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Title: Non-surgical Treatment-induced Reduction in the Biomechanical Risk Factors Related to Knee Osteoarthritis: A systematic review and Bayesian network meta-analysis of randomized controlled trials

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ABSTRACT

Objectives: Do physical therapy and orthopedic equipment efficiency in reducing the biomechanical risk factors in people with knee osteoarthritis (KOA)? Is one therapy better than the others for improving these outcomes?

Design: Systematic review with network meta-analysis of randomised trials.

Participants: People with KOA.

Intervention: Physical therapy, orthopedic equipment and control (no/sham exercise or placebo).

Outcome measures: First and second peak knee adduction moment (KAM), and knee adduction angular impulse (KAAI)

Results. Eighteen randomized controlled trials, including 944 participants, met the inclusion criteria. Based on the collective probability of being the overall best therapy for reducing the first peak KAM, lateral wedge insoles (LWI) plus knee brace was closely followed by gait retraining, and knee brace only. Although no significant difference was observed among the eight interventions, variable-stiffness shoe and neuromuscular exercise exhibited a lower rate of reducing the first peak KAM. And based on the collective probability of being the overall best therapy for reducing KAAI, gait retraining was followed by LWI only, and lower limb exercise.

Conclusion. The ranking statistics like surface under the cumulative ranking curve values of our Bayesian network meta-analysis support the use of LWI plus knee brace for reducing the first peak KAM. We found gait retraining to be the most effective

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intervention as it could reduce the values for KAM and KAAI at the same time based on cumulative ranking and relative effect estimates.

Registration. INPLASY202090054; Doi:10.37766/inplasy2020.9.0054.

Significance and Innovations

① This Bayesian network meta-analysis is the first review on effect of physical therapy and orthopedic equipment on the biomechanical parameters (KAM & KAAI) of the knee OA.

② This review observes a null statistical reduction in KAM and KAAI for most physical therapies and orthopedic equipment, using these non-surgical treatments clinically could improve symptoms and physical activity level without increasing the biomechanical magnitude; thus, improving the quality of life of patients with KOA.

③ This review suggests that further studies should require more research articles in these areas to further explore the impact of various non-surgical therapies on OA patients.

1. INTRODUCTION

Knee osteoarthritis (KOA), a chronic progressive disease, affects approximately 3.8% of people worldwide, mainly middle-aged and older adults. It is more prevalent in women than in men [1,2]. The main clinical manifestation of KOA is knee pain and is often accompanied by radiographic degeneration of the intra-articular cartilage

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associated with hypertrophic bone changes [3]. With the development of KOA, patients may also report stiffness, locking, instability and function loss. Though it is not fatal, the persistent pain and movement difficulties associated with this condition negatively impact the physical and mental health of the patients; thus, reducing their quality of life [4].

These pathological changes of knee joint structure are the result of the break of biomechanical balance and the progression of the disease is now believed to be associated with malalignment of the lower limb [5]. Of the three compartments of a knee joint, KOA mostly occurs in the medial tibiofemoral compartment as it bears 60-91% of the total body load, higher than the lateral one [6]. The external knee adduction moment (KAM) results from the unequal distribution of the transmitted load on both sides in the normal gait of humans. It is defined as the cross product of the ground reaction force and the distance between the knee joint and the force line [7]. Individuals with obesity or other risk factors tend to have frontal plane knee malalignment, which alters the normal force line, forcing the medial knee joint to bear more load and increased KAM [8,9]. The accumulation effect of the moment is determined by calculating the integral of the moment to time, which is also termed as Knee adduction angular impulse (KAAI). It reflects the change in knee joint rotation state during a stance period of gait [10]. Previous studies have revealed a strong correlation between the peak levels of KAM and KAAI and the severity and progression of the disease, which was reflected and calculated by the loss of medial tibial cartilage[11,12]. Both these biomechanical parameters (KAM and KAAI) are

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commonly used to evaluate the medial knee load and predict the long-term structural deterioration.

Recent advancements in healthcare have resulted in the development of several protocols for the intervention and treatment of KOA. KOA patients are primarily recommended non-surgical treatments with the intention of correcting the deviated force line and delaying the progressive pathological damage inside the knee joint [7]. Several non-surgical treatments, such as exercise therapies and noninvasive orthotic devices, have been introduced in orthopedic clinics. Both these modalities focus on relieving pain and improving patients' symptoms by changing the biomechanical state of the knee joint. The exercise therapies mainly include muscular strengthening and gait modification, while orthotic devices include customized shoes/footwear, wedged insoles, and knee braces.

Previous studies have shown the positive impact of exercise therapy in KOA. The strengthening of related lower limb muscles, which play a vital role in disease progression, are known to reduce pain and improve motor functions and are often recommended to KOA patients [13]. Additionally, gait training presents a viable way to correct the patients' underlying gait pattern, which could also reduce their knee load and pain [14,15]. Further, several kinds of orthotic devices have been introduced for the treatment of KOA. The clinical use of lateral wedge insoles (LWI) has gained immense popularity since its origin in 1987 [16,17]. The insoles work by shifting the lateral part of the foot more than the medial part by a slope. Thus, a slope is created to increase the valgus tendency of lower extremities. The center of

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the ground reaction force is shifted laterally, which induces a reduction in force lever arm length and magnitude. Also, the valgus knee brace is a commonly used device. It applies an external valgus force around the knee joint to reduce the medial knee load.

In the past, several systematic reviews and meta-analysis have been published featuring the medical effects of a single KOA treatment. However, only a few of them have focused on multifaceted interventions. Also, only a few reviews have reported the effects of these changes on the biomechanical parameters. The mechanical changes in the body were not sufficiently investigated. Current reviews on KAM and KAAI have also not compared these changes. Thus, we performed a network meta-analysis (NMA) to appraise the benefits of physical treatments in reducing the biomechanical risk factors in KOA patients to overcome these shortcomings, and to help achieve the goal of reducing pain and improving function.

Therefore the research questions for this systematic review were:

1. Do physical therapy and orthopedic equipment efficiency in reducing the biomechanical risk factors in people with knee osteoarthritis (KOA)?
2. Is one therapy better than the others for improving these outcomes?

2. METHODS

The protocol was registered on the INPLASY (registration number: INPLASY202090054; Doi:10.37766/inplasy2020.9.0054). All pooled analyses were derived from previous studies and, therefore, did not require ethical approval and informed consent.

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2.1 Identification and selection of studies.

We searched the following databases for randomized controlled trials that were published before January 2021, which explored the benefits of using non-surgical treatments in reducing the biomechanical risk factors which included the KAM and the KAAI in patients with KOA: PubMed, Web of Science, Cochrane Library, Embase, and MEDLINE. The search was not restricted by language, date, publication type, or publication status (see Appendix 1). Additionally, we performed manual analyses of the published references regarding the use of non-surgical treatments for treating KOA.

The eligibility of searched publications was independently reviewed by HXM, YZX following the Cochrane manual [18]. Any additional inconsistencies were resolved either by deliberation or by a senior expert (HY). First, the study titles and abstracts, published in the English language, were screened. Next, complete articles were reviewed against the following criteria in Box 1.

Eligible comparison subjects, including standard/conventional care or waiting list control (analgesic advice and education), were defined as "standard care." Standard care treatment also included placebo intervention, no intervention, and sham-exercise. In this network meta-analysis, lower limb exercise was defined as the simultaneous exercise of multiple groups of muscles (including hip abductors, quadriceps, and hamstrings). Since our research needed to maintain clinical and statistical homogeneity and also focus on the left-over biomechanical effects after intervention, we selected articles whose measurements were strictly obtained under

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the condition of bare foot.

The exclusion criteria included: (1) studies that were not consistent with the eligibility criteria; (2) studies that were in the form of the non-trail papers, including abstracts, comments, letters, or reviews; (3) studies including participants who had received surgical treatment in the past; (4) studies that did not report suitable data.

2.2 Data Collection and Quality assessment.

KAM and KAAI were the preferred biomechanical measures used in this meta-analysis. The biomechanical indicators of the included studies were measured on flat ground or treadmills. The number of trials that focused on the second peak of KAM was insufficient to conduct an independent network meta-analysis.

Two authors (HXM, YZX) extracted data independently and then cross-checked the data. A predefined information sheet was used to extract the data, which included the details of the first author (name), country, year of publication, population characteristics, intervention, and the time point. The authors of the original study were contacted if more data was required.

2.3 Assessment of characteristics of studies.

Risk of bias

In this network meta-analysis, we used the Cochrane risk bias tool to assess the risk of bias in randomized controlled trials using the following evaluation indicators: sequence generation, allocation concealment, blinding, incomplete outcome data addressed, selective outcome reporting, and other biases[18]. The judgment of the bias risk of this item was presented as "low," "high," and "unclear." Two authors

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independently evaluated the risk of bias of the included studies. The authors discussed or referred to the opinion of a senior author to resolve any disagreements. Additionally, we evaluated the certainty of evidence which contributed to network estimates of the main outcomes with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.

Intervention

In order to describe the experimental intervention, we extracted the following information: the method of training with relevant further details, the details and characteristics of orthopedic equipment, the frequency and total duration of training or wearing.

Outcome measures

Biomechanical risk factors were extracted from barefoot walking test, including the first peak KAM, the second peak KAM and KAAI. KAM was normalized as %body weight times height, with conversion to Nm/kg where necessary. KAAI was the accumulation effect of the moment which was determined by calculating the integral of the moment to time.

2.4 Statistical Analysis.

We conducted a network meta-analysis to compare multiple interventions, including both direct evidences (where treatments were compared directly) and indirect evidences (where treatments were compared with a common control), maintaining randomization in each independent study. Interventions and demographic characteristics were either consistent or comparable across the

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included studies [19-24].

Due to different units, the continuous data used the standard mean difference (SMD) as the statistical indicator of the effect, and the Frequentist 95% confidence interval (CI) of each effect was calculated. Additionally, the I^2 statistic was used to analyze the overall heterogeneity of the two-arm study and the network. The fixed-effect model was used in case no statistical heterogeneity was found between the studies ($p > 0.05$, $I^2 < 50\%$); else, the random effect model was used, and the source of heterogeneity was analyzed. The Node-Split Model was used for testing consistency. If $p > 0.05$, then the consistency model was used for analysis; else, the inconsistency model was used for analysis. Normal likelihood distributions were assumed, non-informative prior distributions were set, and three Markov chains were run simultaneously. The number of update iterations was 50,000, a total of 5000 simulations were used for annealing, and the subsequent 45,000 iterations were examined. The mean rank and surface under the cumulative ranking curve (SUCRA) were used for reporting the probability values. A SUCRA value of 100% was considered best, whereas 0% indicated the worst treatment.

The data from eligible studies were combined using the Review Manager (RevMan) software v5.3. The contribution of the effect sizes was dependent on the sample size and their estimation accuracy. We performed the Bayesian analyses using WinBUGs v1.4.3. Stata (StataCorp. 2015. Stata Statistical Software: Release 15. College Station, TX: StataCorp LP) was used to conduct the frequentist NMA.

3. RESULTS

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3.1 Flow of studies through the review

Overall, the database search strategy found 4919 citation. After screening articles by title and abstract, and deleting duplicate articles, we identified 526 studies that might meet the criteria for inclusion, and then we searched and evaluated their full text. Figure 1 presents the study selection flow chart. Eighteen randomized controlled trials, including 944 participants, met the inclusion criteria [25-42]. Since the present network meta-analysis only considered trials comparing the nine treatments with usual care or each other, only fourteen trials (792 participants) were included.

3.2 Characteristics of included studies

All studies included the radiologically confirmed tibiofemoral OA. The duration of treatment ranged from 2 weeks to 12 months, although most intervention times were administered over an 8-13-week period. The number of exercises varied from 2-5 times per week, depending on the preparation [31,33,36,37]. Both studies of gait training used the faded feedback paradigm, which meant gradual removal of the real-time biofeedback [27,32]. Of the fourteen studies that were included in NMA, nine were classified as Kellgren/Lawrence grade 2 and above. All studies reported either the BMI or the values for height and weight, and in some studies recruiting a general population, the mean BMI was classified as overweight or obese. One study included in NMA had a randomized crossover design [25]. After referring to the manual and consulting a professional statistician, the mean and standard deviation of the experimental and the control groups were analyzed in this network meta-

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analysis [18]. Tables 1 and 2 summarize the characteristics of the included studies and participants.

3.3 KAM.

A study reported that the VER-brace offers additional advantages on first peak KAM compared to V3P-brace and ACL-brace[42]. No first peak KAM reduction was observed between proprioceptive neuromuscular facilitation group and control group[40] , and the result of the study of minimal footwear was the same[39]. Table 3 shows the NMA results of a comparative analysis of the reduction of the first peak KAM. We found insignificant differences in most of the treatment modalities; however, several interventions (Standard care (A) -1.06, 95% CI -1.63 to -0.49; LWI (B) -1.26, 95% CI -1.90 to -0.61; Knee Brace (C) -1.47, 95% CI -2.29 to -0.66; LWI + Knee Brace (D) -1.98, 95% CI -3.15 to -0.81; Gait retraining (E) -1.59, 95% CI -2.30 to -0.87; Quadriceps strengthening (F) -0.93, 95% CI -1.60 to -0.27; Hip strengthening (H) -0.76, 95% CI -1.49 to -0.03; Lower limb exercise (I) -0.97, 95% CI -1.73 to -0.21; and Neuromuscular exercises (J) -0.69, 95% CI -1.36 to -0.02) showed a statistically significant reduction in the first peak KAM over variable-stiffness shoes (G). The overall difference in first peak KAM (v standard care(A)) was -0.53 (95% CI -0.95 to -0.10) for gait retraining (E), 1.06 (95% CI 0.49 to 1.63) for variable-stiffness shoes (G), and 0.37 (95% CI 0.02 to 0.71) for neuromuscular exercises (J). Based on the collective probability of being the overall best therapy for reducing the first peak KAM, LWI plus knee brace (D) (93.4%) was closely followed by gait retraining (E) (85.7%), and knee brace only(C) (79.3%) (Figure

2). On the other hand, after the electroacupuncture treatment, compared with the control group, the second peak KAM significantly increased immediately when the patient ascended stairs[41].

3.4 KAAI.

KAAI was reported in ten studies[25,27,31,34-39,42]. After wearing the three kinds of brace separately, the KAAI measured under barefoot conditions did not decrease significantly, and there was no significant difference between the groups[42]. Table 3 shows the NMA results of the reduction of KAAI. Most treatments were not statistically different from each other, consistent with the results of the first peak KAM. Only gait retraining (E) has a statistical reduction compared with the standard care treatment (A) (-0.48, 95% CI -0.96 to -0.01). Based on the collective probability of being the overall best therapy for reducing KAAI, gait retraining (E) (90.7%) was followed by LWI only (B) (74.1%), and lower limb exercise (I) (53.8%) (Figure 3).

3.5 Risk of bias.

Figure 4 presents a summary of the quality of methods used in this analysis. Nine studies presented a clear description of generating a randomization sequence[29-31,33,36-39,41]. The study by Hinman et al. was the only double-blinded study, while other studies were either single-blinded or did not clearly describe their blind design. All trials provided follow-up data on their outcomes. Six studies did not report the number or the reason for lost visits due to the length of follow-up [25,29,30,32,33,36]. Consequently, all studies were included in the synthesis evaluation and qualified

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329 for literature assessment.And we prepared comparison-adjusted funnel plots that represented different comparisons with different colors. The funnel plots were symmetrically distributed based on a visual inspection, which suggested the absence of small-sample effects for our outcomes (see Appendix 5).

4. DISCUSSION

Our results did not show significant differences regarding the superiority of intervention among different types of non-surgical therapies. This lack of difference was attributed to the fact that the number of studies for several pairwise comparisons was small. However, some of these therapies were still worth recommending. Due to the small number of studies studying the outcome of the KAAI，We found gait retraining to be the relatively more convincing intervention as it could reduce the values for KAM and KAAI at the same time based on cumulative ranking and relative effect estimates. Due to the lack of significant differences among the exercise interventions, we were not able to conclusively accept the cumulative ranking obtained by the network meta-analysis. For example, gait retraining, which occupied the first rank position (90.7%) for reducing the KAAI, was only superior to the neuromuscular exercise interventions.

This study had several strengths and limitations. Eligible RCT studies were identified by conducting a comprehensive search on several databases and resources. Additionally, two independent reviewers scanned through the search output, extracted data, classified interventions, and evaluated the methodological quality of each trial to minimize potential bias.

351 This network meta-analysis is the first report on the effects of physical therapy and orthopedic equipment on the parameters of knee load (KAM, KAAI). Since non-surgical therapy is a complex intervention with a small number of trials comparing the different types of interventions, network meta-analysis appeared to be the most relevant form of analysis. The results of this meta-analysis would be more useful for the decision-makers, service specialists, and caregivers to choose among the various available options, compared with multiple separate pairwise meta-analyses [43]. Additionally, this network meta-analysis conducted each comparison separately with both direct and indirect statistical effects, deriving statistical power from all included data [43]. Also, the Bayesian method provided the probability estimates regarding the superior efficacy of specific exercise interventions, even though the standard methods described the absence of a significant difference between them. In addition, we calculated alternative rankings (second, third best, etc), because in some cases the best exercise intervention might be unavailable, more costly, or contraindicated in some patients.

366 As with most meta-analyses on non-surgical therapies for osteoarthritis, one of the limitations of this network meta-analysis includes the inclusion of trials that had variable periods of follow-up, which could have introduced heterogeneity into the study analysis. Although there was no study that exclusively reported the immediate effect, the span in follow-up periods cannot be ignored. There exist several methods of analyzing and comparing trials with multiple durations of follow-up, as recommended by the Cochrane handbook, such as performing individual patient

373 data meta-analysis and evaluating at a particular time point. However, methods are
374 being developed that would include all time points in a network meta-analysis [18].
375 We removed a study which had a short follow-up time and might cause
376 heterogeneity[25], and performed another network meta-analysis. There is no
377 difference between the results of the reanalysis and the current ranking (see
378 Appendix 7). We were not able to evaluate the influence of population
379 characteristics (such as mean age, the severity of osteoarthritis), as the number of
380 the included studies was not large enough [45-47]. Additionally, other parameters, such
381 as the external knee flexion moment to joint load, should have been studied.
382 However, due to the small number of related articles, we were temporarily unable
383 to include them. By the way, according to the GRADE framework (see Appendix
384 6), the quality of the most comparisons was assessed as low or very low, which
385 might affect the reliability of the evidence.

386 A previous review showed that LWIs were able to reduce the KAM at baseline [48];
387 however, the effect was no longer observed after a period of time. One study
388 showed that a 1-month wear-in period was the longest time period studied where
389 no reduction in biochemical risk factors was observed despite continued wear[49].
390 Besides, several systematic reviews had concluded that exercise and gait retraining
391 could reduce pain and improve motor functioning in people with KOA [50-52], it was
392 possible that any clinical changes in previous studies may due to the increased
393 physical activity levels, and not have been the results of altered loading environment
394 within the knee joint. Furthermore, another study revealed that an increase in the

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amount of reduction in peak KAM in LWIs plus knee brace group was observed after 4 weeks [53].

On the other hand, physical therapies and orthopedic equipment also need to be considered for relieving patients' pain, which has been the focus of several reviews in the past. As an important factor in kinetics and kinematics of gait, the joint pain can affect the kinetics and kinematics of walking[54]. A meta-analysis reported that exercise therapy had a positive impact on knee pain and kinematic function, though this relief of pain subsided with time. After initiation, the efficiency of physical exercise over placebo reached maxima at 2 months [55].

Cumulative loading is another significant parameter regarding knee load exposure in OA[56]. KAAI has been proposed as another indicator to evaluate the duration and intensity of KOA load, despite the association between KAM and disease progression. According to a 12-month study, the loss of medial tibiofemoral cartilage was not directly related to KAM but was related to KAAI[57]. Although the effect of physical therapy and orthopedic equipment on KAM may gradually disappears, it may have a huge cumulative effect on the knee during the early stages of treatment. This should be considered while interpreting the results of this network meta-analysis.

The results presented in this study are both scientifically and clinically instructive. Despite observing a null statistical reduction in KAM and KAAI for most non-surgical therapies, using these treatments clinically could improve symptoms and physical activity level without increasing the biomechanical magnitude; thus,

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improving the quality of life of patients with KOA. Since the studies included in this network meta-analysis mainly involves patients with medial knee osteoarthritis, the results would be more useful for these patients.

On the other hand, previous study reported that the increase in KAAI can explain the significant variation in the uCTX-II levels and the uCTX-II:sCPII ratio in patients with medial tibiofemoral KOA when additional variables are controlled[58]. This showed that intervention in the biomechanical structure of the knee joint in patients with KOA is a potential beneficial role on cartilage structure. Mazzoli et al. pointed out that adopting a modified gait that reduces the KAM can decrease the pain in the medial compartment in KOA more than walking alone[59], which suggests that the KAM and KAAI of patients under non-surgical treatment can be restricted to help reduce pain and improve joint function. More research is needed to further illustrate the impact of changes in knee biomechanics on the prognosis of patients.

Additionally, some other therapies have been reported, such as Taiji, ultrasound, acoustic exercise, etc. However, due to the lack of RCT study design or the report of their biomechanical outcomes, we were not able to include these therapies in our review. Therefore, further studies would require more research articles in these areas to further explore the impact of various non-surgical therapies on OA patients. After accumulating evidence regarding the role of non-surgical therapy in KOA, we could conduct a similar network meta-analysis to understand the relative effectiveness of various types of these interventions in relevant patients.

5. Conclusion

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This network meta-analysis provides valuable insight regarding the alterations in KAM and KAAI of OA patients after non-surgical treatment. The results indicate that lateral wedge insoles plus knee brace was the best therapy for reducing the first peak KAM and gait retraining had the best effect on reducing the KAAI. On the contrary, variable-stiffness shoe and neuromuscular exercise exhibited an increase in the first peak KAM compared to the standard care group. Taken together, these findings suggest that clinicians should choose carefully when treating OA.

6. Authors' Contributions

HXM and YFZ conceived of the study, and participated in its design and coordination and helped to draft the manuscript; YZX, HY and CRY contributed significantly to analysis and manuscript preparation; YJK and LL helped perform the analysis with constructive discussions and revised it critically for important intellectual content.

7. Competing interests

There were no conflicts of interest.

8. Funding

This work was supported by the National Key R&D Program of China (No.2017YFB1303000).

9. Ethics approval

Not required.

10. Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting,

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Table 1. Characteristics of included studies (1) *

Authors	Country	Clinical criteria†	Radiographic features	Intervention	Comparisons	Follow up
Barrios 2013[34]	US	Medial compartment knee OA; Pain VAS (≥3 of 10 upon walking)	K/L grade ≥2, medial tibiofemoral compartment	bespoke full-length LWI	Placebo	12 months
Hinman 2016[35]	Australia	Medial compartment knee OA; Pain NRS (> 4 of 11 upon walking) over the previous week	K/L grade ≥2, medial tibiofemoral compartment	5° full-length LWI	Placebo	6 months
Arazpour 2012[28]	Iran	Medial compartment knee OA	K/L grade 1 and 2, medial tibiofemoral compartment	6° full-length LWI	bespoke unloader knee braces	6 weeks
Jones 2013[25]	UK	Medial compartment knee OA	K/L grade 2 and 3, medial JSN	LWI: The heel was inclined at 5° with the inclination reduced to 0° at the 5th metatarsal head with a contoured arch profile	6° valgus knee brace	2 weeks
Khosravi 2019[26]	Iran	Medial compartment knee OA	K/L grade 2 and 3	Full length custom-made LWI; LWI+ knee brace	three-point valgus knee brace	6 weeks

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* OA=osteoarthritis; LWI=lateral wedged insoles; VAS=visual analog scale; NRS=numerical rating scale; K/L=Kellgren/Lawrence; NR=not reported; JSN=joint space narrowing;

Tables

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

Table 1. Characteristics of included studies (2) *

Authors	Country	Clinical criteria†	Radiographic features	Intervention	Comparisons	Follow up
Hunt 2018[27]	US	Medial compartment knee OA; Pain (≥3 of 10) longer than 6 months	K/L grade ≥2, medial tibiofemoral compartment	Toe-out gait modification	Walking without any guidance	4 months
Lim 2008[29]	Australia	Medial compartment knee OA; Medial knee pain	K/L grade ≥2, medial JSN	Quadriceps strengthening	No intervention	12 weeks
Erhart-Hledik 2012[30]	US	Medial compartment knee OA; Medial knee pain	K/L grade ≥1	Variable-stiffness shoe with stiffer soles on the lateral side	Constant-stiffness control shoe	12 months
Bennell 2010[31]	Australia	Medial compartment knee OA; Varus malalignment; Pain (> 3 of 11 upon walking)	K/L grade ≥2, medial JSN	Hip strengthening	No intervention	13 weeks
Cheung 2018[32]	China	Medial compartment knee OA; Knee pain occurred at least one day a week during each of the 8 weeks prior	K/L grade 1 and 2	Gait retraining for KAM reduction	Walking without any guidance	6 weeks

* OA=osteoarthritis; LWI=lateral wedged insoles; VAS=visual analog scale; NRS=numerical rating scale; K/L=Kellgren/Lawrence; NR=not reported; JSN=joint space narrowing;

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

Table 1. Characteristics of included studies (4) *

Authors	Country	Clinical criteria†	Radiographic features	Intervention	Comparisons	Follow up
Foroughi 2011[33]	Australia	Primary knee OA	K/L grade ≥1	Lower limb exercise	Sham-exercise	6 months
Bennell 2014[36]	Australia	Medial compartment knee OA; Pain VAS (≥25 of 100) over the past week	K/L grade ≥2, medial tibiofemoral compartment	Neuromuscular exercise	Quadriceps strengthening	12 weeks
Hunt 2013[37]	Canada	Medial compartment knee OA; Knee pain >3/10 on most days of the previous month	K/L grade ≥2, medial tibiofemoral compartment	Lower limb exercise	No intervention	11 weeks
Holsgaard-Larsen 2017[38]	Denmark	Primary knee OA Pain KOOS(< 80 of 100, at least mild pain)	K/L grade ≤3	Neuromuscular exercise	Analgesic advice	8 weeks

* OA=osteoarthritis; LWI=lateral wedged insoles; VAS=visual analog scale; NRS=numerical rating scale; K/L=Kellgren/Lawrence; NR=not reported; JSN=joint space narrowing;

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Authors	Country	Clinical criteria†	Radiographic features	Intervention	Comparisons	Follow up
Song 2020[40]	China	Medial compartment knee OA in one or both legs.	K/L grade ≤3	PNF (one-hour sessions three times a week)	Watch television or read magazines at the same time	12 weeks
Wang 2017[41]	China	Medial compartment knee OA	K/L grade 2 and 3	Acupuncture with 2 Hz continuous wave in Neixiyan (EX-LE 4), Dubi (ST 35), Yanglingquan (GB 34), Yinlingquan (SP 9), Xuehai (SP 10), Liangqiu (ST 34) and Zusanli (ST 36)	2 cm next to the same acupoints with shallow acupuncture and no current	Immediate
Robert-Lachaine 2020[42]	Canada	Medial compartment knee OA; Pain > 31/100 on WOMAC; Varus knee alignment ≥ 2°	K/L grade 2 and 3	V3P-brace; VER-brace; ACL-brace (wear the brace as often as possible)	/	3 months
Trombini-Souza 2015[39]	Brazil	Medial compartment knee OA; Knee pain between 3 and 8 on VAS	K/L grade 2 and 3	Minimalist footwear (Moleca®)	Standard, neutral tennis shoe	6 months

* OA=osteoarthritis; LWI=lateral wedged insoles; VAS=visual analog scale; NRS=numerical rating scale; K/L=Kellgren/Lawrence; NR=not reported; JSN=joint space narrowing; PNF= Proprioceptive neuromuscular facilitation; V3P-brace= three-point bending system valgus knee brace; VER-brace= unloader brace with valgus and external rotation functions; ACL-brace= functional medial-lateral stabilization brace used after ligament injuries; The Moleca® shoe is a low-cost women's double canvas, flexible, flat, walking shoe without heels, with a 5-mm anti-slip rubber sole and a 3-mm flat insole of ethylene vinyl acetate that provides only protection but no correction of any kind.

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

Table 2. Characteristics of participants in included studies (1) *

Authors	No.	Sex, M:F	Age, years	Height, meters	Body mass, kg	BMI, kg/m²	Bilateral knee OA included	K/L grade, no.				Main outcomes
								1	2	3	4	
Barrios 2013[34]	38	NR	61.90±8.37	NR	NR	32.00±7.43	NR	0	17	14	7	1st KAM; KAAI
Hinman 2016[35]	164	20:21	64.30±7.45	1.67 ± 0.10	82.95±14.76	29.70±3.64	NR	0	49	52	63	1st KAM; KAAI
Arazpour 2012[28]	24	3:4	59.29±2.37	NR	NR	27.01±1.71	Yes	9	15	0	0	1st KAM
Jones 2013[25]	28	4:3	66.30±8.20	1.75±0.13	88.7±15.10	NR	No	0	10	18	0	1st and 2nd KAM; KAAI
Khosravi 2019[26]	21	13:8	58.97±6.80	1.62±0.11	79.11±9.35	NR	NR	0	9	12	0	1st KAM

* Values are the mean±SD unless indicated otherwise. BMI=body mass index; K/L=Kellgren/Lawrence; NR=not reported; JSN=joint space narrowing; KAM=knee adduction moment; KAAI=knee adduction angular impulse.

Table 2. Characteristics of participants in included studies (2) *

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

Authors	No.	Sex, M:F	Age, years	Height, meters	Body mass, kg	BMI, kg/m^2	Bilateral knee OA included	K/L grade, no.				Main outcomes
								1	2	3	4	
Hunt 2018[27]	79	24:55	64.99±8.60	1.65±0.10	74.59±13.15	27.35±3.48	Yes	0	37	31	11	1st and 2nd KAM; KAAI
Lim 2008[29]	107	48:59	64.60±8.51	1.65±0.10	79.41±15.32	28.96±4.85	Yes	0	34	29	44	1st KAM
Erhart-Hledik 2012[30]	79	41:38	61.70±9.43	1.69±0.08	79.50±15.07	27.51±4.87	Yes	NR	NR	NR	NR	1st KAM
Bennell 2010[31]	89	46:43	64.55±8.34	NR	NR	27.94±4.41	Yes	0	30	29	30	1st KAM; KAAI
Cheung 2018[32]	20	1:1	61.95±6.11	1.63±0.09	65.85±6.64	27.35±3.48	NR	5	15	0	0	1st KAM

* Values are the mean±SD unless indicated otherwise. BMI=body mass index; K/L=Kellgren/Lawrence; NR=not reported; JSN=joint space narrowing; KAM=knee adduction moment; KAAI=knee adduction angular impulse.

Table 2. Characteristics of participants in included studies (3) *

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

Authors	No.	Sex, M:F	Age, years	Height, meters	Body mass, kg	BMI, kg/m^2	Bilateral knee OA included	K/L grade, no.				Main outcomes
								1	2	3	4	
Foroughi 2011[33]	54	0:54	65.48±7.44	NR	82.87±18.43	32.07±7.08	Yes	20	7	20	1	1st and 2nd KAM
Bennell 2014[36]	100	48:52	62.45±7.32	1.67±0.10	82.70±14.29	29.65±4.08	Yes	0	22	43	35	1st KAM; KAAI
Hunt 2013[37]	17	8:9	66.10±11.3	NR	NR	27.00±4.50	Yes	0	10	5	2	1st KAM; KAAI
Holsgaard-Larsen 2017[38]	93	39:54	58.10±7.96	NR	79.64±12.49	26.90±3.09	NR	45	31	17	0	1st KAM; KAAI

* Values are the mean±SD unless indicated otherwise. BMI=body mass index; K/L=Kellgren/Lawrence; NR=not reported; JSN=joint space narrowing; KAM=knee adduction moment; KAAI=knee adduction angular impulse.

Table 2. Characteristics of participants in included studies (4) *

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

Authors	No.	Sex, M:F	Age, years	Height, meters	Body mass, kg	BMI, kg/m^2	Bilateral knee OA included	K/L grade, no.				Main outcomes
								1	2	3	4	
Song 2020[40]	36	1:1	68.01±3.91	1.62±0.07	68.16±6.77	NR	Yes	9	20	7	0	1st KAM
Wang 2017[41]	36	1:5	63.50±7.95	NR	NR	23.75±2.66	Yes	0	19	17	0	1st and 2nd KAM
Robert-Lachaine 2020[42]	24	7:5	57.20±8.60	1.68±0.09	89.30±18.70	31.40±5.00	NR	0	15	8	0	1st and 2nd KAM; KAAI
Trombini-Souza 2015[39]	56	NR	66.00±5.00	1.60±0.10	73.40±13.10	NR	NR	0	NR	NR	0	1st KAM; KAAI

* Values are the mean±SD unless indicated otherwise. BMI=body mass index; K/L=Kellgren/Lawrence; NR=not reported; JSN=joint space narrowing; KAM=knee adduction moment; KAAI=knee adduction angular impulse.

J	0.41 (-0.66,1.49)	0.16 (-0.46,0.79)	-	0.20 (-0.23,0.64)	**0.81 (0.17,1.45)**	-	0.30 (-0.61,1.21)	**0.54 (0.02,1.07)**	0.32 (-0.10,0.75)

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

0.28 (-0.34,0.89)	**I**	-0.25 (-1.33,0.84)	-	-0.21 (-1.37,0.95)	0.40 (-0.70,1.49)	-	-0.12 (-1.39,1.16)	0.13 (-0.90,1.16)	-0.09 (-1.08,0.90)
0.07 (-0.50,0.64)	-0.21 (-0.89,0.47)	**H**	-	0.04 (-0.72,0.80)	0.64 (-0.01,1.30)	-	0.13 (-0.79,1.05)	0.38 (-0.16,0.92)	0.16 (-0.29,0.61)
-0.69 (-1.36,-0.02)	**-0.97 (-1.73,-0.21)**	**-0.76 (-1.49,-0.03)**	**G**	-	-	-	-	-	-
0.24 (-0.11,0.59)	-0.04 (-0.64,0.57)	0.17 (-0.39,0.74)	**0.93 (0.27,1.60)**	**F**	0.61 (-0.17,1.38)	-	0.09 (-0.91,1.10)	0.34 (-0.34,1.02)	0.12 (-0.49,0.73)
0.89 (0.35,1.44)	0.62 (-0.04,1.28)	**0.83 (0.20,1.45)**	**1.59 (0.87,2.30)**	**0.65 (0.11,1.19)**	**E**	-	-0.51 (-1.45,0.42)	-0.27 (-0.83,0.30)	**-0.48 (-0.96,-0.01)**
1.28 (0.21,2.36)	1.01 (-0.13,2.14)	**1.22 (0.10,2.33)**	**1.98 (0.81,3.15)**	1.04 (-0.03,2.11)	0.39 (-0.71,1.49)	**D**	-	-	-
0.78 (0.11,1.45)	0.50 (-0.26,1.27)	0.71 (-0.02,1.44)	**1.47 (0.66,2.29)**	0.54 (-0.12,1.20)	-0.11 (-0.83,0.60)	-0.50 (-1.46,0.46)	**C**	0.25 (-0.50,0.99)	0.03 (-0.77,0.83)
0.56 (0.10,1.02)	0.29 (-0.30,0.87)	0.49 (-0.05,1.04)	**1.26 (0.61,1.90)**	0.32 (-0.13,0.77)	-0.33 (-0.85,0.19)	-0.72 (-1.70,0.25)	-0.22 (-0.71,0.27)	**B**	-0.22 (-0.52,0.08)
0.37 (0.02,0.71)	0.09 (-0.42,0.60)	0.30 (-0.15,0.75)	**1.06 (0.49,1.63)**	0.13 (-0.21,0.46)	**-0.53 (-0.95,-0.10)**	-0.92 (-1.94,0.10)	-0.41 (-0.99,0.16)	-0.19 (-0.49,0.10)	**A**

Table 3. Detailed results of network meta-analysis for the First peak KAM (grey) and KAAI (white). Data are SMDs (from the top left to the bottom right, higher comparator versus lower comparator) and their related 95%CI. Bold texts in the table mean SMDs are statistically significant.

A= Standard care; B= Lateral Wedge Insole; C= Knee Brace; D= Lateral Wedge Insole+ Knee Brace; E= Gait retraining; F= Quadriceps strengthening; G= Variable-stiffness shoe; H= Hip strengthening; I= Lower limb exercise; J= Neuromuscular exercise.

Box

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

Box 1. Inclusion criteria

Design
- Randomised controlled trial

Participants
- People with radiologically confirmed knee osteoarthritis

Intervention
- Manual therapy
- Aerobic exercise
- Pulsed electrical stimulation (PES)
- Acupuncture
- Knee braces
- Ice/cooling treatment
- Pulsed electromagnetic fields (PEMF)
- Balneotherapy
- Interferential therapy
- Transcutaneous electric Nerve stimulation (TENS)
- Heat treatment
- Foot orthoses
- Laser/light therapy
- Muscle-strengthening exercise
- Static magnets
- Tai Chi
- Athletic tape
- Neuromuscular electrical stimulation (NMES)

Comparator
- Control group (no/sham exercise or placebo)

Outcome measures
- KAM and KAAI obtained under the condition of bare foot.

Comparisons
- All interventions compared to the comparator and to each other

Figure Legends

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

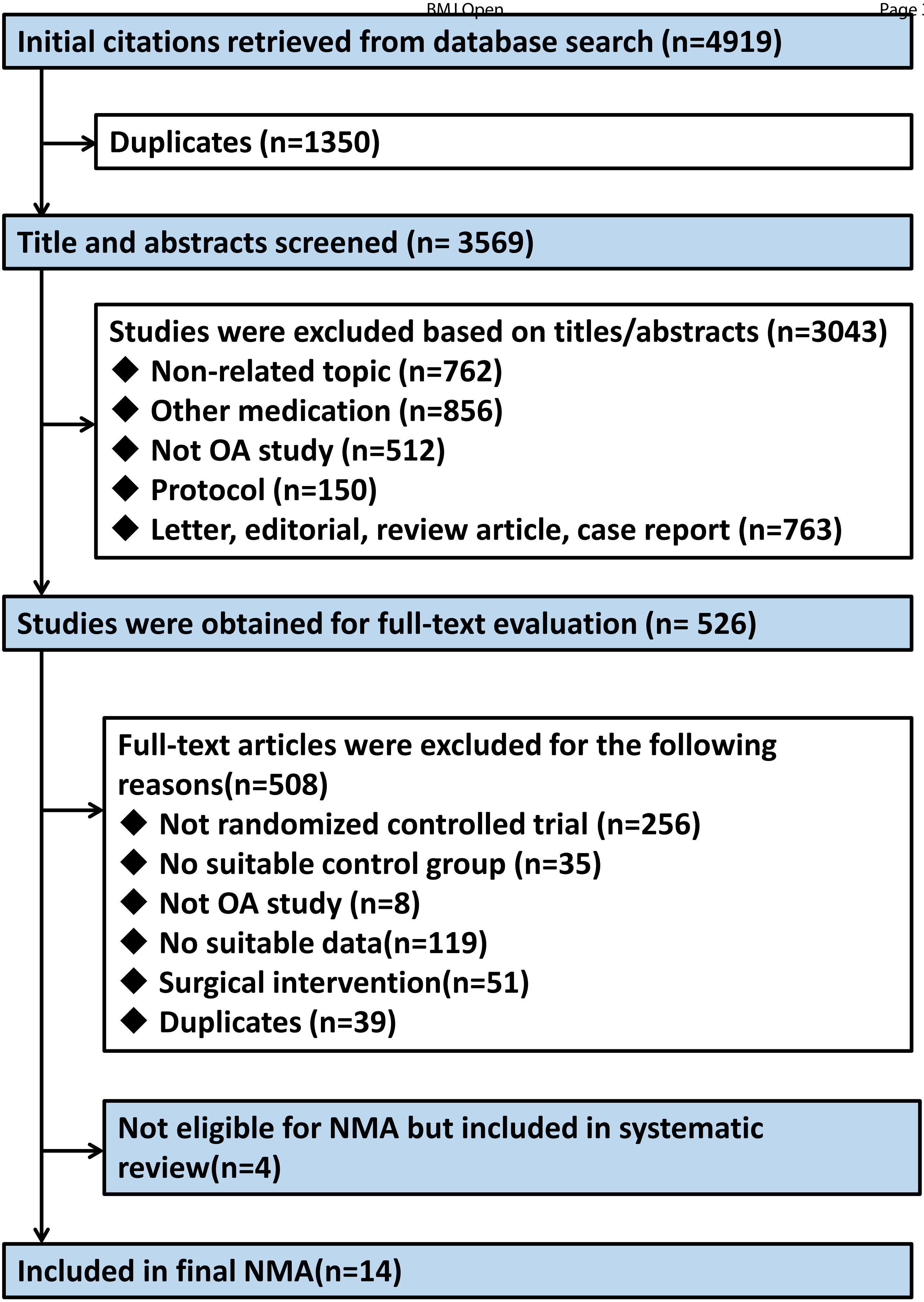
Figure 1. Flow chart of the study selection

Figure 2. Rankings for effects on First peak KAM. Graph displays distribution of probabilities for each treatment. X-axis represents the possible rank of each treatment (from the best to worst according to the outcomes), Y-axis represents the cumulative probability for each treatment to be the best option, among the best two options, among the best three options, and so on. A= Standard care; B= Lateral Wedge Insole; C= Knee Brace; D= Lateral Wedge Insole+ Knee Brace; E= Gait retraining; F= Quadriceps strengthening; G= Variable-stiffness shoe; H= Hip strengthening; I= Lower limb exercise; J= Neuromuscular exercise.

Figure 3. Rankings for effects on KAAI. Graph displays distribution of probabilities for each treatment. X-axis represents the possible rank of each treatment (from the best to worst according to the outcomes), Y-axis represents the cumulative probability for each treatment to be the best option, among the best two options, among the best three options, and so on. A= Standard care; B= Lateral Wedge Insole; C= Knee Brace; E= Gait retraining; F= Quadriceps strengthening; H= Hip strengthening; I= Lower limb exercise; J= Neuromuscular exercise.

