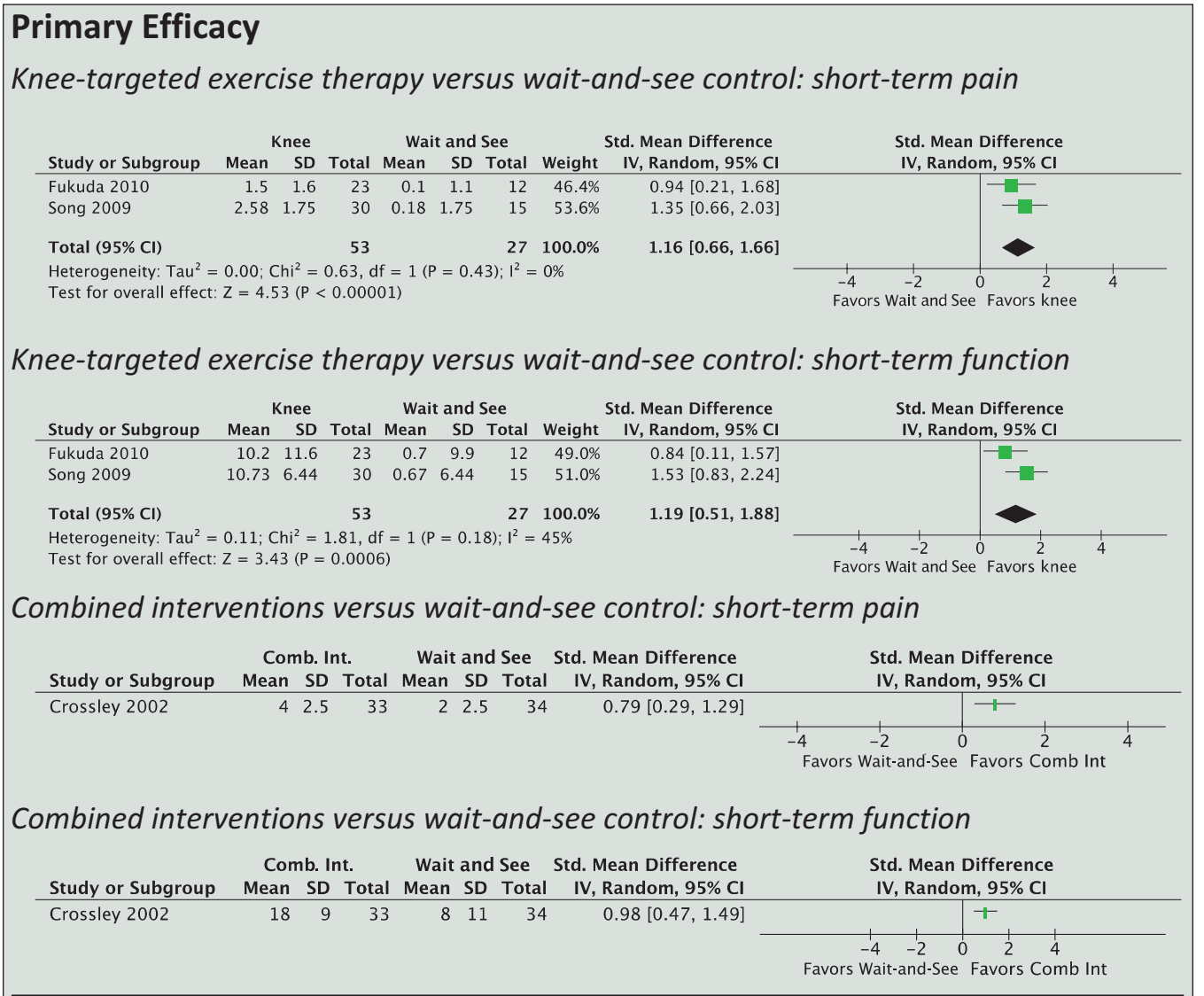


FIGURE 3. Forest plots for primary efficacy outcomes.

GROC score (OR = 1.99; 95% CI: 0.69, 5.75).

Lower-Quadrant Manual Therapy Versus a Wait-and-See Control Based on pooling data from 1 adequately and 1 inadequately powered RCT,[103,116] there was moderate-certainty evidence that lower-quadrant manual therapy had no indication of efficacy compared to wait-and-see control at short-term follow-up for pain (SMD, 2.19; 95% CI: −1.02, 5.41; I^2 = 97%).

Dry Needling Versus Sham Needling Based on data from 1 adequately powered RCT,[100] there was very low certainty of evidence that dry needling had no indication of efficacy compared to sham needling at short-term follow-up for pain (SMD, −0.19; 95% CI: −0.73, 0.35) and function (SMD, 0.02; 95% CI: −0.51, 0.55).

Inadequately Tested

Twenty interventions or combinations of interventions had been inadequately tested in isolation because of the absence of comparison against an intervention with primary efficacy, or wait-and-see control, sham, or placebo, or low sample size (n<23 per group; **APPENDIX E**, available at www.jospt.org), including the following:

1. Education
2. Hip-and-knee-targeted exercise therapy and education
3. Hip-and-knee-targeted exercise therapy and Pilates
4. Hip-and-knee-targeted exercise therapy and placebo taping
5. Hip-and-knee-targeted exercise therapy and patellar taping

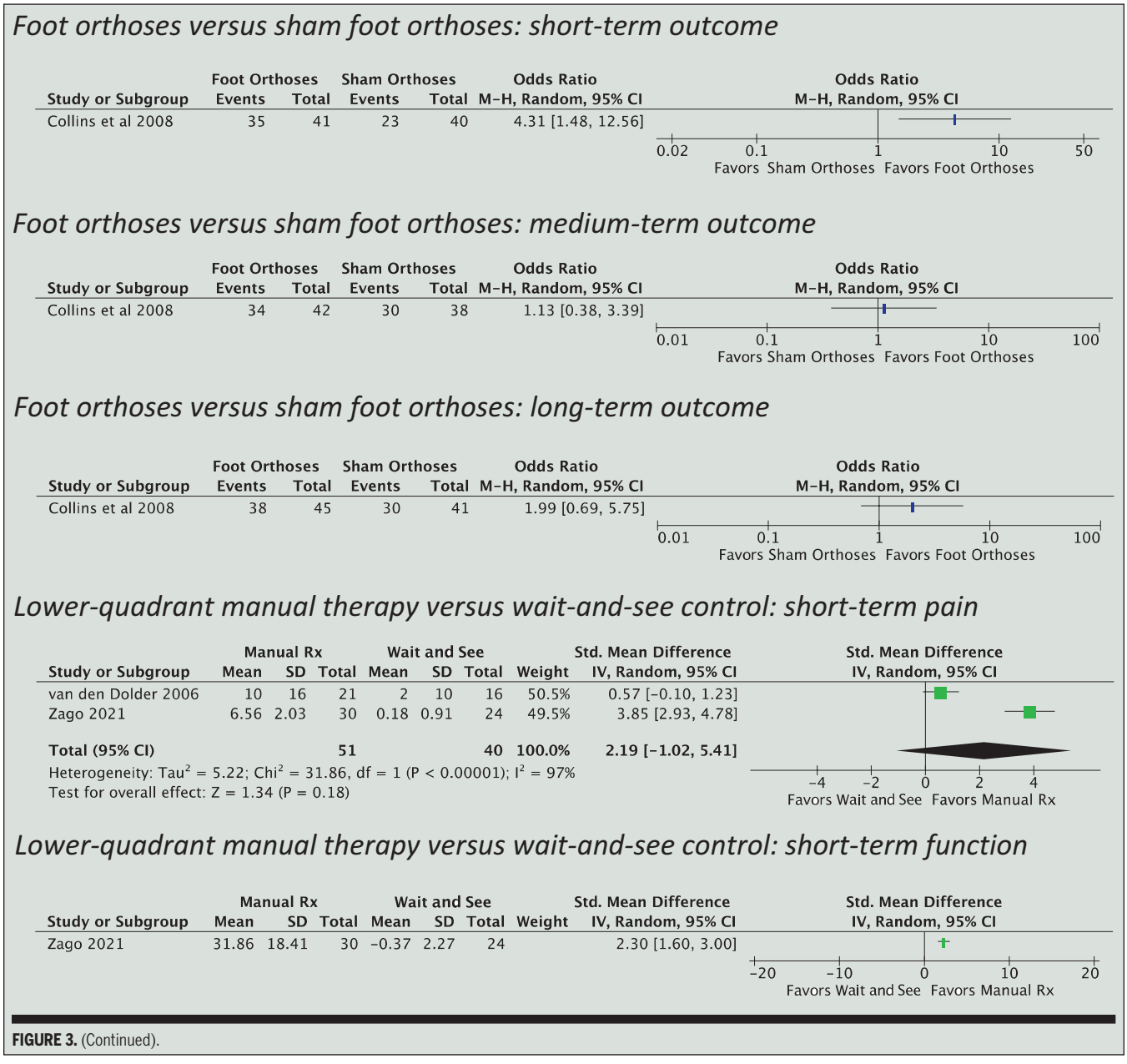


FIGURE 3. (Continued).