Figure 4. Risk of bias summary

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)


Initial citations retrieved from database search (n=4919)
Duplicates (n=1350)
Title and abstracts screened (n= 3569)
Studies were excluded based on titles/abstracts (n=3043)
Non-related topic (n=762)
Other medication (n=856)
Not OA study (n=512)
Protocol (n=150)
Letter, editorial, review article, case report (n=763)
Studies were obtained for full-text evaluation (n= 526)
Full-text articles were excluded for the following reasons(n=508)
Not randomized controlled trial (n=256)
No suitable control group (n=35)
Not OA study (n=8)
No suitable data(n=119)
Surgical intervention(n=51)
Duplicates (n=39)
Not eligible for NMA but included in systematic review(n=4)
Included in final NMA(n=14)

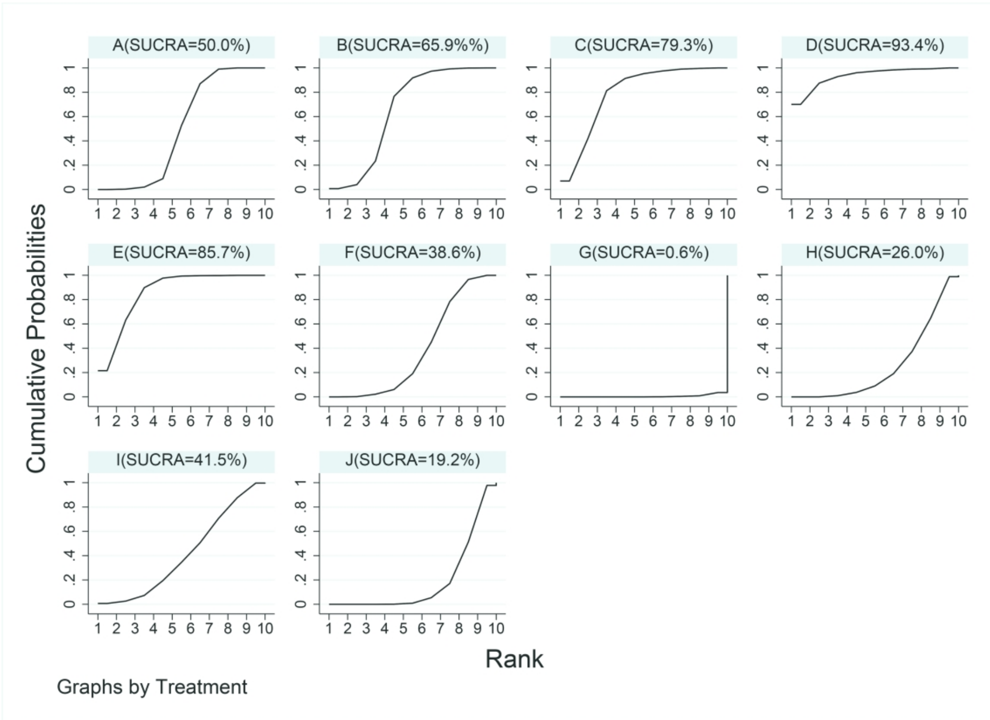


Figure 2

139x101mm (600 x 600 DPI)

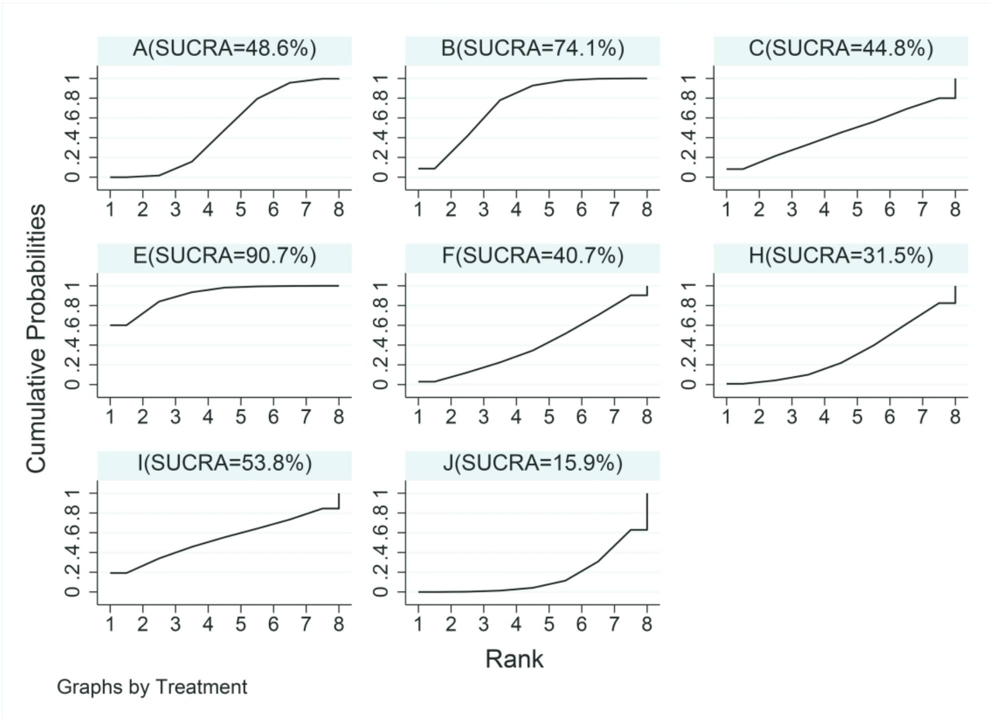
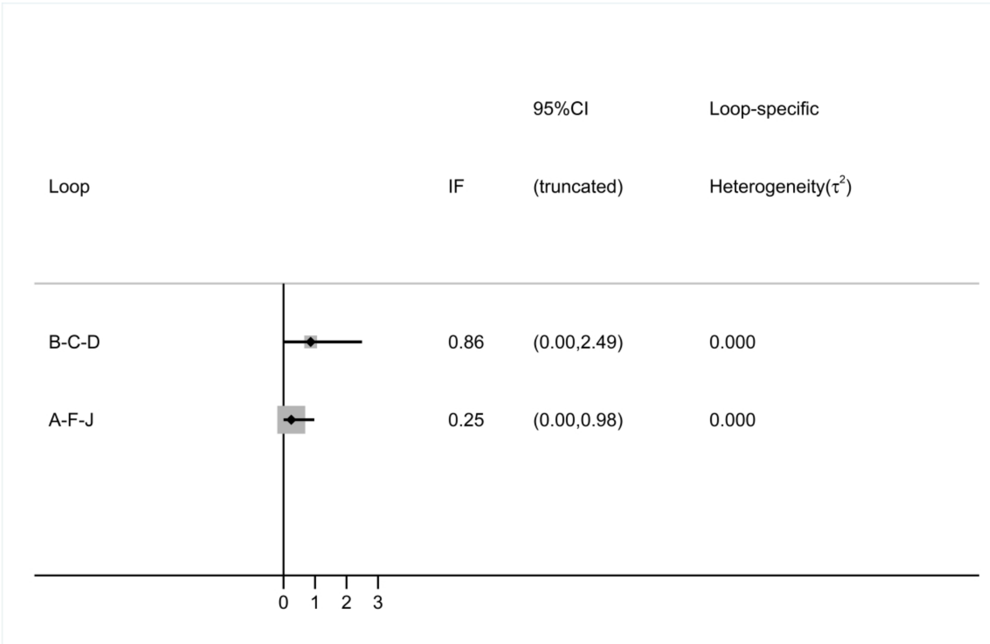


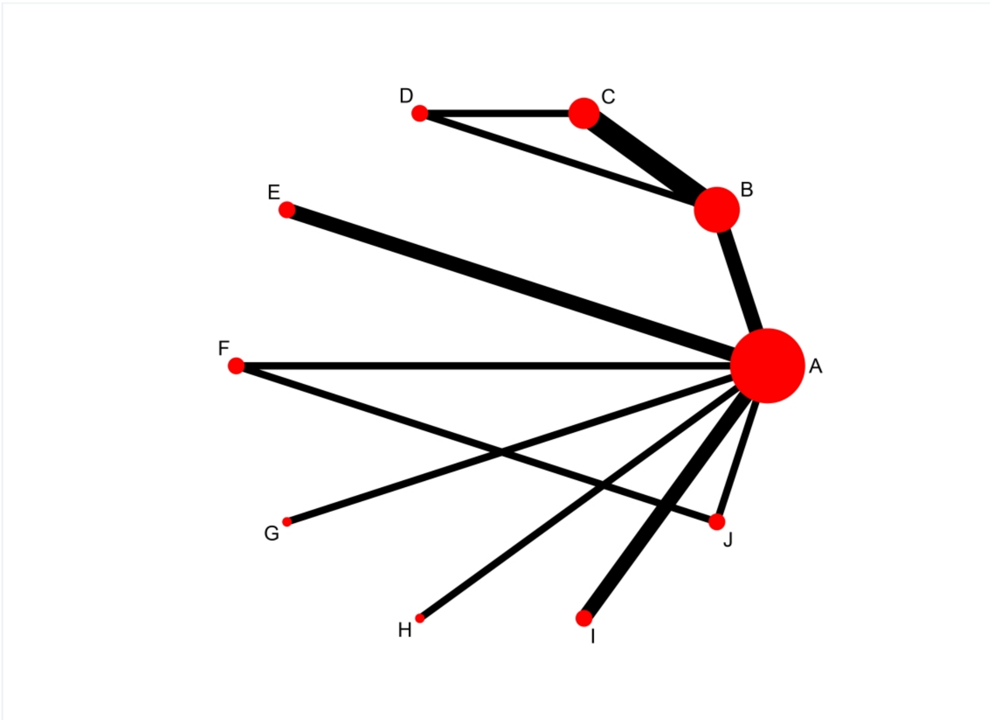
Figure 3

139x101mm (600 x 600 DPI)



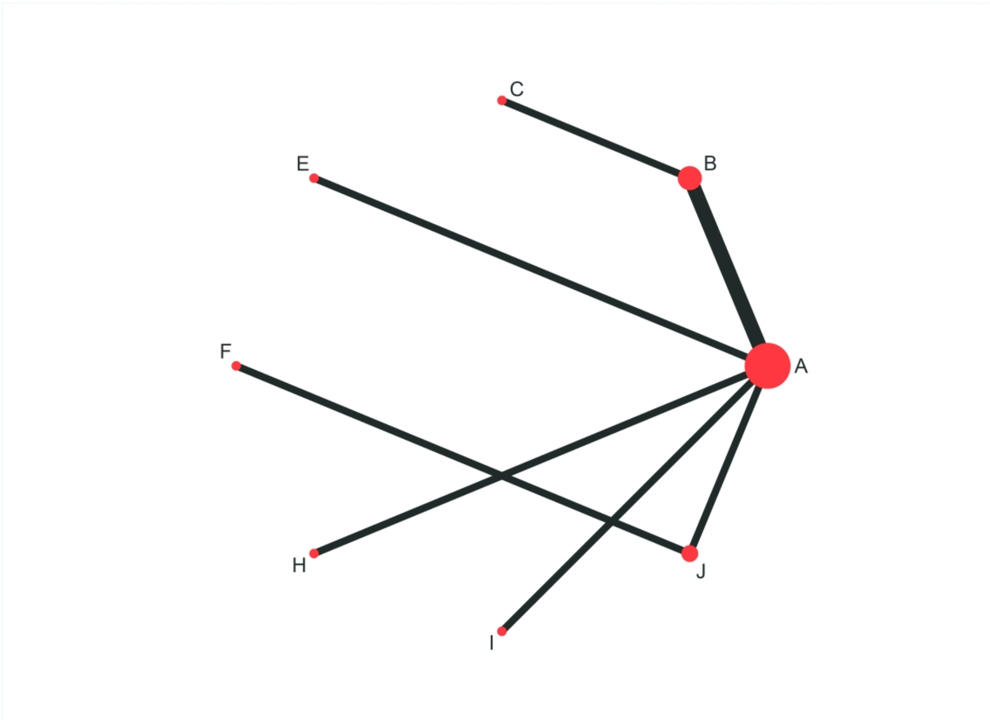
eFigure 1

146x95mm (600 x 600 DPI)



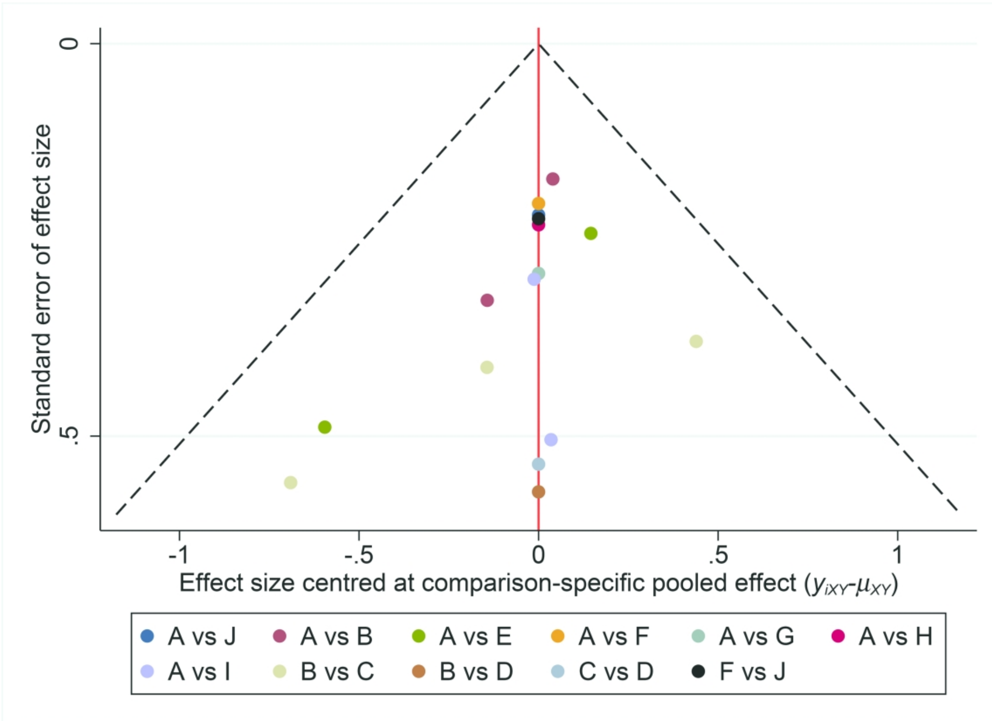
eFigure 2a

139x101mm (600 x 600 DPI)



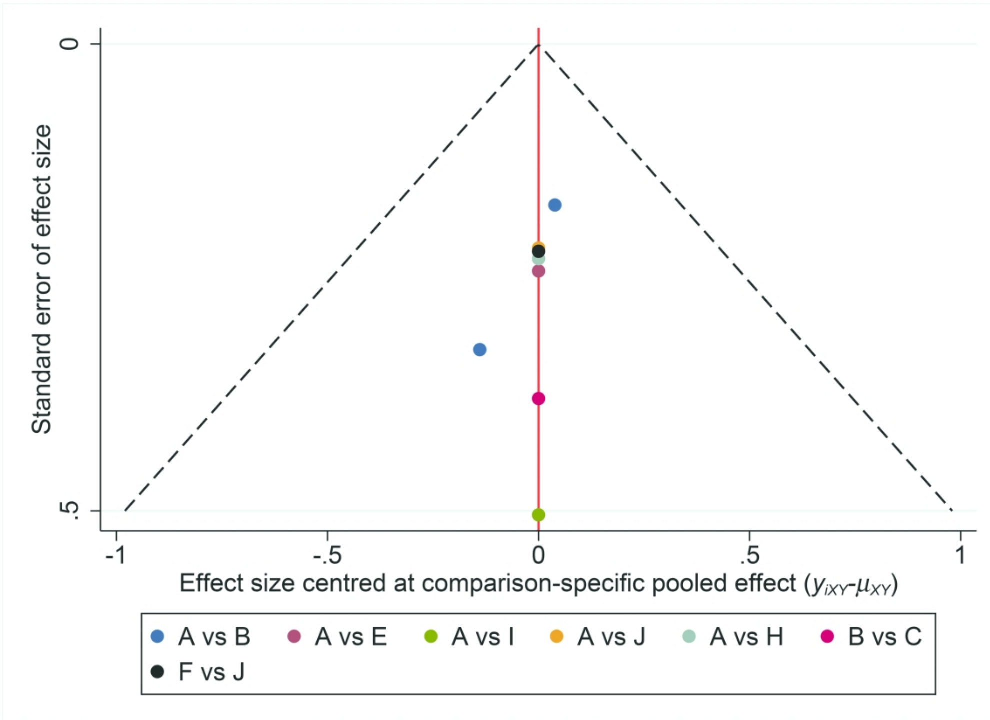
eFigure 2b

139x101mm (600 x 600 DPI)



eFigure 4a

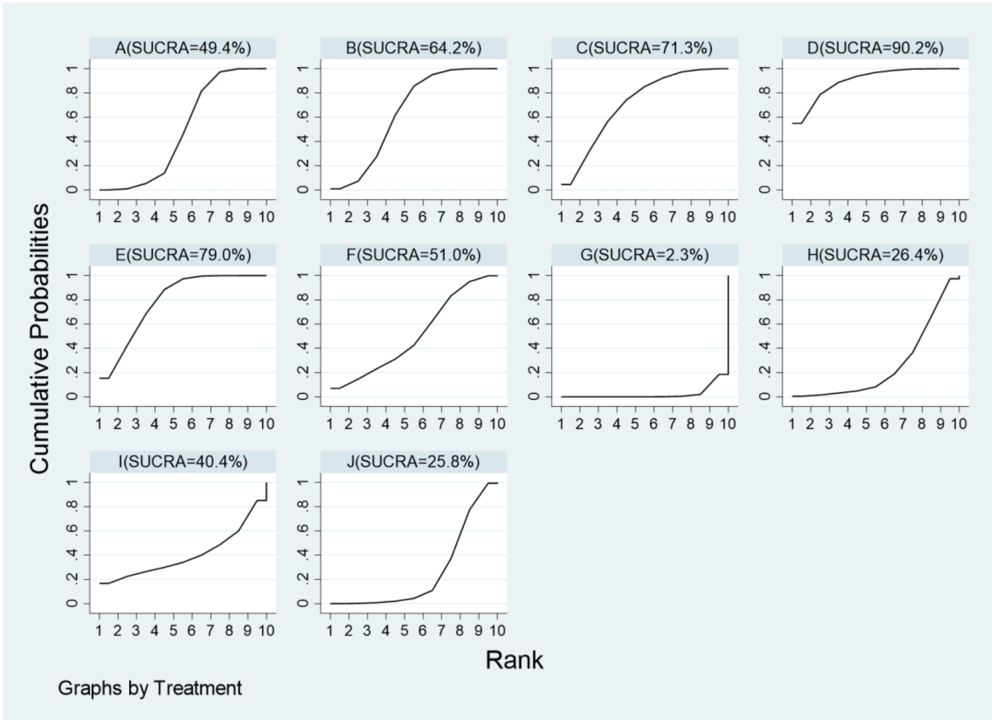
139x101mm (600 x 600 DPI)



eFigure 4b

139x101mm (600 x 600 DPI)

eFigure 5



eFigure 6

349x254mm (120 x 120 DPI)

Appendix

Appendix 1 Search strategies

Search strategies for randomized controlled trials

Pubmed

1. (((((((("Osteoarthritis, Knee"[Mesh]) OR Knee Osteoarthritides[Title/Abstract]) OR Knee Osteoarthritis[Title/Abstract]) OR Osteoarthritis of Knee[Title/Abstract]) OR Osteoarthritis of the Knee[Title/Abstract])))) AND (((((((((((((("Physical Therapy Modalities"[Mesh]) OR (Modalities, Physical Therapy[Title/Abstract])) OR (Modality, Physical Therapy[Title/Abstract])) OR (Physical Therapy Modality[Title/Abstract])) OR (Physiotherapy (Techniques)[Title/Abstract])) OR (Physiotherapies (Techniques)[Title/Abstract])) OR (Physical Therapy Techniques[Title/Abstract])) OR (Physical Therapy Technique[Title/Abstract])) OR (Techniques, Physical Therapy[Title/Abstract])) OR (Group Physiotherapy[Title/Abstract])) OR (Group Physiotherapies[Title/Abstract])) OR (Physiotherapies, Group[Title/Abstract])) OR (Physiotherapy, Group[Title/Abstract])) OR (Neurological Physiotherapy[Title/Abstract])) OR (Physiotherapy, Neurological[Title/Abstract])) OR (Neurophysiotherapy[Title/Abstract])
2. ((((((((("Osteoarthritis, Knee"[Mesh]) OR Knee Osteoarthritides[Title/Abstract]) OR Knee Osteoarthritis[Title/Abstract]) OR Osteoarthritis of Knee[Title/Abstract]) OR Osteoarthritis of the Knee[Title/Abstract])))))) AND (((("Orthopedic Equipment"[Mesh]) OR (Equipment, Orthopedic[Title/Abstract])) OR (Equipments, Orthopedic[Title/Abstract])) OR (Orthopedic Equipments[Title/Abstract]))

Embase

1. ('physiotherapy'/exp OR 'physical therapy':ab,ti OR 'physical therapy (speciality)':ab,ti OR 'physical therapy (specialty)':ab,ti OR 'physical therapy modalities ':ab,ti OR 'physical therapy service':ab,ti OR 'physical therapy speciality':ab,ti OR 'physical therapy specialty ':ab,ti OR 'physical treatment':ab,ti OR ' physio therapy ':ab,ti OR 'physical therapy techniques':ab,ti OR 'physical treatment':ab,ti OR 'physiotherapy department':ab,ti OR 'therapy, physical':ab,ti) AND ('knee osteoarthritis'/exp OR 'arthrosis, knee':ab,ti OR 'femorotibial arthrosis':ab,ti OR 'gonarthrosis':ab,ti OR 'knee arthrosis':ab,ti OR 'knee joint arthrosis':ab,ti OR 'knee joint osteoarthritis':ab,ti OR 'knee osteo-arthritis':ab,ti OR 'knee osteo-arthrosis':ab,ti OR 'knee osteoarthrosis':ab,ti OR 'osteoarthritis, knee':ab,ti OR 'osteoarthrosis, knee':ab,ti)
2. ('orthosis'/exp OR 'device, orthotic':ab,ti OR 'devices, orthotic':ab,ti OR 'orthesis':ab,ti OR 'orthopeadic support device':ab,ti OR 'orthopedic support device':ab,ti OR 'orthoses':ab,ti OR 'orthotic device (physical object)':ab,ti OR 'orthotic devices':ab,ti) AND ('knee osteoarthritis'/exp OR 'arthrosis, knee':ab,ti OR 'femorotibial arthrosis':ab,ti OR 'gonarthrosis':ab,ti OR 'knee arthrosis':ab,ti OR 'knee joint arthrosis':ab,ti OR 'knee joint osteoarthritis':ab,ti OR 'knee osteo-arthritis':ab,ti OR 'knee osteo-arthrosis':ab,ti OR 'knee

osteoarthrosis':ab,ti OR 'osteoarthritis, knee':ab,ti OR 'osteoarthrosis, knee':ab,ti)

Web of Science

1. AB=(physical therapy OR physiotherapy OR physio therapy OR physical treatment OR physiotherapy department OR physical therapy techniques)
2. TI=(physical therapy OR physiotherapy OR physio therapy OR physical treatment OR physiotherapy department OR physical therapy techniques)
3. AB=(orthosis OR device OR orthesis OR orthoses OR orthopeadic support device OR orthotic device)
4. TI=(orthosis OR device OR orthesis OR orthoses OR orthopeadic support device OR orthotic device)
5. #4 OR #3 OR #2 OR #1
6. AB=(knee osteoarthritis OR femorotibial arthrosis OR gonarthrosis OR knee arthrosis OR knee osteo-arthritis OR knee osteoarthrosis OR osteoarthrosis)
7. TI=(knee osteoarthritis OR femorotibial arthrosis OR gonarthrosis OR knee arthrosis OR knee osteo-arthritis OR knee osteoarthrosis OR osteoarthrosis)
8. #6 OR #7
9. #8 AND #5

Cochrane Library

1. (MeSH descriptor: [Physical Therapy Modalities] explode all trees OR (Neurological Physiotherapy):ti,ab,kw OR (Physiotherapy, Neurological):ti,ab,kw OR (Neurophysiotherapy):ti,ab,kw OR (Techniques, Physical Therapy):ti,ab,kw OR (Physiotherapies (Techniques)):ti,ab,kw OR (Physical Therapy Techniques):ti,ab,kw OR (Physiotherapy (Techniques)):ti,ab,kw OR (Modality, Physical Therapy):ti,ab,kw OR (Physical Therapy Modality):ti,ab,kw OR (Physical Therapy Technique):ti,ab,kw OR (Modalities, Physical Therapy):ti,ab,kw OR (Group Physiotherapies):ti,ab,kw OR (Physiotherapy, Group):ti,ab,kw OR (Group Physiotherapy):ti,ab,kw OR (Physiotherapies, Group):ti,ab,kw) AND ((Osteoarthritis of Knee):ti,ab,kw OR (Knee Osteoarthritides):ti,ab,kw OR (Knee Osteoarthritis):ti,ab,kw OR (Osteoarthritis of the Knee):ti,ab,kw) OR MeSH descriptor: [Osteoarthritis, Knee] explode all trees)
2. (MeSH descriptor: [Orthopedic Equipment] explode all trees OR (Orthopedic Equipments):ti,ab,kw OR (Equipment, Orthopedic):ti,ab,kw OR (Equipments, Orthopedic):ti,ab,kw) AND ((Osteoarthritis of Knee):ti,ab,kw OR (Knee Osteoarthritides):ti,ab,kw OR (Knee Osteoarthritis):ti,ab,kw OR (Osteoarthritis of the Knee):ti,ab,kw) OR MeSH descriptor: [Osteoarthritis, Knee] explode all trees)

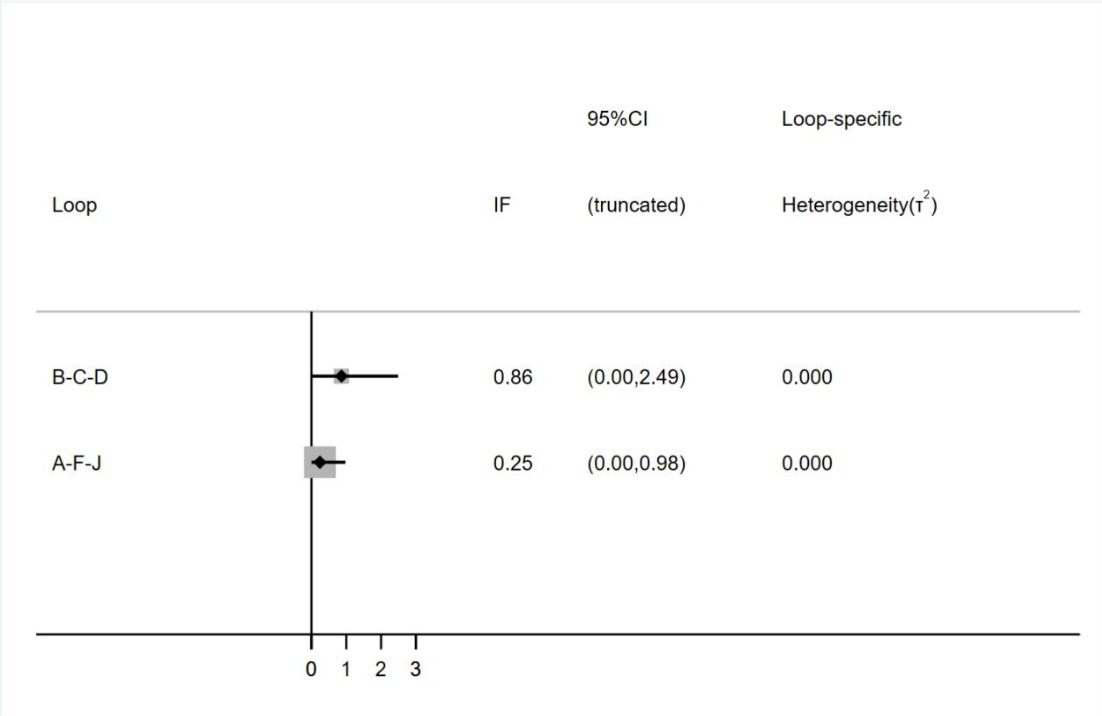
MEDLINE

1. (knee osteoarthritis) OR (femorotibial arthrosis) OR (gonarthrosis) OR (knee arthrosis) OR (knee osteo-arthritis) OR (knee osteoarthrosis) OR (osteoarthrosis)
2. (physical therapy) OR (physiotherapy) OR (physio therapy) OR (physical treatment) OR (physiotherapy department) OR (physical therapy techniques)
3. (orthotic devices) OR (Orthopedic Equipment) OR (orthosis) OR (device) OR (orthesis)

OR (orthoses) OR (orthopeadic support device)

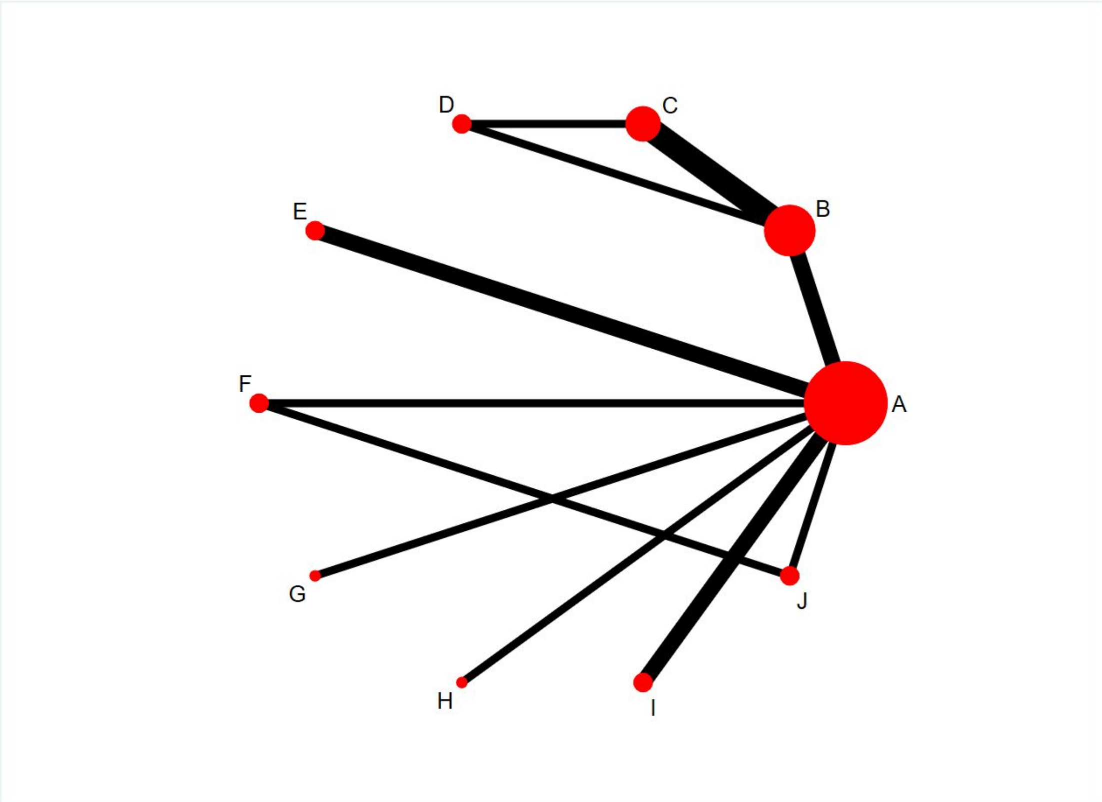
4. #2 OR #3
5. #1 AND #4

Appendix 2 Results of Inconsistency



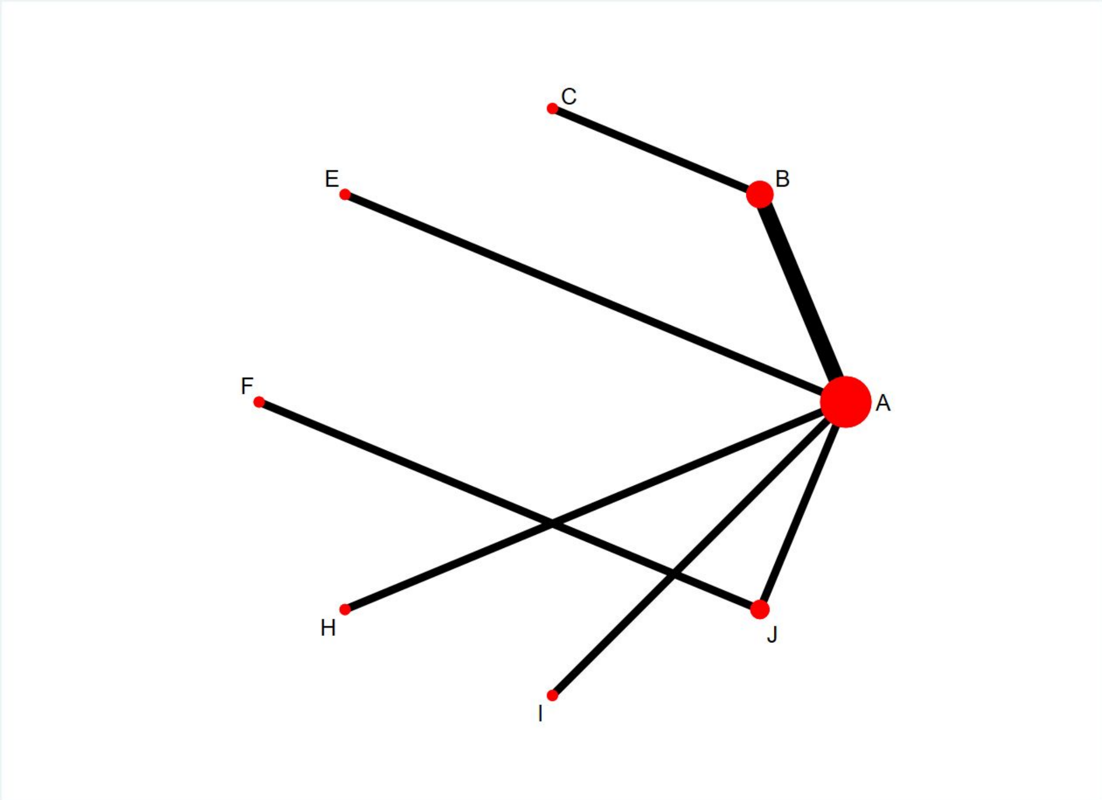
eFigure 1. Inconsistency for triangular loops in First peak KAM.

Appendix 3 Network Diagram



eFigure 2a. Structure of network formed by interventions and their direct comparisons (First peak KAM). A= Standard care; B= Lateral Wedge Insole; C= Knee Brace; D= Lateral Wedge Insole+ Knee Brace; E= Gait retraining; F= Quadriceps strengthening; G= Variable-stiffness shoe; H= Hip strengthening; I= Lower limb exercise; J= Neuromuscular exercise.

Footnote: Width of the lines is proportional to the number of trials comparing every pair of treatments. Size of every circle is proportional to the number of randomly assigned participants (ie, sample size).

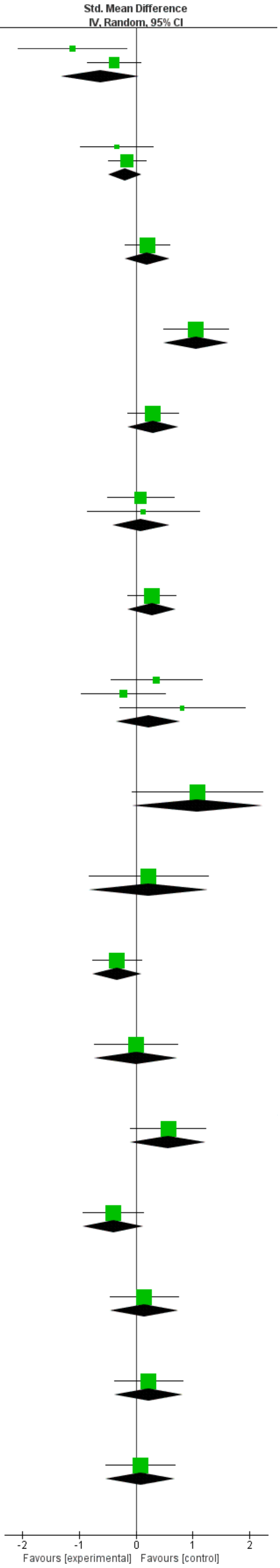


eFigure 2b. Structure of network formed by interventions and their direct comparisons (KAAI). A= Standard care; B= Lateral Wedge Insole; C= Knee Brace; E= Gait retraining; F= Quadriceps strengthening; H= Hip strengthening; I= Lower limb exercise; J= Neuromuscular exercise.

Footnote: Width of the lines is proportional to the number of trials comparing every pair of treatments. Size of every circle is proportional to the number of randomly assigned participants (ie, sample size).

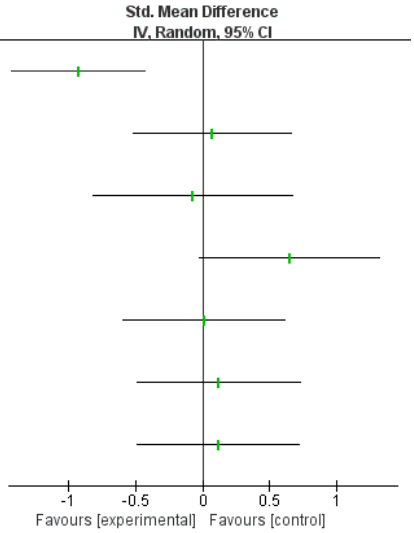
Appendix 4 Conventional meta-analyses results

	Experimental			Control				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
1.1.1 Gait retraining vs Standard Care								
Cheung 2018	-0.078	0.0839	10	0.005	0.0547	10	33.5%	-1.12 [-2.08, -0.16]
Hunt 2018	-0.01	0.3599	37	0.13	0.3666	33	66.5%	-0.38 [-0.86, 0.09]
Subtotal (95% CI)			**47**			**43**	**100.0%**	**-0.63 [-1.32, 0.06]**
Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 1.85$, df = 1 (P = 0.17); $I^2 = 46\%$								
Test for overall effect: Z = 1.80 (P = 0.07)								
1.1.2 LWI vs Standard Care								
Barrios 2013	-0.011	0.1351	19	0.032	0.1133	19	21.7%	-0.34 [-0.98, 0.30]
Hinman 2016	0.26	1.3295	68	0.46	1.234	67	78.3%	-0.16 [-0.49, 0.18]
Subtotal (95% CI)			**87**			**86**	**100.0%**	**-0.19 [-0.49, 0.10]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.24$, df = 1 (P = 0.62); $I^2 = 0\%$								
Test for overall effect: Z = 1.28 (P = 0.20)								
1.1.3 Quadriceps strengthening vs Standard Care								
Lim 2008	0.1	0.9685	49	-0.087	0.8962	48	100.0%	0.20 [-0.20, 0.60]
Subtotal (95% CI)			**49**			**48**	**100.0%**	**0.20 [-0.20, 0.60]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.98 (P = 0.33)								
1.1.4 Variable-stiffness shoes vs Standard Care								
Erhart-Hledik 2012	0.338	0.3763	32	-0.072	0.3878	23	100.0%	1.06 [0.49, 1.63]
Subtotal (95% CI)			**32**			**23**	**100.0%**	**1.06 [0.49, 1.63]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.62 (P = 0.0003)								
1.1.5 Hip strengthening vs Standard Care								
Bennell 2010	0.15	0.4371	39	0.02	0.4258	37	100.0%	0.30 [-0.15, 0.75]
Subtotal (95% CI)			**39**			**37**	**100.0%**	**0.30 [-0.15, 0.75]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.29 (P = 0.20)								
1.1.6 Lower limb exercise vs Standard Care								
Foroughi 2011	-0.02	1.26	20	-0.11	1.0223	25	73.9%	0.08 [-0.51, 0.67]
Hunt 2013	-0.05	0.91	9	-0.17	0.9044	7	26.1%	0.13 [-0.86, 1.11]
Subtotal (95% CI)			**29**			**32**	**100.0%**	**0.09 [-0.42, 0.60]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.01$, df = 1 (P = 0.94); $I^2 = 0\%$								
Test for overall effect: Z = 0.35 (P = 0.73)								
1.1.7 Neuromuscular exercise vs Standard Care								
Holsgaard-Larsen 2017	0.12	0.3125	44	0.03	0.3168	41	100.0%	0.28 [-0.14, 0.71]
Subtotal (95% CI)			**44**			**41**	**100.0%**	**0.28 [-0.14, 0.71]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.30 (P = 0.19)								
1.1.8 LWI vs Knee Brace								
Arazpour 2012	-0.07	0.0324	12	-0.08	0.019	12	36.6%	0.36 [-0.44, 1.17]
Jones 2013	-0.075	0.1296	14	-0.045	0.1346	14	41.3%	-0.22 [-0.96, 0.52]
Khosravi 2019	-0.08	0.1752	7	-0.22	0.1442	7	22.1%	0.82 [-0.29, 1.92]
Subtotal (95% CI)			**33**			**33**	**100.0%**	**0.22 [-0.34, 0.79]**
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 2.58$, df = 2 (P = 0.28); $I^2 = 22\%$								
Test for overall effect: Z = 0.77 (P = 0.44)								
1.1.9 LWI vs LWI+Knee Brace								
Khosravi 2019	-0.08	0.1752	7	-0.251	0.1153	7	100.0%	1.08 [-0.07, 2.23]
Subtotal (95% CI)			**7**			**7**	**100.0%**	**1.08 [-0.07, 2.23]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.84 (P = 0.07)								
1.1.10 Knee Brace vs LWI+Knee Brace								
Khosravi 2019	-0.22	0.1442	7	-0.251	0.1153	7	100.0%	0.22 [-0.83, 1.27]
Subtotal (95% CI)			**7**			**7**	**100.0%**	**0.22 [-0.83, 1.27]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.41 (P = 0.68)								
1.1.11 Quadriceps strengthening vs Neuromuscular exercise								
Bennell 2014	-0.04	0.4605	44	0.12	0.502	38	100.0%	-0.33 [-0.77, 0.11]
Subtotal (95% CI)			**44**			**38**	**100.0%**	**-0.33 [-0.77, 0.11]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.48 (P = 0.14)								
1.1.12 PNF vs Standard Care								
Song 2020	0.01	0.13	13	0.01	0.13	16	100.0%	0.00 [-0.73, 0.73]
Subtotal (95% CI)			**13**			**16**	**100.0%**	**0.00 [-0.73, 0.73]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
1.1.13 Electroacupuncture vs Sham-acupuncture								
Wang 2017	0.019	0.095	18	-0.036	0.094	18	100.0%	0.57 [-0.10, 1.24]
Subtotal (95% CI)			**18**			**18**	**100.0%**	**0.57 [-0.10, 1.24]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.67 (P = 0.09)								
1.1.14 Minimalist footwear vs Standard, neutral tennis shoe								
Trombini-Souza 2015	-0.23	0.84	28	0.18	1.15	28	100.0%	-0.40 [-0.93, 0.13]
Subtotal (95% CI)			**28**			**28**	**100.0%**	**-0.40 [-0.93, 0.13]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.49 (P = 0.14)								
1.1.15 ACL-brace vs V3P-brace								
Robert-Lachaine 2020	0.005	0.0991	21	-0.01	0.0967	21	100.0%	0.15 [-0.46, 0.76]
Subtotal (95% CI)			**21**			**21**	**100.0%**	**0.15 [-0.46, 0.76]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.49 (P = 0.63)								
1.1.16 ACL-brace vs VER-brace								
Robert-Lachaine 2020	0.005	0.0991	21	-0.018	0.1043	21	100.0%	0.22 [-0.39, 0.83]
Subtotal (95% CI)			**21**			**21**	**100.0%**	**0.22 [-0.39, 0.83]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.72 (P = 0.47)								
1.1.17 V3P-brace vs VER-brace								
Robert-Lachaine 2020	-0.01	0.0967	21	-0.018	0.1043	21	100.0%	0.08 [-0.53, 0.68]
Subtotal (95% CI)			**21**			**21**	**100.0%**	**0.08 [-0.53, 0.68]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.25 (P = 0.80)								



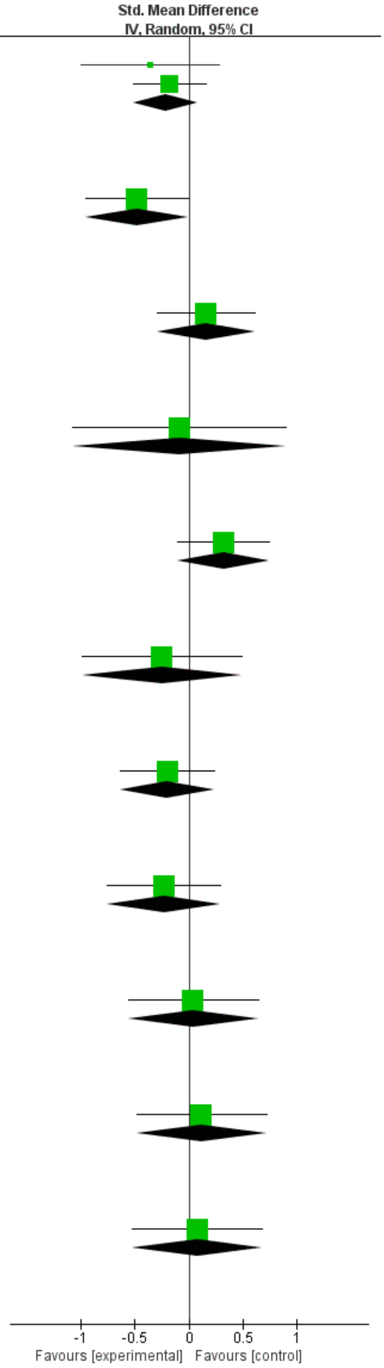
eFigure 3a. Conventional meta-analysis of treatment effects on First peak KAM.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Std. Mean Difference IV, Random, 95% CI
1.2.1 Gait retraining vs Standard Care							
Hunt 2018	-0.24	0.2699	37	0.02	0.2849	33	-0.93 [-1.42, -0.43]
1.2.2 Lower limb exercise vs Standard Care							
Foroughi 2011	0.14	1.311	20	0.06	0.9254	25	0.07 [-0.52, 0.66]
1.2.3 LWI vs Knee Brace							
Jones 2013	-0.06	0.144	14	-0.05	0.12	14	-0.07 [-0.81, 0.67]
1.2.4 Electroacupuncture vs Sham-acupuncture							
Wang 2017	-0.002	0.093	18	-0.046	0.012	18	0.65 [-0.02, 1.32]
1.2.5 ACL-brace vs V3P-brace							
Robert-Lachaine 2020	-0.001	0.106	21	-0.002	0.0989	21	0.01 [-0.60, 0.61]
1.2.6 ACL-brace vs VER-brace							
Robert-Lachaine 2020	-0.001	0.106	21	-0.014	0.1043	21	0.12 [-0.48, 0.73]
1.2.7 V3P-brace vs VER-brace							
Robert-Lachaine 2020	-0.002	0.0989	21	-0.014	0.1043	21	0.12 [-0.49, 0.72]



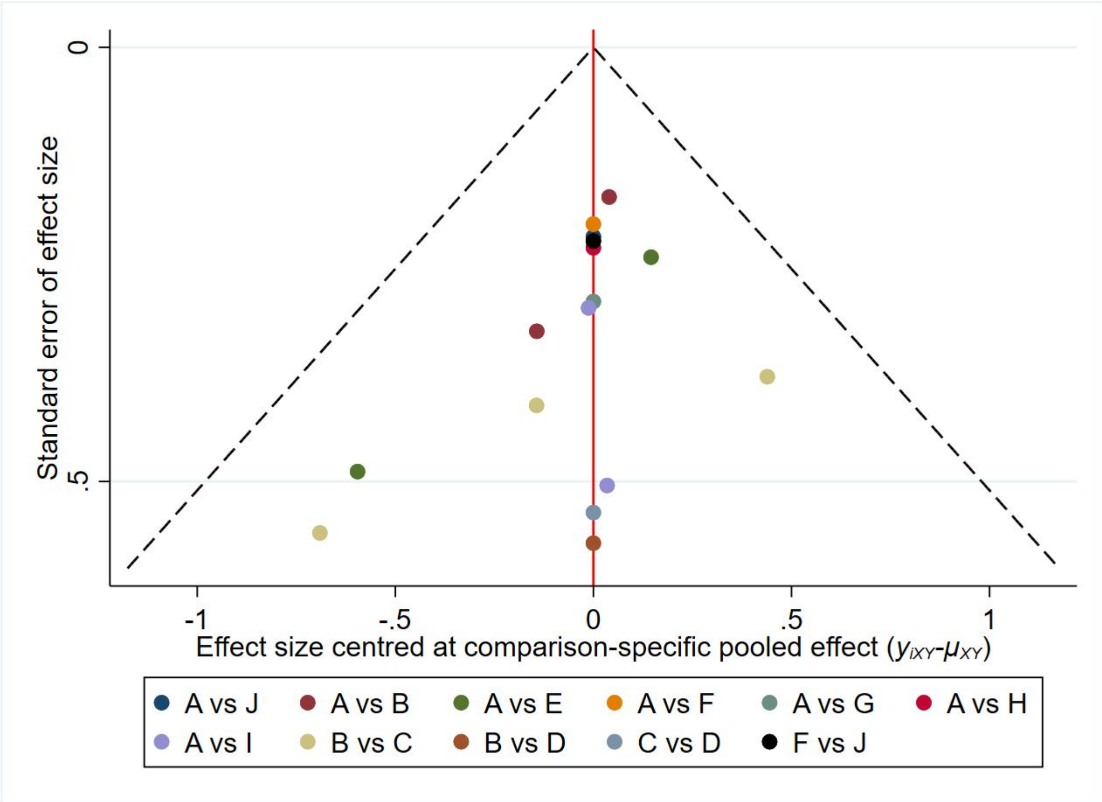
eFigure 3b. Conventional meta-analysis of treatment effects on Second peak KAM.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.3.1 LWI vs Standard Care								
Barrios 2013	-0.009	0.0727	19	0.016	0.064	19	21.7%	-0.36 [-1.00, 0.28]
Hinman 2016	0.07	0.451	68	0.15	0.435	67	78.3%	-0.18 [-0.52, 0.16]
Subtotal (95% CI)			**87**			**86**	**100.0%**	**-0.22 [-0.52, 0.08]**
Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 1 (P = 0.63); I² = 0%								
Test for overall effect: Z = 1.43 (P = 0.15)								
1.3.2 Gait retraining vs Standard Care								
Hunt 2018	-0.04	0.105	37	0.01	0.0987	33	100.0%	-0.48 [-0.96, -0.01]
Subtotal (95% CI)			**37**			**33**	**100.0%**	**-0.48 [-0.96, -0.01]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.99 (P = 0.05)								
1.3.3 Hip strengthening vs Standard Care								
Bennell 2010	0.05	0.1873	39	0.02	0.1825	37	100.0%	0.16 [-0.29, 0.61]
Subtotal (95% CI)			**39**			**37**	**100.0%**	**0.16 [-0.29, 0.61]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.70 (P = 0.48)								
1.3.4 Lower limb exercise vs Standard Care								
Hunt 2013	-0.12	0.3775	9	-0.08	0.4951	7	100.0%	-0.09 [-1.08, 0.90]
Subtotal (95% CI)			**9**			**7**	**100.0%**	**-0.09 [-1.08, 0.90]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.17 (P = 0.86)								
1.3.5 Neuromuscular exercise vs Standard Care								
Holsgaard-Larsen 2017	0.05	0.1316	44	0.01	0.1109	41	100.0%	0.32 [-0.10, 0.75]
Subtotal (95% CI)			**44**			**41**	**100.0%**	**0.32 [-0.10, 0.75]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.49 (P = 0.14)								
1.3.6 LWI vs Knee Brace								
Jones 2013	-0.0395	0.0687	14	-0.0215	0.0726	14	100.0%	-0.25 [-0.99, 0.50]
Subtotal (95% CI)			**14**			**14**	**100.0%**	**-0.25 [-0.99, 0.50]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.65 (P = 0.51)								
1.3.7 Quadriceps strengthening vs Neuromuscular exercise								
Bennell 2014	-0.02	0.1809	44	0.02	0.213	38	100.0%	-0.20 [-0.64, 0.23]
Subtotal (95% CI)			**44**			**38**	**100.0%**	**-0.20 [-0.64, 0.23]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.91 (P = 0.36)								
1.3.8 Minimalist footwear vs Standard, neutral tennis shoe								
Trombini-Souza 2015	-0.09	0.3652	28	0.01	0.4803	28	100.0%	-0.23 [-0.76, 0.29]
Subtotal (95% CI)			**28**			**28**	**100.0%**	**-0.23 [-0.76, 0.29]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.86 (P = 0.39)								
1.3.9 ACL-brace VS V3P-brace								
Robert-Lachaine 2020	0.2	4.9428	21	0	4.8368	21	100.0%	0.04 [-0.56, 0.65]
Subtotal (95% CI)			**21**			**21**	**100.0%**	**0.04 [-0.56, 0.65]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.13 (P = 0.90)								
1.3.10 ACL-brace vs VER-brace								
Robert-Lachaine 2020	0.2	4.9428	21	-0.4	4.9624	21	100.0%	0.12 [-0.49, 0.72]
Subtotal (95% CI)			**21**			**21**	**100.0%**	**0.12 [-0.49, 0.72]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.38 (P = 0.70)								
1.3.11 V3P-brace vs VER-brace								
Robert-Lachaine 2020	0	4.8368	21	-0.4	4.9624	21	100.0%	0.08 [-0.53, 0.69]
Subtotal (95% CI)			**21**			**21**	**100.0%**	**0.08 [-0.53, 0.69]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.26 (P = 0.80)								

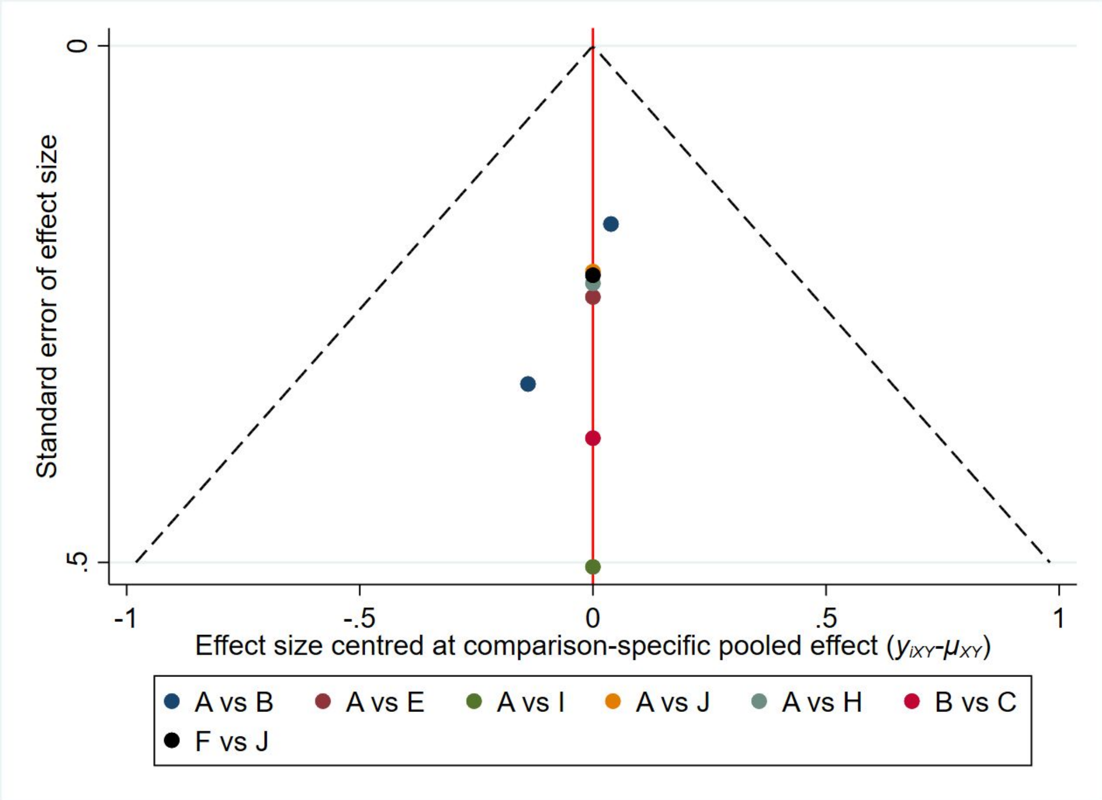


eFigure 3c. Conventional meta-analysis of treatment effects on KAAI.

Appendix 5 Comparison-adjusted funnel plot for each outcome from the network meta-analysis



eFigure 4a. Comparison-adjusted funnel plot for First peak KAM.
A= Standard care; B= Lateral Wedge Insole; C= Knee Brace; D= Lateral Wedge Insole+ Knee Brace; E= Gait retraining; F= Quadriceps strengthening; G= Variable-stiffness shoe; H= Hip strengthening; I= Lower limb exercise; J= Neuromuscular exercise.



eFigure 4b. Comparison-adjusted funnel plot for KAAI.
A= Standard care; B= Lateral Wedge Insole; C= Knee Brace; E= Gait retraining; F= Quadriceps strengthening; H= Hip strengthening; I= Lower limb exercise; J= Neuromuscular exercise.

Appendix 6 Table of GRADE

Based on all the above information, we GRADEd each network estimate according to the following criteria:

1) Study limitations: We downgraded by one level when the contributions from low RoB comparisons were less than 30% and contributions from moderate RoB comparisons were 70% or greater. And we downgraded by two level when the contributions from low RoB comparisons were more than 30%.
2) Imprecision: We considered a clinically meaningful threshold for CI to be 0 and did not downgrade the estimate if the upper limit is below 0; or if the lower limit is above 0.
3) Inconsistency: We rated two concepts, heterogeneity and incoherence (inconsistency), in this domain. For heterogeneity, we did not downgrade any network estimate for heterogeneity, because we looked at the common tau and found that it is low. For

inconsistency, we looked at the results of inconsistency (Appendix 2), where we have not downgraded for imprecision.

4) Indirectness: We have assured transitivity in our network by limiting the included studies to patients with knee osteoarthritis. Evaluation of transitivity for singly-connected nodes is unclear, so we downgraded such nodes for indirectness.

5) Publication bias: The comparison-adjusted funnel plot (Appendix 5) did not suggest presence of overall publication bias. We managed to retrieve supplementary and unpublished information included in the available systematic reviews and network meta-analyses, and we are confident that we have all available information that is possible to capture from clinical trial registries. Although we cannot completely rule out the possibility that some research is still missing, we still believe that the project does not need to be downgraded.

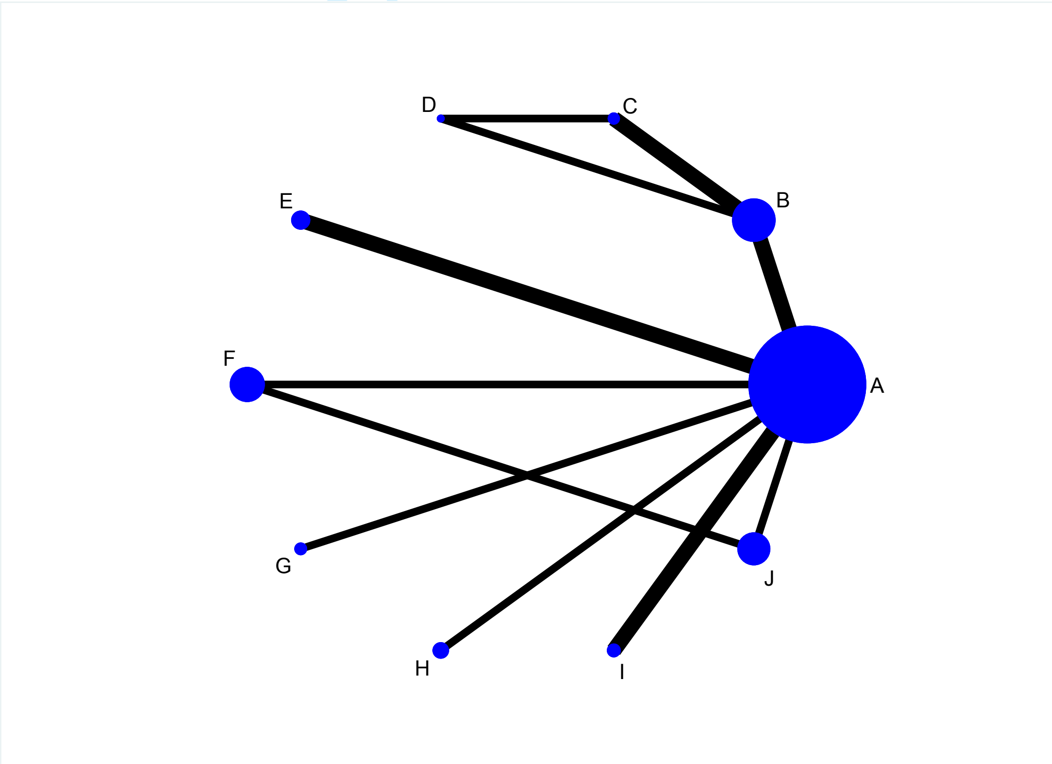
Comparison	Nature of the Evidence	GRADE	Downgarding due to
AB: Placebo *vs* LWI	Mixed	LOW	Study limitations; Imprecision
AC: Placebo *vs* Knee Brace	Indirect	LOW	Study limitations; Imprecision
AD: Placebo *vs* LWI+Knee Brace	Indirect	LOW	Study limitations; Imprecision
AE: Placebo *vs* Gait Retraining	Mixed	VERY LOW	Study limitations; Indirectness
AF: Placebo *vs* Quadriceps Strengthening	Mixed	VERY LOW	Study limitations; Imprecision
AG: Placebo *vs* Variable-Stiffness Shoes	Mixed	VERY LOW	Study limitations; Indirectness;
AH: Placebo *vs* Hip Strengthening	Mixed	VERY LOW	Study limitations; Indirectness; Imprecision
AI: Placebo *vs* Lower Limb Exercise	Mixed	VERY LOW	Study limitations; Indirectness; Imprecision
AJ: Placebo *vs* Neuromuscular Exercise	Mixed	MODERATE	Study limitations
BC: LWI *vs* Knee Brace	Mixed	VERY LOW	Study limitations; Imprecision
BD: LWI *vs* LWI+Knee Brace	Mixed	VERY LOW	Study limitations; Imprecision

BE: LWI *vs* Gait Retraining	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
BF: LWI *vs* Quadriceps Strengthening	Indirect	LOW	Study limitations; Imprecision
BG: LWI *vs* Variable-Stiffness Shoes	Indirect	LOW	Study limitations; Indirectness
BH: LWI *vs* Hip Strengthening	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
BI: LWI *vs* Lower Limb Exercise	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
BJ: LWI *vs* Neuromuscular Exercise	Indirect	MODERATE	Study limitations
CD: Knee Brace *vs* LWI+Knee Brace	Mixed	VERY LOW	Study limitations; Imprecision
CE: Knee Brace *vs* Gait Retraining	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
CF: Knee Brace *vs* Quadriceps Strengthening	Indirect	LOW	Study limitations; Imprecision
CG: Knee Brace *vs* Variable-Stiffness Shoes	Indirect	LOW	Study limitations; Indirectness
CH: Knee Brace *vs* Hip Strengthening	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
CI: Knee Brace *vs* Lower Limb Exercise	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
CJ: Knee Brace *vs* Neuromuscular Exercise	Indirect	MODERATE	Study limitations
DE: LWI+Knee Brace *vs* Gait Retraining	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
DF: LWI+Knee Brace *vs* Quadriceps Strengthening	Indirect	LOW	Study limitations; Imprecision
DG: LWI+Knee Brace *vs* Variable-Stiffness Shoes	Indirect	VERY LOW	Study limitations; Indirectness
DH: LWI+Knee Brace *vs* Hip	Indirect	LOW	Study limitations; Indirectness

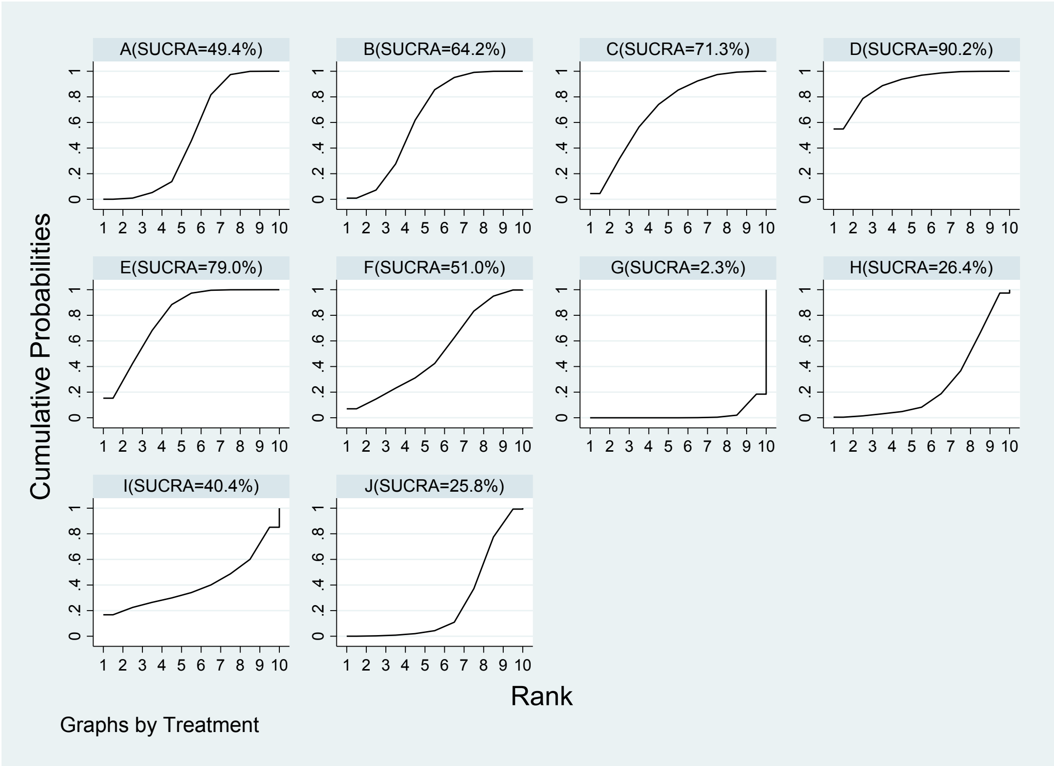
Strengthening			
DI: LWI+Knee Brace *vs* Lower Limb Exercise	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
DJ: LWI+Knee Brace *vs* Neuromuscular Exercise	Indirect	MODERATE	Study limitations
EF: Gait Retraining *vs* Quadriceps Strengthening	Indirect	VERY LOW	Study limitations; Indirectness
EG: Gait Retraining *vs* Variable-Stiffness Shoes	Indirect	VERY LOW	Study limitations; Indirectness
EH: Gait Retraining *vs* Hip Strengthening	Indirect	LOW	Study limitations; Indirectness
EI: Gait Retraining *vs* Lower limb Exercise	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
EJ: Gait Retraining *vs* Neuromuscular Exercise	Indirect	LOW	Study limitations; Indirectness
FG: Quadriceps Strengthening *vs* Variable-Stiffness Shoes	Indirect	VERY LOW	Study limitations; Indirectness
FH: Quadriceps Strengthening *vs* Hip Strengthening	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
FI: Quadriceps Strengthening *vs* Lower Limb Exercise	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
FJ: Quadriceps Strengthening *vs* Neuromuscular Exercise	Mixed	LOW	Study limitations; Imprecision
GH: Variable-Stiffness Shoes *vs* Hip Strengthening	Indirect	LOW	Study limitations; Indirectness
GI: Variable-Stiffness Shoes *vs* Lower Limb Exercise	Indirect	VERY LOW	Study limitations; Indirectness
GJ: Variable-Stiffness Shoes *vs* Neuromuscular Exercise	Indirect	LOW	Study limitations; Indirectness

HI: Hip Strengthening *vs* Lower Limb Exercise	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
HJ: Hip Strengthening *vs* Neuromuscular Exercise	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
IJ: Lower Limb Exercise *vs* Neuromuscular Exercise	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision

Appendix 7 Results of re-analysis



eFigure 5. Structure of network formed by interventions and their direct comparisons on First peak KAM (re-analysis). A= Standard care; B= Lateral Wedge Insole; C= Knee Brace; D= Lateral Wedge Insole+ Knee Brace; E= Gait retraining; F= Quadriceps strengthening; G= Variable-stiffness shoe; H= Hip strengthening; I= Lower limb exercise; J= Neuromuscular exercise.



eFigure 6. Rankings for effects on First peak KAM (re-analysis). Graph displays distribution of probabilities for each treatment. X-axis represents the possible rank of each treatment (from the best to worst according to the outcomes), Y-axis represents the cumulative probability for each treatment to be the best option, among the best two options, among the best three options, and so on. A= Standard care; B= Lateral Wedge Insole; C= Knee Brace; D= Lateral Wedge Insole+ Knee Brace; E= Gait retraining; F= Quadriceps strengthening; G= Variable-stiffness shoe; H= Hip strengthening; I= Lower limb exercise; J= Neuromuscular exercise.

PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction, paragraph 1-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction, paragraph 5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	METHODS, paragraph1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	METHODS, Identification and selection of studies
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	METHODS, Identification and selection of studies, paragraph 1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1 Search strategies
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Results, figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	METHODS, Identification

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			and selection of studies, paragraph 2
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	METHODS, Identification and selection of studies, paragraph 2, 3 & Data Collection and Quality assessment
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	METHODS, Assessment of characteristics of studies & Results, Figure 4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	METHODS, Statistical analysis
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	METHODS, Statistical analysis

Section/Topic	#	Checklist Item	Reported on Page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	METHODS, Assessment of characteristics of studies
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	METHODS, Statistical

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			Analysis
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Results, Characteristics of included studies & Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Results, Characteristics of included studies & Table 1, 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Results, Risk of bias & Figure 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Results, KAM & KAAI & Appendix 4
Synthesis of results	21	Present the main results of the review. If meta-analyses done, include for each, confidence intervals and measures of consistency.	Results, KAM & KAAI (Table 3 & Figure 2, 3)
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Results, Risk of bias & Appendix 5 & 6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Appendix 2 & 5 & 6
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion, paragraph 1 & Conclusion

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Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion, paragraph 4
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Conclusion & Discussion, paragraph 8 & 9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Funding

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Dear Editors,

We would like to submit the enclosed Original Article entitled "Non-surgical Treatment-induced Reduction in the Biomechanical Risk Factors Related to Knee Osteoarthritis: A systematic review and Bayesian network meta-analysis of randomized controlled trials", which we wish to be considered for publication in "*BMJ Open*".

No conflict of interest exits in the submission of this manuscript, and manuscript is approved by all authors for publication. All authors contributed to the creation of this manuscript for important intellectual content. I would like to declare on behalf of my co-authors that the work described was original research that has not been published previously, and not under consideration for publication elsewhere, in whole or in part. All the authors listed have approved the manuscript that is enclosed.

This study aims to evaluate the effects of non-surgical treatment in reducing the biomechanical risk factors related to knee osteoarthritis (KOA) and this Bayesian network meta-analysis is the first review on effect of physical therapy on the biomechanical parameters (KAM & KAAI) of the knee OA. The review observes a null statistical reduction in KAM and KAAI for most therapies, using these non-surgical treatments clinically could improve symptoms and physical activity level without increasing the biomechanical magnitude; thus, improving the quality of life of patients with KOA. I hope this paper is suitable for "*BMJ Open*".

We deeply appreciate your consideration of our manuscript, and we look forward to receiving comments from the reviewers. If you have any queries, please don't hesitate to contact me at the address below.

Thank you and best regards.

Jia-Kuo Yu, MD&PhD, is the corresponding author and his address and other information is as follows,

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Yours sincerely,

Dr. Huang

BMJ Open

Physical Therapy and Orthopedic Equipment-induced Reduction in the Biomechanical Risk Factors Related to Knee Osteoarthritis: A systematic review and Bayesian network meta-analysis of randomized controlled trials

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Primary Subject Heading:	Sports and exercise medicine
Secondary Subject Heading:	Evidence based practice, Rehabilitation medicine
Keywords:	Biophysics < NATURAL SCIENCE DISCIPLINES, Adult orthopaedics < ORTHOPAEDIC & TRAUMA SURGERY, Knee < ORTHOPAEDIC & TRAUMA SURGERY, REHABILITATION MEDICINE

Title: Physical Therapy and Orthopedic Equipment-induced Reduction in the Biomechanical Risk Factors Related to Knee Osteoarthritis: A systematic review and Bayesian network meta-analysis of randomized controlled trials

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Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

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Abbreviated title: Biomechanical Phenomena, Osteoarthritis, Knee, Physical and Rehabilitation Medicine

Key words: Physical Therapy; Orthopedic Equipment; Knee Osteoarthritis; KAM; KAAI; Bayesian Network Meta-analysis.

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Competing interests: Nil

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Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

ABSTRACT

Objective: Are physical therapy and orthopedic equipment efficacious in reducing the biomechanical risk factors in people with tibiofemoral OA? Is there a better treatment than others to improve these outcomes?

Design: Systematic review with network meta-analysis of randomised trials.

Data sources: PubMed, Web of Science, Cochrane Library, Embase, and MEDLINE were searched through January 2021.

Eligibility criteria for selecting studies: We included randomised controlled trials exploring the benefits of using physical therapy and orthopedic equipment in reducing the biomechanical risk factors which included the KAM and the KAAI in patients with tibiofemoral OA.

Data extraction and synthesis: Two authors extracted data independently and assessed risk of bias. We conducted a network meta-analysis to compare multiple interventions, including both direct evidences and indirect evidences. Heterogeneity was assessed (sensitivity analysis) and quantified (I^2 statistic). GRADE assessed the certainty of the evidence.

Results: Eighteen randomized controlled trials, including 944 participants, met the inclusion criteria. Based on the collective probability of being the overall best therapy for reducing the first peak KAM, lateral wedge insoles (LWI) plus knee brace was closely followed by gait retraining, and knee brace only. Although no significant difference was observed among the eight interventions, variable-stiffness shoe and

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

neuromuscular exercise exhibited an increase in the first peak KAM compared to the standard care group. And based on the collective probability of being the overall best therapy for reducing KAAI, gait retraining was followed by LWI only, and lower limb exercise.

Conclusion: The ranking statistics like surface under the cumulative ranking curve values of our Bayesian network meta-analysis support the use of LWI plus knee brace for reducing the first peak KAM. We found gait retraining to be the most efficacious intervention as it could reduce the values for KAM and KAAI at the same time based on cumulative ranking and relative effect estimates.

Strengths and limitations

① This Bayesian network meta-analysis is the first review on efficacy of physical therapy and orthopedic equipment on the biomechanical parameters (KAM & KAAI) of the knee OA.

② the Bayesian method provided the probability estimates regarding the superior efficacy of specific interventions, even though the standard methods described the absence of a significant difference between them.

③ Physical therapies and orthopedic equipment are complex interventions with a small number of trials comparing the different types of interventions.

④ Besides KAM and KAAI, we were temporarily unable to include other biomechanical risk factors, such as the external knee flexion moment to joint load.

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

1. INTRODUCTION

Knee osteoarthritis (KOA), a chronic progressive disease, affects approximately 3.8% of people worldwide, mainly middle-aged and older adults.[1,2] The main clinical manifestation of KOA is knee pain and is often accompanied by radiographic degeneration of the intra-articular cartilage associated with hypertrophic bone changes.[3] With the development of KOA, patients may also report stiffness, locking, instability and function loss. Though it is not fatal, the persistent pain and movement difficulties associated with this condition negatively impact the physical and mental health of the patients; thus, reducing their quality of life.[4]

These pathological changes of knee joint structure are the result of the break of biomechanical balance and the progression of the disease is now believed to be associated with malalignment of the lower limb.[5] Of the three compartments of a knee joint, KOA mostly occurs in the medial tibiofemoral compartment as it bears 60-91% of the total body load, higher than the lateral one.[6] The external knee adduction moment (KAM) results from the unequal distribution of the transmitted load on both sides in the normal gait of humans. It is defined as the cross product of the ground reaction force and the distance between the knee joint and the force line.[7] Individuals with obesity,[8] meniscal lesions,[9] occupational load[10] or other risk factors tend to have frontal plane knee malalignment, which alters the normal force line, forcing the medial knee joint to bear more load and increased KAM.[11,12] The accumulation effect of the moment is determined by calculating the integral of the moment to time, which is also termed as knee adduction angular impulse (KAAI).

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

It reflects the change in knee joint rotation state during a stance period of gait.[13] Previous studies have revealed a strong correlation between the peak levels of KAM and KAAI and the severity and progression of the disease, which was reflected and calculated by the loss of medial tibial cartilage.[14,15] Both these biomechanical parameters (KAM and KAAI) are commonly used to evaluate the medial knee load and predict the long-term structural deterioration.

Recent advancements in healthcare have resulted in the development of several protocols for the intervention and treatment of KOA. KOA patients are primarily recommended physical therapy and orthopedic equipment with the intention of correcting the deviated force line and delaying the progressive pathological damage inside the knee joint.[7] Both these modalities focus on relieving pain and improving patients' symptoms by changing the biomechanical state of the knee joint. The physical therapy mainly includes muscular strengthening, exercise therapy, electric stimulation therapy, extracorporeal shockwave therapy and gait modification, while orthopedic equipment mainly includes customized shoes/footwear, wedged insoles, and knee braces.

Previous studies have shown the positive impact of physical therapy and orthopedic equipment in KOA. The strengthening of related lower limb muscles, which play a vital role in disease progression, are known to reduce instability and abnormal stresses across the joint. Previous studies have shown that a lower knee joint loading rate in patients with stronger quadriceps and hamstring.[16] Additionally, gait training presents a viable way to correct the patients' underlying gait pattern, which could

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

also reduce their knee load and pain.[17,18] Further, several kinds of orthotic devices have been introduced for the treatment of KOA. The clinical use of lateral wedge insoles (LWI) has gained immense popularity since its origin in 1987.[19,20] The insoles work by shifting the lateral part of the foot more than the medial part by a slope. Thus, a slope is created to increase the valgus tendency of lower extremities. The center of the ground reaction force is shifted laterally, which induces a reduction in force lever arm length and magnitude. Also, the valgus knee brace is a commonly used device. It applies an external valgus force around the knee joint to reduce the medial knee load.

In the past, several systematic reviews and meta-analysis have been published featuring the medical effects of a single KOA treatment. However, only a few of them have focused on multifaceted interventions. Also, only a few reviews have reported the effects of these changes on the biomechanical parameters. The mechanical changes in the body were not sufficiently investigated. Current reviews on KAM and KAAI have also not compared these changes. Thus, we performed a network meta-analysis (NMA) to appraise the benefits of physical treatments and orthopedic equipment in reducing the biomechanical risk factors in KOA patients to overcome these shortcomings, and to help achieve the goal of reducing pain and improving function.

Therefore the research questions for this systematic review were:

1. Are physical therapy and orthopedic equipment efficacious in reducing the biomechanical risk factors in people with KOA?

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2. Is there a better treatment than others to improve these outcomes?

2. METHODS

All pooled analyses were derived from previous studies and, therefore, did not require ethical approval and informed consent.

2.1 Identification and selection of studies.

We searched the following databases for randomized controlled trials that were published before January 2021, which explored the benefits of using physical therapy and orthopedic equipment in reducing the biomechanical risk factors which included the KAM and the KAAI in patients with tibiofemoral OA: PubMed, Web of Science, Cochrane Library, Embase, and MEDLINE. The search was not restricted by date, publication type, or publication status (see Appendix 1). Additionally, we performed manual analyses of the published references regarding the use of physical therapy and orthopedic equipment for treating KOA.

The eligibility of searched publications was independently reviewed by HXM, YZX following the Cochrane manual.[21] Any additional inconsistencies were resolved either by deliberation or by a senior expert (HY). First, the study titles and abstracts, published in the English language, were screened. Next, complete articles were reviewed against the following criteria in Box 1.

Eligible comparison subjects, including standard/conventional care or waiting list control (analgesic advice and education), were defined as "standard care." Standard care treatment also included placebo intervention, no intervention, and sham-exercise. In this network meta-analysis, lower limb exercise was defined as the

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simultaneous exercise of multiple groups of muscles (including hip abductors, quadriceps, and hamstrings). Since our research needed to maintain clinical and statistical homogeneity and also focus on the left-over biomechanical effects after intervention, we selected articles whose measurements were strictly obtained under the condition of bare foot.

The exclusion criteria included: (1) studies that were not consistent with the eligibility criteria; (2) studies that were in the form of the non-experimental papers, including abstracts, comments, letters, or reviews; (3) studies including participants who had received surgical treatment in the past; (4) studies that did not report suitable data which included the KAM or the KAAI.

2.2 Data Collection and Quality assessment.

KAM and KAAI were the preferred biomechanical measures used in this meta-analysis. The biomechanical indicators of the studies included in the Bayesian network meta-analysis were measured on flat ground or treadmills. The number of trials that focused on the second peak of KAM was insufficient to conduct an independent network meta-analysis.

Two authors (HXM, YZX) extracted data independently and then cross-checked the data. A predefined information sheet was used to extract the data, which included the details of the first author (name), country, year of publication, population characteristics, intervention, and the time point. The authors of the original study were contacted if more data was required.

2.3 Assessment of characteristics of studies.

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Risk of bias

In this network meta-analysis, we used the Cochrane Risk of Bias tool 2 (RoB2) to assess the risk of bias in randomized controlled trials using the following evaluation indicators: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.[21] The judgment of the bias risk of this item was presented as "low," "high," and " some concerns." Two authors independently evaluated the risk of bias of the included studies. The authors discussed or referred to the opinion of a senior author to resolve any disagreements. Additionally, we evaluated the certainty of evidence which contributed to network estimates of the main outcomes with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.

Intervention

In order to describe the experimental intervention, we extracted the following information: the method of training with relevant further details, the details and characteristics of orthopedic equipment, the frequency and total duration of training or wearing.

Outcome measures

Baseline biomechanical risk factors were extracted from walking test without any orthopedic equipment before intervention, and post-intervention biomechanical risk factors were extracted from walking test with orthopedic equipment. Biomechanical risk factors included the first peak KAM, the second peak KAM and KAAI. KAM

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was normalized as %body weight times height, with conversion to Nm/kg where necessary. KAAI was the accumulation effect of the moment which was determined by calculating the integral of the moment to time.

2.4 Statistical Analysis.

We conducted a network meta-analysis to compare multiple interventions, including both direct evidences (where treatments were compared directly) and indirect evidences (where treatments were compared with a common control), maintaining randomization in each independent study.[22-24] Interventions and demographic characteristics were either consistent or comparable across the included studies.[25-30] At the same time, we did not include the studies that only reported the immediate effect into meta-analysis.

Due to different units, the continuous data used the standard mean difference (SMD) as the statistical indicator of the effect, and the Frequentist 95% confidence interval (CI) of each effect was calculated. Additionally, the I^2 statistic was used to analyze the overall heterogeneity of the two-arm study and the network. The fixed-effect model was used in case no statistical heterogeneity was found between the studies ($p > 0.05$, $I^2 < 50\%$); given the heterogeneity between studies, a random-effects model for meta-analysis was used.[31] A sensitivity analysis (see Appendix 2, eFigure 1 and 2) was conducted by omitting one study and investigating the influence of a single study on the overall pooled estimate to evaluate the source of heterogeneity. The Node-Split Model was used for testing consistency (see Appendix 3, eFigure 3). If $p > 0.05$, then the consistency model was used for analysis; else, the

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inconsistency model was used for analysis.[32] Normal likelihood distributions were assumed, non-informative prior distributions were set, and three Markov chains were run simultaneously. The number of update iterations was 50,000, a total of 5000 simulations were used for annealing, and the subsequent 45,000 iterations were examined. The mean rank and surface under the cumulative ranking curve (SUCRA) were used for reporting the probability values. A SUCRA value of 100% was considered best, whereas 0% indicated the worst treatment.[33] Besides, we also made a conventional meta-analysis (see Appendix 4, eFigure 4a, 4b and 4c).

The data from eligible studies were combined using the Review Manager (RevMan) software v5.3. The contribution of the effect sizes was dependent on the sample size and their estimation accuracy. We performed the Bayesian analyses using WinBUGs v1.4.3. Stata (StataCorp. 2015. Stata Statistical Software: Release 15. College Station, TX: StataCorp LP) was used to conduct the frequentist NMA.

3. RESULTS

3.1 Flow of studies through the review

Overall, the database search strategy found 4919 citation. After screening articles by title and abstract, and deleting duplicate articles, we identified 526 studies that might meet the criteria for inclusion, and then we searched and evaluated their full text. Figure 1 presents the study selection flow chart. Eighteen randomized controlled trials, including 944 participants, met the inclusion criteria.[34-51] Since the present network meta-analysis only considered trials comparing the nine treatments with usual care or each other (see Appendix 5, eFigure 5a and 5b), only fourteen trials (792 participants) were included.

3.2 Characteristics of included studies

All studies included the radiologically confirmed tibiofemoral OA. The duration of treatment ranged from 2 weeks to 12 months, although most intervention times were administered over an 8-13-week period. The number of exercises varied from 2-5 times per week, depending on the preparation.[40,42,45,46] Both studies of gait training used the faded feedback paradigm, which meant gradual removal of the real-time biofeedback.[36,41] Of the fourteen studies that were included in NMA, nine were classified as Kellgren/Lawrence grade 2 and above. All studies reported either the BMI or the values for height and weight, and in some studies recruiting a general population, the mean BMI was classified as overweight or obese. One study included in NMA had a randomized crossover design.[34] After referring to the manual and consulting a professional statistician, the mean and standard deviation of the experimental and the control groups were analyzed in this network meta-analysis.[21] Tables 1 and 2 summarize the characteristics of the included studies and participants.

3.3 KAM.

A study reported that the VER-brace offers additional advantages on first peak KAM compared to V3P-brace and ACL-brace.[51] No first peak KAM reduction was observed between proprioceptive neuromuscular facilitation group and control group,[49] and the result of the study of minimal footwear was the same.[48] On the other hand, after the electroacupuncture treatment, compared with the control group,

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the second peak KAM significantly increased immediately when the patient ascended stairs.[50] Table 3 shows the NMA results of a comparative analysis of the reduction of the first peak KAM. We found insignificant differences in most of the treatment modalities; however, variable-stiffness shoes showed a statistically significant increase in the first peak KAM over the rest of the included interventions. Neuromuscular exercise was better than variable-stiffness shoes, but was still inferior to most other interventions. At the same time, lateral wedge insole plus knee brace and gait retraining performed relatively well in reducing the first peak KAM compared with standard care and other treatments. Based on the collective probability of being the overall best therapy for reducing the first peak KAM, LWI plus knee brace (93.4%) was closely followed by gait retraining (85.7%), and knee brace only (79.3%) (Figure 2).