6. Hip-and-knee-targeted exercise therapy and femoral taping
7. Patellar bracing
8. Hip-and-knee-targeted exercise therapy and mindfulness meditation
9. Foot orthoses and foot exercises
10. Pulsed shortwave diathermy
11. Pulsed shortwave diathermy and exercise therapy
12. Laser
13. Knee-targeted exercise therapy and Botox injection
14. Spinal manipulation
15. Ankle mobilization with movement
16. Trigger point therapy
17. Hip-and-knee-targeted exercise therapy with neuromuscular stimulation
18. Step rate retraining and education
19. Step rate retraining and minimalist footwear
20. Psychologically informed intervention (video)

DISCUSSION

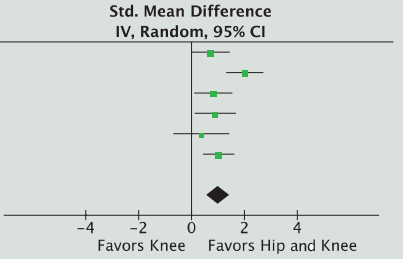
Nonsurgical interventions are appropriate treatment options for people with PFP. Knee-targeted exercise therapy, combined interventions, foot orthoses, and lower-quadrant

(A) Secondary Efficacy

Hip-and-knee-targeted exercise therapy versus knee-targeted exercise therapy: short-term pain

Study or Subgroup	Hip and Knee Mean	SD	Total	Knee Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Baldon 2014	5.7	2.3	15	3.6	3.3	16	17.2%	0.71 [−0.01, 1.44]
Fukuda 2012	4.2	1.7	25	1.4	0.9	24	17.9%	2.01 [1.32, 2.71]
Ismail 2013	3.2	0.9	16	2.26	1.3	16	17.3%	0.82 [0.09, 1.54]
Motealleh et al 2019	40.71	14.39	14	28.57	11.67	14	16.0%	0.90 [0.12, 1.68]
Nakagawa 2008	2.6	2.5	7	1.3	3.9	7	11.2%	0.37 [−0.69, 1.43]
Sahin 2016	3	1.21	25	1	2.43	25	20.5%	1.03 [0.43, 1.62]
Total (95% CI)			**102**			**102**	**100.0%**	**1.02 [0.58, 1.46]**

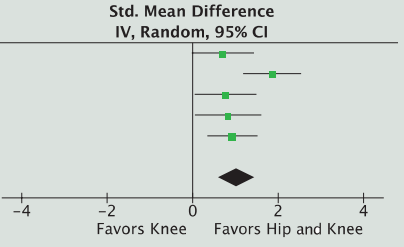
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 10.25$, df = 5 (P = 0.07); $I^2 = 51\%$
Test for overall effect: Z = 4.59 (P < 0.00001)



Hip-and-knee-targeted exercise therapy versus knee-targeted exercise therapy: short-term function

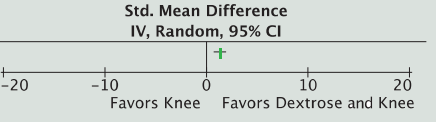
Study or Subgroup	Hip and Knee Mean	SD	Total	Knee Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Baldon 2014	19.5	11.9	15	12.7	6.2	16	19.0%	0.70 [−0.02, 1.43]
Fukuda 2012	19.8	9.1	25	2.8	8.9	24	20.5%	1.86 [1.18, 2.54]
Ismail 2013	13.7	5.5	16	8.6	7.3	16	19.2%	0.77 [0.05, 1.49]
Motealleh et al 2019	19.42	7.96	14	13.21	6.53	14	17.6%	0.83 [0.05, 1.61]
Sahin 2016	11.6	5.8	25	5.6	6.9	25	23.7%	0.93 [0.34, 1.51]
Total (95% CI)			**95**			**95**	**100.0%**	**1.03 [0.61, 1.45]**

Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 7.36$, df = 4 (P = 0.12); $I^2 = 46\%$
Test for overall effect: Z = 4.79 (P < 0.00001)



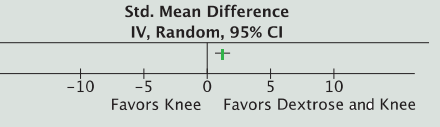
Knee-targeted exercise therapy and dextrose injection versus knee-targeted exercise therapy: short-term pain

Study or Subgroup	Dextrose and Knee Mean	SD	Total	Knee Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Garcia Triana 2021	5.2	2	25	2.5	1.98	25		1.34 [0.72, 1.95]



Knee-targeted exercise therapy and dextrose injection versus knee-targeted exercise therapy: short-term function

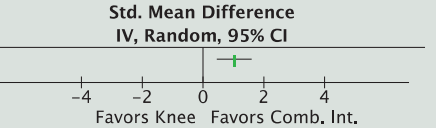
Study or Subgroup	Dextrose and Knee Mean	SD	Total	Knee Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Garcia Triana 2021	23.2	10.7	25	11.1	8.9	25		1.21 [0.60, 1.82]



(B) Superiority

Combined interventions versus knee-targeted exercise therapy: short-term pain

Study or Subgroup	Comb. Int. Mean	SD	Total	Knee Mean	SD	Total	Std. Mean Difference IV, Random, 95% CI
Halabachi 2015	3.74	2.09	26	1.97	1.2	27	1.03 [0.45, 1.60]



Combined interventions versus knee-targeted exercise therapy: short-term function

Study or Subgroup	Comb. Int. Mean	SD	Total	Knee Mean	SD	Total	Std. Mean Difference IV, Random, 95% CI
Halabachi 2015	20.42	11.57	26	10.25	7.15	27	1.05 [0.47, 1.62]

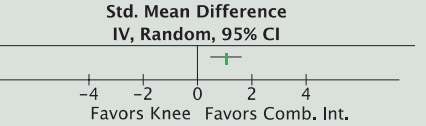
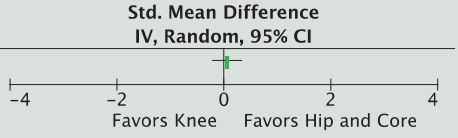


FIGURE 4. Forest plots for (A) secondary efficacy, (B) superiority, and (C) equivalence outcomes.

(C) Equivalence

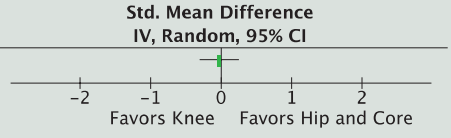
Hip-targeted exercise therapy versus knee-targeted exercise therapy: short-term pain

Study or Subgroup	Hip and Core Mean	Hip and Core SD	Hip and Core Total	Knee Mean	Knee SD	Knee Total	Std. Mean Difference IV, Random, 95% CI
Bolgla 2016	3.11	2.22	111	2.98	2.08	88	0.06 [−0.22, 0.34]



Hip-targeted exercise therapy versus knee-targeted exercise therapy: short-term function

Study or Subgroup	Hip and Core Mean	Hip and Core SD	Hip and Core Total	Knee Mean	Knee SD	Knee Total	Std. Mean Difference IV, Random, 95% CI
Bolgla 2016	12.58	11.93	111	12.9	13.55	88	−0.03 [−0.30, 0.25]



Foot orthoses versus hip-targeted exercise therapy: short-term outcome

Study or Subgroup	Foot Orthoses Events	Foot Orthoses Total	Hip Exercise Events	Hip Exercise Total	Odds Ratio M-H, Random, 95% CI
Matthews et al 2020	48	100	46	92	0.92 [0.52, 1.63]

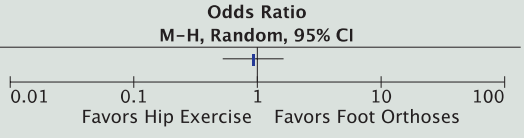


FIGURE 4. (Continued).

manual therapy all have primary efficacy (ie, superior to placebo, sham, or wait-and-see) in the short-term when compared to a wait-and-see approach. Hip-and-knee-targeted exercise therapy and knee-targeted exercise therapy combined with perineural dextrose injection have secondary efficacy (ie, superior to an intervention with established efficacy) in the short-term when compared to knee-targeted exercise therapy alone. Combined interventions produced superior outcomes compared to knee-targeted exercise, suggesting that providing more care may improve outcomes in the short term. Only foot orthoses and hip-and-knee-targeted exercise therapy combined with hyaluronic acid injection have been adequately tested beyond a short-term follow-up.

Interventions With Proof of Efficacy

There is a dearth of evidence to guide clinical practice, service design, and policy recommendations when considering longer-term outcomes. We sought to include a broad range of outcomes from high-quality RCTs in our data synthesis. Recent data syntheses of PFP treatments have focused on a narrow range of outcomes from RCTs of variable quality,[110] or all available RCTs combined with expert consensus[21] have been used to formulate recommendations. Our results support previous work:[21,110] a wait-and-see approach is not appropriate given the number of interventions with short-term efficacy, and people with PFP should be referred for active rehabilitation. Our results do not agree with previous conclusions that there is evidence for medium- and long-term efficacy for exercise therapy[21] or combined interventions and education[110] because of the absence of adequately tested primary or comparator interventions against a true, no-intervention, wait-and-see control. From the high-quality RCTs included in our review, 6 of 7 efficacious or equivalent interventions were inadequately tested beyond short-term follow-up, and a further 18 interventions were inadequately tested at all time points.

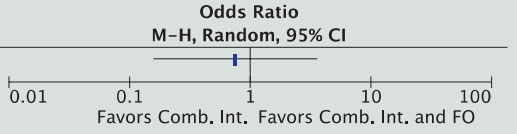
Although combined hip-and-knee-targeted exercise therapy has benefit compared to knee-targeted exercise therapy at short-term follow-up, it has not been adequately tested beyond this time point. One in 2 people with PFP report persistent pain up to 8 years postdiagnosis,[65] so treatments with a long-term effect are clearly required. The dearth of high-quality exercise therapy trials with an adequate control arm beyond a short-term follow-up highlights the disparity between reported symptom persistence[65] and follow-up duration in current RCTs intended to underpin clinical practice. Exercise therapy RCTs that do include a long-term follow-up[41,105] have not involved an appropriate control and are inadequate for guiding high-quality decisions.