3.4 KAAI.

KAAI was reported in ten studies.[34,36,40,43-48,51] After wearing the three kinds of brace separately, the KAAI measured without brace did not decrease significantly, and there was no significant difference between the groups.[51] Table 3 shows the NMA results of the reduction of KAAI. Most treatments were not statistically different from each other, consistent with the results of the first peak KAM. Only gait retraining has a statistical reduction compared with the standard care treatment. The aggregated results suggested that gait retraining is efficient in reducing the KAAI, while neuromuscular exercise will relatively increase the KAAI compared with some treatment. Based on the collective probability of being the overall best

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therapy for reducing KAAI, gait retraining (90.7%) was followed by LWI only (74.1%), and lower limb exercise (53.8%) (Figure 3).

3.5 Heterogeneity.

We removed a study which had a short follow-up time and might cause heterogeneity,[34] and performed another network meta-analysis. There is no difference between the results of the reanalysis and the current ranking (see Appendix 2, eFigure 1 and 2).

3.6 GRADE assessment

According to the GRADE framework (see Appendix 6), the quality of the most comparisons was assessed as low or very low. Only neuromuscular exercise compared with standard care, neuromuscular exercise compared with LWI, neuromuscular exercise compared with knee brace, and neuromuscular exercise compared with LWI plus knee brace were evaluated as a moderate-grade comparison.

3.7 Risk of bias.

Figure 4 depicts a summary of the risk-of-bias scores for the included RCTs in this analysis. Nine studies presented a clear description of generating a randomization sequence.[38-40,42,45-48,50] The study by Hinman et al. was the only double-blinded study, while other studies were either single-blinded or did not clearly describe their blind design. All trials provided follow-up data on their outcomes. Six studies did not report the number or the reason for lost visits due to the length of follow-up.[34,38,39,41,42,45] Consequently, all studies were included in the synthesis evaluation

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and qualified for literature assessment. And we prepared comparison-adjusted funnel plots that represented different comparisons with different colors. The funnel plots were symmetrically distributed based on a visual inspection, which suggested the absence of small-sample effects for our outcomes (see Appendix 7, eFigure 6a and 6b).

4. DISCUSSION

Our results did not show significant differences regarding the superiority of intervention among different types of physical therapies and orthopedic equipment. This lack of difference was attributed to the fact that the number of studies for several pairwise comparisons was small. However, some of these therapies were still worth recommending. Due to the small number of studies studying the outcome of the KAAI, we found gait retraining to be the relatively more convincing intervention as it could reduce the values for KAM and KAAI at the same time based on cumulative ranking and relative effect estimates. Due to the lack of significant differences among the interventions, we were not able to conclusively accept the cumulative ranking obtained by the network meta-analysis. For example, gait retraining, which occupied the first rank position (90.7%) for reducing the KAAI, was only superior to the neuromuscular exercise interventions.

This study had several strengths and limitations. This network meta-analysis is the first report on the effects of physical therapy and orthopedic equipment on the parameters of knee load (KAM, KAAI). Since physical therapies and orthopedic equipment are complex interventions with a small number of trials comparing the

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different types of interventions, network meta-analysis appeared to be the most relevant form of analysis. The results of this meta-analysis would be more useful for the decision-makers, service specialists, and caregivers to choose among the various available options, compared with multiple separate pairwise meta-analyses.[52] Additionally, this network meta-analysis conducted each comparison separately with both direct and indirect statistical effects, deriving statistical power from all included data.[52] Also, the Bayesian method provided the probability estimates regarding the superior efficacy of specific interventions, even though the standard methods described the absence of a significant difference between them. In addition, we calculated alternative rankings (second, third best, etc), because in some cases the best intervention might be unavailable, more costly, or contraindicated in some patients. As with most meta-analyses on non-surgical therapies for osteoarthritis, one of the limitations of this network meta-analysis includes the inclusion of trials that had variable periods of follow-up, which could have introduced heterogeneity into the study analysis. There exist several methods of analyzing and comparing trials with multiple durations of follow-up, as recommended by the Cochrane handbook, such as performing individual patient data meta-analysis and evaluating at a particular time point. However, methods are being developed that would include all time points in a network meta-analysis.[21] We were not able to evaluate the influence of population characteristics (such as mean age, the severity of osteoarthritis), as the number of the included studies was not large enough.[53-55] Additionally, other parameters, such as the external knee

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flexion moment to joint load, should have been studied. However, due to the small number of related articles, we were temporarily unable to include them.

A previous review showed that LWIs were able to reduce the KAM at baseline;[56] however, the effect was no longer observed after a period. One study showed that a 1-month wear-in period was the longest time period studied where no reduction in biochemical risk factors was observed despite continued wear.[57] Besides, several systematic reviews had concluded that exercise and gait retraining could reduce pain and improve motor functioning in people with KOA,[58-60] it was possible that any clinical changes in previous studies may due to the increased physical activity levels, and not have been the results of altered loading environment within the knee joint. Furthermore, another study revealed that an increase in the amount of reduction in peak KAM in LWIs plus knee brace group was observed after 4 weeks.[61] In this network meta-analysis, we focused on the studies of non-immediate effect, removed the research with a follow-up time of less than one month in the sensitivity analysis, and made the final rank. The results showed that only gait training produces a significant reduction in KAM and KAAI, indicating that the biomechanical reduction effect of orthopedic equipment cannot be maintained for a long time when they are donned. Once the time of the treatment was extended, the biomechanical reduction effect might lessen. The reason may be that orthopedic equipment deform and render them less effective mechanically, although typically made of high density materials.

On the other hand, physical therapies and orthopedic equipment also need to be

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considered for relieving patients' pain, which has been the focus of several reviews in the past. As an important factor in kinetics and kinematics of gait, the joint pain can affect the kinetics and kinematics of walking.[62] A meta-analysis reported that exercise therapy had a positive impact on knee pain and kinematic function, though this relief of pain subsided with time. After initiation, the efficiency of physical exercise over placebo reached maxima at 2 months.[63]

Cumulative loading is another significant parameter regarding knee load exposure in OA.[64] KAAI has been proposed as another indicator to evaluate the duration and intensity of KOA load, despite the association between KAM and disease progression. According to a 12-month study, the loss of medial tibiofemoral cartilage was not directly related to KAM but was related to KAAI.[65] Although the effect of physical therapy and orthopedic equipment on KAM may gradually disappears, it may have a huge cumulative effect on the knee during the early stages of treatment. This should be considered while interpreting the results of this network meta-analysis.

The results presented in this study are both scientifically and clinically instructive. Despite observing a null statistical reduction in KAM and KAAI for most therapies, using these treatments clinically could improve symptoms and physical activity level without increasing the biomechanical magnitude; thus, improving the quality of life of patients with KOA. Although the results of this study suggested that wearing variable-stiffness shoes is not a good choice for long-term reduction of KAM, current study have pointed out that variable-stiffness shoe will have greater

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439 benefits in reducing KAM for patients with increasing walking speed.[66] At the same
440 time, variable-stiffness shoes had relatively weaker discomfort than equipment such
441 as LWI. Since the studies included in this network meta-analysis mainly involves
442 patients with medial knee osteoarthritis, the results would be more useful for these
443 patients.

444 On the other hand, previous study reported that the increase in KAAI can explain
445 the significant variation in the uCTX-II levels and the uCTX-II:sCPII ratio in
446 patients with medial tibiofemoral KOA when additional variables are controlled.[67]
447 This showed that intervention in the biomechanical structure of the knee joint in
448 patients with KOA is a potential beneficial role on cartilage structure. Maleki et al.
449 pointed out that adopting a modified gait that reduces the KAM can decrease the
450 pain in the medial compartment in KOA more than walking alone,[68] which suggests
451 that the KAM and KAAI of patients under non-surgical treatment can be restricted
452 to help reduce pain and improve joint function. More research is needed to further
453 illustrate the impact of changes in knee biomechanics on the prognosis of patients.
454 Additionally, some other therapies have been reported, such as Taiji, ultrasound,
455 acoustic exercise, etc. However, due to the lack of RCT study design or the report
456 of their biomechanical outcomes, we were not able to include these therapies in our
457 review. Therefore, further studies would require more research articles in these
458 areas to further explore the impact of various non-surgical therapies on OA patients.
459 After accumulating evidence regarding the role of non-surgical therapy in KOA, we
460 could conduct a similar network meta-analysis to understand the relative

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effectiveness of various types of these interventions in relevant patients.

5. Conclusion

This network meta-analysis provides valuable insight regarding the alterations in KAM and KAAI of OA patients after physical therapy and orthopedic equipment. After integrating cumulative ranking and relative effect estimates, gait retraining was the most recommended therapy for reducing the biomechanical risk factors. On the contrary, variable-stiffness shoe and neuromuscular exercise needed to be used with caution in clinical treatment. Taken together, these findings suggest that clinicians should choose carefully when treating OA.

6. Authors' Contributions

HXM and YFZ conceived of the study, and participated in its design and coordination and helped to draft the manuscript; YZX, HY and CRY contributed significantly to analysis and manuscript preparation; YJK and LL helped perform the analysis with constructive discussions and revised it critically for important intellectual content.

7. Competing interests

There were no conflicts of interest.

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9. Ethics approval

Not required.

10. Data availability statement

No data are available.

11. Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

Table 1. Characteristics of included studies (1) *

Authors	Country	Clinical criteria†	Radiographic features	Intervention	Comparisons	Follow up
Barrios 2013[43]	US	Medial compartment knee OA; Pain VAS (≥3 of 10 upon walking)	K/L grade ≥2, medial tibiofemoral compartment	bespoke full-length LWI	Placebo	12 months
Hinman 2016[44]	Australia	Medial compartment knee OA; Pain NRS (> 4 of 11 upon walking) over the previous week	K/L grade ≥2, medial tibiofemoral compartment	5° full-length LWI	Placebo	6 months
Arazpour 2012[37]	Iran	Medial compartment knee OA	K/L grade 1 and 2, medial tibiofemoral compartment	6° full-length LWI	bespoke unloader knee braces	6 weeks
Jones 2013[34]	UK	Medial compartment knee OA	K/L grade 2 and 3, medial JSN	LWI: The heel was inclined at 5° with the inclination reduced to 0° at the 5th metatarsal head with a contoured arch profile	6° valgus knee brace	2 weeks
Khosravi 2019[35]	Iran	Medial compartment knee OA	K/L grade 2 and 3	Full length custom-made LWI; LWI+ knee brace	three-point valgus knee brace	6 weeks

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

* OA=osteoarthritis; LWI=lateral wedged insoles; VAS=visual analog scale; NRS=numerical rating scale; K/L=Kellgren/Lawrence; NR=not reported; JSN=joint space narrowing;

Tables

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

Table 1. Characteristics of included studies (2) *

Authors	Country	Clinical criteria†	Radiographic features	Intervention	Comparisons	Follow up
Hunt 2018[36]	US	Medial compartment knee OA; Pain (≥3 of 10) longer than 6 months	K/L grade ≥2, medial tibiofemoral compartment	Toe-out gait modification	Walking without any guidance	4 months
Lim 2008[38]	Australia	Medial compartment knee OA; Medial knee pain	K/L grade ≥2, medial JSN	Quadriceps strengthening	No intervention	12 weeks
Erhart-Hledik 2012[39]	US	Medial compartment knee OA; Medial knee pain	K/L grade ≥1	Variable-stiffness shoe with stiffer soles on the lateral side	Constant-stiffness control shoe	12 months
Bennell 2010[40]	Australia	Medial compartment knee OA; Varus malalignment; Pain (> 3 of 11 upon walking)	K/L grade ≥2, medial JSN	Hip strengthening	No intervention	13 weeks
Cheung 2018[41]	China	Medial compartment knee OA; Knee pain occurred at least one day a week during each of the 8 weeks prior	K/L grade 1 and 2	Gait retraining for KAM reduction	Walking without any guidance	6 weeks

* OA=osteoarthritis; LWI=lateral wedged insoles; VAS=visual analog scale; NRS=numerical rating scale; K/L=Kellgren/Lawrence; NR=not reported; JSN=joint space narrowing;

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

Table 1. Characteristics of included studies (4) *

Authors	Country	Clinical criteria†	Radiographic features	Intervention	Comparisons	Follow up
Foroughi 2011[42]	Australia	Primary knee OA	K/L grade ≥1	Lower limb exercise	Sham-exercise	6 months
Bennell 2014[45]	Australia	Medial compartment knee OA; Pain VAS (≥25 of 100) over the past week	K/L grade ≥2, medial tibiofemoral compartment	Neuromuscular exercise	Quadriceps strengthening	12 weeks
Hunt 2013[46]	Canada	Medial compartment knee OA; Knee pain >3/10 on most days of the previous month	K/L grade ≥2, medial tibiofemoral compartment	Lower limb exercise	No intervention	11 weeks
Holsgaard-Larsen 2017[47]	Denmark	Primary knee OA Pain KOOS(< 80 of 100, at least mild pain)	K/L grade ≤3	Neuromuscular exercise	Analgesic advice	8 weeks

* OA=osteoarthritis; LWI=lateral wedged insoles; VAS=visual analog scale; NRS=numerical rating scale; K/L=Kellgren/Lawrence; NR=not reported; JSN=joint space narrowing;

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

Authors	Country	Clinical criteria†	Radiographic features	Intervention	Comparisons	Follow up
Song 2020[49]	China	Medial compartment knee OA in one or both legs.	K/L grade ≤3	PNF (one-hour sessions three times a week)	Watch television or read magazines at the same time	12 weeks
Wang 2017[50]	China	Medial compartment knee OA	K/L grade 2 and 3	Acupuncture with 2 Hz continuous wave in Neixiyan (EX-LE 4), Dubi (ST 35), Yanglingquan (GB 34), Yinlingquan (SP 9), Xuehai (SP 10), Liangqiu (ST 34) and Zusanli (ST 36)	2 cm next to the same acupoints with shallow acupuncture and no current	Immediate
Robert-Lachaine 2020[51]	Canada	Medial compartment knee OA; Pain > 31/100 on WOMAC; Varus knee alignment ≥ 2°	K/L grade 2 and 3	V3P-brace; VER-brace; ACL-brace (wear the brace as often as possible)	/	3 months
Trombini-Souza 2015[48]	Brazil	Medial compartment knee OA; Knee pain between 3 and 8 on VAS	K/L grade 2 and 3	Minimalist footwear (Moleca®)	Standard, neutral tennis shoe	6 months

* OA=osteoarthritis; LWI=lateral wedged insoles; VAS=visual analog scale; NRS=numerical rating scale; K/L=Kellgren/Lawrence; NR=not reported; JSN=joint space narrowing; PNF= Proprioceptive neuromuscular facilitation; V3P-brace= three-point bending system valgus knee brace; VER-brace= unloader brace with valgus and external rotation functions; ACL-brace= functional medial-lateral stabilization brace used after ligament injuries; The Moleca® shoe is a low-cost women's double canvas, flexible, flat, walking shoe without heels, with a 5-mm anti-slip rubber sole and a 3-mm flat insole of ethylene vinyl acetate that provides only protection but no correction of any kind.

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

Table 2. Characteristics of participants in included studies (1) *

Authors	No.	Sex, M:F	Age, years	Height, meters	Body mass, kg	BMI, kg/m²	Bilateral knee OA included	K/L grade, no.				Main outcomes
								1	2	3	4	
Barrios 2013[43]	38	NR	61.90±8.37	NR	NR	32.00±7.43	NR	0	17	14	7	1st KAM; KAAI
Hinman 2016[44]	164	20:21	64.30±7.45	1.67 ± 0.10	82.95±14.76	29.70±3.64	NR	0	49	52	63	1st KAM; KAAI
Arazpour 2012[37]	24	3:4	59.29±2.37	NR	NR	27.01±1.71	Yes	9	15	0	0	1st KAM
Jones 2013[34]	28	4:3	66.30±8.20	1.75±0.13	88.7±15.10	NR	No	0	10	18	0	1st and 2nd KAM; KAAI
Khosravi 2019[35]	21	13:8	58.97±6.80	1.62±0.11	79.11±9.35	NR	NR	0	9	12	0	1st KAM

* Values are the mean±SD unless indicated otherwise. BMI=body mass index; K/L=Kellgren/Lawrence; NR=not reported; JSN=joint space narrowing; KAM=knee adduction moment; KAAI=knee adduction angular impulse.

Table 2. Characteristics of participants in included studies (2) *

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

Authors	No.	Sex, M:F	Age, years	Height, meters	Body mass, kg	BMI, kg/m²	Bilateral knee OA included	K/L grade, no.				Main outcomes
								1	2	3	4	
Hunt 2018[36]	79	24:55	64.99±8.60	1.65±0.10	74.59±13.15	27.35±3.48	Yes	0	37	31	11	1st and 2nd KAM; KAAI
Lim 2008[38]	107	48:59	64.60±8.51	1.65±0.10	79.41±15.32	28.96±4.85	Yes	0	34	29	44	1st KAM
Erhart-Hledik 2012[39]	79	41:38	61.70±9.43	1.69±0.08	79.50±15.07	27.51±4.87	Yes	NR	NR	NR	NR	1st KAM
Bennell 2010[40]	89	46:43	64.55±8.34	NR	NR	27.94±4.41	Yes	0	30	29	30	1st KAM; KAAI
Cheung 2018[41]	20	1:1	61.95±6.11	1.63±0.09	65.85±6.64	27.35±3.48	NR	5	15	0	0	1st KAM

* Values are the mean±SD unless indicated otherwise. BMI=body mass index; K/L=Kellgren/Lawrence; NR=not reported; JSN=joint space narrowing; KAM=knee adduction moment; KAAI=knee adduction angular impulse.

Table 2. Characteristics of participants in included studies (3) *

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

Authors	No.	Sex, M:F	Age, years	Height, meters	Body mass, kg	BMI, kg/m²	Bilateral knee OA included	K/L grade, no.				Main outcomes
								1	2	3	4	
Foroughi 2011[42]	54	0:54	65.48±7.44	NR	82.87±18.43	32.07±7.08	Yes	20	7	20	1	1st and 2nd KAM
Bennell 2014[45]	100	48:52	62.45±7.32	1.67±0.10	82.70±14.29	29.65±4.08	Yes	0	22	43	35	1st KAM; KAAI
Hunt 2013[46]	17	8:9	66.10±11.3	NR	NR	27.00±4.50	Yes	0	10	5	2	1st KAM; KAAI
Holsgaard-Larsen 2017[47]	93	39:54	58.10±7.96	NR	79.64±12.49	26.90±3.09	NR	45	31	17	0	1st KAM; KAAI

* Values are the mean±SD unless indicated otherwise. BMI=body mass index; K/L=Kellgren/Lawrence; NR=not reported; JSN=joint space narrowing; KAM=knee adduction moment; KAAI=knee adduction angular impulse.

Table 2. Characteristics of participants in included studies (4) *

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

Authors	No.	Sex, M:F	Age, years	Height, meters	Body mass, kg	BMI, kg/m^2	Bilateral knee OA included	K/L grade, no.				Main outcomes
								1	2	3	4	
Song 2020[49]	36	1:1	68.01±3.91	1.62±0.07	68.16±6.77	NR	Yes	9	20	7	0	1st KAM
Wang 2017[50]	36	1:5	63.50±7.95	NR	NR	23.75±2.66	Yes	0	19	17	0	1st and 2nd KAM
Robert-Lachaine 2020[51]	24	7:5	57.20±8.60	1.68±0.09	89.30±18.70	31.40±5.00	NR	0	15	8	0	1st and 2nd KAM; KAAI
Trombini-Souza 2015[48]	56	NR	66.00±5.00	1.60±0.10	73.40±13.10	NR	NR	0	NR	NR	0	1st KAM; KAAI

* Values are the mean±SD unless indicated otherwise. BMI=body mass index; K/L=Kellgren/Lawrence; NR=not reported; JSN=joint space narrowing; KAM=knee adduction moment; KAAI=knee adduction angular impulse.

J	0.41 (-0.66,1.49)	0.16 (-0.46,0.79)	-	0.20 (-0.23,0.64)	**0.81 (0.17,1.45)**	-	0.30 (-0.61,1.21)	**0.54 (0.02,1.07)**	0.32 (-0.10,0.75)

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

0.28 (-0.34,0.89)	**I**	-0.25 (-1.33,0.84)	-	-0.21 (-1.37,0.95)	0.40 (-0.70,1.49)	-	-0.12 (-1.39,1.16)	0.13 (-0.90,1.16)	-0.09 (-1.08,0.90)
0.07 (-0.50,0.64)	-0.21 (-0.89,0.47)	**H**	-	0.04 (-0.72,0.80)	0.64 (-0.01,1.30)	-	0.13 (-0.79,1.05)	0.38 (-0.16,0.92)	0.16 (-0.29,0.61)
-0.69 (-1.36,-0.02)	**-0.97 (-1.73,-0.21)**	**-0.76 (-1.49,-0.03)**	**G**	-	-	-	-	-	-
0.24 (-0.11,0.59)	-0.04 (-0.64,0.57)	0.17 (-0.39,0.74)	**0.93 (0.27,1.60)**	**F**	0.61 (-0.17,1.38)	-	0.09 (-0.91,1.10)	0.34 (-0.34,1.02)	0.12 (-0.49,0.73)
0.89 (0.35,1.44)	0.62 (-0.04,1.28)	**0.83 (0.20,1.45)**	**1.59 (0.87,2.30)**	**0.65 (0.11,1.19)**	**E**	-	-0.51 (-1.45,0.42)	-0.27 (-0.83,0.30)	**-0.48 (-0.96,-0.01)**
1.28 (0.21,2.36)	1.01 (-0.13,2.14)	**1.22 (0.10,2.33)**	**1.98 (0.81,3.15)**	1.04 (-0.03,2.11)	0.39 (-0.71,1.49)	**D**	-	-	-
0.78 (0.11,1.45)	0.50 (-0.26,1.27)	0.71 (-0.02,1.44)	**1.47 (0.66,2.29)**	0.54 (-0.12,1.20)	-0.11 (-0.83,0.60)	-0.50 (-1.46,0.46)	**C**	0.25 (-0.50,0.99)	0.03 (-0.77,0.83)
0.56 (0.10,1.02)	0.29 (-0.30,0.87)	0.49 (-0.05,1.04)	**1.26 (0.61,1.90)**	0.32 (-0.13,0.77)	-0.33 (-0.85,0.19)	-0.72 (-1.70,0.25)	-0.22 (-0.71,0.27)	**B**	-0.22 (-0.52,0.08)
0.37 (0.02,0.71)	0.09 (-0.42,0.60)	0.30 (-0.15,0.75)	**1.06 (0.49,1.63)**	0.13 (-0.21,0.46)	**-0.53 (-0.95,-0.10)**	-0.92 (-1.94,0.10)	-0.41 (-0.99,0.16)	-0.19 (-0.49,0.10)	**A**

Table 3. Detailed results of network meta-analysis for the First peak KAM (grey) and KAAI (white). Data are SMDs (from the top left to the bottom right, higher comparator versus lower comparator) and their related 95%CI. Bold texts in the table mean SMDs are statistically significant.

A= Standard care; B= Lateral Wedge Insole; C= Knee Brace; D= Lateral Wedge Insole+ Knee Brace; E= Gait retraining; F= Quadriceps strengthening; G= Variable-stiffness shoe; H= Hip strengthening; I= Lower limb exercise; J= Neuromuscular exercise.

Box

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

Box 1. Inclusion criteria

Design
- Randomised controlled trial

Participants
- People with radiologically confirmed knee osteoarthritis

Intervention
- Manual therapy
- Aerobic exercise
- Pulsed electrical stimulation (PES)
- Acupuncture
- Knee braces
- Ice/cooling treatment
- Pulsed electromagnetic fields (PEMF)
- Balneotherapy
- Interferential therapy
- Transcutaneous electric Nerve stimulation (TENS)
- Heat treatment
- Foot orthoses
- Laser/light therapy
- Muscle-strengthening exercise
- Static magnets
- Tai Chi
- Athletic tape
- Neuromuscular electrical stimulation (NMES)

Comparator
- Control group (standard/conventional care, placebo intervention, no intervention, sham-exercise, analgesic advice and education)

Outcome measures
- KAM and KAAI.

Comparisons
- All interventions compared to the comparator and to each other

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

Figure Legends

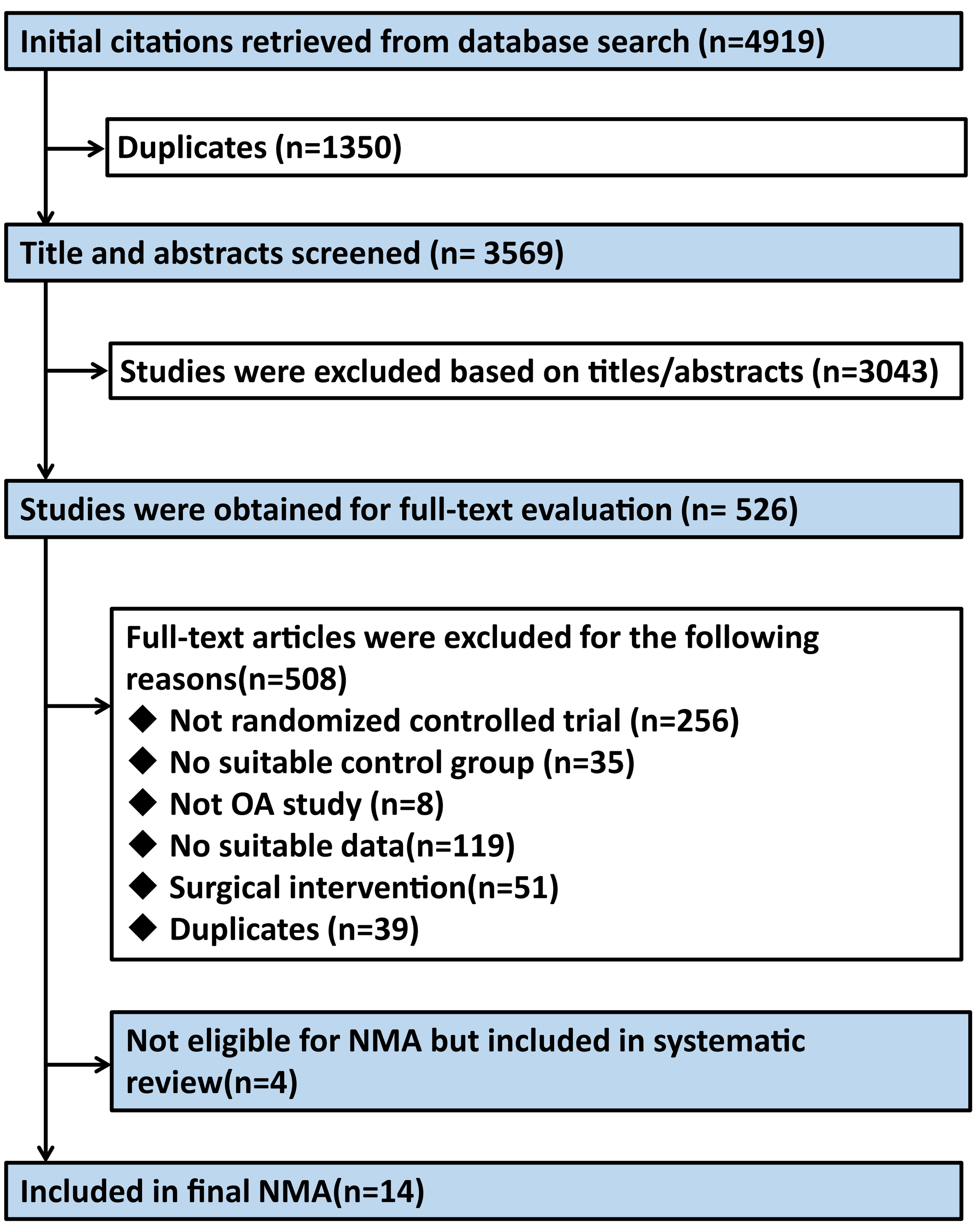
Figure 1. Flow chart of the study selection

Figure 2. Rankings for effects on First peak KAM. Graph displays distribution of probabilities for each treatment. X-axis represents the possible rank of each treatment (from the best to worst according to the outcomes), Y-axis represents the cumulative probability for each treatment to be the best option, among the best two options, among the best three options, and so on. A= Standard care; B= Lateral Wedge Insole; C= Knee Brace; D= Lateral Wedge Insole+ Knee Brace; E= Gait retraining; F= Quadriceps strengthening; G= Variable-stiffness shoe; H= Hip strengthening; I= Lower limb exercise; J= Neuromuscular exercise.

Figure 3. Rankings for effects on KAAI. Graph displays distribution of probabilities for each treatment. X-axis represents the possible rank of each treatment (from the best to worst according to the outcomes), Y-axis represents the cumulative probability for each treatment to be the best option, among the best two options, among the best three options, and so on. A= Standard care; B= Lateral Wedge Insole; C= Knee Brace; E= Gait retraining; F= Quadriceps strengthening; H= Hip strengthening; I= Lower limb exercise; J= Neuromuscular exercise.

Figure 4. Risk of bias summary

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)


Initial citations retrieved from database search (n=4919)
Duplicates (n=1350)
Title and abstracts screened (n= 3569)
Studies were excluded based on titles/abstracts (n=3043)
Studies were obtained for full-text evaluation (n= 526)
Full-text articles were excluded for the following reasons(n=508)
Not randomized controlled trial (n=256)
No suitable control group (n=35)
Not OA study (n=8)
No suitable data(n=119)
Surgical intervention(n=51)
Duplicates (n=39)
Not eligible for NMA but included in systematic review(n=4)
Included in final NMA(n=14)

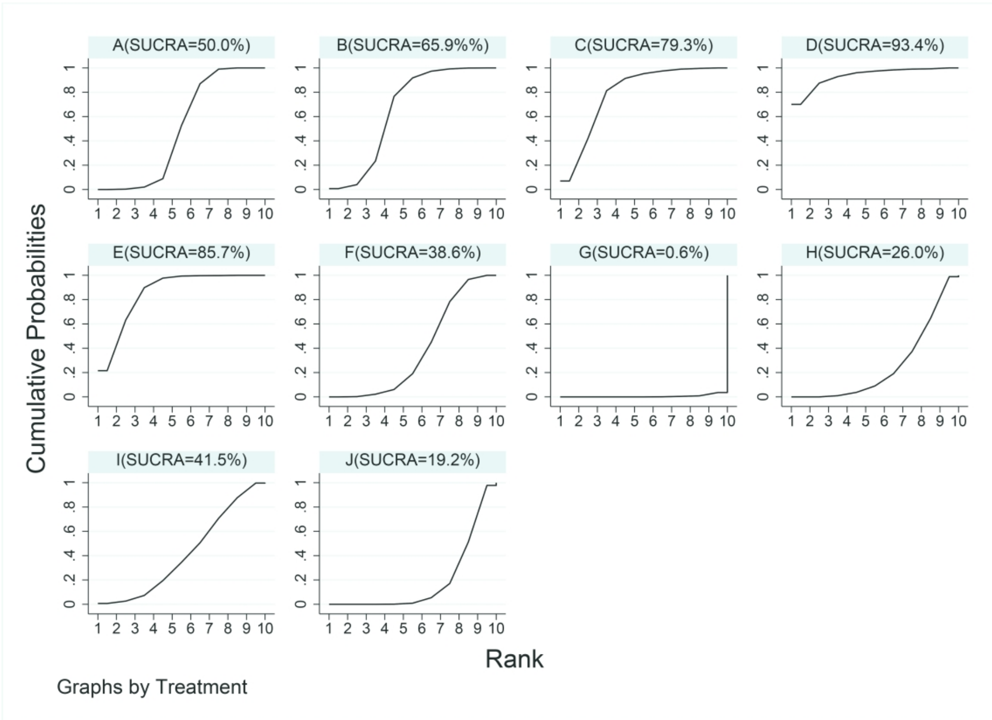
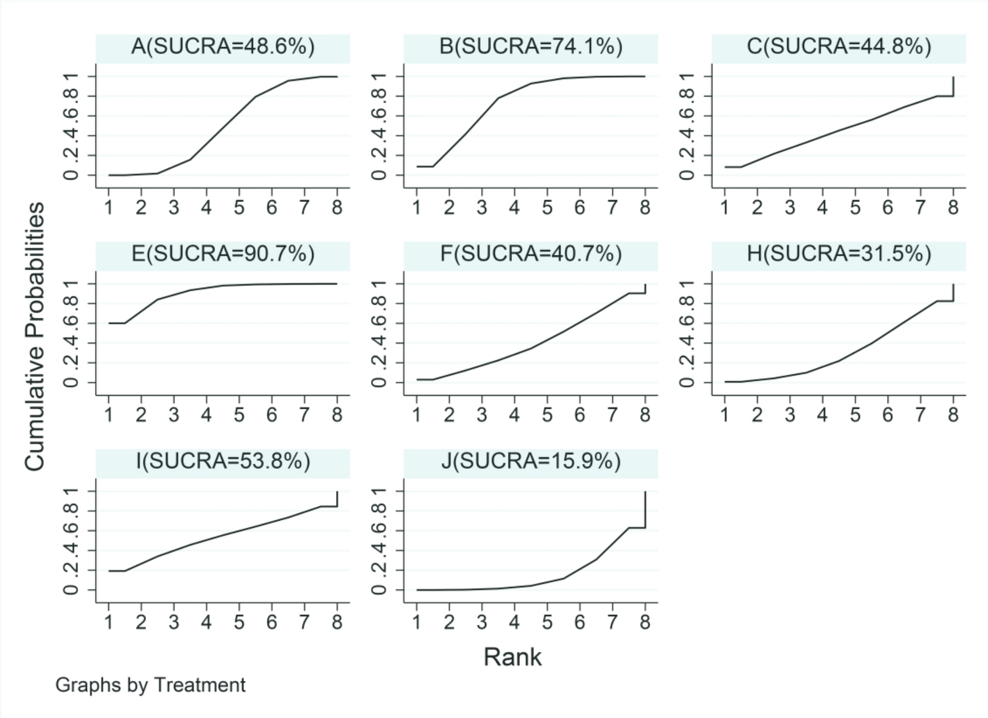

A(SUCRA=50.0%)
B(SUCRA=65.9%%)
C(SUCRA=79.3%)
D(SUCRA=93.4%)
E(SUCRA=85.7%)
F(SUCRA=38.6%)
G(SUCRA=0.6%)
H(SUCRA=26.0%)
I(SUCRA=41.5%)
J(SUCRA=19.2%)
Cumulative Probabilities
Rank
Graphs by Treatment

Figure 2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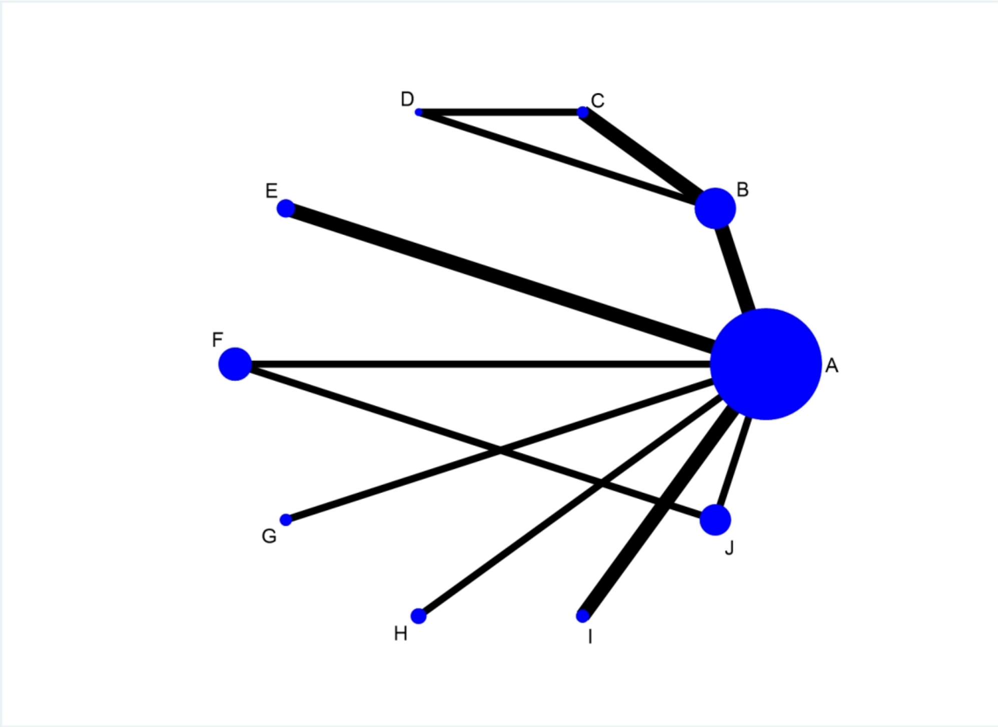
B(SUCRA=74.1%)
C(SUCRA=44.8%)
E(SUCRA=90.7%)
F(SUCRA=40.7%)
H(SUCRA=31.5%)
I(SUCRA=53.8%)
J(SUCRA=15.9%)
Cumulative Probabilities
0 .2 .4 .6 .8 1
1 2 3 4 5 6 7 8
Rank
Graphs by Treatment

Figure 3

Study ID	Randomization process	Deviations from intended i	Missing outcome data	Measurement of the outcome	Selection of the reported	Overall
Arazpour 2012	?	?	?	+	+	!
Barrios 2013	?	+	+	+	+	!
Bennell 2010	+	+	+	+	+	+
Bennell 2014	+	+	?	+	+	?
Cheung 2018	?	?	?	+	?	?
Erhart-Hledik 2012	?	+	?	+	?	?
Foroughi 2011	?	+	?	+	+	?
Hinman 2016	?	+	?	+	+	!
Holsgaard-Larsen 2017	+	+	+	+	+	+
Hunt 2013	+	+	+	+	?	!
Hunt 2018	?	?	+	+	?	?
Jones 2013	?	?	?	+	?	?
Khosravi 2019	?	?	?	?	?	!
Lim 2008	+	?	?	+	?	?
Robert-Lachaine 2020	?	?	+	+	+	?
Song 2020	?	?	?	+	?	?
Trombini-Souza 2015	?	+	+	+	+	!
Wang 2017	+	?	+	+	?	?



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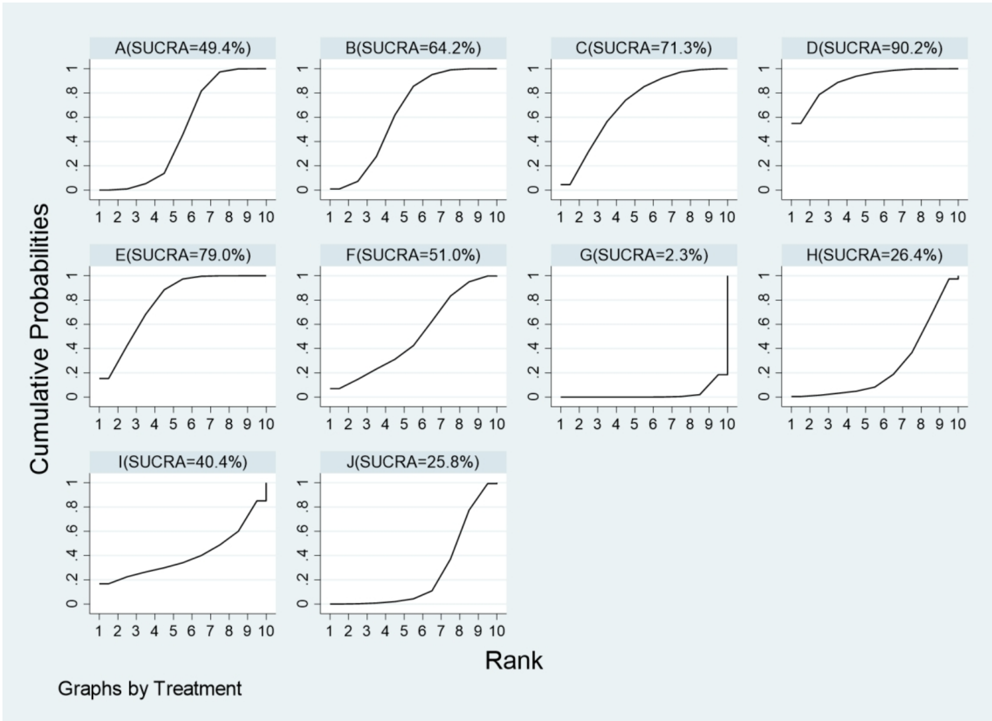

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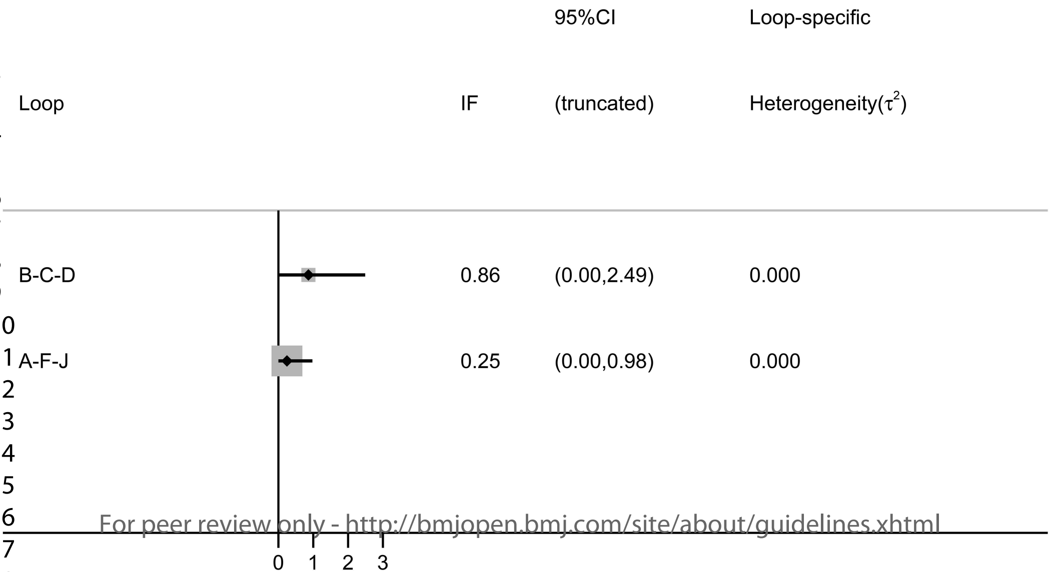
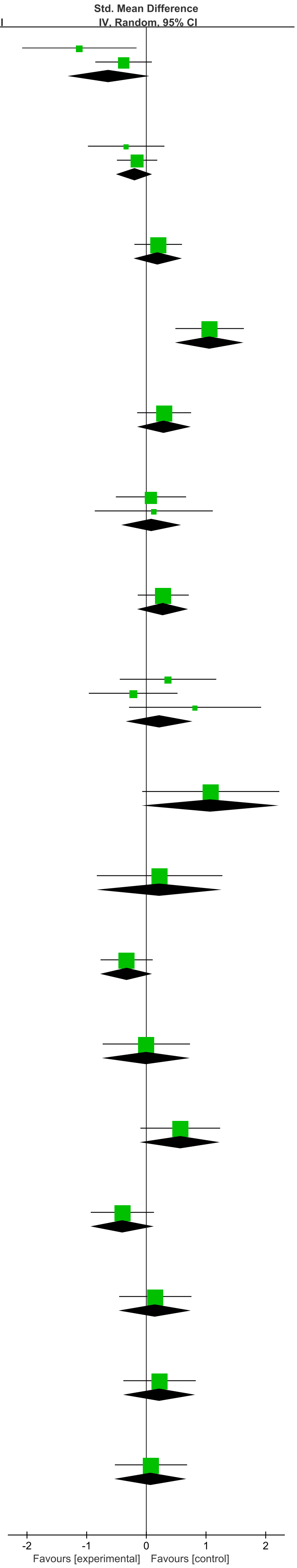
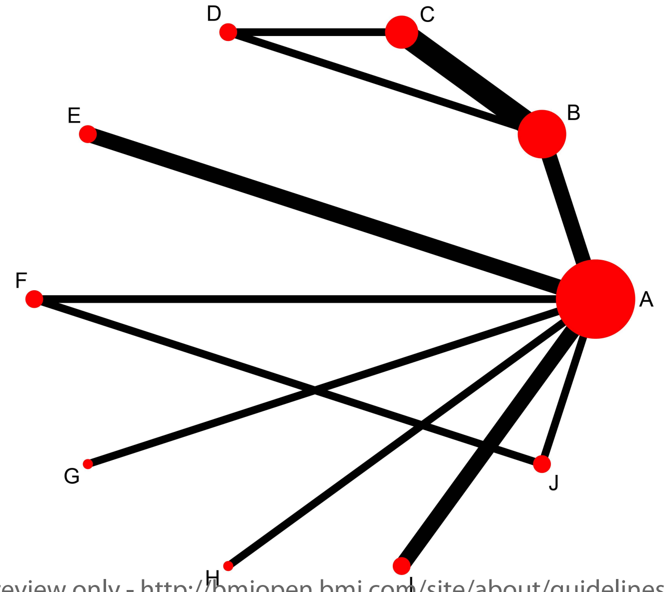

95%CI
Loop-specific
Loop
IF
(truncated)
Heterogeneity(τ^2)
B-C-D
0.86
(0.00,2.49)
0.000
A-F-J
0.25
(0.00,0.98)
0.000
0
1
2
3

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Gait retraining vs Standard Care								
Cheung 2018	-0.078	0.0839	10	0.005	0.0547	10	33.5%	-1.12 [-2.08, -0.16]
Hunt 2018	-0.01	0.3599	37	0.13	0.3666	33	66.5%	-0.38 [-0.86, 0.09]
Subtotal (95% CI)			**47**			**43**	**100.0%**	**-0.63 [-1.32, 0.06]**
Heterogeneity: Tau² = 0.13; Chi² = 1.85, df = 1 (P = 0.17); I² = 46%								
Test for overall effect: Z = 1.80 (P = 0.07)								
1.1.2 LWI vs Standard Care								
Barrios 2013	-0.011	0.1351	19	0.032	0.1133	19	21.7%	-0.34 [-0.98, 0.30]
Hinman 2016	0.26	1.3295	68	0.46	1.234	67	78.3%	-0.16 [-0.49, 0.18]
Subtotal (95% CI)			**87**			**86**	**100.0%**	**-0.19 [-0.49, 0.10]**
Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.62); I² = 0%								
Test for overall effect: Z = 1.28 (P = 0.20)								
1.1.3 Quadriceps strengthening vs Standard Care								
Lim 2008	0.1	0.9685	49	-0.087	0.8962	48	100.0%	0.20 [-0.20, 0.60]
Subtotal (95% CI)			**49**			**48**	**100.0%**	**0.20 [-0.20, 0.60]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.98 (P = 0.33)								
1.1.4 Variable-stiffness shoes vs Standard Care								
Erhart-Hledik 2012	0.338	0.3763	32	-0.072	0.3878	23	100.0%	1.06 [0.49, 1.63]
Subtotal (95% CI)			**32**			**23**	**100.0%**	**1.06 [0.49, 1.63]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.62 (P = 0.0003)								
1.1.5 Hip strengthening vs Standard Care								
Bennell 2010	0.15	0.4371	39	0.02	0.4258	37	100.0%	0.30 [-0.15, 0.75]
Subtotal (95% CI)			**39**			**37**	**100.0%**	**0.30 [-0.15, 0.75]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.29 (P = 0.20)								
1.1.6 Lower limb exercise vs Standard Care								
Foroughi 2011	-0.02	1.26	20	-0.11	1.0223	25	73.9%	0.08 [-0.51, 0.67]
Hunt 2013	-0.05	0.91	9	-0.17	0.9044	7	26.1%	0.13 [-0.86, 1.11]
Subtotal (95% CI)			**29**			**32**	**100.0%**	**0.09 [-0.42, 0.60]**
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%								
Test for overall effect: Z = 0.35 (P = 0.73)								
1.1.7 Neuromuscular exercise vs Standard Care								
Holsgaard-Larsen 2017	0.12	0.3125	44	0.03	0.3168	41	100.0%	0.28 [-0.14, 0.71]
Subtotal (95% CI)			**44**			**41**	**100.0%**	**0.28 [-0.14, 0.71]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.30 (P = 0.19)								
1.1.8 LWI vs Knee Brace								
Arazpour 2012	-0.07	0.0324	12	-0.08	0.019	12	36.6%	0.36 [-0.44, 1.17]
Jones 2013	-0.075	0.1296	14	-0.045	0.1346	14	41.3%	-0.22 [-0.96, 0.52]
Khosravi 2019	-0.08	0.1752	7	-0.22	0.1442	7	22.1%	0.82 [-0.29, 1.92]
Subtotal (95% CI)			**33**			**33**	**100.0%**	**0.22 [-0.34, 0.79]**
Heterogeneity: Tau² = 0.06; Chi² = 2.58, df = 2 (P = 0.28); I² = 22%								
Test for overall effect: Z = 0.77 (P = 0.44)								
1.1.9 LWI vs LWI+Knee Brace								
Khosravi 2019	-0.08	0.1752	7	-0.251	0.1153	7	100.0%	1.08 [-0.07, 2.23]
Subtotal (95% CI)			**7**			**7**	**100.0%**	**1.08 [-0.07, 2.23]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.84 (P = 0.07)								
1.1.10 Knee Brace vs LWI+Knee Brace								
Khosravi 2019	-0.22	0.1442	7	-0.251	0.1153	7	100.0%	0.22 [-0.83, 1.27]
Subtotal (95% CI)			**7**			**7**	**100.0%**	**0.22 [-0.83, 1.27]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.41 (P = 0.68)								
1.1.11 Quadriceps strengthening vs Neuromuscular exercise								
Bennell 2014	-0.04	0.4605	44	0.12	0.502	38	100.0%	-0.33 [-0.77, 0.11]
Subtotal (95% CI)			**44**			**38**	**100.0%**	**-0.33 [-0.77, 0.11]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.48 (P = 0.14)								
1.1.12 PNF vs Standard Care								
Song 2020	0.01	0.13	13	0.01	0.13	16	100.0%	0.00 [-0.73, 0.73]
Subtotal (95% CI)			**13**			**16**	**100.0%**	**0.00 [-0.73, 0.73]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
1.1.13 Electroacupuncture vs Sham-acupuncture								
Wang 2017	0.019	0.095	18	-0.036	0.094	18	100.0%	0.57 [-0.10, 1.24]
Subtotal (95% CI)			**18**			**18**	**100.0%**	**0.57 [-0.10, 1.24]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.67 (P = 0.09)								
1.1.14 Minimalist footwear vs Standard, neutral tennis shoe								
Trombini-Souza 2015	-0.23	0.84	28	0.18	1.15	28	100.0%	-0.40 [-0.93, 0.13]
Subtotal (95% CI)			**28**			**28**	**100.0%**	**-0.40 [-0.93, 0.13]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.49 (P = 0.14)								
1.1.15 ACL-brace vs V3P-brace								
Robert-Lachaine 2020	0.005	0.0991	21	-0.01	0.0967	21	100.0%	0.15 [-0.46, 0.76]
Subtotal (95% CI)			**21**			**21**	**100.0%**	**0.15 [-0.46, 0.76]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.49 (P = 0.63)								
1.1.16 ACL-brace vs VER-brace								
Robert-Lachaine 2020	0.005	0.0991	21	-0.018	0.1043	21	100.0%	0.22 [-0.39, 0.83]
Subtotal (95% CI)			**21**			**21**	**100.0%**	**0.22 [-0.39, 0.83]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.72 (P = 0.47)								
1.1.17 V3P-brace vs VER-brace								
Robert-Lachaine 2020	-0.01	0.0967	21	-0.018	0.1043	21	100.0%	0.08 [-0.53, 0.68]
Subtotal (95% CI)			**21**			**21**	**100.0%**	**0.08 [-0.53, 0.68]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.25 (P = 0.80)								




D
C
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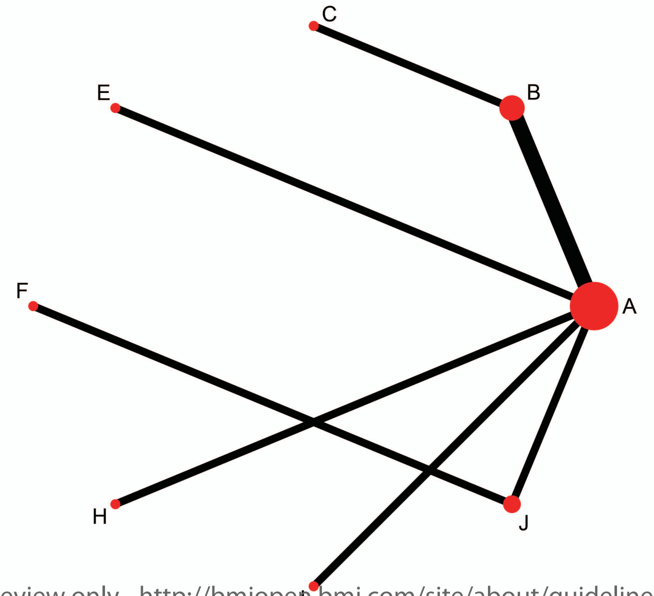
H
I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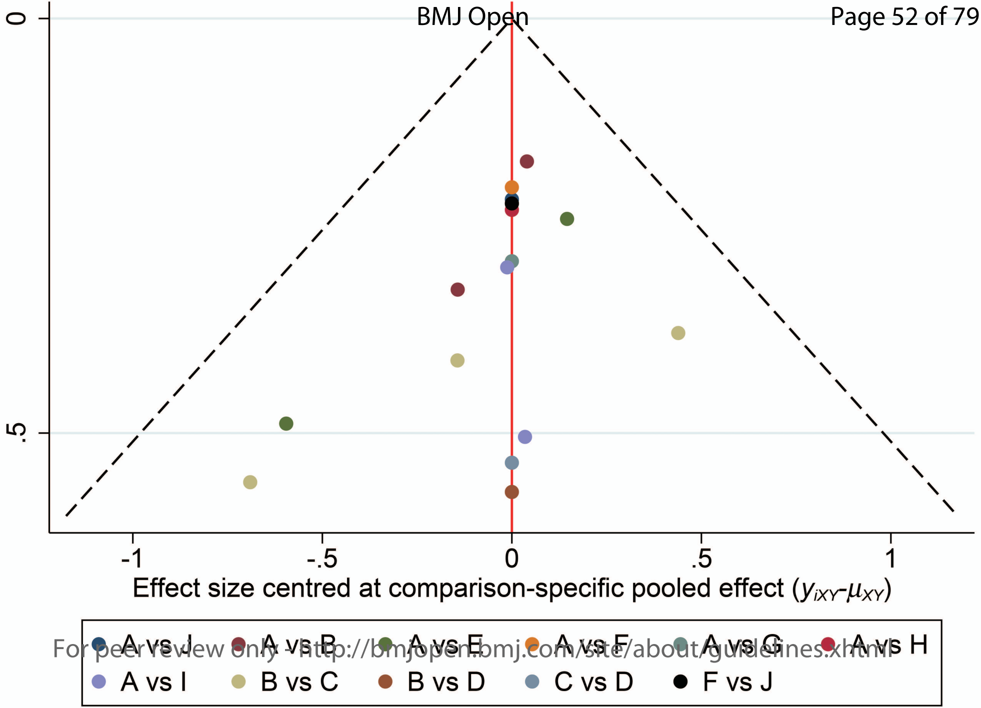
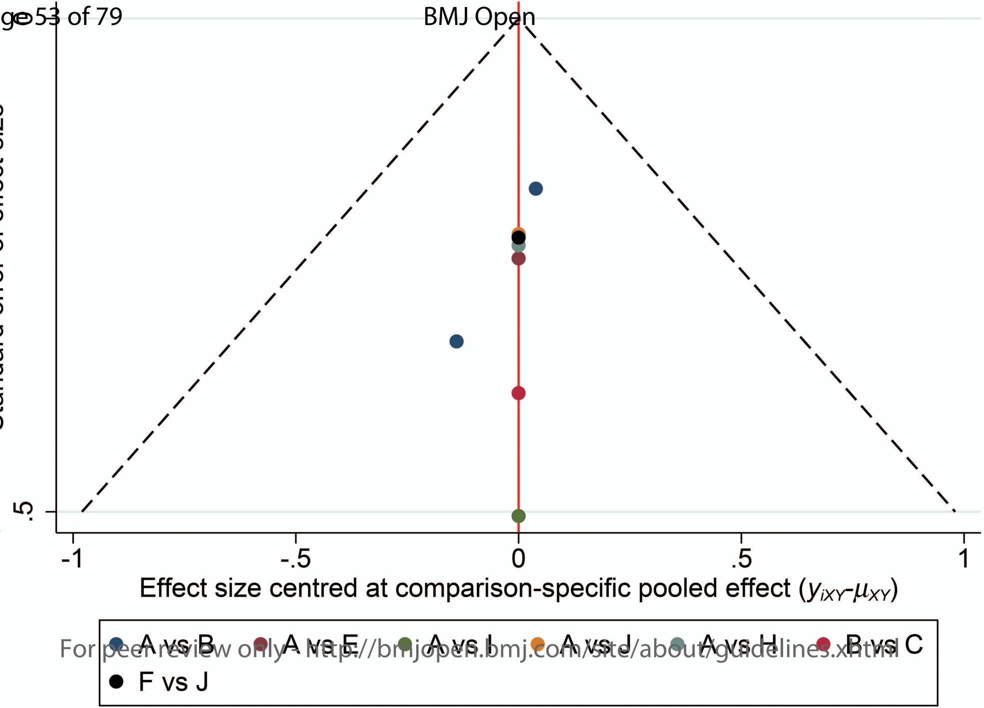

0
.5
Standard error of effect size
-1
-.5
0
.5
1
Effect size centred at comparison-specific pooled effect (y_{iXY}-μ_{XY})
A vs J
A vs B
A vs E
A vs F
A vs G
A vs H
A vs I
B vs C
B vs D
C vs D
F vs J


0
.5
Standard error of effect size
-1
-.5
0
.5
1
Effect size centred at comparison-specific pooled effect (y_{iXY}-μ_{XY})
A vs B
A vs E
A vs I
A vs J
A vs H
B vs C
F vs J

Appendix

Appendix 1 Search strategies

Search strategies for randomized controlled trials

Pubmed

1. (((((((("Osteoarthritis, Knee"[Mesh]) OR Knee Osteoarthritides[Title/Abstract]) OR Knee Osteoarthritis[Title/Abstract]) OR Osteoarthritis of Knee[Title/Abstract]) OR Osteoarthritis of the Knee[Title/Abstract])))) AND ((((((((((((((("Physical Therapy Modalities"[Mesh]) OR (Modalities, Physical Therapy[Title/Abstract])) OR (Modality, Physical Therapy[Title/Abstract])) OR (Physical Therapy Modality[Title/Abstract])) OR (Physiotherapy (Techniques)[Title/Abstract])) OR (Physiotherapies (Techniques)[Title/Abstract])) OR (Physical Therapy Techniques[Title/Abstract])) OR (Physical Therapy Technique[Title/Abstract])) OR (Techniques, Physical Therapy[Title/Abstract])) OR (Group Physiotherapy[Title/Abstract])) OR (Group Physiotherapies[Title/Abstract])) OR (Physiotherapies, Group[Title/Abstract])) OR (Physiotherapy, Group[Title/Abstract])) OR (Neurological Physiotherapy[Title/Abstract])) OR (Physiotherapy, Neurological[Title/Abstract])) OR (Neurophysiotherapy[Title/Abstract])
2. ((((((((("Osteoarthritis, Knee"[Mesh]) OR Knee Osteoarthritides[Title/Abstract]) OR Knee Osteoarthritis[Title/Abstract]) OR Osteoarthritis of Knee[Title/Abstract]) OR Osteoarthritis of the Knee[Title/Abstract]))))) AND (((("Orthopedic Equipment"[Mesh]) OR (Equipment, Orthopedic[Title/Abstract])) OR (Equipments, Orthopedic[Title/Abstract])) OR (Orthopedic Equipments[Title/Abstract]))

Embase

1. ('physiotherapy'/exp OR 'physical therapy':ab,ti OR 'physical therapy (speciality)':ab,ti OR 'physical therapy (specialty)':ab,ti OR 'physical therapy modalities ':ab,ti OR 'physical therapy service':ab,ti OR 'physical therapy speciality':ab,ti OR 'physical therapy specialty ':ab,ti OR 'physical treatment':ab,ti OR ' physio therapy ':ab,ti OR 'physical therapy techniques':ab,ti OR 'physical treatment':ab,ti OR 'physiotherapy department':ab,ti OR 'therapy, physical':ab,ti) AND ('knee osteoarthritis'/exp OR 'arthrosis, knee':ab,ti OR 'femorotibial arthrosis':ab,ti OR 'gonarthrosis':ab,ti OR 'knee arthrosis':ab,ti OR 'knee joint arthrosis':ab,ti OR 'knee joint osteoarthritis':ab,ti OR 'knee osteo-arthritis':ab,ti OR 'knee osteo-arthrosis':ab,ti OR 'knee osteoarthrosis':ab,ti OR 'osteoarthritis, knee':ab,ti OR 'osteoarthrosis, knee':ab,ti)
2. ('orthosis'/exp OR 'device, orthotic':ab,ti OR 'devices, orthotic':ab,ti OR 'orthesis':ab,ti OR 'orthopeadic support device':ab,ti OR 'orthopedic support device':ab,ti OR 'orthoses':ab,ti OR 'orthotic device (physical object)':ab,ti OR 'orthotic devices':ab,ti) AND ('knee osteoarthritis'/exp OR 'arthrosis, knee':ab,ti OR 'femorotibial arthrosis':ab,ti OR 'gonarthrosis':ab,ti OR 'knee arthrosis':ab,ti OR 'knee joint arthrosis':ab,ti OR 'knee joint osteoarthritis':ab,ti OR 'knee osteo-arthritis':ab,ti OR 'knee osteo-arthrosis':ab,ti OR 'knee osteoarthrosis':ab,ti OR 'osteoarthritis, knee':ab,ti OR 'osteoarthrosis, knee':ab,ti)

Web of Science

1. AB=(physical therapy OR physiotherapy OR physio therapy OR physical treatment OR physiotherapy department OR physical therapy techniques)
2. TI=(physical therapy OR physiotherapy OR physio therapy OR physical treatment OR physiotherapy department OR physical therapy techniques)
3. AB=(orthosis OR device OR orthesis OR orthoses OR orthopeadic support device OR orthotic device)
4. TI=(orthosis OR device OR orthesis OR orthoses OR orthopeadic support device OR orthotic device)
5. #4 OR #3 OR #2 OR #1
6. AB=(knee osteoarthritis OR femorotibial arthrosis OR gonarthrosis OR knee arthrosis OR knee osteo-arthritis OR knee osteoarthrosis OR osteoarthrosis)
7. TI=(knee osteoarthritis OR femorotibial arthrosis OR gonarthrosis OR knee arthrosis OR knee osteo-arthritis OR knee osteoarthrosis OR osteoarthrosis)
8. #6 OR #7
9. #8 AND #5

Cochrane Library

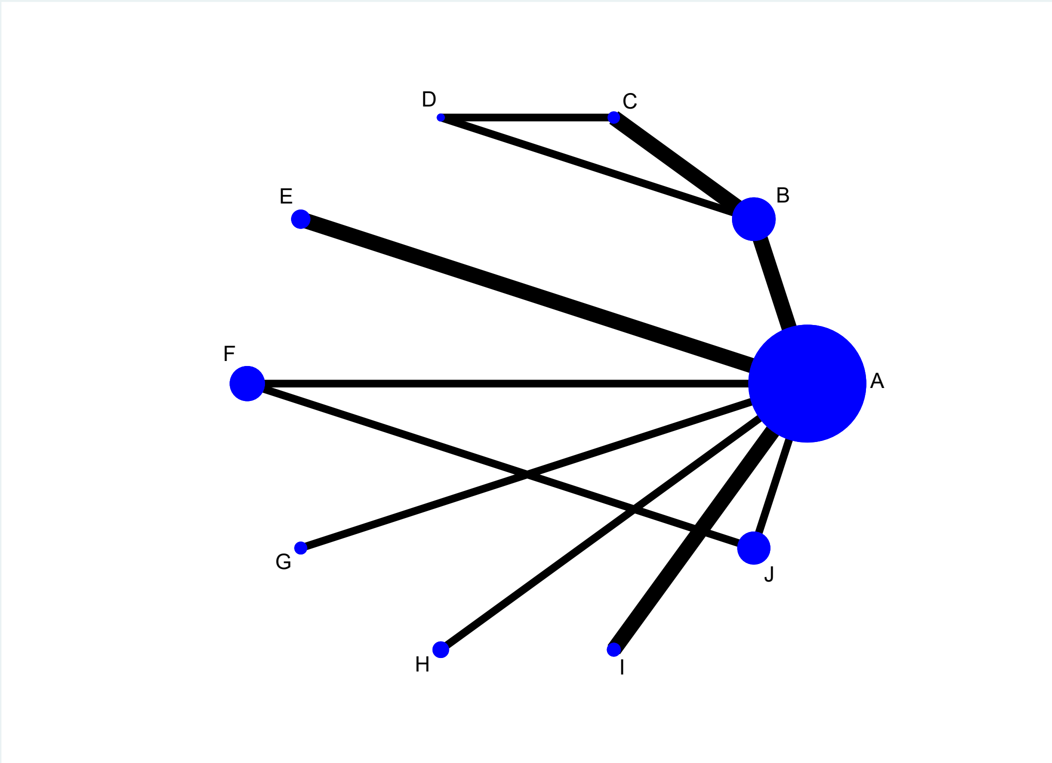
1. (MeSH descriptor: [Physical Therapy Modalities] explode all trees OR (Neurological Physiotherapy):ti,ab,kw OR (Physiotherapy, Neurological):ti,ab,kw OR (Neurophysiotherapy):ti,ab,kw OR (Techniques, Physical Therapy):ti,ab,kw OR (Physiotherapies (Techniques)):ti,ab,kw OR (Physical Therapy Techniques):ti,ab,kw OR (Physiotherapy (Techniques)):ti,ab,kw OR (Modality, Physical Therapy):ti,ab,kw OR (Physical Therapy Modality):ti,ab,kw OR (Physical Therapy Technique):ti,ab,kw OR (Modalities, Physical Therapy):ti,ab,kw OR (Group Physiotherapies):ti,ab,kw OR (Physiotherapy, Group):ti,ab,kw OR (Group Physiotherapy):ti,ab,kw OR (Physiotherapies, Group):ti,ab,kw) AND ((Osteoarthritis of Knee):ti,ab,kw OR (Knee Osteoarthritides):ti,ab,kw OR (Knee Osteoarthritis):ti,ab,kw OR (Osteoarthritis of the Knee):ti,ab,kw) OR MeSH descriptor: [Osteoarthritis, Knee] explode all trees)
2. (MeSH descriptor: [Orthopedic Equipment] explode all trees OR (Orthopedic Equipments):ti,ab,kw OR (Equipment, Orthopedic):ti,ab,kw OR (Equipments, Orthopedic):ti,ab,kw) AND ((Osteoarthritis of Knee):ti,ab,kw OR (Knee Osteoarthritides):ti,ab,kw OR (Knee Osteoarthritis):ti,ab,kw OR (Osteoarthritis of the Knee):ti,ab,kw) OR MeSH descriptor: [Osteoarthritis, Knee] explode all trees)

MEDLINE

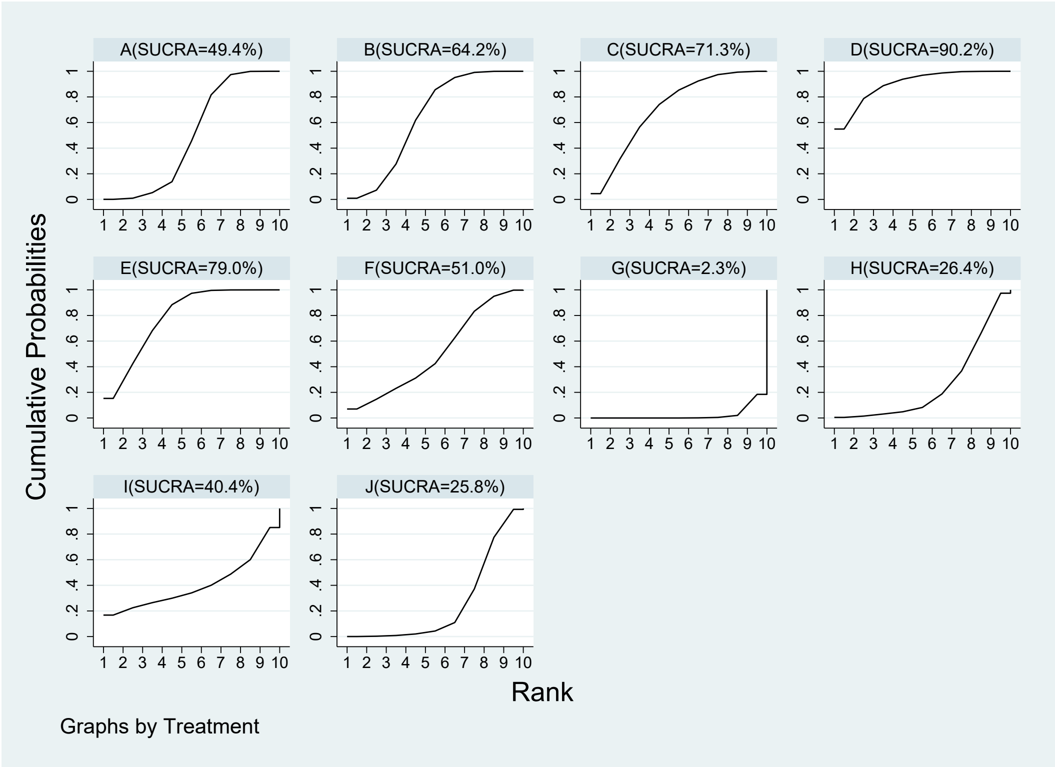
1. (knee osteoarthritis) OR (femorotibial arthrosis) OR (gonarthrosis) OR (knee arthrosis) OR (knee osteo-arthritis) OR (knee osteoarthrosis) OR (osteoarthrosis)
2. (physical therapy) OR (physiotherapy) OR (physio therapy) OR (physical treatment) OR (physiotherapy department) OR (physical therapy techniques)
3. (orthotic devices) OR (Orthopedic Equipment) OR (orthosis) OR (device) OR (orthesis) OR (orthoses) OR (orthopeadic support device)
4. #2 OR #3

5. #1 AND #4

Appendix 2 Results of re-analysis

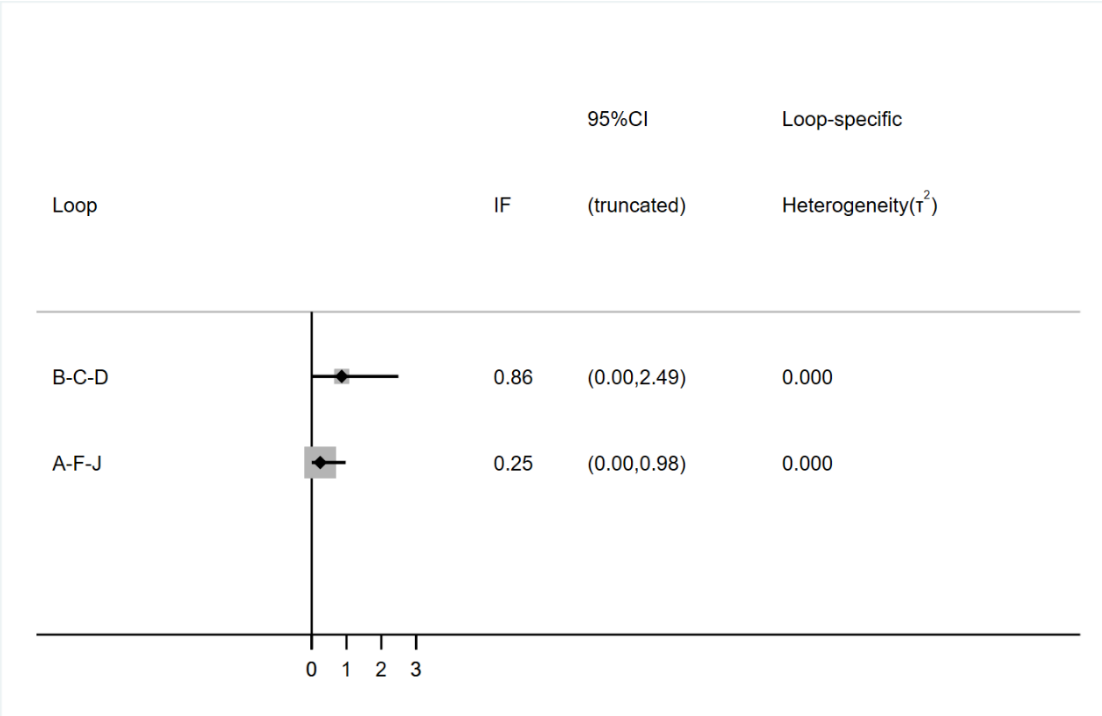


eFigure 1. Structure of network formed by interventions and their direct comparisons on First peak KAM (re-analysis). A= Standard care; B= Lateral Wedge Insole; C= Knee Brace; D= Lateral Wedge Insole+ Knee Brace; E= Gait retraining; F= Quadriceps strengthening; G= Variable-stiffness shoe; H= Hip strengthening; I= Lower limb exercise; J= Neuromuscular exercise.



eFigure 2. Rankings for effects on First peak KAM (re-analysis). Graph displays distribution of probabilities for each treatment. X-axis represents the possible rank of each treatment (from the best to worst according to the outcomes), Y-axis represents the cumulative probability for each treatment to be the best option, among the best two options, among the best three options, and so on. A= Standard care; B= Lateral Wedge Insole; C= Knee Brace; D= Lateral Wedge Insole+ Knee Brace; E= Gait retraining; F= Quadriceps strengthening; G= Variable-stiffness shoe; H= Hip strengthening; I= Lower limb exercise; J= Neuromuscular exercise.

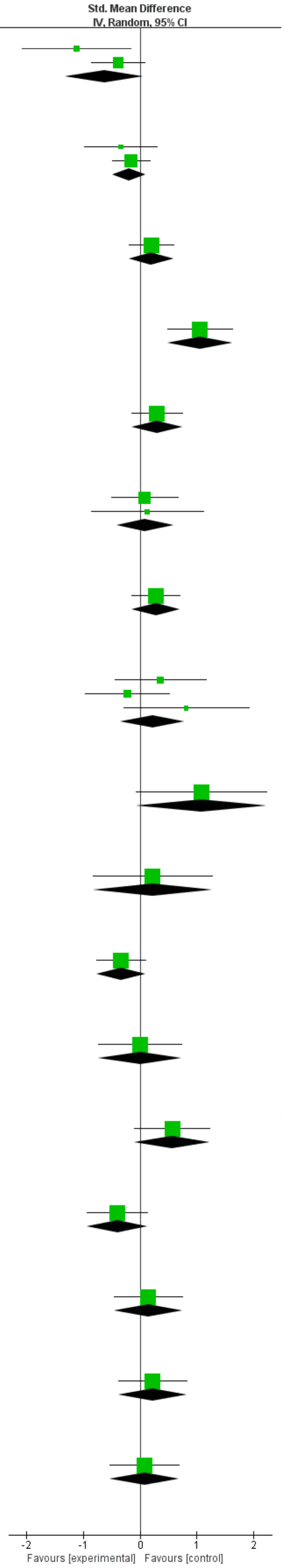
Appendix 3 Results of Inconsistency



eFigure 3. Inconsistency for triangular loops in First peak KAM.

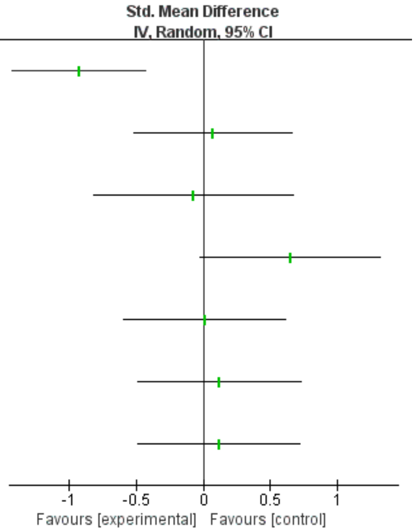
Appendix 4 Conventional meta-analyses results

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Gait retraining vs Standard Care								
Cheung 2018	-0.078	0.0839	10	0.005	0.0547	10	33.5%	-1.12 [-2.08, -0.16]
Hunt 2018	-0.01	0.3599	37	0.13	0.3666	33	66.5%	-0.38 [-0.86, 0.09]
Subtotal (95% CI)			**47**			**43**	**100.0%**	**-0.63 [-1.32, 0.06]**
Heterogeneity: Tau² = 0.13; Chi² = 1.85, df = 1 (P = 0.17); I² = 46%								
Test for overall effect: Z = 1.80 (P = 0.07)								
1.1.2 LWI vs Standard Care								
Barrios 2013	-0.011	0.1351	19	0.032	0.1133	19	21.7%	-0.34 [-0.98, 0.30]
Hinman 2016	0.26	1.3295	68	0.46	1.234	67	78.3%	-0.16 [-0.49, 0.18]
Subtotal (95% CI)			**87**			**86**	**100.0%**	**-0.19 [-0.49, 0.10]**
Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.62); I² = 0%								
Test for overall effect: Z = 1.28 (P = 0.20)								
1.1.3 Quadriceps strengthening vs Standard Care								
Lim 2008	0.1	0.9685	49	-0.087	0.8962	48	100.0%	0.20 [-0.20, 0.60]
Subtotal (95% CI)			**49**			**48**	**100.0%**	**0.20 [-0.20, 0.60]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.98 (P = 0.33)								
1.1.4 Variable-stiffness shoes vs Standard Care								
Erhart-Hledik 2012	0.338	0.3763	32	-0.072	0.3878	23	100.0%	1.06 [0.49, 1.63]
Subtotal (95% CI)			**32**			**23**	**100.0%**	**1.06 [0.49, 1.63]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.62 (P = 0.0003)								
1.1.5 Hip strengthening vs Standard Care								
Bennell 2010	0.15	0.4371	39	0.02	0.4258	37	100.0%	0.30 [-0.15, 0.75]
Subtotal (95% CI)			**39**			**37**	**100.0%**	**0.30 [-0.15, 0.75]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.29 (P = 0.20)								
1.1.6 Lower limb exercise vs Standard Care								
Foroughi 2011	-0.02	1.26	20	-0.11	1.0223	25	73.9%	0.08 [-0.51, 0.67]
Hunt 2013	-0.05	0.91	9	-0.17	0.9044	7	26.1%	0.13 [-0.86, 1.11]
Subtotal (95% CI)			**29**			**32**	**100.0%**	**0.09 [-0.42, 0.60]**
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%								
Test for overall effect: Z = 0.35 (P = 0.73)								
1.1.7 Neuromuscular exercise vs Standard Care								
Holsgaard-Larsen 2017	0.12	0.3125	44	0.03	0.3168	41	100.0%	0.28 [-0.14, 0.71]
Subtotal (95% CI)			**44**			**41**	**100.0%**	**0.28 [-0.14, 0.71]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.30 (P = 0.19)								
1.1.8 LWI vs Knee Brace								
Arazpour 2012	-0.07	0.0324	12	-0.08	0.019	12	36.6%	0.36 [-0.44, 1.17]
Jones 2013	-0.075	0.1296	14	-0.045	0.1346	14	41.3%	-0.22 [-0.96, 0.52]
Khosravi 2019	-0.08	0.1752	7	-0.22	0.1442	7	22.1%	0.82 [-0.29, 1.92]
Subtotal (95% CI)			**33**			**33**	**100.0%**	**0.22 [-0.34, 0.79]**
Heterogeneity: Tau² = 0.06; Chi² = 2.58, df = 2 (P = 0.28); I² = 22%								
Test for overall effect: Z = 0.77 (P = 0.44)								
1.1.9 LWI vs LWI+Knee Brace								
Khosravi 2019	-0.08	0.1752	7	-0.251	0.1153	7	100.0%	1.08 [-0.07, 2.23]
Subtotal (95% CI)			**7**			**7**	**100.0%**	**1.08 [-0.07, 2.23]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.84 (P = 0.07)								
1.1.10 Knee Brace vs LWI+Knee Brace								
Khosravi 2019	-0.22	0.1442	7	-0.251	0.1153	7	100.0%	0.22 [-0.83, 1.27]
Subtotal (95% CI)			**7**			**7**	**100.0%**	**0.22 [-0.83, 1.27]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.41 (P = 0.68)								
1.1.11 Quadriceps strengthening vs Neuromuscular exercise								
Bennell 2014	-0.04	0.4605	44	0.12	0.502	38	100.0%	-0.33 [-0.77, 0.11]
Subtotal (95% CI)			**44**			**38**	**100.0%**	**-0.33 [-0.77, 0.11]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.48 (P = 0.14)								
1.1.12 PNF vs Standard Care								
Song 2020	0.01	0.13	13	0.01	0.13	16	100.0%	0.00 [-0.73, 0.73]
Subtotal (95% CI)			**13**			**16**	**100.0%**	**0.00 [-0.73, 0.73]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
1.1.13 Electroacupuncture vs Sham-acupuncture								
Wang 2017	0.019	0.095	18	-0.036	0.094	18	100.0%	0.57 [-0.10, 1.24]
Subtotal (95% CI)			**18**			**18**	**100.0%**	**0.57 [-0.10, 1.24]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.67 (P = 0.09)								
1.1.14 Minimalist footwear vs Standard, neutral tennis shoe								
Trombini-Souza 2015	-0.23	0.84	28	0.18	1.15	28	100.0%	-0.40 [-0.93, 0.13]
Subtotal (95% CI)			**28**			**28**	**100.0%**	**-0.40 [-0.93, 0.13]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.49 (P = 0.14)								
1.1.15 ACL-brace vs V3P-brace								
Robert-Lachaine 2020	0.005	0.0991	21	-0.01	0.0967	21	100.0%	0.15 [-0.46, 0.76]
Subtotal (95% CI)			**21**			**21**	**100.0%**	**0.15 [-0.46, 0.76]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.49 (P = 0.63)								
1.1.16 ACL-brace vs VER-brace								
Robert-Lachaine 2020	0.005	0.0991	21	-0.018	0.1043	21	100.0%	0.22 [-0.39, 0.83]
Subtotal (95% CI)			**21**			**21**	**100.0%**	**0.22 [-0.39, 0.83]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.72 (P = 0.47)								
1.1.17 V3P-brace vs VER-brace								
Robert-Lachaine 2020	-0.01	0.0967	21	-0.018	0.1043	21	100.0%	0.08 [-0.53, 0.68]
Subtotal (95% CI)			**21**			**21**	**100.0%**	**0.08 [-0.53, 0.68]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.25 (P = 0.80)								



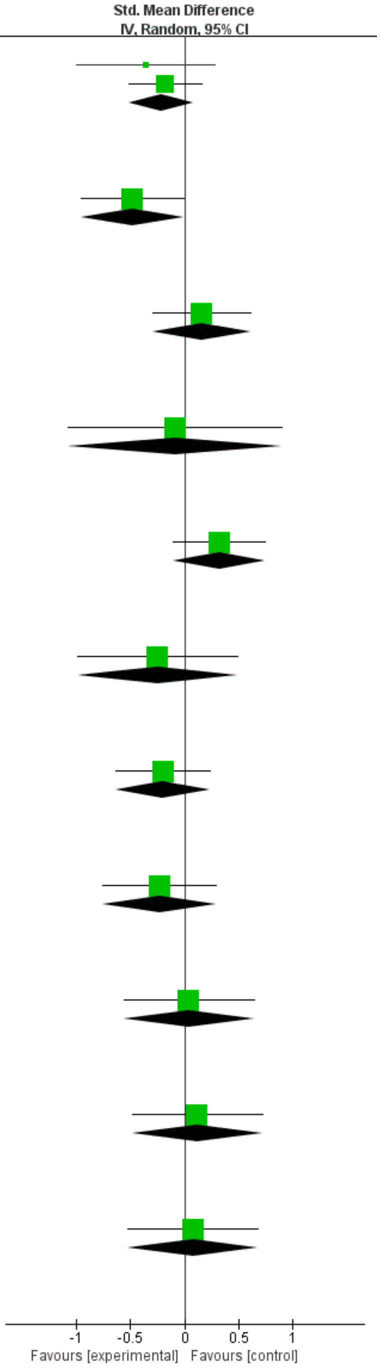
eFigure 4a. Conventional meta-analysis of treatment effects on First peak KAM.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Std. Mean Difference IV, Random, 95% CI
1.2.1 Gait retraining vs Standard Care							
Hunt 2018	-0.24	0.2699	37	0.02	0.2849	33	-0.93 [-1.42, -0.43]
1.2.2 Lower limb exercise vs Standard Care							
Foroughi 2011	0.14	1.311	20	0.06	0.9254	25	0.07 [-0.52, 0.66]
1.2.3 LWI vs Knee Brace							
Jones 2013	-0.06	0.144	14	-0.05	0.12	14	-0.07 [-0.81, 0.67]
1.2.4 Electroacupuncture vs Sham-acupuncture							
Wang 2017	-0.002	0.093	18	-0.046	0.012	18	0.65 [-0.02, 1.32]
1.2.5 ACL-brace vs V3P-brace							
Robert-Lachaine 2020	-0.001	0.106	21	-0.002	0.0989	21	0.01 [-0.60, 0.61]
1.2.6 ACL-brace vs VER-brace							
Robert-Lachaine 2020	-0.001	0.106	21	-0.014	0.1043	21	0.12 [-0.48, 0.73]
1.2.7 V3P-brace vs VER-brace							
Robert-Lachaine 2020	-0.002	0.0989	21	-0.014	0.1043	21	0.12 [-0.49, 0.72]