There are ethical challenges associated with having a true wait-and-see group (ie, no treatment) in a long-term follow-up trial, with some treatment (eg, basic education) considered a more ethical comparison. Funding and conducting high-quality trials of adequately developed

(A) No Additional Benefit

Combined interventions and foot orthoses versus combined interventions: short-term outcome

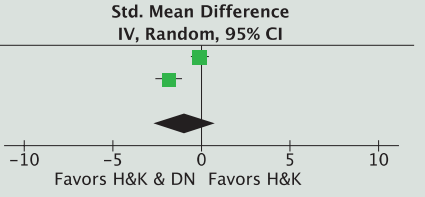
Study or Subgroup	Comb. Int. and FO Events	Total	Comb. Int. Events	Total	Odds Ratio M-H, Random, 95% CI
Collins et al 2008	38	42	38	41	0.75 [0.16, 3.58]



Hip-and-knee-targeted exercise therapy and dry needling versus hip-and-knee-targeted exercise therapy: short-term pain

Study or Subgroup	H&K Mean	SD	Total	H&K & DN Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Espi-Lopez 2017	1.3	2.68	30	1.6	3.75	30	51.3%	−0.09 [−0.60, 0.42]
Zarei 2019	1	2.5	20	4.5	0.76	20	48.7%	−1.86 [−2.61, −1.10]
Total (95% CI)			**50**			**50**	**100.0%**	**−0.95 [−2.68, 0.78]**

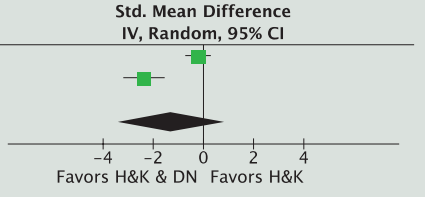
Heterogeneity: Tau² = 1.45; Chi² = 14.53, df = 1 (P = 0.0001); I² = 93%
Test for overall effect: Z = 1.08 (P = 0.28)



Hip-and-knee-targeted exercise therapy and dry needling versus hip-and-knee-targeted exercise therapy: short-term function

Study or Subgroup	H&K Mean	SD	Total	H&K & DN Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Espi-Lopez 2017	9.2	12	30	12	13.93	30	51.2%	−0.21 [−0.72, 0.30]
Zarei 2019	3.01	7.95	20	18.15	3.91	20	48.8%	−2.37 [−3.20, −1.54]
Total (95% CI)			**50**			**50**	**100.0%**	**−1.26 [−3.38, 0.85]**

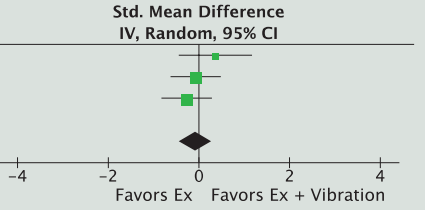
Heterogeneity: Tau² = 2.20; Chi² = 18.99, df = 1 (P < 0.0001); I² = 95%
Test for overall effect: Z = 1.17 (P = 0.24)



Hip-and-knee-targeted exercise therapy and vibration versus hip-and-knee-targeted exercise therapy: short-term pain

Study or Subgroup	Ex + Vibration Mean	SD	Total	Ex Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Rasti 2020	2.66	0.88	12	2.23	1.35	12	19.1%	0.36 [−0.44, 1.17]
Wu 2021	23.9	20.47	25	25.4	20.47	25	40.6%	−0.07 [−0.63, 0.48]
Yanez Alvarez 2021	0.05	8.5	25	4.6	21.8	25	40.2%	−0.27 [−0.83, 0.29]
Total (95% CI)			**62**			**62**	**100.0%**	**−0.07 [−0.42, 0.28]**

Heterogeneity: Tau² = 0.00; Chi² = 1.61, df = 2 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.38 (P = 0.70)



Hip-and-knee-targeted exercise therapy and vibration versus hip-and-knee-targeted exercise therapy: short-term function

Study or Subgroup	Ex + Vibration Mean	SD	Total	Ex Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Wu 2021	10.2	10.53	25	10.8	10.53	25	50.5%	−0.06 [−0.61, 0.50]
Yanez Alvarez 2021	21	16.9	25	0	7.3	25	49.5%	1.59 [0.95, 2.23]
Total (95% CI)			**50**			**50**	**100.0%**	**0.76 [−0.85, 2.37]**

Heterogeneity: Tau² = 1.26; Chi² = 14.42, df = 1 (P = 0.0001); I² = 93%
Test for overall effect: Z = 0.92 (P = 0.36)

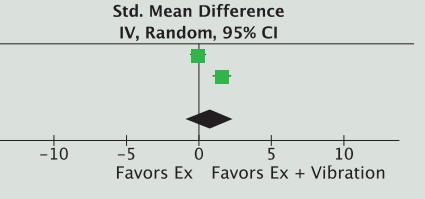


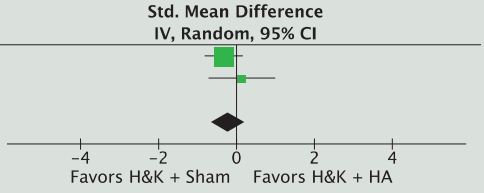
FIGURE 5. Forest plots (A) for no additional benefit outcomes and (B) for nonefficacy outcomes. Abbreviations: DN, dry needling; Ex, exercise; FO, foot orthoses; HA, hyaluronic acid; H&K, hip and knee.

(B) Interventions With No Indication of Efficacy

Hip-and-knee-targeted exercise therapy and hyaluronic acid injection versus hip-and-knee-targeted exercise & sham injection: short-term pain

Study or Subgroup	H&K + HA Mean	SD	Total	H&K + Sham Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Hart 2019 (F)	2.65	2.87	34	3.6	2.84	31	75.4%	−0.33 [−0.82, 0.16]
Hart 2019 (M)	3.34	3.02	11	2.91	2.86	10	24.6%	0.14 [−0.72, 1.00]
Total (95% CI)			**45**			**41**	**100.0%**	**−0.21 [−0.64, 0.21]**

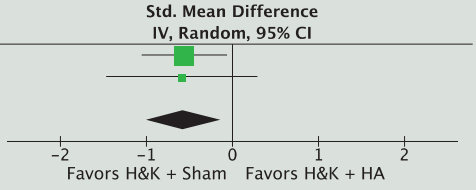
Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 0.98 (P = 0.33)



Hip-and-knee-targeted exercise therapy and hyaluronic acid injection versus hip-and-knee-targeted exercise and sham injection: short-term function

Study or Subgroup	H&K + HA Mean	SD	Total	H&K + Sham Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Hart 2019 (F)	7.85	14.24	34	16.2	15.25	31	75.8%	−0.56 [−1.06, −0.06]
Hart 2019 (M)	9.63	11.67	11	17.26	13.24	10	24.2%	−0.59 [−1.47, 0.29]
Total (95% CI)			**45**			**41**	**100.0%**	**−0.57 [−1.00, −0.13]**

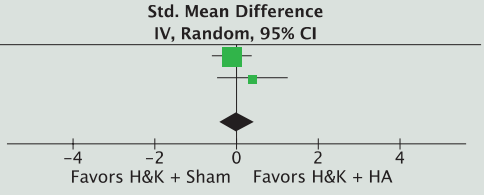
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0%
Test for overall effect: Z = 2.57 (P = 0.01)



Hip-and-knee-targeted exercise therapy and hyaluronic acid injection versus hip-and-knee-targeted exercise and sham injection: medium-term pain

Study or Subgroup	H&K + HA Mean	SD	Total	H&K + Sham Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Hart 2019 (F)	3.19	3.16	34	3.57	3.27	31	76.0%	−0.12 [−0.60, 0.37]
Hart 2019 (M)	4.16	3	11	2.97	2.89	10	24.0%	0.39 [−0.48, 1.25]
Total (95% CI)			**45**			**41**	**100.0%**	**0.00 [−0.42, 0.43]**

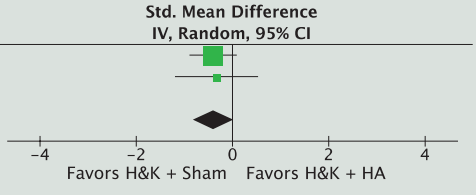
Heterogeneity: Tau² = 0.00; Chi² = 0.99, df = 1 (P = 0.32); I² = 0%
Test for overall effect: Z = 0.02 (P = 0.98)



Hip-and-knee-targeted exercise therapy and hyaluronic acid injection versus hip-and-knee-targeted exercise and sham injection: medium-term function

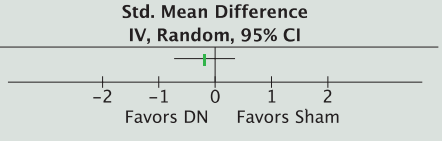
Study or Subgroup	H&K + HA Mean	SD	Total	H&K + Sham Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Hart 2019 (F)	9.74	15.56	34	16.4	17.04	31	75.5%	−0.40 [−0.90, 0.09]
Hart 2019 (M)	10.47	38.15	11	20.41	10.79	10	24.5%	−0.33 [−1.20, 0.53]
Total (95% CI)			**45**			**41**	**100.0%**	**−0.39 [−0.81, 0.04]**

Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%
Test for overall effect: Z = 1.77 (P = 0.08)



Dry needling versus sham needling: short-term pain

Study or Subgroup	Sham Mean	SD	Total	DN Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Sutlive 2018	1.42	2.23	26	1.81	1.84	27		−0.19 [−0.73, 0.35]



Dry needling versus sham needling: short-term function

Study or Subgroup	Sham Mean	SD	Total	DN Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Sutlive 2018	6.63	9.87	26	6.41	8.37	29		0.02 [−0.51, 0.55]

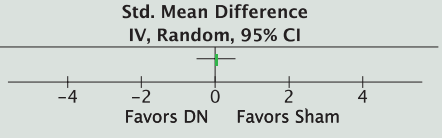


FIGURE 5. (Continued).

interventions with long-term follow-up (≥12 months) is an urgent research priority.