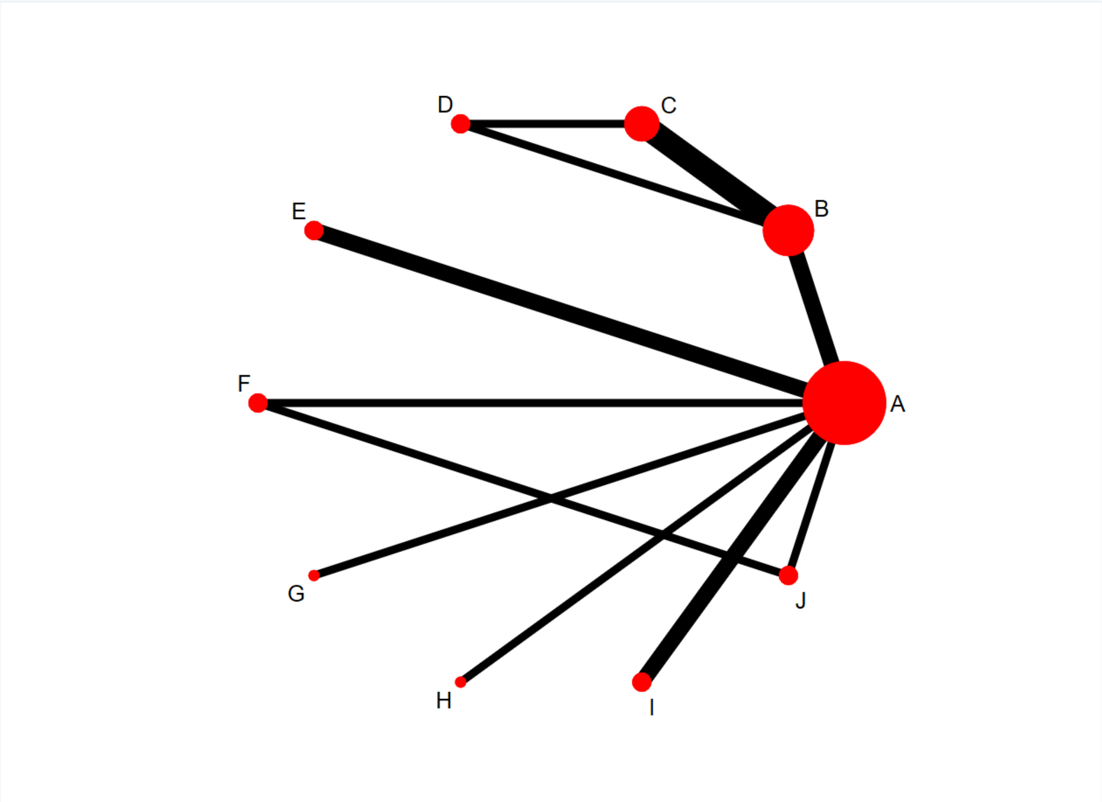
eFigure 4b. Conventional meta-analysis of treatment effects on Second peak KAM.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.3.1 LWI vs Standard Care								
Barrios 2013	-0.009	0.0727	19	0.016	0.064	19	21.7%	-0.36 [-1.00, 0.28]
Hinman 2016	0.07	0.451	68	0.15	0.435	67	78.3%	-0.18 [-0.52, 0.16]
Subtotal (95% CI)			**87**			**86**	**100.0%**	**-0.22 [-0.52, 0.08]**
Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 1 (P = 0.63); I² = 0%								
Test for overall effect: Z = 1.43 (P = 0.15)								
1.3.2 Gait retraining vs Standard Care								
Hunt 2018	-0.04	0.105	37	0.01	0.0987	33	100.0%	-0.48 [-0.96, -0.01]
Subtotal (95% CI)			**37**			**33**	**100.0%**	**-0.48 [-0.96, -0.01]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.99 (P = 0.05)								
1.3.3 Hip strengthening vs Standard Care								
Bennell 2010	0.05	0.1873	39	0.02	0.1825	37	100.0%	0.16 [-0.29, 0.61]
Subtotal (95% CI)			**39**			**37**	**100.0%**	**0.16 [-0.29, 0.61]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.70 (P = 0.48)								
1.3.4 Lower limb exercise vs Standard Care								
Hunt 2013	-0.12	0.3775	9	-0.08	0.4951	7	100.0%	-0.09 [-1.08, 0.90]
Subtotal (95% CI)			**9**			**7**	**100.0%**	**-0.09 [-1.08, 0.90]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.17 (P = 0.86)								
1.3.5 Neuromuscular exercise vs Standard Care								
Holsgaard-Larsen 2017	0.05	0.1316	44	0.01	0.1109	41	100.0%	0.32 [-0.10, 0.75]
Subtotal (95% CI)			**44**			**41**	**100.0%**	**0.32 [-0.10, 0.75]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.49 (P = 0.14)								
1.3.6 LWI vs Knee Brace								
Jones 2013	-0.0395	0.0687	14	-0.0215	0.0726	14	100.0%	-0.25 [-0.99, 0.50]
Subtotal (95% CI)			**14**			**14**	**100.0%**	**-0.25 [-0.99, 0.50]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.65 (P = 0.51)								
1.3.7 Quadriceps strengthening vs Neuromuscular exercise								
Bennell 2014	-0.02	0.1809	44	0.02	0.213	38	100.0%	-0.20 [-0.64, 0.23]
Subtotal (95% CI)			**44**			**38**	**100.0%**	**-0.20 [-0.64, 0.23]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.91 (P = 0.36)								
1.3.8 Minimalist footwear vs Standard, neutral tennis shoe								
Trombini-Souza 2015	-0.09	0.3652	28	0.01	0.4803	28	100.0%	-0.23 [-0.76, 0.29]
Subtotal (95% CI)			**28**			**28**	**100.0%**	**-0.23 [-0.76, 0.29]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.86 (P = 0.39)								
1.3.9 ACL-brace VS V3P-brace								
Robert-Lachaine 2020	0.2	4.9428	21	0	4.8368	21	100.0%	0.04 [-0.56, 0.65]
Subtotal (95% CI)			**21**			**21**	**100.0%**	**0.04 [-0.56, 0.65]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.13 (P = 0.90)								
1.3.10 ACL-brace vs VER-brace								
Robert-Lachaine 2020	0.2	4.9428	21	-0.4	4.9624	21	100.0%	0.12 [-0.49, 0.72]
Subtotal (95% CI)			**21**			**21**	**100.0%**	**0.12 [-0.49, 0.72]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.38 (P = 0.70)								
1.3.11 V3P-brace vs VER-brace								
Robert-Lachaine 2020	0	4.8368	21	-0.4	4.9624	21	100.0%	0.08 [-0.53, 0.69]
Subtotal (95% CI)			**21**			**21**	**100.0%**	**0.08 [-0.53, 0.69]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.26 (P = 0.80)								



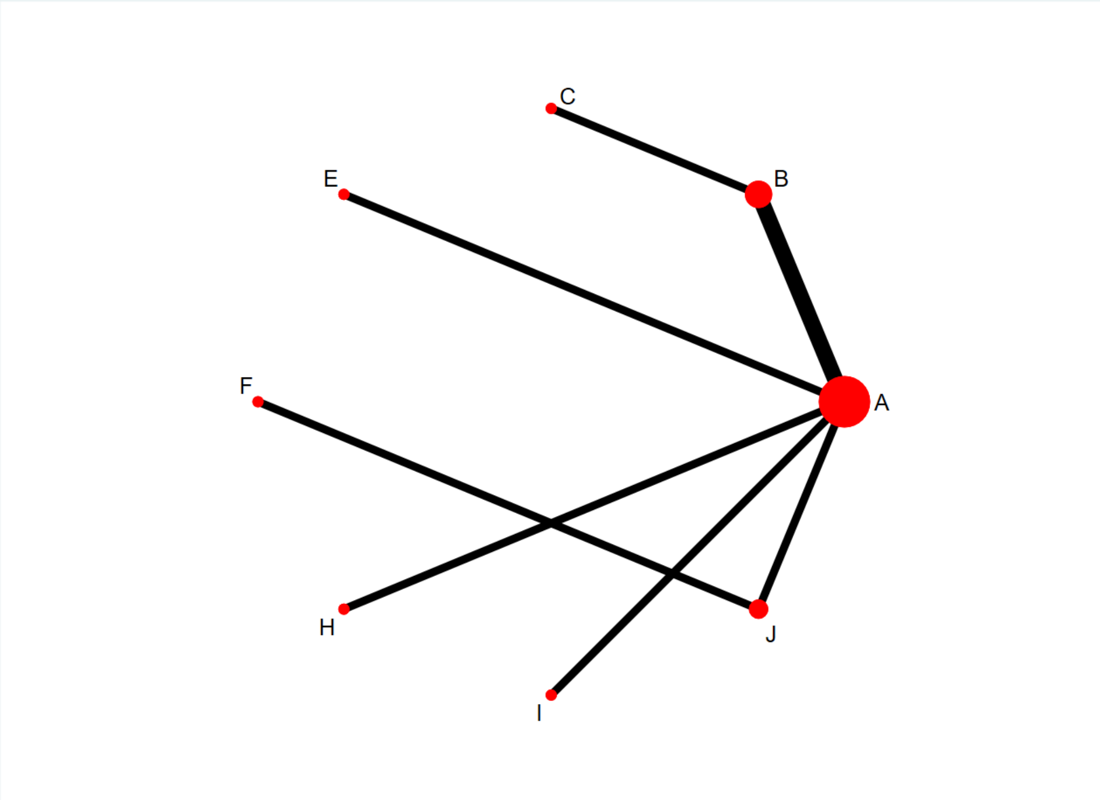
eFigure 4c. Conventional meta-analysis of treatment effects on KAAI.

Appendix 5 Network Diagram



eFigure 5a. Structure of network formed by interventions and their direct comparisons (First peak KAM). A= Standard care; B= Lateral Wedge Insole; C= Knee Brace; D= Lateral Wedge Insole+ Knee Brace; E= Gait retraining; F= Quadriceps strengthening; G= Variable-stiffness shoe; H= Hip strengthening; I= Lower limb exercise; J= Neuromuscular exercise.

Footnote: Width of the lines is proportional to the number of trials comparing every pair of treatments. Size of every circle is proportional to the number of randomly assigned participants (ie, sample size).



eFigure 5b. Structure of network formed by interventions and their direct comparisons (KAAI). A= Standard care; B= Lateral Wedge Insole; C= Knee Brace; E= Gait retraining; F= Quadriceps strengthening; H= Hip strengthening; I= Lower limb exercise; J= Neuromuscular exercise.

Footnote: Width of the lines is proportional to the number of trials comparing every pair of treatments. Size of every circle is proportional to the number of randomly assigned participants (ie, sample size).

Appendix 6 Table of GRADE

Based on all the above information, we GRADEd each network estimate according to the following criteria:

1) Study limitations: We downgraded by one level when the contributions from low RoB comparisons were less than 30% and contributions from moderate RoB comparisons were 70% or greater. And we downgraded by two level when the contributions from low RoB comparisons were more than 30%.
2) Imprecision: We considered a clinically meaningful threshold for CI to be 0 and did not

downgrade the estimate if the upper limit is below 0; or if the lower limit is above 0.

3) Inconsistency: We rated two concepts, heterogeneity and incoherence (inconsistency), in this domain. For heterogeneity, we did not downgrade any network estimate for heterogeneity, because we looked at the common tau and found that it is low. For inconsistency, we looked at the results of inconsistency (Appendix 2), where we have not downgraded for imprecision.

4) Indirectness: We have assured transitivity in our network by limiting the included studies to patients with knee osteoarthritis. Evaluation of transitivity for singly-connected nodes is unclear, so we downgraded such nodes for indirectness.

5) Publication bias: The comparison-adjusted funnel plot (Appendix 5) did not suggest presence of overall publication bias. We managed to retrieve supplementary and unpublished information included in the available systematic reviews and network meta-analyses, and we are confident that we have all available information that is possible to capture from clinical trial registries. Although we cannot completely rule out the possibility that some research is still missing, we still believe that the project does not need to be downgraded.

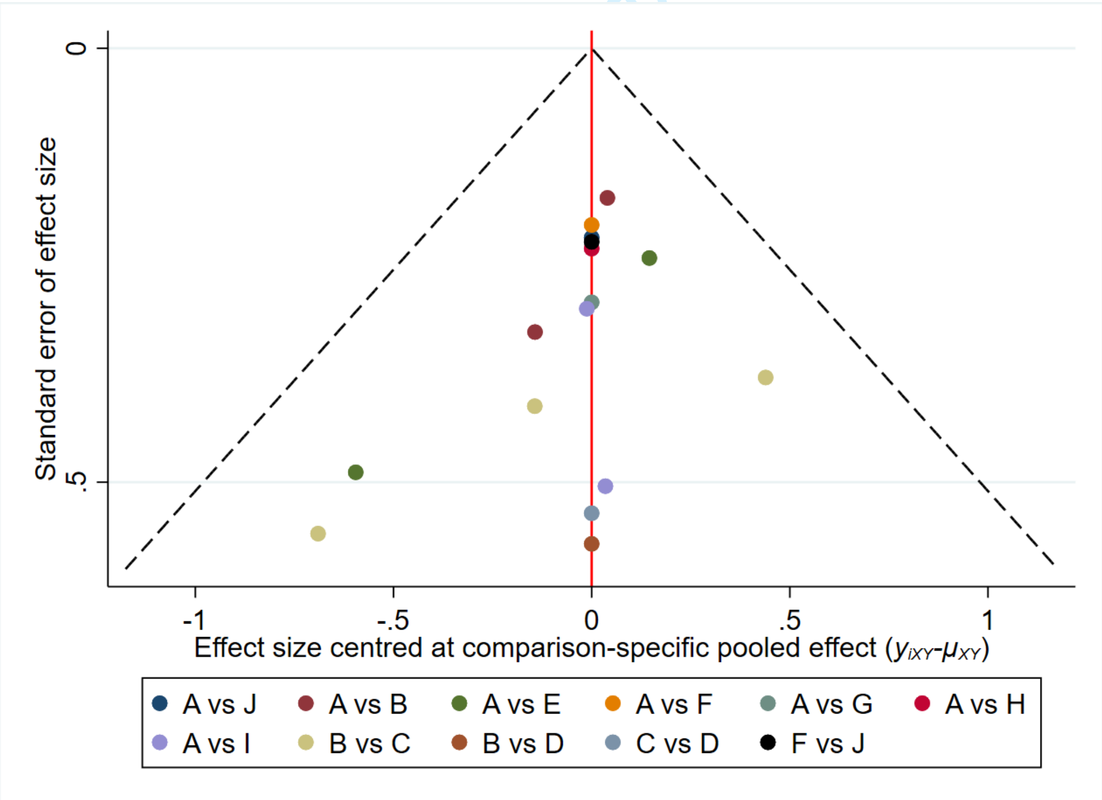
Comparison	Nature of the Evidence	GRADE	Downgarding due to
AB: Standard Care *vs* LWI	Mixed	LOW	Study limitations; Imprecision
AC: Standard Care *vs* Knee Brace	Indirect	LOW	Study limitations; Imprecision
AD: Standard Care *vs* LWI+Knee Brace	Indirect	LOW	Study limitations; Imprecision
AE: Standard Care *vs* Gait Retraining	Mixed	VERY LOW	Study limitations; Indirectness
AF: Standard Care *vs* Quadriceps Strengthening	Mixed	VERY LOW	Study limitations; Imprecision
AG: Standard Care *vs* Variable-Stiffness Shoes	Mixed	VERY LOW	Study limitations; Indirectness;
AH: Standard Care *vs* Hip Strengthening	Mixed	VERY LOW	Study limitations; Indirectness; Imprecision
AI: Standard Care *vs* Lower Limb	Mixed	VERY LOW	Study limitations; Indirectness;

Exercise			Imprecision
AJ: Standard Care *vs* Neuromuscular Exercise	Mixed	MODERATE	Study limitations
BC: LWI *vs* Knee Brace	Mixed	VERY LOW	Study limitations; Imprecision
BD: LWI *vs* LWI+Knee Brace	Mixed	VERY LOW	Study limitations; Imprecision
BE: LWI *vs* Gait Retraining	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
BF: LWI *vs* Quadriceps Strengthening	Indirect	LOW	Study limitations; Imprecision
BG: LWI *vs* Variable-Stiffness Shoes	Indirect	LOW	Study limitations; Indirectness
BH: LWI *vs* Hip Strengthening	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
BI: LWI *vs* Lower Limb Exercise	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
BJ: LWI *vs* Neuromuscular Exercise	Indirect	MODERATE	Study limitations
CD: Knee Brace *vs* LWI+Knee Brace	Mixed	VERY LOW	Study limitations; Imprecision
CE: Knee Brace *vs* Gait Retraining	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
CF: Knee Brace *vs* Quadriceps Strengthening	Indirect	LOW	Study limitations; Imprecision
CG: Knee Brace *vs* Variable-Stiffness Shoes	Indirect	LOW	Study limitations; Indirectness
CH: Knee Brace *vs* Hip Strengthening	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
CI: Knee Brace *vs* Lower Limb Exercise	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
CJ: Knee Brace *vs* Neuromuscular Exercise	Indirect	MODERATE	Study limitations
DE: LWI+Knee Brace *vs* Gait Retraining	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision

DF: LWI+Knee Brace *vs* Quadriceps Strengthening	Indirect	LOW	Study limitations; Imprecision
DG: LWI+Knee Brace *vs* Variable-Stiffness Shoes	Indirect	VERY LOW	Study limitations; Indirectness
DH: LWI+Knee Brace *vs* Hip Strengthening	Indirect	LOW	Study limitations; Indirectness
DI: LWI+Knee Brace *vs* Lower Limb Exercise	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
DJ: LWI+Knee Brace *vs* Neuromuscular Exercise	Indirect	MODERATE	Study limitations
EF: Gait Retraining *vs* Quadriceps Strengthening	Indirect	VERY LOW	Study limitations; Indirectness
EG: Gait Retraining *vs* Variable-Stiffness Shoes	Indirect	VERY LOW	Study limitations; Indirectness
EH: Gait Retraining *vs* Hip Strengthening	Indirect	LOW	Study limitations; Indirectness
EI: Gait Retraining *vs* Lower limb Exercise	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
EJ: Gait Retraining *vs* Neuromuscular Exercise	Indirect	LOW	Study limitations; Indirectness
FG: Quadriceps Strengthening *vs* Variable-Stiffness Shoes	Indirect	VERY LOW	Study limitations; Indirectness
FH: Quadriceps Strengthening *vs* Hip Strengthening	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
FI: Quadriceps Strengthening *vs* Lower Limb Exercise	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
FJ: Quadriceps Strengthening *vs* Neuromuscular Exercise	Mixed	LOW	Study limitations; Imprecision
GH: Variable-Stiffness Shoes *vs* Hip	Indirect	LOW	Study limitations; Indirectness

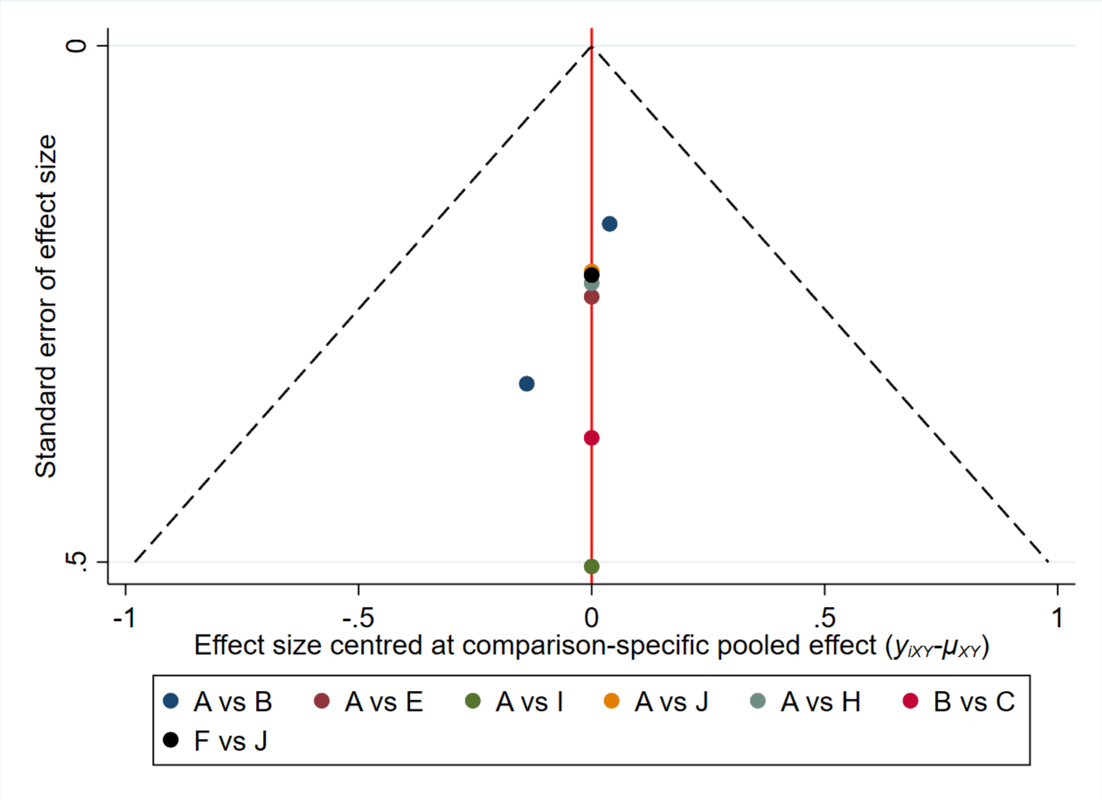
Strengthening			
GI: Variable-Stiffness Shoes *vs* Lower Limb Exercise	Indirect	VERY LOW	Study limitations; Indirectness
GJ: Variable-Stiffness Shoes *vs* Neuromuscular Exercise	Indirect	LOW	Study limitations; Indirectness
HI: Hip Strengthening *vs* Lower Limb Exercise	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
HJ: Hip Strengthening *vs* Neuromuscular Exercise	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
IJ: Lower Limb Exercise *vs* Neuromuscular Exercise	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision

Appendix 7 Comparison-adjusted funnel plot for each outcome from the network meta-analysis



eFigure 6a. Comparison-adjusted funnel plot for First peak KAM.

A= Standard care; B= Lateral Wedge Insole; C= Knee Brace; D= Lateral Wedge Insole+ Knee Brace; E= Gait retraining; F= Quadriceps strengthening; G= Variable-stiffness shoe; H= Hip strengthening; I= Lower limb exercise; J= Neuromuscular exercise.



eFigure 6b. Comparison-adjusted funnel plot for KAAI.

A= Standard care; B= Lateral Wedge Insole; C= Knee Brace; E= Gait retraining; F= Quadriceps strengthening; H= Hip strengthening; I= Lower limb exercise; J= Neuromuscular exercise.

PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction, paragraph 1-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction, paragraph 5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	METHODS, paragraph1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	METHODS, Identification and selection of studies
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	METHODS, Identification and selection of studies, paragraph 1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1 Search strategies
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Results, figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	METHODS, Identification

PRISMA 2009 Checklist

			and selection of studies, paragraph 2
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	METHODS, Identification and selection of studies, paragraph 2, 3 & Data Collection and Quality assessment
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	METHODS, Assessment of characteristics of studies & Results, Figure 4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	METHODS, Statistical analysis
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	METHODS, Statistical analysis

Section/Topic	#	Checklist Item	Reported on Page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	METHODS, Assessment of characteristics of studies
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	METHODS, Statistical

PRISMA 2009 Checklist

			Analysis
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Results, Characteristics of included studies & Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Results, Characteristics of included studies & Table 1, 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Results, Risk of bias & Figure 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Results, KAM & KAAI & Appendix 4
Synthesis of results	21	Present the main results of the review. If meta-analyses done, include for each, confidence intervals and measures of consistency.	Results, KAM & KAAI (Table 3 & Figure 2, 3)
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Results, Risk of bias & Appendix 6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Appendix 2 & 3 & 7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion, paragraph 1 & Conclusion

PRISMA 2009 Checklist

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion, paragraph 4
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Conclusion & Discussion, paragraph 8 & 9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Funding

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

List of Responses

Dear Editors and Reviewer:

Thank you very much for your kind advice and valuable comments in helping us improve our manuscript. We have substantially modified the manuscript, according to the questions raised by the Editor and Reviewers. All the modified words, sentences and paragraphs were labeled with red fonts. A point-to-point response to highlight how we have addressed each of the comments is listed below.

Comments and Suggestions for Authors：

-Please remove the "significance and Innovations' section, and replace it with a 'Strengths and limitations' section (after the abstract). This section should contain up to five short bullet points, no longer than one sentence each, that relate specifically to the methods. The results of the study should not be summarised here.

-Please remove any references to your INPLASY registration from your manuscript.

Response 1: Thank you for your thoughtful suggestion. We re-written this part as required. (Line 70-80, 95-105).

Reviewer: 1

Dr. Erin Macri, Erasmus MC, The University of British Columbia

Comments to the Author:

This study is a systematic review and network meta-analysis comparing the efficacy of physical therapy and orthopaedic equipment on KAM and KAII in individuals with predominantly medial tibiofemoral joint osteoarthritis. The research question is clinically relevant given that biomechanics are believed to be a key cause of OA and OA-related symptoms.

Overall, the analysis appears to be sound but the interpretation needs more clinical perspective and the writing is difficult to follow in some sections. Below I provide some suggestions that I hope the authors will find useful.

Abstract.

Please reword the research question for grammar and accuracy. Instead of efficiency, I think the authors mean efficacy. Please be specific with which biomechanical risk factors (i.e. only KAM and KAII). Also, I believe the authors have only included studies of tibiofemoral joint osteoarthritis, so they may wish to consider being more specific. These changes should be done throughout the text.

Response 2: Yes, your opinion is very rigorous. We carefully considered the wording according to the purpose of the article and revised them to be more specific. (Line 1, 66-68, 92, 139, 147-148, 169, 181-182, 183, 187, 353, 366-367, 457)

Line 81 - please clarify that variable stiffness shoes made the KAM worse (lower rate of KAM reduction is misleading).

Response 3: The statements have been corrected. We will be happy to edit the text further, based on helpful comments from the reviewers.

Methods (e.g. Bayesion NMA) are provided in the conclusion section instead of Methods section. Please report results and conclusions in a way that balances statistical significance and clinical relevance. Further comments regarding this are provided below.

Introduction.

In general the Introduction wanders around the topic but needs more focus to guide the reader to the research question. More original references are required to justify some of the comments. For example, first sentence 3.8% OA prevalence - where did this number come from? What evidence has shown that obesity is associated with frontal plane knee alignment? What specific other risk factors have evidence showing that they are associated with knee alignment?

Response 4: We agree, we have deleted some redundant sentences in this part to make it read closer to the core of this article. At the same time, we also added more original references as evidence. (Line 109-110, 125-127)

Please provide a rationale why the authors think that exercises might alter knee alignment. Please also be sure to introduce the concept of physical therapy into the introduction, and again provide a rationale as to why the authors think that modalities such as ultrasound and so forth might affect biomechanics? Provide references to justify this. If such a rationale does not exist, then consider limiting this study to gait retraining and orthopaedic devices which have a rationale and evidence to support a link to biomechanics.

Response 5: We thank the reviewer for the suggestion. Previous studies have shown that a lower knee joint loading rate in patients with stronger quadriceps and hamstring. And the strengthening of related lower limb muscles may play a vital role in disease progression [4] (Line 147-150). Although the effects of gait retraining and orthopedic devices on biomechanics are more direct than the effects of modalities such as ultrasound and Taiji, some studies have shown that the joint pain can affect the kinetics and kinematics of walking [2]. These modalities such as ultrasound and Taiji had a certain effect on pain relief [5], so we didn't want to miss any treatment which can affect biomechanics when we set the topic. Besides, we introduce the concept of physical therapy and orthopedic equipment into the introduction (Line 141-145).

Avoid the term 'non-surgical' since this is not accurate for this paper. Non-surgical treatments would also include medications, injections and other treatments not included under physical therapy and orthopaedic devices. Please be specific.

Response 6: We replaced this word with "physical treatments and orthopedic equipment".

Please reword research questions so that they are grammatically correct and accurate and specific to the present study.

Response 7: We apologize for our carelessness. Thank you for your thoughtful suggestion. We have corrected it. (Line 172-174)

Methods

Line 180 and 187: Please clarify if the eligible studies were in English language only or not and be consistent here.

Response 8: We apologize for our carelessness. We normalized the language to make it clear that the eligible studies were in English language only (Line 184, 190).

Clarify if eligible studies were limited to tibiofemoral OA only. There don't appear to be any studies on patellofemoral OA included in this study.

Response 9: We thank this reviewer for pointing out this critical point. The eligible studies were indeed limited to tibiofemoral OA only. We changed this section in the method and abstract.

Line 189. Placebo, no intervention, and sham are not standard care and should therefore not be labelled as such. Box 1 is worded in a way that suggests that actual standard care was not included. Please reword and clarify.

Response 10: We thank the reviewer for pointing out this issue. In fact, we named standard care as a summative name for a variety of control interventions with high homogeneity such as placebo, no intervention, sham, standard / conventional care or waiting list control (analytical advice and education). We also considered whether this word fully fit each treatment it contains. Although these treatments were roughly the same, there were still some differences. Using standard care to summarize these treatments may not completely and accurately describe each included intervention, but we consider that it is a more appropriate description and a more understandable description. At the same time, we also replaced the description in box 1 with a more comprehensive description.

Line 199. “non-trail papers” – do the authors mean papers that were not peer-reviewed? Please clarify.

Response 11: We replaced this word with " non-experimental".

Line 201. What constitutes “studies that did not report suitable data”. Please be concrete about what this means.

Response 12: The “studies that did not report suitable data” corresponds to “studies that did not report KAM or KAAI” (this is now clarified in the text) (Line 205).

Line 214. Please justify why Cochrane ROB version 1 was used, or consider updating to use the current ROB version 2 which is currently recommended by Cochrane.

Response 13: We agree, and we have used ROB version 2 to replace the previous version.

Line 229. Please be specific about the conditions and time of assessments of the outcomes. Some RCTs only measure biomechanics as immediate effects with and without the knee brace on, for example, and they do so prior to the actual clinical trial. For all studies in which devices were worn (braces, insoles, etc), be sure to report whether the outcomes were measured before or after treatment, and whether the device was worn or not at the time of evaluation.

Response 14: We apologize for our carelessness. We have already described the conditions and time of assessments of the outcomes in more detail. “ Baseline biomechanical risk factors were extracted from walking test without any orthopedic equipment before intervention, and biomechanical risk factors after intervention were extracted from walking test with orthopedic equipment.” (Line 236-238).

Statistical analyses.

Please include references for all statistical tests and methods employed.

Response 15: Revised.

Line 247. What methods were employed to evaluate the source of heterogeneity? Also, remember to report in the results with a result was based on FE or RE, and the results of these additional analyses to evaluate source of heterogeneity.

Response 16: We used a random-effects model for meta-analysis, and a sensitivity analysis to evaluate the source of heterogeneity (this is now added in the text). (Line 254-259). At the same time, we added heterogeneity evaluation to the results (Line 328-332).

Figure 1. Using the PRISMA guidelines, it is not required to report reasons for exclusion at the title/abstract screen. Please update Figure 1 to adhere to PRISMA guidelines.

Response 17: We agree with the reviewer’s assessment and have implemented their suggestion.

Results.

For orthopaedic interventions, please remember to discuss whether biomechanical effects were preand post-intervention, or if they were done at a single time point with orthopaedic device off and then on.

Response 18: We have added a detailed description of this (Line 236-238).

Section 3.3 KAM, 3.4 KAII

Please rewrite this section to provide a narrative synthesis/summary of the results in a way that is understandable to the reader. Effect sizes do not need to be repeated in the text since they are already in Table 3, so use this space to help the reader understand the results. Please make sure to emphasize that despite the rankings at the end of each section, they are not significant and therefore not clinically relevant. For any results that are statistically significant, be sure to also consider their clinical interpretation – are any of the results clinically important?

Response 19: We have made correction according to the Reviewer's comments. We have re-written the result section to help readers understand the final clinically significance of our study. At the same time, we have increased the clinical interpretation of the results (Line 403-411).

Line 307. This sentence should be removed regarding stair ambulation. Stairs was not included in the eligibility criteria of this analysis.

Response 20: We are very sorry for the misunderstanding of our previous description. This article met our eligibility criteria. However, considering that its inclusion in meta-analysis will lead to excessive heterogeneity, we excluded it from the network meta-analysis. Our intention is that the biomechanical indicators of the studies included in the Bayesian network meta-analysis were measured on flat ground or treadmills. Other studies that cannot be included in the network meta-analysis were included in the systematic review. We have corrected this imprecise sentence (Line 208-209).

Risk of Bias.

Figure 4 seems to be missing – the only Figure 4 I can see if the funnel plot, not the ROB table. ROB is not the same thing as quality. Be sure to use accurate and consistent language.

Response 21: We apologize for our carelessness. We uploaded the Figure 4 according to ROB 2.0. At the same time, we have refined the language (Line 341-342).

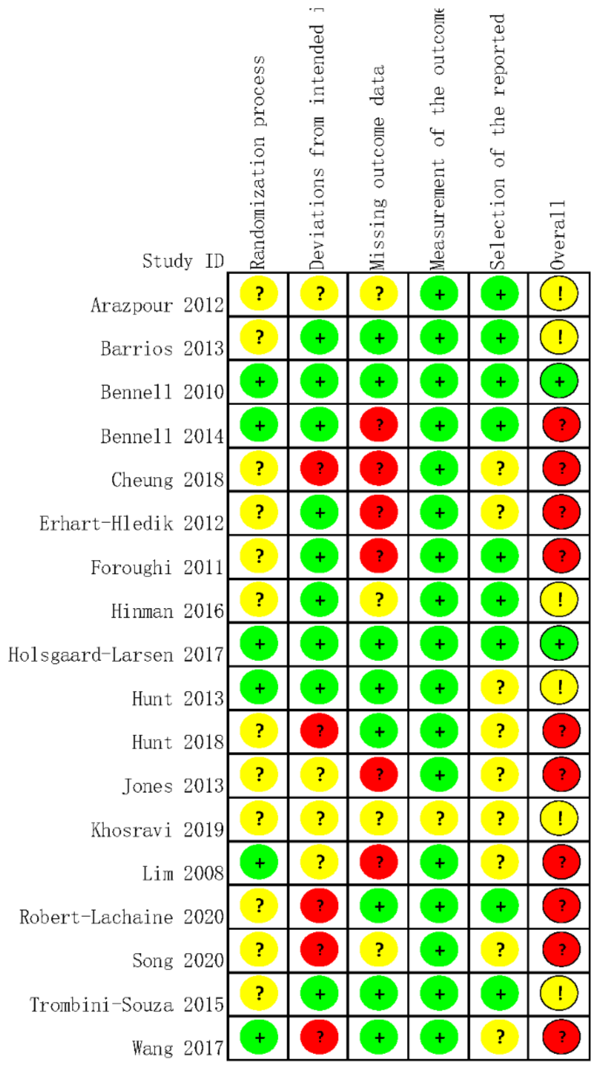


Figure 4

Be sure to include the GRADE results in the Results section.

Response 22: We have added the grade section (Line 333-339).

Discussion.

The authors have used up more than 2 pages of writing to discuss “strengths and limitations”. This should be reduced to 1 paragraph maximum, and should focus on limitations more so than strengths. Much of this writing could be moved to the methods section to justify choices of methods.

Response 23: Yes, your opinion is very rigorous. We carefully deleted some sentences according to the purpose of the article and revised them to be more specific.

Line 369. “there was no study that reported the immediate effect” – what about Wang 2017? Table reports these were immediate effects.

Response 24: We thank the reviewer for pointing out this issue. Our intention was that immediate effect were not included in this network meta-analysis. We have deleted this sentence to avoid ambiguity.

Line 375. Sensitivity analyses should be reported in the methods and results section, no in the Discussion section.

Response 25: We have moved this section to the results section (Line 329-332).

Please include some discussion as to whether the condition of device wear during biomechanics testing might influence the results. Do the authors think that LWI and braces only work if they are donned, or would a period of wear result in changes to biomechanics even after the devices are removed?

Response 26: We have added this part to the discussion (Line 394-396, 403-411). The results of current study showed that there is no statistically significant reduction in biomechanics after taking off the LWI after one year of treatment, which is contrary to the results of donning it[1]. Therefore, as the reviewer said, we believe that once the LWI and braces are removed, they do not work anymore. This is the reason that we recommend gait training - it not only has better long-term effect, but also is more comfortable than wearing equipment for OA patients who need a long-term therapy.

Line 424. Mazzoli references is Maleki.

Response 27: We apologize for our carelessness, and we have corrected it.

Line 430. Please justify why the authors think that Taiji, ultrasound and acoustic exercises might alter biomechanics. Are these studies really necessary?

Response 28: As mentioned earlier, we still believe that Taiji and ultrasound have some effects on pain relief and muscle strength, which can affect the kinetics and kinematics of walking. So we didn't want to miss any treatment that can affect biomechanics when we set the topic.

Variable-stiffness shoes appear to make KAM worse. Would the authors recommend against use of these as a treatment for OA? Is there other evidence showing efficacy for other outcomes like pain or OA structural features that might still support the use of this intervention?

Response 29: It is really true as Reviewer suggested that variable-stiffness shoes may make KAM worse. We have expressed our attitude of recommending against use of these in the discussion and conclusion. As Reviewer suggested that we have added other evidence which still support the use of this intervention (Line 432-437). Although the results of this study suggested that wearing variable-stiffness shoes is not a good choice for long-term reduction of KAM, current study have pointed out that variable-stiffness shoe will have greater benefits in reducing KAM for patients with increasing walking speed. At the same time, variable-stiffness shoes had relatively weaker discomfort than equipment such as LWI[3]. Perhaps with the increase of the number of participants and the gradual rigor of the study process, the results of variable-stiffness shoes may be completely different in the future.

Conclusion. Please provide concrete conclusions. "The best" therapy according to NMA ranking does not necessarily mean effective. Integrate statistical significant, clinical importance of effect size, and rankings and provide the reader with concrete recommendations.

Response 30: We have re-written this part according to the Reviewer's suggestion (Line 458-462).

Thank you for the opportunity to review this work.

Special thanks to you for your good comments.

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Physical Therapy and Orthopedic Equipment-induced Reduction in the Biomechanical Risk Factors Related to Knee Osteoarthritis: A systematic review and Bayesian network meta-analysis of randomized controlled trials

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Manuscripts

Title: Physical Therapy and Orthopedic Equipment-induced Reduction in the Biomechanical Risk Factors Related to Knee Osteoarthritis: A systematic review and Bayesian network meta-analysis of randomized controlled trials

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ABSTRACT

Objective: Are physical therapy or orthopedic equipment efficacious in reducing the biomechanical risk factors in people with tibiofemoral OA? Is there a better therapeutic intervention than others to improve these outcomes?

Design: Systematic review with network meta-analysis of randomized trials.

Data sources: PubMed, Web of Science, Cochrane Library, Embase, and MEDLINE were searched through January 2021.

Eligibility criteria for selecting studies: We included randomized controlled trials exploring the benefits of using physical therapy or orthopedic equipment in reducing the biomechanical risk factors which included KAM and KAAI in individuals with tibiofemoral OA.

Data extraction and synthesis: Two authors extracted data independently and assessed risk of bias. We conducted a network meta-analysis to compare multiple interventions, including both direct and indirect evidences. Heterogeneity was assessed (sensitivity analysis) and quantified (I^2 statistic). GRADE assessed the certainty of the evidence.

Results: Eighteen randomized controlled trials, including 944 participants, met the inclusion criteria, of which 14 trials could be included in the NMA. Based on the collective probability of being the overall best therapy for reducing the first peak KAM, lateral wedge insoles (LWI) plus knee brace was closely followed by gait retraining, and knee brace only. Although no significant difference was observed among the eight interventions, variable-stiffness shoes and neuromuscular exercise exhibited an increase in the first peak KAM compared to the control condition group. And based on

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the collective probability of being the overall best therapy for reducing KAAI, gait retraining was followed by LWI only, and lower limb exercise.

Conclusion: The results of our study support the use of LWI plus knee brace for reducing the first peak KAM. Gait retraining did not rank highest but it influenced both KAM and KAAI and therefore it was the most recommended therapy for reducing the biomechanical risk factors.

Strengths and limitations

① The Bayesian method provided the probability estimates regarding the relative efficacy of specific interventions, even though standard methods found no significant differences among them.

② Physical therapies and orthopedic equipment are complex interventions with a small number of trials comparing the different types of interventions.

③ Besides KAM and KAAI, we were unable to include other biomechanical risk factors, such as the external knee flexion moment to joint load, because the number of these studies was not enough to form a complete NMA.

④ Heterogeneity in NMA may reduce the validity of the results.

1. INTRODUCTION

Knee osteoarthritis (KOA), an chronic progressive disease, affects approximately 3.8% of people worldwide and frequently occurs in the middle-aged and the elderly population.[1] The main clinical manifestation of KOA is knee pain and is often

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accompanied by radiographic degeneration of the intra-articular cartilage associated with hypertrophic bone changes.[2] Furthermore, the KOA development often leads to knee stiffness, joint locking, and instability, along with functional loss. Though it is not fatal, the persistent pain and movement restrictions associated with this condition negatively impact the physical and mental health of the patients, thus, reducing their quality of life.[3]

These pathological changes in knee joints are a cumulative result of various biomechanical imbalances leading to the progression of the disease and are now believed to be associated with malalignment of the lower limb.[4] Tibiofemoral OA most commonly occurs in the medial compartment, since several studies have stated that patellofemoral compartment is as prevalent as medial tibiofemoral joint.[5,6] The external knee adduction moment (KAM) results from the unequal distribution of the transmitted load on both sides in the normal gait of humans. It is defined as the cross product of the ground reaction force and the distance between the knee joint and the force line.[7] Individuals with obesity,[8] meniscal lesions,[9] occupational loads,[10] or other associated risk factors tend to have a frontal plane knee malalignment, which alters the normal force line and forces the medial knee joint to bear more load and thus, leads to increased KAM.[11,12] The accumulation effect of the moment is determined by calculating the integral of the moment to time, which is also called knee adduction angular impulse (KAAI). It reflects the change in knee joint rotation state during a stance period of gait.[13] Previous studies have revealed a strong correlation between the peak levels of KAM and KAAI and the

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severity and progression of the disease, which was reflected and calculated by the loss of medial tibial cartilage.[14,15] Both these biomechanical parameters (KAM and KAAI) are commonly utilized to evaluate the medial knee load and predict the long-term structural deterioration of the knee.

Recent advancements in healthcare have resulted in the development of several protocols for the intervention and treatment of KOA. KOA patients are primarily recommended physical therapy or orthopedic equipment with the intention of correcting the deviated force line and delaying the progressive pathological damage inside the knee joint.[7] Some other modalities, such as ultrasound and Taiji programs, primarily focus on relieving the pain, and therefore, this might improve the biomechanical state of the knee joint.[16,17] The physical therapy mainly includes muscular strengthening, exercise therapy, electric stimulation therapy, extracorporeal shockwave therapy and gait modification, while orthopedic equipment mainly incorporates customized shoes/footwear, wedged insoles, and knee braces.

Several literary insights have shown the positive impact of physical therapy or orthopedic equipment in KOA patients.[13,18,19] The strengthening of related lower limb muscles, which play a vital role in disease progression, are known to reduce instability and abnormal stresses across the joint.[20,21] Another study displayed a lower knee joint loading rate in patients with stronger quadriceps and hamstrings.[22] Additionally, gait training presents a viable way for correcting the patients' underlying gait pattern, thus, further reducing their knee load and pain.[23,24]

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Furthermore, various kinds of orthotic devices have been introduced for the treatment of KOA. The clinical use of lateral wedge insoles (LWI) has gained immense popularity since its origin in 1987.[25,26] The insoles tends to shift the lateral part of the foot more than the medial part by a slope that increases the valgus tendency of lower extremities. The center of the ground reaction force is shifted laterally, which induces a reduction in force lever arm length and magnitude.[27] Also, the valgus knee brace is a commonly used device. It applies an external valgus force around the knee joint to reduce the medial knee load.

In the past, several systematic reviews and meta-analyses have been published featuring the medical effects of a single KOA treatment. However, only a few of them have focused on multifaceted interventions. Also, only a few reviews have reported the effects on biomechanical parameters. The mechanical changes in the body were not sufficiently investigated. Current reviews on KAM and KAAI have also not compared these changes. Thus, a network meta-analysis (NMA) was performed to appraise the benefits of physical treatments or orthopedic equipment in reducing biomechanical risk factors in KOA patients.

Therefore, the research questions for this systematic review were:

1. Are physical therapies or orthopedic equipment efficacious in reducing the biomechanical risk factors in people with KOA?
2. Is there a better therapeutic intervention than others to improve these outcomes?

2. METHODS

All pooled analyses were derived from previous studies and, therefore, did not

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require ethical approval and informed consent.

2.1 Identification and selection of studies.

The following databases were searched for listed randomized controlled trials that were published before January 2021: PubMed, Web of Science, Cochrane Library, Embase, and MEDLINE. These studies explored the benefits of using physical therapy or orthopedic equipment in reducing the biomechanical risk factors including KAM and KAAI in patients with tibiofemoral OA. The search was not restricted by date, publication type, or status (see Appendix 1). Additionally, we performed manual analyses of the published references regarding the use of physical therapy or orthopedic equipment for treating KOA.

The eligibility of searched publications was independently reviewed by HXM and YZX following the Cochrane manual directives.[28] Any additional inconsistencies were resolved either by deliberation or by a senior expert (HY). Firstly, the study titles and abstracts, published in English literature, were screened. Next, the complete articles were reviewed against the directed criteria described in box 1.

Eligible comparison subjects, including standard/conventional care or waiting list control (analgesic advice and education), were defined as "control condition." Control condition also included placebo intervention, no intervention, and sham-exercise. This NMA defined lower limb exercise as the simultaneous exercise of multiple muscle groups that included hip abductors, quadriceps, and hamstrings. Since our research needed to maintain clinical and statistical homogeneity and focus on the residual biomechanical effects after the intervention, only those articles were

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selected whose measurements were strictly obtained under the condition of going barefoot.

The exclusion criteria included: (1) studies that were not consistent with the eligibility criteria; (2) experimental peer-reviewed studies; (3) studies that included participants who had received surgical treatment in the past; (4) studies that did not report KAM or KAAI.

2.2 Data Collection and Quality assessment.

KAM and KAAI were the preferred biomechanical measures used in this meta-analysis. The biomechanical outcomes of the studies included in the Bayesian network meta-analysis were measured on flat ground or treadmills. Additionally, the number of trials focusing on the second peak of KAM was insufficient to conduct an independent NMA.

The data were extracted independently by two authors (HXM, YZX) and were cross-checked. A predefined information sheet was used for data extraction, which included the details of the first author (name), country, the year of publication, population characteristics, intervention, and the time points. The authors of the original study were contacted in the cases requiring more data.

2.3 Assessment of characteristics of studies.

Risk of bias

This NMA utilized the Cochrane Risk of Bias 2 (RoB2) to assess the risk of bias in randomized controlled trials using the following evaluation indicators: randomization process, deviations from the intended interventions, missing

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outcome data, outcome measurement, and selection of the reported results.[21] The judgment of the bias risk of this item was presented as "low," "high," and "some concerns." Two authors independently evaluated the risk of bias in all the included studies. The authors discussed or referred to the opinion of a senior author to resolve any disagreements. Additionally, the certainty of evidence the evidence was also evaluated, which contributed to network estimates of the main outcomes with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.[29]

Intervention

In order to describe the experimental interventions, the following information was extracted: the training method with further relevant details, the details and characteristics of orthopedic equipment, and the frequency as well as the total duration of training or wearing.

Outcome measures

Baseline biomechanical risk factors were extracted from the walking trials without any orthopedic equipment before the intervention, while post-intervention biomechanical risk factors were extracted from walking trials that incorporated orthopedic equipment. Biomechanical risk factors included in the study were the first peak KAM, the second peak KAM and KAAI. KAM was normalized as %body weight times height, with conversion to Nm/kg wherever necessary. KAAI was designated as the moment accumulation rate, which was determined by calculating the integral of the moment to time.

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2.4 Statistical Analysis.

A network meta-analysis was carried out for comparing multiple interventions, including both direct (direct comparison of treatment modalities) and indirect evidence (indirect comparison of various treatments with a common control), maintaining randomization in each independent study.[30-32] Interventions, as well as different demographic characteristics were either consistent or comparable in all included studies,[30,33-37] while those studies were excluded that reported immediate treatment effects.

Due to different units, the continuous data used the standard mean difference (SMD) as the statistical indicator of the effect, and the Frequentist 95% confidence interval (CI) of each effect was calculated. Additionally, the I^2 statistic was utilized to analyze the overall heterogeneity of the two-arm study and the network. The fixed-effect model was suggested to be used in cases of the absence of statistical heterogeneity($p > 0.05$, $I^2 < 50\%$); however, given the heterogeneity among the studies, a random-effects model for meta-analysis was used.[38] A sensitivity analysis (see Appendix 2, eFigure 1 and 2) was conducted by omitting one study and investigating the influence of the single study on the overall pooled estimate to evaluate the source of heterogeneity. The node-split model was used for evaluating the testing consistency (see Appendix 3, eFigure 3). If $p > 0.05$, then the consistency model was used for analysis; otherwise, the inconsistency model was utilized.[39] Normal likelihood distributions were assumed, non-informative prior distributions were set, and three Markov chains were run simultaneously. Since the number of

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update iterations was 50,000, a total of 5000 simulations were used for annealing, and the subsequent 45,000 iterations were examined. The mean rank and surface under the cumulative ranking curve (SUCRA) were used for reporting the probability values. A SUCRA value of 100% was considered best, whereas 0% indicated the worst treatment.[40] Besides, a conventional meta-analysis was also carried out (see Appendix 4, eFigure 4a, b, and c). Comparison-adjusted funnel plots were prepared that represented different comparisons with different colors.

The data from the eligible studies were combined using the Review Manager (RevMan) software v5.3. The contribution of the effect sizes was dependent on the sample size and their estimation accuracy. The Bayesian analyses were carried out using WinBUGs v1.4.3. Stata (StataCorp. 2015. Stata Statistical Software: Release 15. College Station, TX: StataCorp LP) was employed to conduct the frequentist NMA.

2.5 Patient and Public Involvement.

No patients were directly involved in the development of the study question, selection of the outcome measures, design and implementation of the study, or explanation of the results.

3. RESULTS

3.1 Flow of studies through the review

A comprehensive investigation of databases retrieved 4919 citations. After screening articles by title and abstract, and deleting duplicate articles, we identified 526 studies that might meet the criteria for inclusion, and then we searched and

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evaluated their full text. Figure 1 presents the study selection flow chart. Eighteen randomized controlled trials, including 944 participants, met the inclusion criteria.[23,41-57] Since the present NMA only considered trials comparing the nine treatments with control condition or each other (see Appendix 5, eFigure 5a and b), only fourteen trials (792 participants) were included. Furthermore, four trials were excluded from the NMA considering their excessive heterogeneity and inability to form NMA with other studies.[54-57]

3.2 Characteristics of included studies

All studies included tibiofemoral OA cases, which were radiologically confirmed. Although most interventions were administered over an 8–13week period, the treatment duration ranged from 2 weeks to 12 months. The number of exercises varied from 2-5 times per week, depending on the initial preparation.[43,44,46,49] Both gait training studies used the faded feedback paradigm, which meant gradual removal of the real-time biofeedback.[23,48] As NMA included fourteen studies, nine were classified as Kellgren/Lawrence grade 2 and above. All studies reported either the values for BMI or height and weight, while the studies recruiting a general population classified the mean BMI as overweight or obese. Additionally, one NMA study had a randomized crossover design.[50] After consulting a reference manual along with a professional statistician, the mean and standard deviation of the experimental and the control groups were analyzed in this network meta-analysis.[28] Tables 1 and 2 summarize the characteristics of the included studies and their participants.

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3.3 KAM.

According to the collective probability of being the overall best therapy for reducing the first peak KAM, LWI plus knee brace (93.4%) was closely followed by gait retraining (85.7%), and knee brace only (79.3%) (Figure 2). A study reported that the VER-brace offers additional advantages on first peak KAM compared to V3P-brace and ACL-brace.[54] No first peak KAM reduction was observed between proprioceptive neuromuscular facilitation group and controls,[55] and the result of the study of minimal footwear was the same.[56] On the other hand, after the electroacupuncture treatment, compared with the control group, the second peak KAM significantly increased immediately when the patient ascended stairs.[57] Table 3 shows the NMA results of a comparative analysis of the reduction of the first peak KAM. We found no differences in most of the treatment modalities; however, variable-stiffness shoes showed a statistically significant increase in the first peak KAM over the rest of the included interventions. Neuromuscular exercise was better than variable-stiffness shoes, but was still inferior to most other interventions. At the same time, lateral wedge insole plus knee brace and gait retraining performed relatively well in reducing the first peak KAM compared with control condition and other treatments.

3.4 KAAI.

Based on the collective probability of being the overall best therapy for reducing KAAI, gait retraining (90.7%) was followed by LWI only (74.1%), and lower limb exercise (53.8%) (Figure 3). KAAI was reported in ten studies.[42-44,47-50,53,54,56] After

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wearing the three kinds of brace separately, the KAAI measured without brace did not decrease significantly, and there was no significant difference between the groups.[54] Table 3 shows the NMA results of the reduction of KAAI. Most treatments were not statistically different from each other, consistent with the results of the first peak KAM. Only gait retraining had a statistical reduction compared with control condition. The aggregated results suggested that gait retraining is efficacious in reducing the KAAI, while neuromuscular exercise increased the KAAI compared with gait retraining and knee brace.

3.5 Heterogeneity.

We removed a study which had a short follow-up time and might cause heterogeneity,[50] and performed another network meta-analysis. There was no difference between the results of the reanalysis and the current ranking (see Appendix 2, eFigure 1 and 2).

3.6 GRADE assessment

According to the GRADE framework (see Appendix 6), the quality of most comparisons was assessed as low or very low. Only neuromuscular exercise compared with control condition, neuromuscular exercise compared with LWI, neuromuscular exercise compared with knee brace, and neuromuscular exercise compared with LWI plus knee brace were evaluated as a moderate-grade comparison.

3.7 Risk of bias.

Figure 4 depicts a summary of the risk-of-bias scores for the included RCTs in this

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analysis. Nine studies presented a clear description of generating a randomization sequence.[43-47,49,52,56,57] The study by Hinman et al. was the only double-blinded study, while other studies were either single-blinded or did not clearly describe their blind design. All trials provided follow-up data on their outcomes. Six studies did not report the patient number or the reason for lost visits due to the length of follow-up.[23,44-46,50,52] All studies were included in the synthesis evaluation. The comparison-adjusted funnel plots were symmetrically distributed based on a visual inspection, which suggested the absence of small-sample effects for our study outcomes (see Appendix 7, eFigure 6a and 6b).

4. DISCUSSION

Our study results did not show any significant difference regarding the relative efficacy of intervention among different types of physical therapies or orthopedic equipment. This lack of difference might be attributed to the fact that the number of studies for several pairwise comparisons was small. However, some of these therapies were still worth recommending. Due to a small number of studies studying the outcome of the KAAI, we found gait retraining to be the relatively more convincing intervention as it could simultaneously reduce the values for KAM and KAAI values based on cumulative ranking and relative effect estimates. Due to the lack of significant differences among the interventions, the cumulative ranking obtained by the network meta-analysis could not be conclusively accepted. For example, gait retraining, which was employed as the foremost intervention (90.7%) for KAAI reduction, was only superior to the neuromuscular exercise interventions.

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This study had several strengths and limitations. This NMA is the first report on the effects of physical therapy or orthopedic equipment on the parameters of knee load (KAM, KAAI). Since physical therapies and orthopedic equipment are complex interventions with a small number of trials comparing the different types of interventions, network meta-analysis was deemed as the most relevant form of analysis. The results of this meta-analysis could be more useful for the decision-makers and primary service providers for choosing wisely among the various available options, as compared to the multiple separate pairwise meta-analyses.[58] Additionally, this NMA conducted each comparison distinctly with both direct and indirect statistical effects, deriving statistical power from all included data.[58] Also, the Bayesian method provided the probability estimates regarding the relative efficacy of specific interventions, even though the standard methods described the absence of a significant difference between them. Furthermore, alternative rankings (second, third best, etc.) were calculated to provide overall feasibility due to unavailability of the best-suited interventions, more expensive therapies, or contraindications in some cases. As with most meta-analyses based on non-surgical therapies for osteoarthritis, one of the limitations of this NMA was the inclusion of trials that had variable periods of follow-up, which might have introduced heterogeneity into the study analyses. The Cochrane handbook recommends several methods for analyzing and comparing trials with multiple durations of follow-up, as recommended by the Cochrane handbook, such as performing individual patient data meta-analysis and a precise evaluation at a particular time point. However,

396 newer approaches are now being developed that would include all the time points
397 in a NMA.[28] Our study was unable to evaluate the influence of population
398 characteristics (such as mean age, the severity of osteoarthritis), as the number of
399 the included studies was not large enough.[59-61] Additionally, other parameters, such
400 as the external knee flexion moment to joint load, should have been studied in detail.
401 However, due to lesser available literature, our study was unable to include them.
402 Finally, standard/conventional care, placebo intervention, no intervention, sham-
403 exercise, analgesic advice and education were all considered as the same parameter
404 in defining the 'control condition'. Therefore, the relative rankings in our study
405 might not represent the true factual rankings as compared to actual standard care
406 due to lack of consideration of bias introduced by heterogeneity and lack of blinding.
407 A previous review reported that LWIs were able to reduce the KAM at the
408 baseline;[13] however, the effect was no longer observed after a specific period.
409 Another study displayed that a month wear-in period was the longest study time in
410 which no reduction in biochemical risk factors was observed despite continued
411 wear.[18] Besides, several other systematic reviews stated that exercise and gait
412 retraining could further reduce pain and improve motor functioning in people with
413 KOA.[62-64] There is a high probability that any clinical changes occurring in previous
414 studies might be due to increased physical activity levels, and not owing to the
415 altered loading environment within the knee joint. Furthermore, another study
416 revealed that an increase in the amount of reduction in peak KAM in LWIs plus
417 knee brace group was observed after four weeks.[65] In our NMA, we focused on the

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418 studies of non-immediate effect, removed the research with a follow-up time of less
419 than one month in the sensitivity analysis, and made the final rank. Our results
420 showed that only gait training produces a significant reduction in KAM and KAAI
421 when compared with control condition, indicating that the biomechanical reduction
422 effect of orthopedic equipment cannot be maintained for a long time when they are
423 donned. It was evident that an extension of the treatment time led to a decrease in
424 the biomechanical reduction effect, which might be due to the gradual deformation
425 of the orthopedic equipment that renders them ineffective, despite being made from
426 high-density materials.

427 On the other hand, various physical therapies and orthopedic equipment also should
428 be considered for relieving patients' pain, which has been the focus of several past
429 reviews. As an important gait parameter, the joint pain can affect the kinetics and
430 kinematics of walking.[19] A meta-analysis reported that exercise therapy had a
431 positive impact on knee pain and kinematic function, though this relief of pain
432 subsided with time. After proper initiation, the efficiency of physical exercise over
433 placebo reached a maximum level at two months.[66]

434 Cumulative loading is another significant parameter regarding knee load exposure
435 in OA.[67] KAAI has been proposed as another indicator for evaluating the duration
436 and intensity of KOA load, despite the association between KAM and disease
437 progression. According to a study lasting for a year, the loss of medial tibiofemoral
438 cartilage was not directly linked to KAM but was promptly related to KAAI.[14]
439 Although the effect of physical therapy or orthopedic equipment on KAM are short-

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lived, it might have a huge cumulative effect on the knee during the early stages of treatment and should be considered while interpreting our NMA results.

Our study results are both scientifically and clinically instructive. Despite a majority of therapies displaying a null statistical KAM and KAAI reduction, the clinical usage of these treatment modalities could significantly improve the presenting symptoms and physical activity level without increasing the biomechanical magnitude; thus, improving the quality of life of patients with KOA. Although the results of this study suggested that wearing variable-stiffness shoes is not preferable for long-term KAM reduction, our current study explained that variable-stiffness shoes displayed a major advantage in reducing KAM for patients with increasing walking speed.[68] At the same time, variable-stiffness shoes had relatively less discomfort than equipment such as LWI. Since the studies included in this network meta-analysis mainly involves patients with medial KOA, the consolidated results would be more useful for such patients.

On the other hand, a previous study reported that an increase in KAAI can explain the significant variation in the uCTX-II levels as well as the uCTX-II:sCPII ratio in medial tibiofemoral KOA patients after controlling additional variables.[49] It was evident that appropriate intervention in the biomechanical structure of the knee joint in KOA patients exert a potential beneficial role on cartilage structure. Maleki et al. reported that adopting a modified gait for reducing the KAM can decrease the pain in the medial compartment in KOA more than walking alone,[69] which suggests that the KAM and KAAI of patients undergoing non-surgical approaches could be

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462 restricted to reduce pain and improve the joint function. More research is further needed to promptly illustrate the impact of changes in knee biomechanics on the prognosis of such patients.

465 Additionally, some other therapies have also been reported, such as Taiji, ultrasound, acoustic exercises, etc. However, due to the lack of RCT study design or the report of their biomechanical outcomes, these therapies were not included in our review. Therefore, further studies would require more research articles in these areas for exploring the impact of various non-surgical therapies on OA patients. After accumulating evidence regarding the role of non-surgical therapy in KOA, another similar network meta-analysis to understand the relative effectiveness of various treatment in the relevant patients.

5. Conclusion

To conclude, this network meta-analysis provides valuable insights regarding the KAM and KAAI alterations in OA patients after the usage of physical therapy or orthopedic equipment. After integrating cumulative ranking and relative effect estimates, LWI plus knee brace was the highest-ranking intervention despite an absence of statistical significance. Although gait retraining did not score a higher rank, it remarkably influenced both KAM and KAAI values and, therefore, was the most recommended therapy for reducing the biomechanical risk factors. On the contrary, variable-stiffness shoe and neuromuscular exercise should be used with caution in clinical practice. Taken together, these findings suggest that clinicians should carefully consider all appropriate treatment modalities when treating OA

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patients.

6. Authors' Contributions

HXM and YFZ conceived of the study, and participated in its design and coordination and helped to draft the manuscript; YZX, HY and CRY contributed significantly to analysis and manuscript preparation; YJK and LL helped perform the analysis with constructive discussions and revised it critically for important intellectual content.

7. Competing interests

There were no conflicts of interest.

8. Funding

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9. Ethics approval

Not required.

10. Data availability statement

No data are available.

11. Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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Tables

Table 1. Characteristics of included studies (1) *

Authors	Country	Clinical criteria†	Radiographic features	Intervention	Comparisons	Follow up
Barrios 2013[42]	US	Medial compartment knee OA; Pain VAS (≥3 of 10 upon walking)	K/L grade ≥2, medial tibiofemoral compartment	bespoke full-length LWI	Placebo	12 months
Hinman 2016[53]	Australia	Medial compartment knee OA; Pain NRS (> 4 of 11 upon walking) over the previous week	K/L grade ≥2, medial tibiofemoral compartment	5° full-length LWI	Placebo	6 months
Arazpour 2012[41]	Iran	Medial compartment knee OA	K/L grade 1 and 2, medial tibiofemoral compartment	6° full-length LWI	bespoke unloader knee braces	6 weeks
Jones 2013[50]	UK	Medial compartment knee OA	K/L grade 2 and 3, medial JSN	LWI: The heel was inclined at 5° with the inclination reduced to 0° at the 5th metatarsal head with a contoured arch profile	6° valgus knee brace	2 weeks
Khosravi 2019[51]	Iran	Medial compartment knee OA	K/L grade 2 and 3	Full length custom-made LWI; LWI+ knee brace	three-point valgus knee brace	6 weeks

* OA=osteoarthritis; LWI=lateral wedged insoles; VAS=visual analog scale; NRS=numerical rating scale; K/L=Kellgren/Lawrence; NR=not reported; JSN=joint space narrowing;

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Table 1. Characteristics of included studies (2) *

Authors	Country	Clinical criteria†	Radiographic features	Intervention	Comparisons	Follow up
Hunt 2018[48]	US	Medial compartment knee OA; Pain (≥3 of 10) longer than 6 months	K/L grade ≥2, medial tibiofemoral compartment	Toe-out gait modification	Walking without any guidance	4 months
Lim 2008[52]	Australia	Medial compartment knee OA; Medial knee pain	K/L grade ≥2, medial JSN	Quadriceps strengthening	No intervention	12 weeks
Erhart-Hledik 2012[45]	US	Medial compartment knee OA; Medial knee pain	K/L grade ≥1	Variable-stiffness shoe with stiffer soles on the lateral side	Constant-stiffness control shoe	12 months
Bennell 2010[43]	Australia	Medial compartment knee OA; Varus malalignment; Pain (> 3 of 11 upon walking)	K/L grade ≥2, medial JSN	Hip strengthening	No intervention	13 weeks
Cheung 2018[23]	China	Medial compartment knee OA; Knee pain occurred at least one day a week during each of the 8 weeks prior	K/L grade 1 and 2	Gait retraining for KAM reduction	Walking without any guidance	6 weeks

* OA=osteoarthritis; LWI=lateral wedged insoles; VAS=visual analog scale; NRS=numerical rating scale; K/L=Kellgren/Lawrence; NR=not reported; JSN=joint space narrowing;

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Table 1. Characteristics of included studies (3) *

Authors	Country	Clinical criteria†	Radiographic features	Intervention	Comparisons	Follow up
Foroughi 2011[46]	Australia	Primary knee OA	K/L grade ≥1	Lower limb exercise	Sham-exercise	6 months
Bennell 2014[44]	Australia	Medial compartment knee OA; Pain VAS (≥25 of 100) over the past week	K/L grade ≥2, medial tibiofemoral compartment	Neuromuscular exercise	Quadriceps strengthening	12 weeks
Hunt 2013[49]	Canada	Medial compartment knee OA; Knee pain >3/10 on most days of the previous month	K/L grade ≥2, medial tibiofemoral compartment	Lower limb exercise	No intervention	11 weeks
Holsgaard-Larsen 2017[47]	Denmark	Primary knee OA Pain KOOS(< 80 of 100, at least mild pain)	K/L grade ≤3	Neuromuscular exercise	Analgesic advice	8 weeks

* OA=osteoarthritis; LWI=lateral wedged insoles; VAS=visual analog scale; NRS=numerical rating scale; K/L=Kellgren/Lawrence; NR=not reported; JSN=joint space narrowing;

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Table 1. Characteristics of included studies (4) *

Authors	Country	Clinical criteria†	Radiographic features	Intervention	Comparisons	Follow up
Song 2020[55]	China	Medial compartment knee OA in one or both legs.	K/L grade ≤3	PNF (one-hour sessions three times a week)	Watch television or read magazines at the same time	12 weeks
Wang 2017[57]	China	Medial compartment knee OA	K/L grade 2 and 3	Acupuncture with 2 Hz continuous wave in Neixiyan (EX-LE 4), Dubi (ST 35), Yanglingquan (GB 34), Yinlingquan (SP 9), Xuehai (SP 10), Liangqiu (ST 34) and Zusanli (ST 36)	2 cm next to the same acupoints with shallow acupuncture and no current	Immediate
Robert-Lachaine 2020[54]	Canada	Medial compartment knee OA; Pain > 31/100 on WOMAC; Varus knee alignment ≥ 2°	K/L grade 2 and 3	V3P-brace; VER-brace; ACL-brace (wear the brace as often as possible)	/	3 months
Trombini-Souza 2015[56]	Brazil	Medial compartment knee OA; Knee pain between 3 and 8 on VAS	K/L grade 2 and 3	Minimalist footwear (Moleca®)	Standard, neutral tennis shoe	6 months

* OA=osteoarthritis; LWI=lateral wedged insoles; VAS=visual analog scale; NRS=numerical rating scale; K/L=Kellgren/Lawrence; NR=not reported; JSN=joint space narrowing; PNF= Proprioceptive neuromuscular facilitation; V3P-brace= three-point bending system valgus knee brace; VER-brace= unloader brace with valgus and external rotation functions; ACL-brace= functional medial-lateral stabilization brace used after ligament injuries; The Moleca® shoe is a low-cost women's double canvas, flexible, flat, walking shoe without heels, with a 5-mm anti-slip rubber sole and a 3-mm flat insole of ethylene vinyl acetate that provides only protection but no correction of any kind.

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

Table 2. Characteristics of participants in included studies (1) *

Authors	No.	Sex, M:F	Age, years	Height, meters	Body mass, kg	BMI, kg/m²	Bilateral knee OA included	K/L grade, no.				Main outcomes
								1	2	3	4	
Barrios 2013[42]	38	NR	61.90±8.37	NR	NR	32.00±7.43	NR	0	17	14	7	1st KAM; KAAI
Hinman 2016[53]	164	20:21	64.30±7.45	1.67 ± 0.10	82.95±14.76	29.70±3.64	NR	0	49	52	63	1st KAM; KAAI
Arazpour 2012[41]	24	3:4	59.29±2.37	NR	NR	27.01±1.71	Yes	9	15	0	0	1st KAM
Jones 2013[50]	28	4:3	66.30±8.20	1.75±0.13	88.7±15.10	NR	No	0	10	18	0	1st and 2nd KAM; KAAI
Khosravi 2019[51]	21	13:8	58.97±6.80	1.62±0.11	79.11±9.35	NR	NR	0	9	12	0	1st KAM

* Values are the mean±SD unless indicated otherwise. BMI=body mass index; K/L=Kellgren/Lawrence; NR=not reported; JSN=joint space narrowing; KAM=knee adduction moment; KAAI=knee adduction angular impulse.

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

Table 2. Characteristics of participants in included studies (2) *

Authors	No.	Sex, M:F	Age, years	Height, meters	Body mass, kg	BMI, kg/m^2	Bilateral knee OA included	K/L grade, no.				Main outcomes
								1	2	3	4	
Hunt 2018[48]	79	24:55	64.99±8.60	1.65±0.10	74.59±13.15	27.35±3.48	Yes	0	37	31	11	1st and 2nd KAM; KAAI
Lim 2008[52]	107	48:59	64.60±8.51	1.65±0.10	79.41±15.32	28.96±4.85	Yes	0	34	29	44	1st KAM
Erhart-Hledik 2012[45]	79	41:38	61.70±9.43	1.69±0.08	79.50±15.07	27.51±4.87	Yes	NR	NR	NR	NR	1st KAM
Bennell 2010[43]	89	46:43	64.55±8.34	NR	NR	27.94±4.41	Yes	0	30	29	30	1st KAM; KAAI
Cheung 2018[23]	20	1:1	61.95±6.11	1.63±0.09	65.85±6.64	27.35±3.48	NR	5	15	0	0	1st KAM

* Values are the mean±SD unless indicated otherwise. BMI=body mass index; K/L=Kellgren/Lawrence; NR=not reported; JSN=joint space narrowing; KAM=knee adduction moment; KAAI=knee adduction angular impulse.

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

Table 2. Characteristics of participants in included studies (3) *

Authors	No.	Sex, M:F	Age, years	Height, meters	Body mass, kg	BMI, kg/m^2	Bilateral knee OA included	K/L grade, no.				Main outcomes
								1	2	3	4	
Foroughi 2011[46]	54	0:54	65.48±7.44	NR	82.87±18.43	32.07±7.08	Yes	20	7	20	1	1st and 2nd KAM
Bennell 2014[44]	100	48:52	62.45±7.32	1.67±0.10	82.70±14.29	29.65±4.08	Yes	0	22	43	35	1st KAM; KAAI
Hunt 2013[49]	17	8:9	66.10±11.3	NR	NR	27.00±4.50	Yes	0	10	5	2	1st KAM; KAAI
Holsgaard-Larsen 2017[47]	93	39:54	58.10±7.96	NR	79.64±12.49	26.90±3.09	NR	45	31	17	0	1st KAM; KAAI

* Values are the mean±SD unless indicated otherwise. BMI=body mass index; K/L=Kellgren/Lawrence; NR=not reported; JSN=joint space narrowing; KAM=knee adduction moment; KAAI=knee adduction angular impulse.

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

Table 2. Characteristics of participants in included studies (4) *

Authors	No.	Sex, M:F	Age, years	Height, meters	Body mass, kg	BMI, kg/m^2	Bilateral knee OA included	K/L grade, no.				Main outcomes
								1	2	3	4	
Song 2020[55]	36	1:1	68.01±3.91	1.62±0.07	68.16±6.77	NR	Yes	9	20	7	0	1st KAM
Wang 2017[57]	36	1:5	63.50±7.95	NR	NR	23.75±2.66	Yes	0	19	17	0	1st and 2nd KAM
Robert-Lachaine 2020[54]	24	7:5	57.20±8.60	1.68±0.09	89.30±18.70	31.40±5.00	NR	0	15	8	0	1st and 2nd KAM; KAAI
Trombini-Souza 2015[56]	56	NR	66.00±5.00	1.60±0.10	73.40±13.10	NR	NR	0	NR	NR	0	1st KAM; KAAI

* Values are the mean±SD unless indicated otherwise. BMI=body mass index; K/L=Kellgren/Lawrence; NR=not reported; JSN=joint space narrowing; KAM=knee adduction moment; KAAI=knee adduction angular impulse.

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

J	0.41 (-0.66,1.49)	0.16 (-0.46,0.79)	-	0.20 (-0.23,0.64)	**0.81 (0.17,1.45)**	-	0.30 (-0.61,1.21)	**0.54 (0.02,1.07)**	0.32 (-0.10,0.75)
0.28 (-0.34,0.89)	**I**	-0.25 (-1.33,0.84)	-	-0.21 (-1.37,0.95)	0.40 (-0.70,1.49)	-	-0.12 (-1.39,1.16)	0.13 (-0.90,1.16)	-0.09 (-1.08,0.90)
0.07 (-0.50,0.64)	-0.21 (-0.89,0.47)	**H**	-	0.04 (-0.72,0.80)	0.64 (-0.01,1.30)	-	0.13 (-0.79,1.05)	0.38 (-0.16,0.92)	0.16 (-0.29,0.61)
-0.69 (-1.36,-0.02)	**-0.97 (-1.73,-0.21)**	**-0.76 (-1.49,-0.03)**	**G**	-	-	-	-	-	-
0.24 (-0.11,0.59)	-0.04 (-0.64,0.57)	0.17 (-0.39,0.74)	**0.93 (0.27,1.60)**	**F**	0.61 (-0.17,1.38)	-	0.09 (-0.91,1.10)	0.34 (-0.34,1.02)	0.12 (-0.49,0.73)
0.89 (0.35,1.44)	0.62 (-0.04,1.28)	**0.83 (0.20,1.45)**	**1.59 (0.87,2.30)**	**0.65 (0.11,1.19)**	**E**	-	-0.51 (-1.45,0.42)	-0.27 (-0.83,0.30)	**-0.48 (-0.96,-0.01)**
1.28 (0.21,2.36)	1.01 (-0.13,2.14)	**1.22 (0.10,2.33)**	**1.98 (0.81,3.15)**	1.04 (-0.03,2.11)	0.39 (-0.71,1.49)	**D**	-	-	-
0.78 (0.11,1.45)	0.50 (-0.26,1.27)	0.71 (-0.02,1.44)	**1.47 (0.66,2.29)**	0.54 (-0.12,1.20)	-0.11 (-0.83,0.60)	-0.50 (-1.46,0.46)	**C**	0.25 (-0.50,0.99)	0.03 (-0.77,0.83)
0.56 (0.10,1.02)	0.29 (-0.30,0.87)	0.49 (-0.05,1.04)	**1.26 (0.61,1.90)**	0.32 (-0.13,0.77)	-0.33 (-0.85,0.19)	-0.72 (-1.70,0.25)	-0.22 (-0.71,0.27)	**B**	-0.22 (-0.52,0.08)
0.37 (0.02,0.71)	0.09 (-0.42,0.60)	0.30 (-0.15,0.75)	**1.06 (0.49,1.63)**	0.13 (-0.21,0.46)	**-0.53 (-0.95,-0.10)**	-0.92 (-1.94,0.10)	-0.41 (-0.99,0.16)	-0.19 (-0.49,0.10)	**A**

Table 3. Detailed results of network meta-analysis for the First peak KAM (grey) and KAAI (white). Data are SMDs (from the top left to the bottom right, higher comparator versus lower comparator) and their related 95%CI. Bold texts in the table mean SMDs are statistically significant.

A= Control condition; B= Lateral Wedge Insole; C= Knee Brace; D= Lateral Wedge Insole+ Knee Brace; E= Gait retraining; F= Quadriceps strengthening; G= Variable-stiffness shoe; H= Hip strengthening; I= Lower limb exercise; J= Neuromuscular exercise.

Box

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

Box 1. Inclusion criteria

Design
- Randomized controlled trial

Participants
- People with radiologically confirmed knee osteoarthritis

Intervention
- Manual therapy
- Aerobic exercise
- Pulsed electrical stimulation (PES)
- Acupuncture
- Knee braces
- Ice/cooling treatment
- Pulsed electromagnetic fields (PEMF)
- Balneotherapy
- Interferential therapy
- Transcutaneous electric Nerve stimulation (TENS)
- Heat treatment
- Foot orthoses
- Laser/light therapy
- Muscle-strengthening exercise
- Static magnets
- Tai Chi
- Athletic tape
- Neuromuscular electrical stimulation (NMES)

Comparator
- Control condition (standard/conventional care, placebo intervention, no intervention, sham-exercise, analgesic advice and education)

Outcome measures
- KAM and KAAI.

Comparisons
- All interventions compared to the comparator and to each other

Figure Legends

Figure 1. Flow chart of the study selection

Figure 2. Rankings for effects on First peak KAM. The graph displays the distribution of probabilities for each treatment. The X-axis represents the possible rank of each treatment (from the best to worst according to the outcomes), Y-axis represents the cumulative probability for each treatment to be the best option, among the best two options, among the best three options, and so on. A= Control condition; B= Lateral Wedge Insole; C= Knee Brace; D= Lateral Wedge Insole+ Knee Brace; E= Gait retraining; F= Quadriceps strengthening; G= Variable-stiffness shoe; H= Hip strengthening; I= Lower limb exercise; J= Neuromuscular exercise.

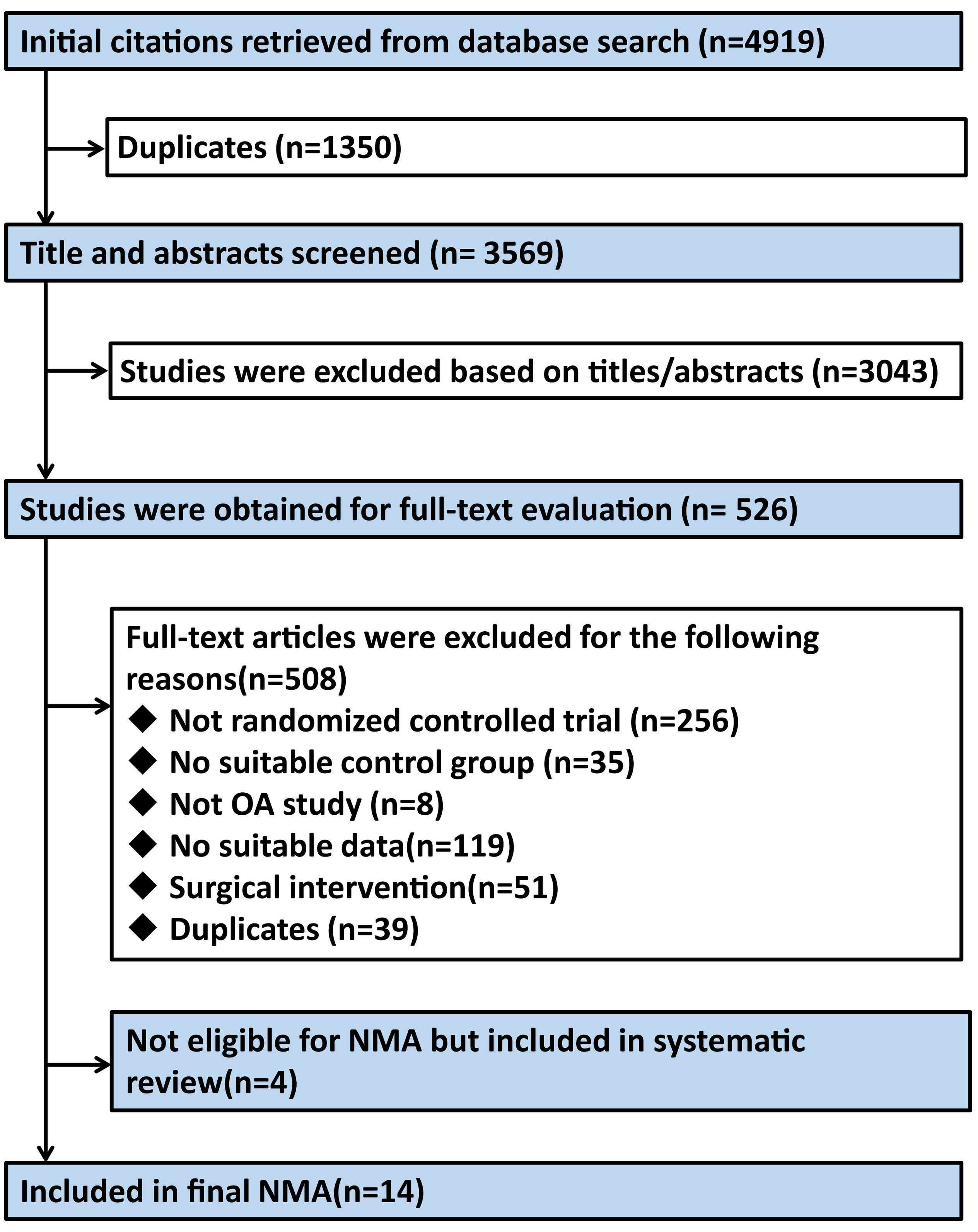
Figure 3. Rankings for effects on KAAI. The graph displays the distribution of probabilities for each treatment. The X-axis represents the possible rank of each treatment (from the

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

best to worst according to the outcomes), Y-axis represents the cumulative probability for each treatment to be the best option, among the best two options, among the best three options, and so on. A= Control condition; B= Lateral Wedge Insole; C= Knee Brace; E= Gait retraining; F= Quadriceps strengthening; H= Hip strengthening; I= Lower limb exercise; J= Neuromuscular exercise.