Both foot orthoses and lower-quadrant manual therapy should be offered to people with PFP, with the variable response and absence of effect beyond the short-term forming part of the shared-decision making between patient and clinician. Prefabricated foot orthoses are efficacious in the short term when compared to sham foot orthoses but not at medium- or long-term follow-up, and they were equivalent to a hip exercise therapy protocol at short-term follow-up. There was greater variability in outcome for lower-quadrant manual therapy when compared to a wait-and-see approach, with a significant short-term improvement in function, but not pain. Wide CIs for both pain and function outcomes following manual therapy suggest variable results across individuals. There are currently limited or no data available to predict response to foot orthoses or manual therapy, respectively, with baseline foot mobility or hip strength recently reported to not mediate treatment outcome.[71] Decisions should not rely solely on clinical trial data, but they should also incorporate clinician experience[28] and patient preferences.[10]

Patellofemoral pain has a multifaceted presentation with a variable aetiology[80] and treatment targets across multiple domains.[40,64,92] A combined interventions approach, encompassing hip-and-knee-targeted exercise therapy, vastus medialis oblique biofeedback, soft tissue stretching, and patellar taping is superior to a wait-and-see control and to knee-targeted exercise therapy in isolation. This variable aetiology may explain why combining multiple interventions results in short-term success. However, the fact that combined interventions used in the included trials do not address all potential treatment targets[64] may explain why short-term success inconsistently translates into long-term resolution.[22,81,111] Developing treatments that target all relevant deficits, such as using graded exposure in the presence of kinesophobia[106] or a strength training programme in the presence of measured muscle weakness,[34] represents a plausible step forward in evidence-informed clinical practice.[10,84]

Interventions With No Indication of Efficacy

There is no role for dry needling, vibration therapy, or hyaluronic acid injection combined with exercise therapy when treating PFP. Dry needling of the quadriceps was no better than sham needling, and dry needling of the quadratus lumborum, gluteus medius, and quadriceps combined with hip-and-knee-targeted exercise therapy had no additional benefit above hip-and-knee-targeted exercise therapy alone. Vasti muscle timing local to the patellofemoral joint has been reported to be associated with a diagnosis of PFP.[4] Isolated interventions aiming to affect these variables did not have indication of efficacy, offered no additional benefit, or have been inadequately tested. These findings agree with the most recently published consensus statement[21] despite the addition of new high-quality RCTs. Vibration therapy offered no additional benefit for either pain or function over and above hip-and-knee targeted exercise therapy. The wide range of mechanisms that purportedly underpin the effects of vibration therapy in healthy people should be investigated in people with PFP prior to further RCTs. We also identified that hyaluronic acid injection combined with hip-and-knee-targeted exercise therapy was ineffective when compared to sham injection combined with hip-and-knee-targeted exercise therapy. Hyaluronic acid is effective for tibiofemoral osteoarthritis[5] when injected locally and may contribute to symptom improvement through the stimulation of native synovial fluid production.[55] While PFP is proposed as part of a continuum with patellofemoral osteoarthritis,[23] the hypothesized synovial fluid production mechanism of hyaluronic acid is of questionable relevance for the typical PFP demographic.

Clinical Implications

People with PFP should not be offered wait-and-see care. Clinicians should strongly consider engaging people with persistent PFP in hip-and/or-knee exercise therapy and combining interventions (ie, exercise plus another intervention) may result in superior short-term outcomes. Foot orthoses, lower-quadrant manual therapy, and perineural dextrose injection (alongside exercise) should also be offered to people with persistent PFP as part of a shared decision-making approach. Clinicians should be open and honest with people with PFP about the absence of supporting evidence for interventions beyond short-term follow-up.

Limitations

We searched MEDLINE, Web of Science, and Scopus, and limited our search to studies published in the English language. Searching alternative or additional databases may have led to the inclusion of additional data, which may have altered the results, but we mitigated this with a citing reference search and by hand searching the reference lists of included studies. Our data extraction was completed by a single author and subsequently checked for accuracy by a second author, and our RoB assessment was completed by a single author. Having second authors perform these tasks independently before reaching consensus may have increased their accuracy. We did not consider publication bias, and it is possible that trials with negative outcomes could have influenced the results of our review.

Given the high number of RCTs in the PFP field, we decided to include only those with high methodological quality defined using the PEDro scale. An alternative approach would be to include all eligible trials and allow study quality and RoB to factor into the certainty of evidence using GRADE, which may have produced different results. The reporting of exercise prescription parameters has previously been highlighted as frequently insufficient[58] to enable clinical translation. We did not appraise included RCTs relative to any reporting guideline(s), which limits any evaluation of the specific parameters that resulted in the reported outcomes.

Thirteen of 65 trials did not provide data in a format suitable for meta-analysis despite multiple requests. One hundred and five RCTs were excluded for inadequate methodological quality. Future RCTs should aim to ensure a robust methodology by concealing allocation, ensuring blinding of outcome assessors, and performing intention-to-treat analyses; to include a long-term follow-up; and to adhere to published reporting guidelines, for example, the recent REPORT-PFP consensus.[11]

Of the 65 retained high-quality RCTs, the minimum mean symptom duration was 6 months. The best approach to managing PFP of a shorter duration is unclear, and careful clinical reasoning is required when applying the outcomes of our review to people with a symptom duration of under 6 months. It is plausible that interventions delivered to people with PFP of a shorter duration would have a different effect to those delivered once symptoms have persisted for a longer period. As a symptom duration of >4 months is associated with a poorer prognosis,[63,70] developing and investigating appropriate interventions that can be delivered and readily accessed by people with PFP of a shorter duration are important.

Knee-targeted exercise therapy was the only intervention with high-certainty evidence, and there is a dearth of RCTs that investigate intervention effects beyond short-term follow-up. We identified 6 interventions with positive effects, yet it remains difficult to determine for whom these interventions are most likely to deliver benefits, or by what mechanism(s). This is in part because RCTs do not translate into clinical practice in isolation.[48] The outcomes of this review need to be synthesized with the preferences of people with PFP[10] and expert clinical reasoning[28] to fully define current best practice for PFP.

CONCLUSIONS

Interventions for persistent PFP that improved pain and function outcomes at short-term follow-up included knee-targeted exercise, combined interventions, foot orthoses, lower-quadrant manual therapy, knee-targeted exercise combined with perineural dextrose injection, and hip-and-knee-targeted exercise. These interventions should be offered to people with persistent PFP. No intervention demonstrated efficacy beyond a short-term follow-up.

KEY POINTS

FINDINGS: Six interventions have positive effects on pain and function outcomes at 3 months for people with persistent PFP (a symptom duration of >6 months). No intervention demonstrated efficacy beyond short-term follow-up, and several interventions are inadequately tested to allow for efficacy evaluation.

IMPLICATIONS: People with persistent PFP should not be offered wait-and-see care given there are appropriate interventions with evidence of benefit available in the short term.

CAUTION: Efficacy statements refer only to short-term follow-up and to people with persistent PFP.

STUDY DETAILS

AUTHOR CONTRIBUTIONS: Drs Neal, Lack, Morrissey, and Barton conceived and designed the study. Drs Neal, Lack, and Bartholomew collected and analyzed data. Drs Neal, Lack, Morrissey, and Barton interpreted the data. Drs Neal and Lack drafted the manuscript with input from all authors who read and approved the final manuscript.

DATA SHARING: All data relevant to the study are included in this article or are available as appendices.

PATIENT AND PUBLIC INVOLVEMENT: No patients or members of the public were involved in this manuscript.

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APPENDIX A

DATA EXTRACTION FROM THE RETAINED HIGH-QUALITY RANDOMIZED CONTROLLED TRIALS

Study	Sample Size (F:M) Age in Years (mean ±) BMI in kg/m2 (mean ±) Symptom Duration in Months (mean ±) Group 1	Group 2	Group 3	Group 4	Furthest Follow-up (Weeks)	Extracted Pain Outcome	Extracted Function Outcome
Exercise therapy							
Aghakeshizadeh[1] **IT**	23 (15:8) 29.9 ±8.0 23.9 ±1.3 74 ±NR	23 (12:11) 28.6 ±7.7 23.7 ±1.9 65 ±NR	24 (13:11) 28.9 ±6.5 23.7 ±1.7 43 ±NR	N/A	6	VAS	Kujala
Almeida[3] **IT**	26 (26:0) 24.9 ±4.6 23.0 ±3.5 50.8 ±38.9	26 (26:0) 24.9 ±5.0 24.8 ±2.6 47.3 ±39.6	N/A	N/A	26	NPRS	Kujala
Azab[7] **IT, DUM**	17 (12:5) 15.2 ±1.1 21.8 ±1.3 26.2 ±6.7	17 (10/7) 15.7 ±1.1 22.1 ±1.2 23.1 ±5.8	N/A	N/A	12	VAS	Kujala
Bagheri[8] **IT**	15 (15:0) 27.9 ±7.5 23.7 ±2.3 NR	14 (14:0) 28.8 ±6.8 23.2 ±2.6 NR	N/A	N/A	26	VAS	KOS-ADLS
Bakhtiary[9] **IT**	16 (16:0) 22.3 ±1.7 NR NR	16 (16:0) 21.8 ±0.6 NR NR	N/A	N/A	5	VAS	NR
Baldon[31] **SE**	15 (15:0) 22.7 ±3.2 20.6 ±2.9 60 ±NR	16 (16:0) 21.3 ±2.6 22.3 ±2.5 27 ±NR	N/A	N/A	12	W-VAS	LEFS
Boitrago[29] **IT**	30 (30:0) NR NR NR	30 (30:0) NR NR NR	N/A	N/A	12	NPRS	Kujala
Bolgla[15] **E**	105 (73:32) 29.4 ±0.7 NR NR	80 (51:29) 29.3 ±0.9 NR NR	N/A	N/A	6	VAS	Kujala
Clark[20] **IT**	20 (10:10) 26.0 ±7.4 24.8 ±5.7 NR	20 (8:12) 29.5 ±6.2 24.9 ±4.2 NR	19 (9:10) 29.3 ±6.8 25.0 ±3.9 NR	22 (9:13) 27.1 ±7.2 25.2 ±4.2 NR	52	VAS	WOMAC
Emamvirdi[36] **IT**	32 (32:0) 22.1 ±5.9 22.1 ±1.6 NR	32 (32:0) 23.1 ±6.5 21.2 ±1.0 NR	N/A	N/A	6	VAS	NR
Fukuda[42] **PE**	23 (23:0) 24.0 ±7.0 NR NR	20 (20:0) 25.0 ±6.0 NR NR	21 (21:0) 25.0 ±7.0 NR NR	N/A	8	NPRS-AS	Kujala

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APPENDIX A (CONTINUED)

Study	Sample Size (F:M) Age in Years (mean ±) BMI in kg/m2 (mean ±) Symptom Duration in Months (mean ±) Group 1	Group 2	Group 3	Group 4	Furthest Follow-up (Weeks)	Extracted Pain Outcome	Extracted Function Outcome
Fukuda[41] **PE**	24 (24:0) 23.0 ±3.0 24.5 ±3.0 21.0 ±17.7	24 (25:0) 22.0 ±3.0 23.6 ±2.7 23.2 +29.0	N/A	N/A	52	NPRS-DS	Kujala
Hott[60] **DUM**	37 (24:13) 28.5 ±6.2 NR NR	39 (25:14) 27.8 ±8.6 NR NR	36 (24:12) 26.3 ±7.0 NR NR	N/A	12	U-VAS	Kujala
Hott[59] **DUM**	37 (24:13) 28.5 ±6.2 NR NR	39 (25:14) 27.8 ±8.6 NR NR	36 (24:12) 26.3 ±7.0 NR NR	N/A	52	U-VAS	Kujala
Ismail[62] **PE**	16 (11:5) 20.8 ±2.7 NR NR	16 (12:4) 21.2 ±3.2 NR NR	N/A	N/A	6	VAS	Kujala
Motealleh[77] **PE**	14 (14:0) 30.4 ±6.1 23.2 ±3.3 NR	14 (14:0) 28.4 ±5.7 22.6 ±3.0 NR	N/A	N/A	4	VAS	Kujala
Nakagawa[78] **PE**	7 (NR) NR NR NR	7 (NR) NR NR NR	N/A	N/A	6	W-VAS	NR
Osteras[82] **IT**	21 (15:6) 33.0 ±12.4 NR 43.2 ±32.4	19 (17:2) 26.8 ±10.5 NR 34.8 ±37.2	N/A	N/A	12	VAS	FIQ
Rabelo[35] **IT**	17 (17:0) 25.3 ±8.1 22.8 ±1.8 49.3 ±40.5	17 (17:0) 25.9 ±5.5 21.8 ±2.8 46.2 ±33.0	N/A	N/A	26	NPRS	Kujala
Rasti[86] **IT**	12 (0:12) 25.9 ±5.2 24.0 ±0.8 NR	12 (0:12) 24.2 ±5.2 24.3 ±0.0 NR	N/A	N/A	4	VAS	NR
Rathleff[87] **IT**	59 (51:8) 17.3 ±0.9 22.4 ±3.1 39 ±NR	62 (46:16) 17.2 ±1.1 21.1 ±2.5 36 ±NR	N/A	N/A	104	W-VAS	KOOS-ADL
Riel[88] **IT**	20 (16:4) 16.5 ±1.5 22.0 ±2.3 NR	20 (19:1) 16.9 ±1.5 22.3 ±3.6 NR	N/A	N/A	6	NR	Kujala
Saad[90] **DUM**	10 (10:0) 23.2 ±2.5 21.8 ±1.7 NR	10 (10:0) 22.5 ±1.1 22.0 ±2.0 NR	10 (10:0) 21.3 ±1.2 21.9 ±1.3 NR	10 (10:0) 23.2 ±1.0 21.3 ±1.3 NR	8	VAS	Kujala

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APPENDIX A (CONTINUED)

Study	Sample Size (F:M) Age in Years (mean ±) BMI in kg/m2 (mean ±) Symptom Duration in Months (mean ±) Group 1	Group 2	Group 3	Group 4	Furthest Follow-up (Weeks)	Extracted Pain Outcome	Extracted Function Outcome
Sahin[91] **SE**	25 (25:0) 35.0 ±5.9 26.4 ±3.5 6 ±NR	25 (25:0) 33.3 ±6.5 25.5 ±4.4 8 ±NR	N/A	N/A	12	VAS	Kujala
Song[98] **PE**	29 (21:8) 38.6 ±10.8 22.2 ±3.2 41.8 ±36.1	30 (22:8) 40.2 ±9.9 23.0 ±3.0 38.3 ±34.2	30 (26:4) 42.9 ±9.8 22.5 ±2.1 27.7 ±41.0	N/A	8	W-VAS	Lysholm
Syme[101] **DUM**	23 (13:10) 28.8 ±8.0 25.5 ±1.3 49.0 ±37.5	23 (13:10) 27.3 ±7.9 25.5 ±1.3 45.5 ±35.3	23 (15:8) 28.5 ±6.4 26.2 ±1.2 50.5 ±41.3	N/A	8	NPRS	FIQ
Van Linschoten[105] **IT**	65 (42:23) 24.7 ±8.6 23.2 ±3.9 NR	66 (42:24) 23.3 ±7.8 23.0 ±3.4 NR	N/A	N/A	52	VAS-A	Kujala
Witvrouw[112] **DUM**	30 (20:10) NR NR NR	30 (20:10) NR NR NR	N/A	N/A	12	VAS	Kujala
Witvrouw[111] **DUM**	30 (20:10) NR NR NR	30 (20:10) NR NR NR	N/A	N/A	260	VAS	Kujala
Yanez-Alvarez[115] **IT**	25 (14:11) 48 ±13.0 27.8 ±3.8 NR	25 (12:13) 52 ±10.7 28.5 ±4.7 NR	N/A	N/A	4	VAS	Kujala
Electrotherapy							
Albornoz-Cabello[2] **IT**	42 (NR) 48 ±15.6 28.3 ±5.3 NR	42 (NR) 52 +10.3 28.2 ±4.7 NR	N/A	N/A	3	VAS	Kujala
Callaghan[18] **IT**	37 (21:16) 36.5 ±13.6 25.7 ±5.7 28.1 ±14.1	37 (22:15) 33.2 ±9.4 25.9 ±5.9 23.7 ±14.3	N/A	N/A	6	VAS	Kujala
Celik[19] **DUM**	15 (11:4) 32.9 ±6.9 24.1 ±3.1 5.7 ±3.9	15 (9:6) 32.7 ±9.7 22.7 ±2.9 7.7 ±4.3	N/A	N/A	5	NR	Lysholm
Das[30] **DUM**	14 (9:5) 39.1 ±9.1 NR NR	13 (6:7) 41.5 ±12.7 NR NR	N/A	N/A	12	VAS	Kujala

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APPENDIX A (CONTINUED)

Study	Sample Size (F:M) Age in Years (mean ±) BMI in kg/m2 (mean ±) Symptom Duration in Months (mean ±) Group 1	Group 2	Group 3	Group 4	Furthest Follow-up (Weeks)	Extracted Pain Outcome	Extracted Function Outcome
Gobbi[47] **IT**	24 (16:8) 35.5 ±9.0 NR NR	17 (12:5) 36.8 ±8.0 NR NR	N/A	N/A	52	NR	Kujala
Glaviano[46] **IT**	11 (8:3) 23.8 ±5.6 NR 26.3 ±26.3	10 (8:2) 23.0 ±3.7 NR 23.0 ±27.8	N/A	N/A	52	U-VAS	Kujala
Iammarrone[94] **DUM**	17 (12:5) 24 ±8 NR NR	13 (10:3) 21 ±7 NR NR	N/A	N/A	52	NR	VISA
Rogvi-Hansen[89] **IT**	19 (11:8) 35 ±NR NR 48 ±NR	17 (9:8) 31 ±NR NR 72 ±NR	N/A	N/A	12	VAS	NR
Wu[113] **NAB**	18 (9:9) 27.3 ±NR 21.7 ±NR NR	18 (8:10) 27.5 ±NR 22.2 ±NR NR	N/A	N/A	12	VAS	Kujala
Manual therapy							
Behrangrad[14] **IT**	15 (12:3) 24.3 ±1.9 19.3 ±2.4 NR	15 (12:3) 24.3 ±1.9 19.4 ±2.2 NR	N/A	N/A	13	NRPS	Kujala
Coelho[66] **IT**	39 (39:0) 25.3 ±5.3 25.1 ±5.2 NR	39 (39:0) 24.6 ±4.3 23.8 ±4.0 NR	39 (39:0) 25.6 ±5.1 24.5 ±5.3 NR	N/A	0.5	NPRS	Kujala
Hains[53] **DUM**	27 (20:7) 25.3 ±NR NR NR	11 (8:3) 25.0 ±NR NR NR	N/A	N/A	4	VAS	NR
Shah[95] **DUM**	30 (19:11) 29 ±1.7 23.6 ±3.9 NR	30 (22:8) 27 ±1.7 26.8 ±3.7 NR	N/A	N/A	6	VAS	FIQ
van den Dolder[103] **NE**	21 (17:4) 55 ±11 NR NR	16 (10:6) 52 ±18 NR NR	N/A	N/A	2	U-VAS	NR
Zago[116] **PE, NE**	30 (NR) 31.4 ±7.2 24.1 ±2.8 NR	28 (NR 34.9 ±10.8 24.0 ±3.8 NR	24 (NR) 32.9 ±8.8 24.1 ±2.2 NR	N/A	4	VAS	Lysholm

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APPENDIX A (CONTINUED)

Study	Sample Size (F:M) Age in Years (mean ±) BMI in kg/m2 (mean ±) Symptom Duration in Months (mean ±) Group 1	Group 2	Group 3	Group 4	Furthest Follow-up (Weeks)	Extracted Pain Outcome	Extracted Function Outcome
Foot orthoses							
Collins[22] **PE, NAB, NE**	46 (25:21) 27.9 ±5.3 26.1 ±5.6 NR	44 (20:24) 29.0 ±6.0 23.9 ±3.5 NR	45 (29:16) 30.9 ±5.8 24.2 ±4.7 NR	44 (26:18) 29.6 ±5.6 24.8 ±6.2 NR	52	GROC	
Matthews[71] **E**	109 (70:39) 28.3 ±6.0 25.5 ±4.9 52.3 ±61.9	109 (81:28) 27.9 ±6.0 24.7 ±4.8 55.4 ±60.8	N/A	N/A	12	GROC	
Mills[72] **IT**	20 (15:5) 30.4 ±5.5 26.4 ±9.7 36 ±NR	20 (14:6) 28.5 ±5.9 23.6 ±2.7 48 ±NR	N/A	N/A	6	GROC	
Molgaard[74] **IT**	20 (NR) NR NR NR	20 (NR) NR NR NR	N/A	N/A	52	KOOS (pain)	KOOS (sport)
Dry needling							
Espi-Lopez[38] **NAB**	30 (15:15) 29.7 ±9.5 NR 114 ±69.6	30 (14:16) 29.2 ±10.5 NR 102 ±75.6	N/A	N/A	12	NPRS	KOOS-ADL
Ma[67] **DUM**	25 (12:13) 22.5 ±2.4 22.7 ±2.7 NR	23 (13:10) 25.1 ±6.0 21.8 ±3.3 NR	N/A	N/A	12	VAS	Kujala
Sutlive[100] **NE**	30 (17:13) 30.3 ±5.5 26.4 ±4.4 27.4 ±29.7	30 (20:10) 31.1 ±5.1 26.8 ±3.2 53.0 ±66.8	N/A	N/A	0.5	NPRS	Kujala
Zarei[117] **NAB**	20 (20:0) 22.3 ±3.3 NR NR	20 (20:0) 25.7 ±8.5 NR NR	N/A	N/A	6	NPRS	Kujala
Injection therapy							
Garcia-Trian[43] **SE**	25 (18:7) 55.5 ±14.8 NR NR	25 (20:5) 53.5 ±14.4 NR NR	N/A	N/A	26	VAS	WOMAC (function)
Hart[55] **NE**	45 (35:11) 26.0 ±7.0 26.4 ±5.3 NR	41 (31:10) 28.1 ±8.4 25.8 ±5.1 NR	N/A	N/A	26	VAS	WOMAC (function)
Singer[96] **IT**	14 (8:6) 31.5 ±NR NR 66 ±NR	10 (9:1) 27.4 ±NR NR 80 ±NR	N/A	N/A	24	VAS	Kujala

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APPENDIX A (CONTINUED)

Study	Sample Size (F:M) Age in Years (mean ±) BMI in kg/m2 (mean ±) Symptom Duration in Months (mean ±) Group 1	Group 2	Group 3	Group 4	Furthest Follow-up (Weeks)	Extracted Pain Outcome	Extracted Function Outcome
Taping and bracing							
Arrebola[6] **IT**	13 (13:0) 30.4 ±8.4 24.6 ±2.6 NR	16 (16:0) 30.3 ±7.9 22.7 ±2.8 NR	14 (14:0) 27.9 ±9.4 23.4 ±3.6 NR	N/A	24	NPRS	Kujala
Priore[85] **IT**	25 (18:7) 22.9 ±4.5 23.8 ±4.3 50.5 ±43.0	25 (19:6) 22.0 ±3.3 23.5 ±2.8 51.2 ±64.0	N/A	N/A	6	VAS	Kujala
Whittingham[108] **IT**	10 (2:8) 18.8 ±1.3 NR NR	10 (2:8) 18.6 ±1.1 NR NR	10 (2:8) 18.7 ±1.4 NR NR	N/A	4	VAS	FIQ
Gait retraining							
Bonacci[16] **IT**	8 (8:0) 34.0 ±9.5 24.0 ±2.7 48.3 ±56.9	8 (4:4) 31.5 ±9.7 22.9 ±3.4 46.5 ±40.7	N/A	N/A	20	GROC	
Esculier[37] **IT**	23 (15:8) 30.7 ±5.3 NR 16.4 ±16.3	23 (14:9) 33.2 ±6.5 NR 42.2 ±47.4	23 (14:9) 28.4 ±6.8 NR 28.0 ±42.4	N/A	20	U-VAS	KOS-ADLS
Combined interventions							
Crossley[25] **PE**	36 (23:13) 29.0 +8.0 23.5 ±3.8 39.0 ±43.0	35 (23:12) 26.0 ±8.0 24.8 ±3.7 31.0 ±32.0	N/A	N/A	6	U-VAS	Kujala
Halabchi[54] **Sup**	30 (17:13) 30.1 ±5.9 24.3 ±3.9 31.9 ±21.2	30 (18:12) 29.3 ±5.9 21.6 ±2.4 30.1 ±22.4	N/A	N/A	12	VAS	Kujala
BFR							
Giles[44] **DUM**	40 (24:16) 28.5 ±5.2 NR 31.6 ±40.9	39 (19:20) 26.7 ±5.5 NR 37.8 ±55.5	N/A	N/A	26	W-VAS	Kujala
Psychological							
Selhorst[93] **IT, DUM**	34 (24:10) 15.3 ±1.7 23.1 ±5.4 NR	32 (19:13) 14.3 ±1.7 22.4 ±5.5 NR	N/A	N/A	12	NPRS	Kujala

Abbreviations: BFR, blood flow restriction training; BMI, body mass index; DUM, data unsuitable for meta-analysis; E, equivalence data; F, female; FIQ, functional index questionnaire; GROC, global rating of change; IT, inadequately tested data; KOOS-ADL, knee injury and osteoarthritis outcome score – activities of daily living; KOS-ADLS, knee outcome survey – activities of daily living scale; LEFS, lower extremity functional scale; M, male; NAB, no additional benefit data; NE, nonefficacy data; NPRS, numerical pain-rating scale; NPRS-AS, numerical pain-rating scale when ascending stairs; NPRS-DS, numerical pain-rating scale when descending stairs; NR, not reported; PE, primary efficacy data; SE, secondary efficacy data; Sup, superiority data; U-VAS, usual visual analogue scale; VAS, visual analogue scale; VAS-A, visual analogue scale during activity; VISA, Victorian Institute of Sports Assessment. W-VAS, worst visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

APPENDIX B

PEDro SCORES FOR THE EXCLUDED LOW-QUALITY RANDOMIZED CONTROLLED TRIALS

Study	A	B	C	D	E	F	G	H	I	J	Total
Abyaneh et al 2016	1	0	1	0	0	0	1	0	1	1	5
Akarcali et al 2002	1	0	0	0	0	0	1	0	1	1	4
Akbas et al 2011	1	0	1	0	0	0	0	0	1	1	4
Alsharani et al 2020	1	0	0	0	0	0	1	0	1	1	4
Astur et al 2019	1	1	1	0	0	0	1	0	1	1	6
Avraham et al 2007	1	0	0	0	0	1	0	0	1	0	3
Azizi et al 2019	1	0	1	0	0	0	0	0	1	1	4
Bazbug et al 2022	1	0	1	0	0	0	1	0	1	1	5
Bedum et al 2020	1	0	0	0	0	1	0	0	1	1	4
Behrangrad et al 2020	1	1	1	0	0	0	1	0	1	1	6
Bily et al 2008	1	1	0	0	0	0	0	0	1	1	4
Boitrago et al 2021	1	0	1	0	0	1	1	0	1	1	6
Brantignham et al 2009	1	1	1	0	0	1	0	0	1	1	6
Callaghan et al 2001	1	0	0	0	0	0	1	0	1	1	4
Can et al 2003	1	0	1	0	0	0	0	0	1	1	4
Chevidikunnan et al 2016	1	1	0	0	0	0	1	0	1	1	5
Constantinou et al 2022	1	0	1	0	0	1	1	0	1	1	6
Corum et al 2018	1	0	1	0	0	1	1	0	1	1	6
De Souza et al 2020	1	0	0	0	0	0	0	0	1	1	3
Demirci et al 2017	1	0	1	0	0	0	1	0	1	1	5
Denton et al 2005	1	0	1	0	0	0	0	0	1	1	4
Dolak et al 2011	1	1	1	0	0	0	0	1	1	1	6
dos Santos et al 2019	1	1	0	0	0	0	1	0	1	1	5
Drew et al 2017	1	1	0	0	0	0	1	0	1	1	5
Dursun et al 2001	1	0	1	0	0	0	1	0	1	1	5
Ebrahimi et al 2021	1	1	1	0	0	1	1	0	0	0	5
Elsayed et al 2014	1	0	1	0	0	0	0	0	0	1	3
Eng et al 1993	1	0	1	0	0	0	0	0	1	0	3
Evcik et al 2010	1	0	0	0	0	1	1	0	1	1	5
Fatimah et al 2021	1	1	1	0	0	0	1	0	1	1	6
Ferber at al 2015	1	1	0	0	0	1	0	1	1	1	6
Foroughi et al 2019	1	0	1	0	0	0	0	0	1	1	4
Ghourbanpour et al 2018	1	0	1	0	0	0	0	0	1	1	4
Gunay et al 2017	1	0	1	0	0	0	0	0	1	1	4
Hafez et al 2006	1	0	0	0	0	0	0	0	0	1	2
Hafez et al 2012	1	0	0	0	0	0	0	0	1	1	3
Herrington et al 2007	1	1	1	0	0	1	1	0	1	1	6
Jellad et al 2021	1	0	1	0	0	0	1	0	1	1	5
Jensen et al 1999	1	0	0	0	0	1	1	0	1	1	5
Kang et al 2014	1	0	0	0	0	0	0	0	1	1	3
Kannus et al 1992	1	0	0	0	0	0	1	0	1	0	3
Kannus et al 1999	1	1	0	0	0	0	1	0	1	0	4
Karamiani et al 2022	1	0	1	0	0	1	1	0	1	1	6
Kaya et al 2013	1	0	0	0	0	0	1	0	1	1	4

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APPENDIX B (CONTINUED)

Study	A	B	C	D	E	F	G	H	I	J	Total
Kayambashi et al 2012	1	0	1	0	0	0	1	0	1	1	5
Kayambashi et al 2014	1	0	1	0	0	0	1	0	1	1	5
Kedroff et al 2019	1										
Kowall et al 1996	1	0	0	0	0	0	0	0	1	0	2
Kim et al 2022	1	0	1	1	0	0	1	0	1	1	6
Kumar et al 2013	1	0	0	0	0	0	0	0	1	1	3
Lee et al 2014	1	0	1	0	0	0	0	0	1	1	4
Lewinson et al 2015	1	0	1	1	0	1	0	0	1	1	6
Loudon et al 2004	1	0	1	0	0	0	1	0	0	1	4
Lun et al 2005	1	0	1	0	0	1	0	0	1	1	4
Maayah et al 2013	1	0	1	0	0	0	1	0	1	1	5
Mahmoud et al 2015	1	0	1	0	0	1	0	0	1	1	5
Maryam et al 2018	1	0	1	0	0	0	0	0	1	0	3
Mason et al 2011	1	1	0	0	0	1	0	0	1	1	5
Melo et al 2018	1	1	1	0	0	0	1	0	1	1	6
Minoonejad et al 2012	1	0	1	0	0	0	0	0	1	1	4
Monika et al 2016	1	0	1	0	0	0	0	0	1	1	4
Moyano et al 2013	1	1	1	0	0	0	1	0	1	1	6
Naidu et al 2018	1	0	0	0	0	0	0	0	1	1	3
Nakhostin-Roohi et al 2016	1	0	1	1	1	1	0	0	1	0	6
Naslund et al 2002	1	0	0	0	0	0	1	0	1	0	3
Nouri et al 2019	1	0	1	1	1	1	1	0	1	0	6
Orscelik et al 2015	1	0	1	0	0	0	0	0	1	1	4
Orscelik et al 2019	1	0	1	1	1	0	1	0	1	0	6
Osteras et al 2012	1	1	1	0	0	1	0	0	1	1	6
O'Sullivan et al 2021	1	1	1	1	0	1	0	0	0	1	6
Petersen et al 2016	1	0	0	0	0	0	0	0	1	0	2
Phillips et al 2009	1	0	1	0	0	0	1	0	1	1	5
Pocai et al 2021	1	0	0	0	0	0	1	0	1	1	4
Qi et al 2007	1	0	0	0	0	0	1	0	1	1	4
Qui et al 2009	1	0	1	0	0	0	0	0	0	1	3
Raatikainen et al 1990	1	0	0	1	1	0	1	0	1	0	5
Rangole et al 2015	1	0	0	0	0	0	0	0	1	1	3
Razeghi et al 2010	1	0	0	0	0	0	1	0	1	1	4
Rehman et al 2021	1	1	0	1	0	0	1	0	1	1	6
Rodrigues et al 2021	1	0	0	0	0	0	0	0	0	0	1
Roh et al 2021	1	1	1	0	0	1	1	0	0	1	6
Roper et al 2016	1	0	1	0	0	0	1	0	1	1	5
Rowlands et al 1990	1	0	0	1	0	0	0	0	1	0	3
Sanchez et al 2017	1	0	0	0	0	1	1	0	1	0	4
Selhorst et al 2018	1	0	0	1	0	1	0	1	1	1	6
Senthil et al 2020	1	0	0	0	0	0	0	0	0	1	2
Shadloo et al 2021	1	0	1	0	0	1	1	0	0	0	4
Shafiei et al 2019	1	0	1	0	0	1	1	0	1	1	6
Sharif et al 2014	1	0	1	0	0	0	0	0	1	1	4
Sharif et al 2020	1	0	1	0	0	0	0	0	1	1	4

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APPENDIX B (CONTINUED)

Study	A	B	C	D	E	F	G	H	I	J	Total
Shetty et al 2016	1	1	0	0	0	0	1	0	1	1	5
Smith et al 2019	1	1	1	0	0	0	0	1	1	1	6
Sokhangooei et al 2010	1	0	0	0	0	0	0	0	1	1	3
Talbot et al 2020	1	1	1	0	0	0	1	0	1	1	6
Tan et al 2010	1	0	1	0	0	0	1	1	1	1	6
Telles et al 2016	1	0	1	0	0	0	0	0	1	1	4
Thomee et al 1997	1	0	0	0	0	0	1	0	1	1	4
Timm et al 1997	1	0	1	0	0	1	0	0	1	1	5
Tramontano et al 2020	1	0	0	0	0	1	1	0	0	1	4
Valera-Calero et al 2021	1	1	1	0	0	0	1	0	1	1	6
Verma et al 2012	1	0	0	0	0	0	0	0	0	1	2
Wiener-Oglive et al 2004	1	1	0	0	0	0	1	0	1	1	5
Yevlar et al 2015	1	0	1	0	0	1	0	0	1	1	5
Yip et al 2006	1	0	0	0	0	1	1	0	1	1	5
Zemadanis et al 2015	1	0	0	0	0	0	1	0	1	0	3

Abbreviations: A, random allocation; B, concealed allocation; C, comparable groups at baseline; D, participant blinding; E, clinician blinding; F, outcome assessor blinding; G, ≥85% data collection; H, intention-to-treat analyses; I, between-group statistical comparisons; J, variability reported.

APPENDIX C

DIAGNOSTIC VALIDITY SCORES FOR THE RETAINED HIGH-QUALITY RANDOMIZED CONTROLLED TRIALS

	Inclusion Criteria			Exclusion Criteria				
Study	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**Total**
Aghakeshizadeh 2021	0	0	1	1	1	1	1	5
Albornoz-Cabello 2020	0	0	0	0	0	0	0	0
Almeida 2021	1	1	1	1	1	1	1	7
Arrebola 2020	0	0	1	1	1	1	1	5
Azab 2022	1	1	1	1	1	1	1	7
Bagheri 2020	1	1	1	1	1	1	1	7
Bakhtiary 2008	0	0	1	0	0	0	0	1
Baldon 2014	1	1	1	1	1	1	1	7
Behrangrad 2017	0	0	1	1	1	1	0	4
Boitrago 2021	0	1	1	1	1	1	1	6
Bolgla 2016	0	0	1	0	0	1	1	3
Bonacci 2018	1	1	1	1	0	0	0	4
Callaghan 2004	1	1	1	0	0	0	0	3
Celik 2020	1	0	1	1	1	1	0	5
Clark 2000	0	0	0	0	1	1	0	2
Coelho 2020	0	1	1	1	1	1	1	6
Collins 2008	1	1	1	1	0	1	0	5
Crossley 2002	1	1	1	1	1	1	1	7
Das 2016	1	0	1	1	1	1	1	6
Emamvirdi 2019	1	1	1	1	1	1	1	7
Esculier 2018	0	1	1	1	1	1	1	6
Espi-Lopez 2017	1	1	1	1	1	1	0	6
Fukuda 2010	0	0	1	1	1	1	1	5
Fukuda 2012	0	0	1	1	1	1	1	5
Garcia-Triana	0	0	0	0	1	1	1	3
Giles 2017	0	1	1	1	0	1	1	5
Glaviano 2019	1	1	1	1	0	1	1	6
Gobbi 2019	0	0	1	1	1	0	0	3
Hains 2010	0	0	0	1	1	0	0	2
Halabchi 2015	1	0	1	1	1	1	1	6
Hart 2019	0	0	0	1	1	1	1	4
Hott 2019	0	0	1	1	1	1	1	5
Hott 2020	0	0	1	1	1	1	1	5
Iammarrone 2016	0	0	1	1	1	0	0	3
Ismail 2013	1	1	1	1	1	1	0	6
Ma 2020	0	1	1	1	1	1	1	6
Matthews 2020	1	1	1	1	0	1	0	5
Mills 2012	1	1	1	1	0	1	1	6
Molgaard 2018	1	0	0	1	1	0	1	4
Motealleh 2019	0	0	1	1	1	1	1	5
Nakagawa 2013	1	1	1	1	1	1	1	7

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APPENDIX C (CONTINUED)

	Inclusion Criteria			Exclusion Criteria				
Study	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**Total**
Osteras 2013	1	1	1	1	1	0	1	6
Priore 2020	0	1	1	1	1	1	1	6
Rabelo 2017	0	0	1	1	1	1	0	4
Rasti 2020	0	1	1	1	1	1	1	6
Rathleff 2015	1	1	1	1	0	1	0	5
Riel 2018	0	1	1	1	1	1	1	6
Rogvi-Hansen 1991	0	0	0	0	0	0	0	0
Saad 2018	1	1	1	1	0	1	0	5
Sahin 2016	1	1	1	1	1	1	1	7
Selhorst 2021	1	0	1	1	0	0	1	4
Shah 2016	1	1	1	1	0	1	0	5
Singer 2011	0	0	0	1	1	1	0	3
Song 2009	1	1	1	1	1	0	1	6
Sutlive 2018	1	0	1	1	1	0	1	5
Syme 2009	1	0	1	1	1	1	1	6
van den Dolder 2006	0	0	0	1	0	0	0	1
Van Linschoten 2009	0	0	1	1	1	0	1	4
Whittingham 2004	0	0	1	1	1	1	0	4
Witvrouw 2000	0	0	0	1	0	0	0	1
Witvrouw 2004	0	0	0	1	1	1	0	3
Yanez-Alvarez 2020	0	1	1	1	1	1	1	6
Zago 2021	0	0	1	0	0	0	0	1
Zarei 2020	1	1	1	0	1	1	1	6
Wu 2021	1	1	1	1	1	1	1	7

Abbreviations: A, pain location; B, insidious onset; C, symptoms consistent with patellofemoral pain; D, previous knee surgery; E, internal derangement; F, ligamentous instability; G, other sources of knee pain.

APPENDIX D

RoB2 SCORES FOR THE RETAINED HIGH-QUALITY RANDOMIZED CONTROLLED TRIALS

APPENDIX E

GAP MAP FOR INADEQUATELY TESTED INTERVENTIONS

Intervention	Control	Outcome Measure	Short Term	Medium Term	Long Term
Interventions with inadequate testing					
Hip-and-knee-targeted exercise therapy	Wait and see	Pain (1 study)	Positive, low certainty 1.05 (0.29, 1.80)		
		Function (1 study)	Positive, high certainty 1.41 (0.61, 2.21)		
Hip-and-knee-targeted exercise therapy	Knee-targeted exercise therapy	Pain (1 study)		Positive, moderate certainty, 2.37 (1.63, 3.12)*	Positive, moderate certainty, 3.22 (2.35, 4.09)*
		Function (1 study)		Positive, moderate certainty, 1.86 (1.18, 2.54)*	Positive, moderate certainty, 1.76 (1.09, 2.42)*
Hip-and-knee-targeted exercise therapy	Education	Pain (4 studies)	Positive, very low certainty 1.17 (0.45, 1.89)		Positive, very low certainty 0.40 (0.05, 0.74)
		Function (3 studies)	Positive, low certainty 1.22 (0.17, 2.27)		Neutral, very low certainty 0.26 (−0.08, 0.61)
Hip-and-knee-targeted exercise therapy	Education	Outcome (1 study)	Positive, moderate certainty OR 28.85 (1.55, 537.96)		
Hip-and-knee-targeted exercise therapy and education	Education	Pain (2 studies)	Positive, moderate certainty 0.34 (0.02, 0.66)	Neutral, moderate certainty 0.17 (−0.14, 0.49)	Neutral, low certainty 0.19 (−0.17, 0.55)
		Function (2 studies)	Neutral, moderate certainty 0.02 (−0.29, 0.34)	Neutral, moderate certainty −0.06 (−0.38, 0.25)	Neutral, low certainty 0.05 (−0.31, 0.40)
Posterior hip-targeted exercise therapy	Anterior hip-targeted exercise therapy	Pain (1 study)	Neutral, very low certainty −0.11 (−0.66, 0.43)	Neutral, very low certainty −0.11 (−0.43, 0.66)	
		Function (1 study)	Neutral, very low certainty −0.03 (−0.88, 0.22)	Neutral, very low certainty −0.33 (−0.65, 0.22)	
Hip-and-knee-targeted exercise therapy and dry needling	Hip-and-knee-targeted exercise therapy	Pain (2 studies)		Neutral, low certainty, −1.17 (−3.25, 0.91)	
		Function (2 studies)			
Hip-and-knee-targeted exercise therapy and vibration therapy	Hip-and-knee-targeted exercise therapy	Pain (2 studies)	Neutral, very low certainty 1.41 (−0.63, 3.44)		
		Function (2 studies)	Positive, very low certainty 1.59 (0.95, 2.23)		
Hip-and-knee-targeted exercise therapy and mindfulness meditation	Hip-and-knee-targeted exercise therapy	Pain (1 study)	Neutral, very low certainty 0.44 (−0.29, 1.17)	Positive, very low certainty 1.07 (0.29, 1.84)	
		Function (1 study)	Neutral, very low certainty 0.02 (−0.70, 0.73)	Positive, very low certainty 0.88 (0.13, 1.64)	
Hip-and-knee-targeted exercise therapy and motor control exercise	Hip-and-knee-targeted exercise therapy	Pain (1 study)	Neutral, very low certainty 0.29 (−0.38, 0.97)	Neutral, very low certainty 0.19 (−0.48, 0.87)	
		Function (1 study)	Neutral, very low certainty 0.50 (−0.19, 1.18)	Neutral, very low certainty 0.31 (−0.36, 0.99)	
Open chain knee-targeted exercise therapy	Closed chain knee-targeted exercise therapy	Pain (1 study)	Neutral, very low certainty 0.15 (−0.54, 0.84)		
		Function			
Exercise therapy with feedback	Exercise therapy without feedback	Pain (1 study)			
		Function (1 study)	Neutral, very low certainty 0.34 (−0.28, 0.97)		
Hip-and-knee-targeted exercise therapy and patellar taping	Hip-and-knee-targeted exercise therapy	Pain (1 study)	Positive, low certainty 1.92 (0.61, 3.31)		
		Function (1 study)	Positive, low certainty 2.13 (0.73, 3.52)		
Hip-and-knee-targeted exercise therapy and placebo taping	Hip-and-knee-targeted exercise therapy	Pain (1 study)	Neutral, very low certainty 0.94 (−0.20, 2.09)		
		Function (1 study)	Neutral, very low certainty −0.07 (−1.14, 1.01)		
Hip-and-knee-targeted exercise therapy and patellar kinesio taping	Hip-and-knee-targeted exercise therapy	Pain (1 study)	Neutral, very low certainty 0.11 (−1.04, 1.26)		
		Function (1 study)	Neutral, very low certainty −0.05 (−1.20, 1.09)		
Hip-and-knee-targeted exercise therapy and femoral kinesio taping	Hip-and-knee-targeted exercise therapy	Pain (1 study)	Neutral, very low certainty 0.14 (−0.92, 1.19)		
		Function (1 study)	Neutral, very low certainty −0.18 (−1.24, 0.88)		
Bracing	Education	Pain (1 study)	Positive, low certainty 1.11 (0.51, 1.71)		
		Function (1 study)	Neutral, very low certainty 0.23 (−0.32, 0.79)		
Foot orthoses	Wait and see	Outcome (1 study)	Positive, low certainty OR 17.10 (1.89, 154.84)		
Combined interventions and foot orthoses	Combined interventions	Outcome (1 study)		Neutral, vey low certainty, OR 3.91 (0.76, 20.13)	Neutral, vey low certainty, OR 1.03 (0.35, 3.05)
Foor orthoses and foot-targeted exercise therapy	Knee-targeted exercise therapy	Pain (1 study)	Positive, low certainty 0.98 (0.24, 1.72)		Neutral, low certainty 0.59 (−0.12, 1.30)
		Function (1 study)	Neutral, low certainty 0.63 (−0.08, 1.35)		Neutral, low certainty 0.37 (−0.33, 1.07)

Intervention	Control	Outcome Measure	Short Term	Medium Term	Long Term
Interventions with inadequate testing					
Pulsed shortwave	Placebo pulsed shortwave	Pain (1 study)			
		Function (1 study)	Positive, low certainty 1.52 (0.81, 2.23)		
Pulsed shortwave and exercise therapy	Exercise therapy	Pain (1 study)	Positive, moderate certainty 2.76 (2.15, 3.36)		
		Function (1 study)	Positive, moderate certainty 1.66 (1.16, 2.16)		
Lazer	Sham lazer	Outcome (1 study)	Neutral, very low certainty OR 2.67 (0.67, 10.58)		
Hip-and-knee-targeted exercise therapy and neuromuscular stimulation	Hip-and-knee-targeted exercise therapy	Pain (1 study)	Neutral, low certainty −0.78 (−1.67, 0.12)	Neutral, very low certainty 0.19 (−0.48, 0.87)	Neutral, very low certainty −0.31 (−1.18, 0.55)
		Function (1 study)	Neutral, low certainty −0.81 (−1.71, 0.09)	Neutral, low certainty −0.61 (−1.49, 0.27)	Neutral, low certainty −0.80 (−1.69, 0.20)
Standard neuromuscular stimulation	Variable neuromuscular stimulation	Pain (1 study)	Neutral, very low certainty 0.00 (−0.46, 0.46)		
		Function (1 study)	Neutral, very low certainty 0.26 (−0.29, 0.62)		
Knee-targeted exercise therapy and botox injection	Knee-targeted exercise therapy and placebo injection	Pain (1 study)	Neutral, very low certainty 0.74 (−0.11, 1.58)		
		Function (1 study)	Positive, very low certainty 0.93 (0.07, 1.79)		
Spinal manipulation	Trigger point therapy	Pain (1 study)	Negative, very low certainty −1.04 (−1.81, −0.27)		
		Function (1 study)	Neutral, very low certainty −1.53 (−2.36, 0.70)		
Step rate retraining combined with education	Education	Pain (1 study)	Neutral, very low certainty −0.18 (−0.88, 0.52)	Neutral, very low certainty −0.28 (−0.99, 0.42)	
		Function (1 study)	Neutral, very low certainty −0.33 (−1.03, 0.38)	Neutral, very low certainty −0.27 (−0.97, 0.42)	
Step rate retraining and minimalist shoes	Foot orthoses	Outcome (1 study)	Positive, low certainty OR 15.00 (1.03, 218.30)		
Psychologically informed video	Sham video	Pain (1 study)	Positive, low certainty 0.47 (0.02, 0.92)		
		Function (1 study)			

Key		
Positive	Neutral	Negative
High	High	High
Moderate	Moderate	Moderate
Low	Low	Low
Very low	Very low	Very low