Figure 4. Risk of bias summary

Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)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Duplicates (n=1350)
Title and abstracts screened (n= 3569)
Studies were excluded based on titles/abstracts (n=3043)
Studies were obtained for full-text evaluation (n= 526)
Full-text articles were excluded for the following reasons(n=508)
◆ Not randomized controlled trial (n=256)
◆ No suitable control group (n=35)
◆ Not OA study (n=8)
◆ No suitable data(n=119)
◆ Surgical intervention(n=51)
◆ Duplicates (n=39)
Not eligible for NMA but included in systematic review(n=4)
Included in final NMA(n=14)

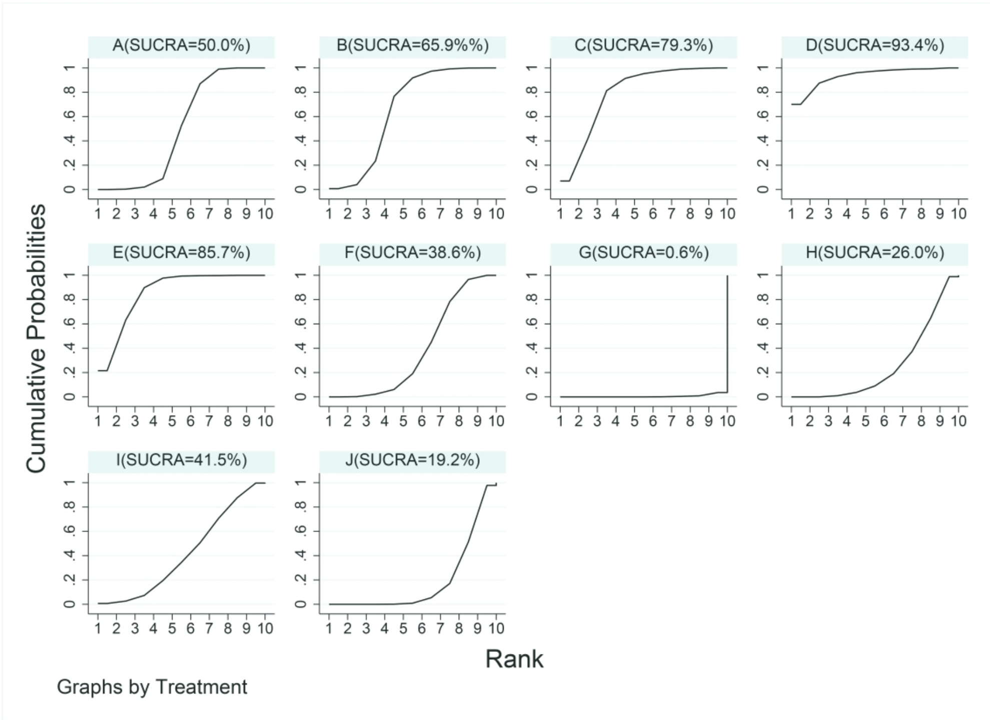

A(SUCRA=50.0%)
B(SUCRA=65.9%%)
C(SUCRA=79.3%)
D(SUCRA=93.4%)
E(SUCRA=85.7%)
F(SUCRA=38.6%)
G(SUCRA=0.6%)
H(SUCRA=26.0%)
I(SUCRA=41.5%)
J(SUCRA=19.2%)
Cumulative Probabilities
Rank
Graphs by Treatment

Figure 2

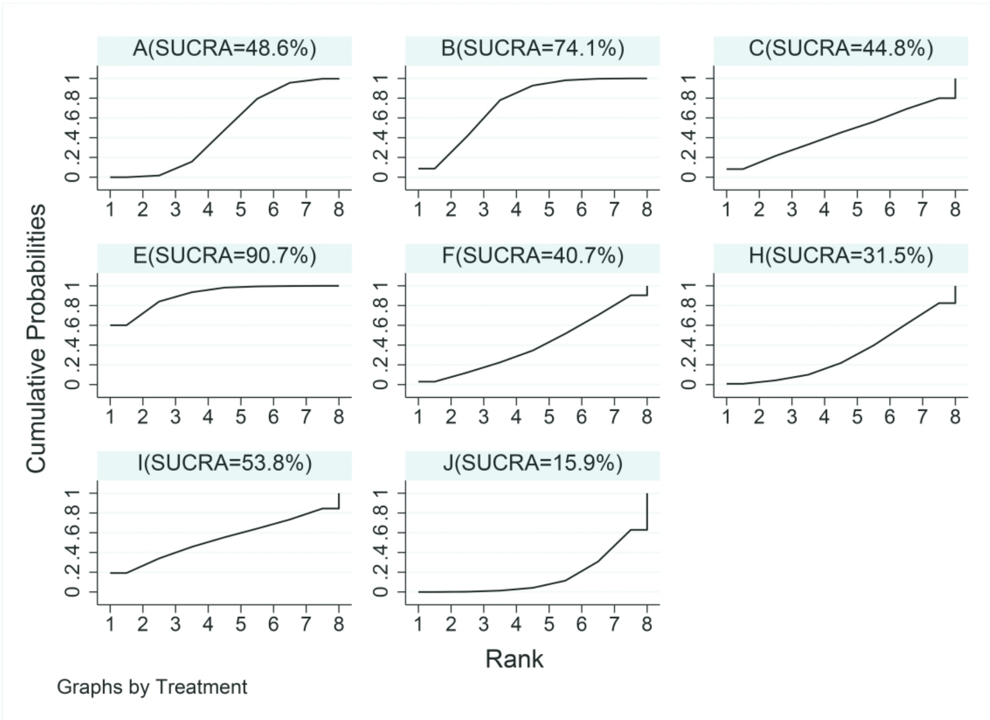
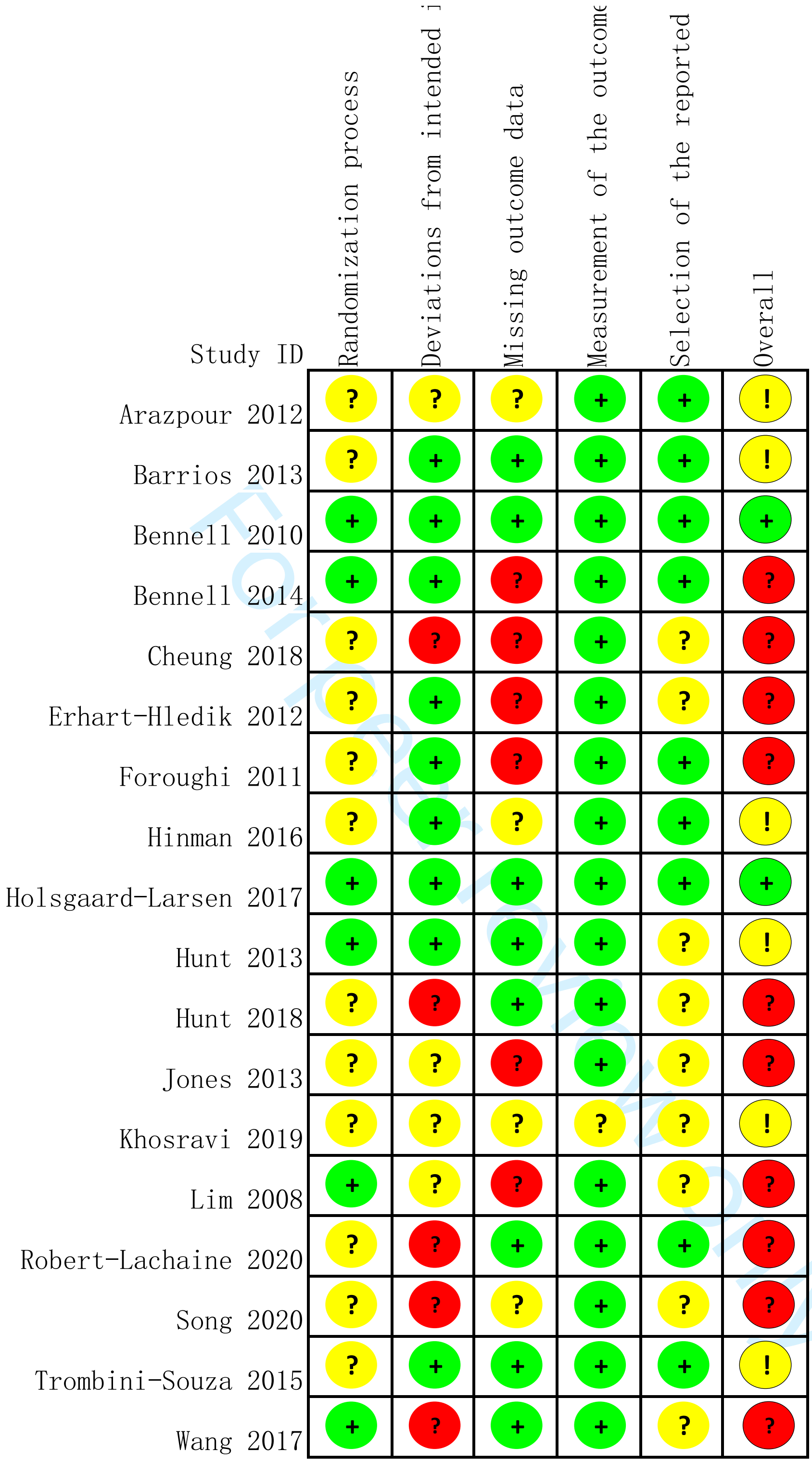
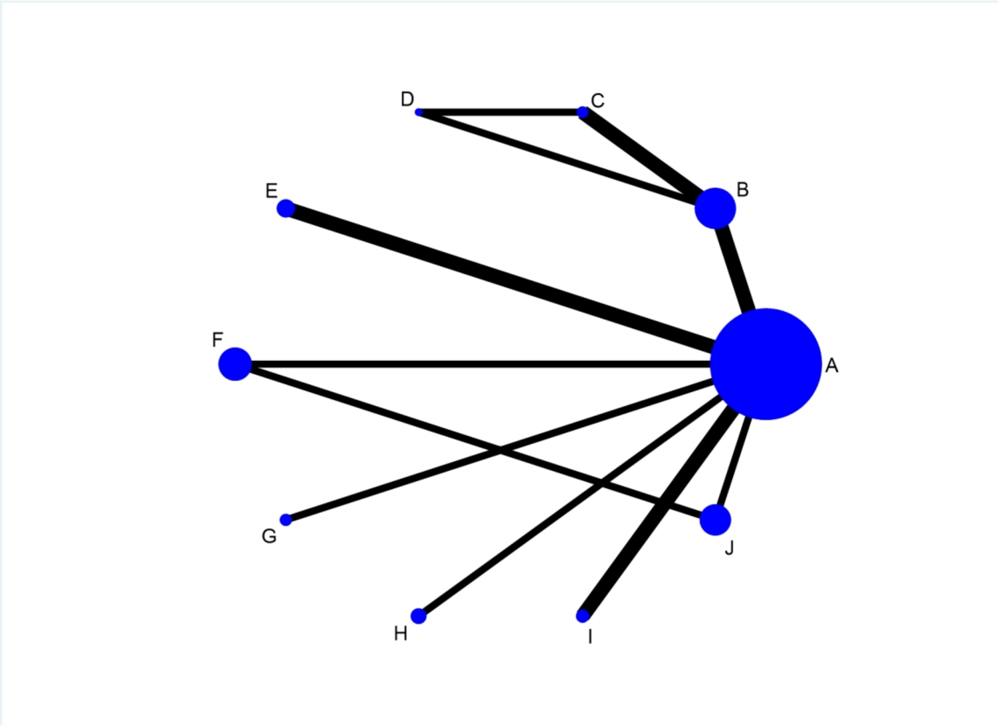

A(SUCRA=48.6%)
B(SUCRA=74.1%)
C(SUCRA=44.8%)
E(SUCRA=90.7%)
F(SUCRA=40.7%)
H(SUCRA=31.5%)
I(SUCRA=53.8%)
J(SUCRA=15.9%)
Cumulative Probabilities
0 .2 .4 .6 .8 1
1 2 3 4 5 6 7 8
Rank
Graphs by Treatment

Figure 3


Study ID
Randomization process
Deviations from intended i
Missing outcome data
Measurement of the outcome
Selection of the reported
Overall
Arazpour 2012
Barrios 2013
Bennell 2010
Bennell 2014
Cheung 2018
Erhart-Hledik 2012
Foroughi 2011
Hinman 2016
Holsgaard-Larsen 2017
Hunt 2013
Hunt 2018
Jones 2013
Khosravi 2019
Lim 2008
Robert-Lachaine 2020
Song 2020
Trombini-Souza 2015
Wang 2017



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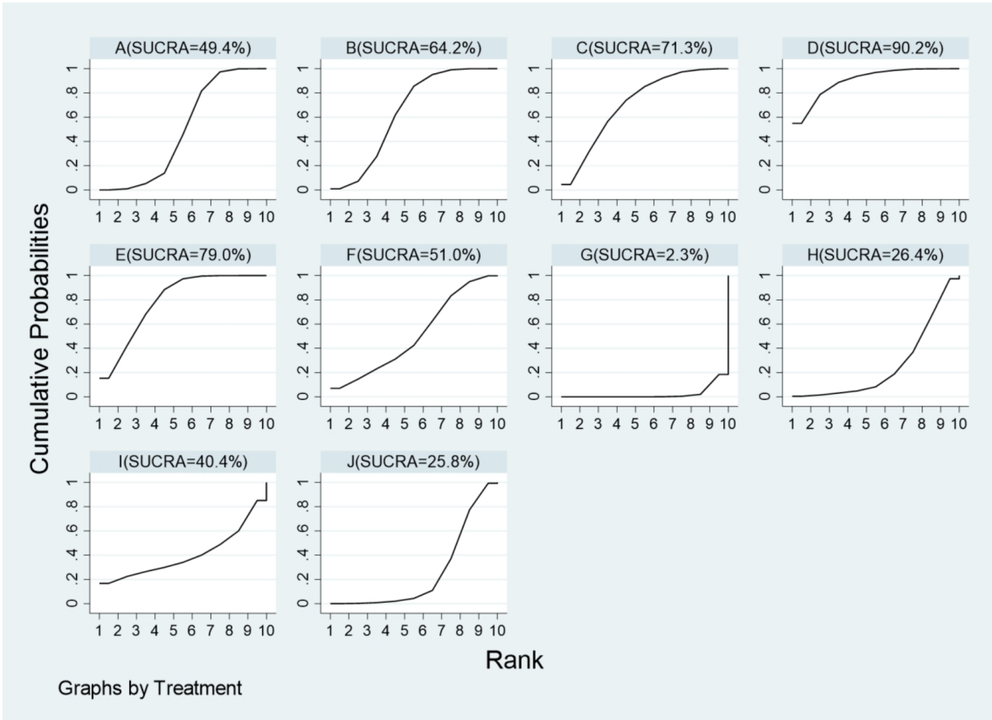

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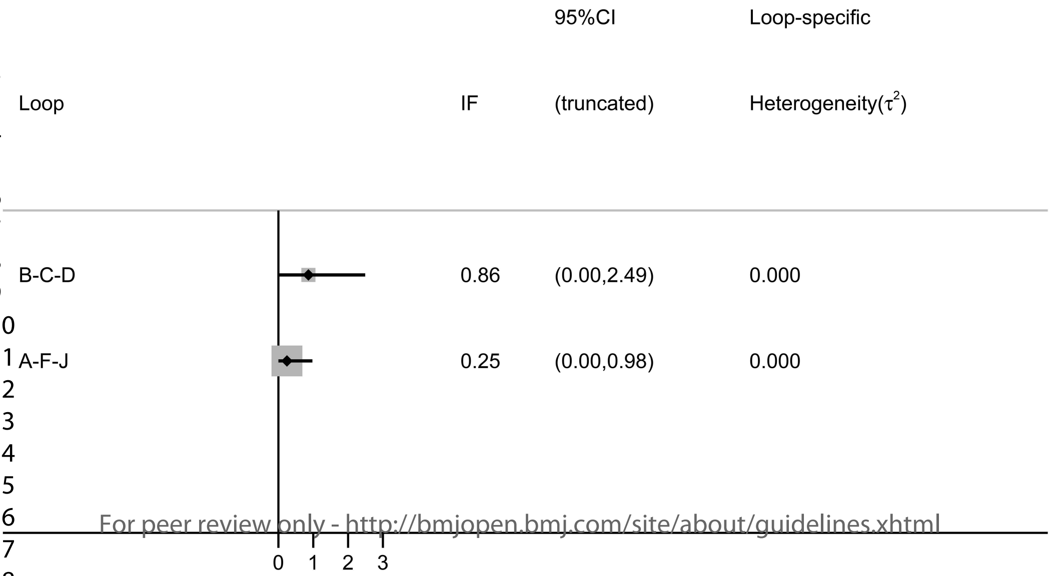
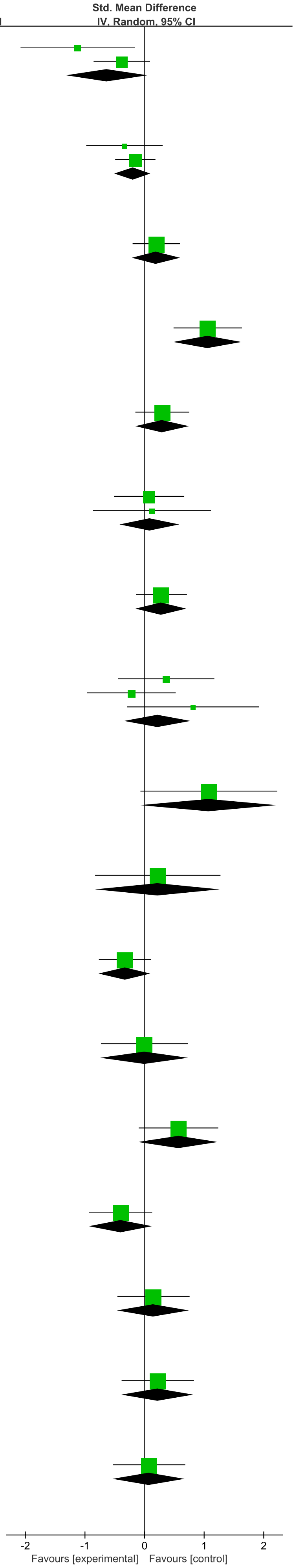
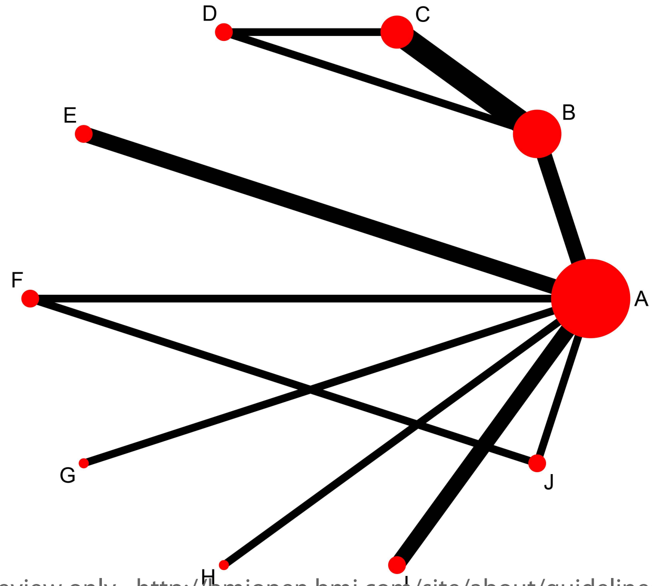

Loop
IF
95%CI (truncated)
Loop-specific Heterogeneity(τ^2)
B-C-D
0.86
(0.00,2.49)
0.000
A-F-J
0.25
(0.00,0.98)
0.000
0
1
2
3

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Gait retraining vs Standard Care								
Cheung 2018	-0.078	0.0839	10	0.005	0.0547	10	33.5%	-1.12 [-2.08, -0.16]
Hunt 2018	-0.01	0.3599	37	0.13	0.3666	33	66.5%	-0.38 [-0.86, 0.09]
Subtotal (95% CI)			**47**			**43**	**100.0%**	**-0.63 [-1.32, 0.06]**
Heterogeneity: Tau² = 0.13; Chi² = 1.85, df = 1 (P = 0.17); I² = 46%								
Test for overall effect: Z = 1.80 (P = 0.07)								
1.1.2 LWI vs Standard Care								
Barrios 2013	-0.011	0.1351	19	0.032	0.1133	19	21.7%	-0.34 [-0.98, 0.30]
Hinman 2016	0.26	1.3295	68	0.46	1.234	67	78.3%	-0.16 [-0.49, 0.18]
Subtotal (95% CI)			**87**			**86**	**100.0%**	**-0.19 [-0.49, 0.10]**
Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.62); I² = 0%								
Test for overall effect: Z = 1.28 (P = 0.20)								
1.1.3 Quadriceps strengthening vs Standard Care								
Lim 2008	0.1	0.9685	49	-0.087	0.8962	48	100.0%	0.20 [-0.20, 0.60]
Subtotal (95% CI)			**49**			**48**	**100.0%**	**0.20 [-0.20, 0.60]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.98 (P = 0.33)								
1.1.4 Variable-stiffness shoes vs Standard Care								
Erhart-Hledik 2012	0.338	0.3763	32	-0.072	0.3878	23	100.0%	1.06 [0.49, 1.63]
Subtotal (95% CI)			**32**			**23**	**100.0%**	**1.06 [0.49, 1.63]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.62 (P = 0.0003)								
1.1.5 Hip strengthening vs Standard Care								
Bennell 2010	0.15	0.4371	39	0.02	0.4258	37	100.0%	0.30 [-0.15, 0.75]
Subtotal (95% CI)			**39**			**37**	**100.0%**	**0.30 [-0.15, 0.75]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.29 (P = 0.20)								
1.1.6 Lower limb exercise vs Standard Care								
Foroughi 2011	-0.02	1.26	20	-0.11	1.0223	25	73.9%	0.08 [-0.51, 0.67]
Hunt 2013	-0.05	0.91	9	-0.17	0.9044	7	26.1%	0.13 [-0.86, 1.11]
Subtotal (95% CI)			**29**			**32**	**100.0%**	**0.09 [-0.42, 0.60]**
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%								
Test for overall effect: Z = 0.35 (P = 0.73)								
1.1.7 Neuromuscular exercise vs Standard Care								
Holsgaard-Larsen 2017	0.12	0.3125	44	0.03	0.3168	41	100.0%	0.28 [-0.14, 0.71]
Subtotal (95% CI)			**44**			**41**	**100.0%**	**0.28 [-0.14, 0.71]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.30 (P = 0.19)								
1.1.8 LWI vs Knee Brace								
Arazpour 2012	-0.07	0.0324	12	-0.08	0.019	12	36.6%	0.36 [-0.44, 1.17]
Jones 2013	-0.075	0.1296	14	-0.045	0.1346	14	41.3%	-0.22 [-0.96, 0.52]
Khosravi 2019	-0.08	0.1752	7	-0.22	0.1442	7	22.1%	0.82 [-0.29, 1.92]
Subtotal (95% CI)			**33**			**33**	**100.0%**	**0.22 [-0.34, 0.79]**
Heterogeneity: Tau² = 0.06; Chi² = 2.58, df = 2 (P = 0.28); I² = 22%								
Test for overall effect: Z = 0.77 (P = 0.44)								
1.1.9 LWI vs LWI+Knee Brace								
Khosravi 2019	-0.08	0.1752	7	-0.251	0.1153	7	100.0%	1.08 [-0.07, 2.23]
Subtotal (95% CI)			**7**			**7**	**100.0%**	**1.08 [-0.07, 2.23]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.84 (P = 0.07)								
1.1.10 Knee Brace vs LWI+Knee Brace								
Khosravi 2019	-0.22	0.1442	7	-0.251	0.1153	7	100.0%	0.22 [-0.83, 1.27]
Subtotal (95% CI)			**7**			**7**	**100.0%**	**0.22 [-0.83, 1.27]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.41 (P = 0.68)								
1.1.11 Quadriceps strengthening vs Neuromuscular exercise								
Bennell 2014	-0.04	0.4605	44	0.12	0.502	38	100.0%	-0.33 [-0.77, 0.11]
Subtotal (95% CI)			**44**			**38**	**100.0%**	**-0.33 [-0.77, 0.11]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.48 (P = 0.14)								
1.1.12 PNF vs Standard Care								
Song 2020	0.01	0.13	13	0.01	0.13	16	100.0%	0.00 [-0.73, 0.73]
Subtotal (95% CI)			**13**			**16**	**100.0%**	**0.00 [-0.73, 0.73]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
1.1.13 Electroacupuncture vs Sham-acupuncture								
Wang 2017	0.019	0.095	18	-0.036	0.094	18	100.0%	0.57 [-0.10, 1.24]
Subtotal (95% CI)			**18**			**18**	**100.0%**	**0.57 [-0.10, 1.24]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.67 (P = 0.09)								
1.1.14 Minimalist footwear vs Standard, neutral tennis shoe								
Trombini-Souza 2015	-0.23	0.84	28	0.18	1.15	28	100.0%	-0.40 [-0.93, 0.13]
Subtotal (95% CI)			**28**			**28**	**100.0%**	**-0.40 [-0.93, 0.13]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.49 (P = 0.14)								
1.1.15 ACL-brace vs V3P-brace								
Robert-Lachaine 2020	0.005	0.0991	21	-0.01	0.0967	21	100.0%	0.15 [-0.46, 0.76]
Subtotal (95% CI)			**21**			**21**	**100.0%**	**0.15 [-0.46, 0.76]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.49 (P = 0.63)								
1.1.16 ACL-brace vs VER-brace								
Robert-Lachaine 2020	0.005	0.0991	21	-0.018	0.1043	21	100.0%	0.22 [-0.39, 0.83]
Subtotal (95% CI)			**21**			**21**	**100.0%**	**0.22 [-0.39, 0.83]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.72 (P = 0.47)								
1.1.17 V3P-brace vs VER-brace								
Robert-Lachaine 2020	-0.01	0.0967	21	-0.018	0.1043	21	100.0%	0.08 [-0.53, 0.68]
Subtotal (95% CI)			**21**			**21**	**100.0%**	**0.08 [-0.53, 0.68]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.25 (P = 0.80)								




D
C
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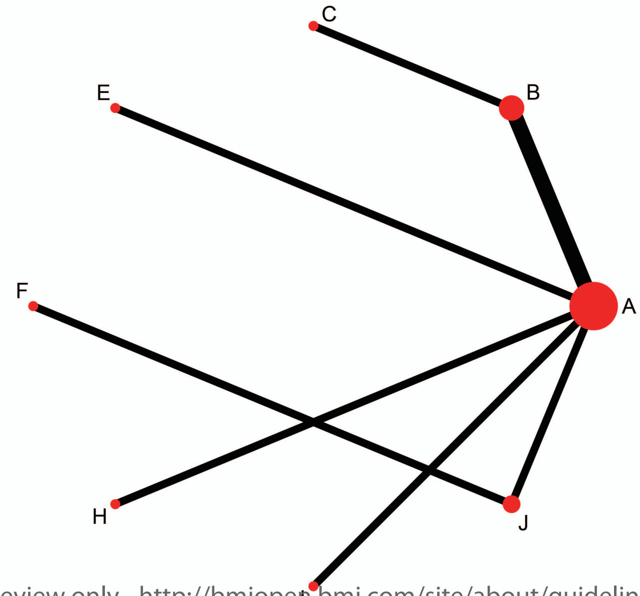
I


C
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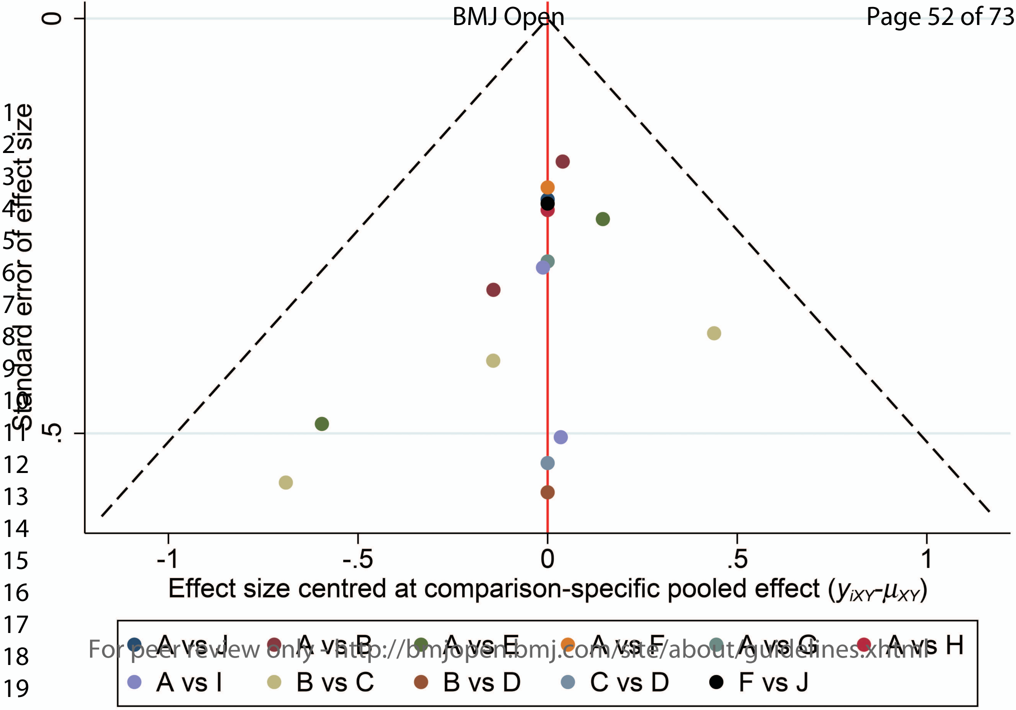
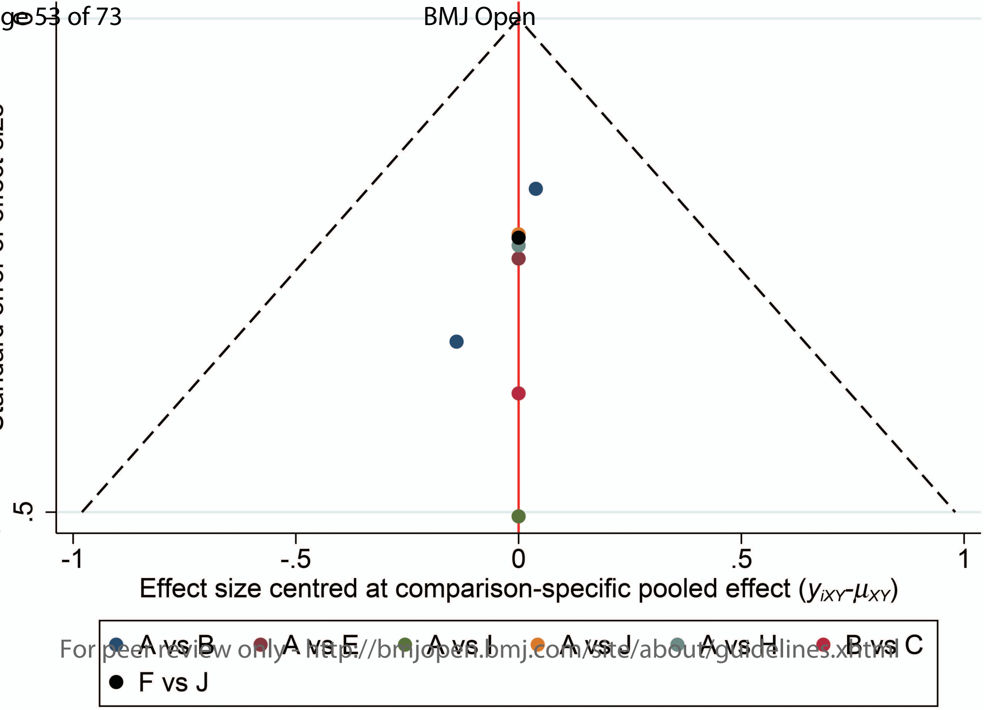

Standard error of effect size
0
.5
-1
-.5
0
.5
1
Effect size centred at comparison-specific pooled effect ($y_{iXY}-\mu_{XY}$)
A vs J
A vs B
A vs E
A vs F
A vs G
A vs H
A vs I
B vs C
B vs D
C vs D
F vs J


Standard error of effect size
.5
-1
-.5
0
.5
1
Effect size centred at comparison-specific pooled effect (y_{iXY}-μ_{XY})
A vs B
A vs E
A vs I
A vs J
A vs H
B vs C
F vs J

Appendix

Appendix 1 Search strategies

Search strategies for randomized controlled trials Pubmed

1. (((((((("Osteoarthritis, Knee"[Mesh]) OR Knee Osteoarthritides[Title/Abstract]) OR Knee Osteoarthritis[Title/Abstract]) OR Osteoarthritis of Knee[Title/Abstract]) OR Osteoarthritis of the Knee[Title/Abstract])))) AND ((((((((((((((("Physical Therapy Modalities"[Mesh]) OR (Modalities, Physical Therapy[Title/Abstract])) OR (Modality, Physical Therapy[Title/Abstract])) OR (Physical Therapy Modality[Title/Abstract])) OR (Physiotherapy (Techniques)[Title/Abstract])) OR (Physiotherapies (Techniques)[Title/Abstract])) OR (Physical Therapy Techniques[Title/Abstract])) OR (Physical Therapy Technique[Title/Abstract])) OR (Techniques, Physical Therapy[Title/Abstract])) OR (Group Physiotherapy[Title/Abstract])) OR (Group Physiotherapies[Title/Abstract])) OR (Physiotherapies, Group[Title/Abstract])) OR (Physiotherapy, Group[Title/Abstract])) OR (Neurological Physiotherapy[Title/Abstract])) OR (Physiotherapy, Neurological[Title/Abstract])) OR (Neurophysiotherapy[Title/Abstract])
2. ((((((((("Osteoarthritis, Knee"[Mesh]) OR Knee Osteoarthritides[Title/Abstract]) OR Knee Osteoarthritis[Title/Abstract]) OR Osteoarthritis of Knee[Title/Abstract]) OR Osteoarthritis of the Knee[Title/Abstract]))))) AND (((("Orthopedic Equipment"[Mesh]) OR(Equipment,Orthopedic[Title/Abstract]))OR(Equipments,

1. ('physiotherapy'/exp OR 'physical therapy':ab,ti OR 'physical therapy (speciality)':ab,ti OR 'physical therapy (specialty)':ab,ti OR 'physical therapy modalities ':ab,ti OR 'physical therapy service':ab,ti OR 'physical therapy speciality':ab,ti OR 'physical therapy specialty ':ab,ti OR 'physical treatment':ab,ti OR ' physio therapy ':ab,ti OR 'physical therapy techniques':ab,ti OR 'physical treatment':ab,ti OR 'physiotherapy department':ab,ti OR 'therapy, physical':ab,ti) AND ('knee osteoarthritis'/exp OR 'arthrosis, knee':ab,ti OR 'femorotibial arthrosis':ab,ti OR 'gonarthrosis':ab,ti OR 'knee arthrosis':ab,ti OR 'knee joint arthrosis':ab,ti OR 'knee joint osteoarthritis':ab,ti OR 'knee osteo-arthritis':ab,ti OR 'knee osteo-arthrosis':ab,ti OR 'knee osteoarthrosis':ab,ti OR 'osteoarthritis, knee':ab,ti OR 'osteoarthrosis, knee':ab,ti)
2. ('orthosis'/exp OR 'device, orthotic':ab,ti OR 'devices, orthotic':ab,ti OR 'orthesis':ab,ti OR 'orthopeadic support device':ab,ti OR 'orthopedic support device':ab,ti OR 'orthoses':ab,ti OR 'orthotic device (physical object)':ab,ti OR 'orthotic devices':ab,ti) AND ('knee osteoarthritis'/exp OR 'arthrosis, knee':ab,ti OR 'femorotibial arthrosis':ab,ti OR 'gonarthrosis':ab,ti OR 'knee arthrosis':ab,ti OR 'knee joint arthrosis':ab,ti OR 'knee joint osteoarthritis':ab,ti OR 'knee osteo-arthritis':ab,ti OR 'knee osteo-arthrosis':ab,ti OR 'knee osteoarthrosis':ab,ti OR 'osteoarthritis, knee':ab,ti OR 'osteoarthrosis, knee':ab,ti)

Web of Science

1. AB=(physical therapy OR physiotherapy OR physio therapy OR physical treatment OR physioth erapy department OR physical therapy techniques)
2. TI=(physical therapy OR physiotherapy OR physio therapy OR physical treatment OR physiotherapy department OR physical therapy techniques)
3. AB=(orthosis OR device OR orthesis OR orthoses OR orthopeadic support device OR orthotic device)
4. TI=(orthosis OR device OR orthesis OR orthoses OR orthopeadic support device OR orthotic device)
5. #4 OR #3 OR #2 OR #1
6. AB=(knee osteoarthritis OR femorotibial arthrosis OR gonarthrosis OR knee arthrosis OR knee osteo-arthritis OR knee osteoarthrosis OR osteoarthrosis)
7. TI=(knee osteoarthritis OR femorotibial arthrosis OR gonarthrosis OR knee arthrosis OR knee osteo-arthritis OR knee osteoarthrosis OR osteoarthrosis)
8. #6 OR #7
9. #8 AND #5

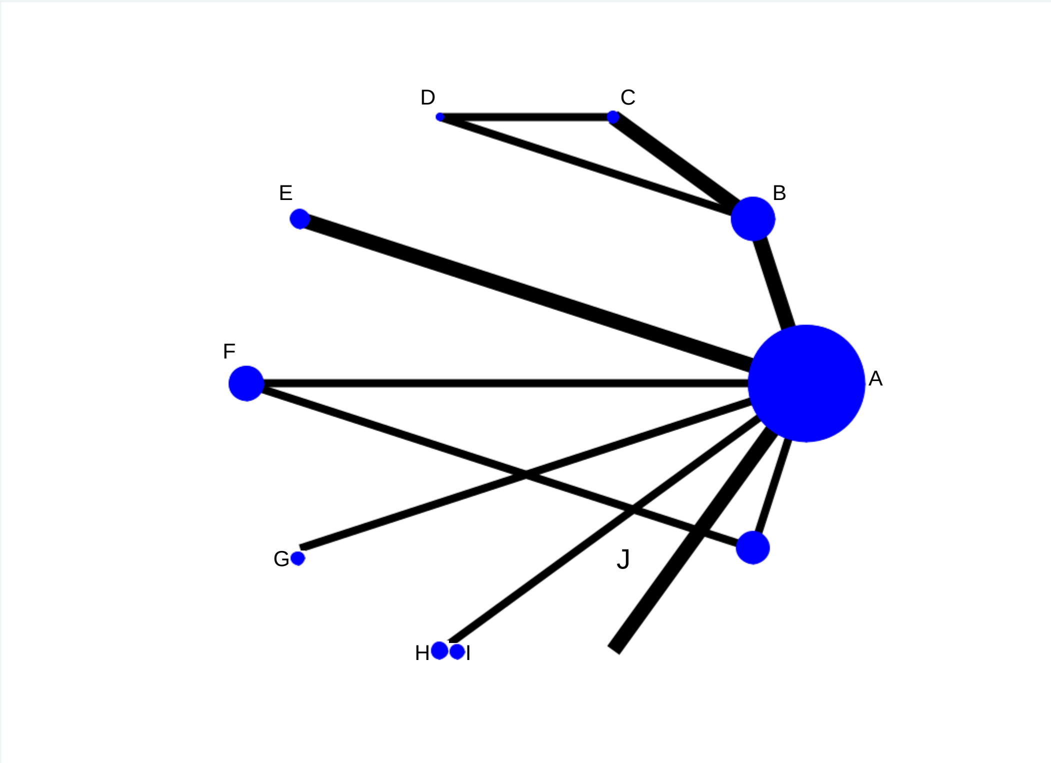
1. (MeSH descriptor: [Physical Therapy Modalities] explode all trees OR (Neurological Physiotherapy):ti,ab,kw OR (Physiotherapy, Neurological):ti,ab,kw OR (Neurophysiotherapy):ti,ab,kw OR (Techniques, Physical Therapy):ti,ab,kw OR (Physiotherapies (Techniques)):ti,ab,kw OR (Physical Therapy Techniques):ti,ab,kw OR (Physiotherapy (Techniques)):ti,ab,kw OR (Modality, Physical Therapy):ti,ab,kw OR (Physical Therapy Modality):ti,ab,kw OR (Physical Therapy Technique):ti,ab,kw OR (Modalities, Physical Therapy):ti,ab,kw OR (Group Physiotherapies):ti,ab,kw OR (Physiotherapy, Group):ti,ab,kw OR (Group Physiotherapy):ti,ab,kw OR (Physiotherapies, Group):ti,ab,kw) AND ((Osteoarthritis of Knee):ti,ab,kw OR (Knee Osteoarthritides):ti,ab,kw OR (Knee Osteoarthritis):ti,ab,kw OR (Osteoarthritis of the Knee):ti,ab,kw) OR MeSH descriptor: [Osteoarthritis, Knee] explode all trees)
2. (MeSH descriptor: [Orthopedic Equipment] explode all trees OR (Orthopedic Equipments):ti,ab,kw OR (Equipment, Orthopedic):ti,ab,kw OR (Equipments, Orthopedic):ti,ab,kw) AND ((Osteoarthritis of Knee):ti,ab,kw OR (Knee Osteoarthritides):ti,ab,kw OR (Knee Osteoarthritis):ti,ab,kw OR (Osteoarthritis of the Knee):ti,ab,kw) OR MeSH descriptor: [Osteoarthritis, Knee] explode all trees)

MEDLINE

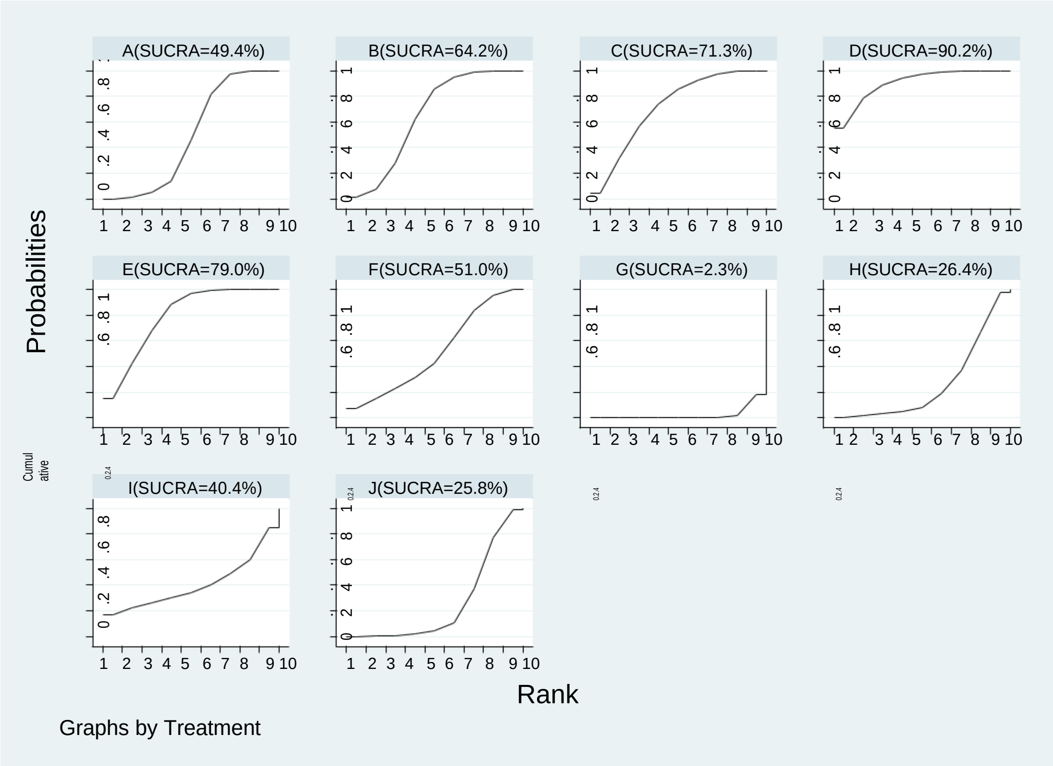
1. (knee osteoarthritis) OR (femorotibial arthrosis) OR (gonarthrosis) OR (knee arthrosis) OR (knee osteo-arthritis) OR (knee osteoarthrosis) OR (osteoarthrosis)
2. (physical therapy) OR (physiotherapy) OR (physio therapy) OR (physical treatment) OR (physioth erapy department) OR (physical therapy techniques)
3. (orthotic devices) OR (Orthopedic Equipment) OR (orthosis) OR (device) OR (orthesis) OR (orthoses) OR (orthopeadic support device)
4. #2 OR #3

5. #1 AND #4

Appendix 2 Results of re-analysis

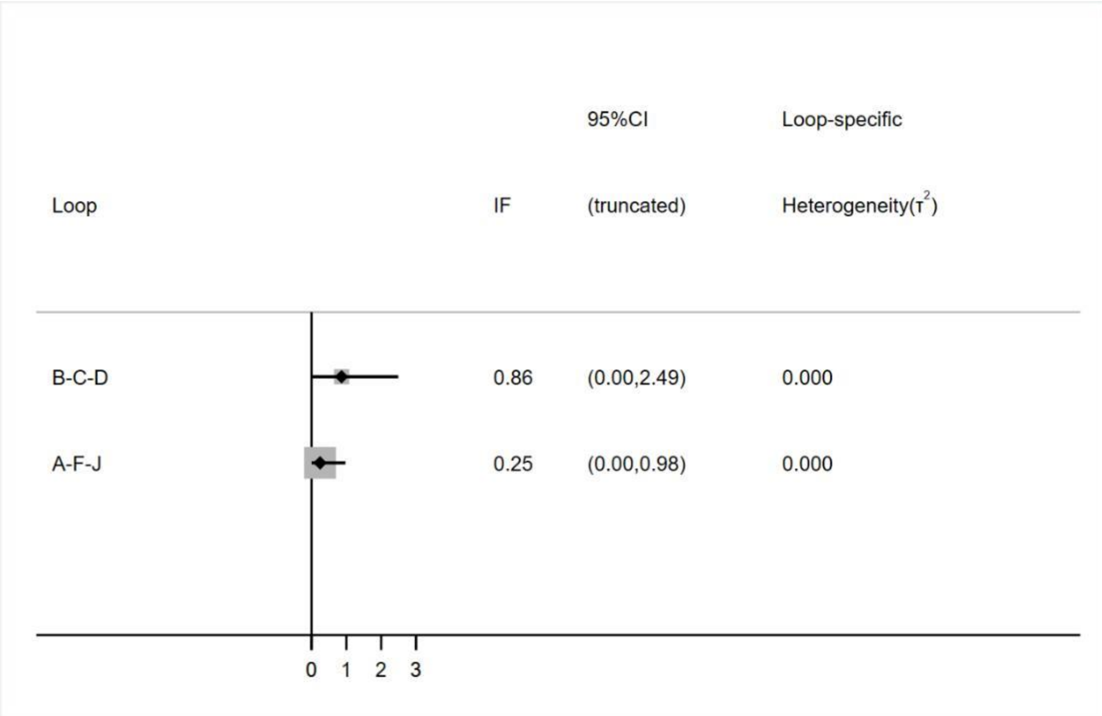


eFigure 1. Structure of network formed by interventions and their direct comparisons on First peak KAM (re-analysis). A= Control condition; B= Lateral Wedge Insole; C= Knee Brace; D= Lateral Wedge Insole+ Knee Brace; E= Gait retraining; F= Quadriceps strengthening; G= Variable-stiffness shoe; H= Hip strengthening; I= Lower limb exercise; J= Neuromuscular exercise.



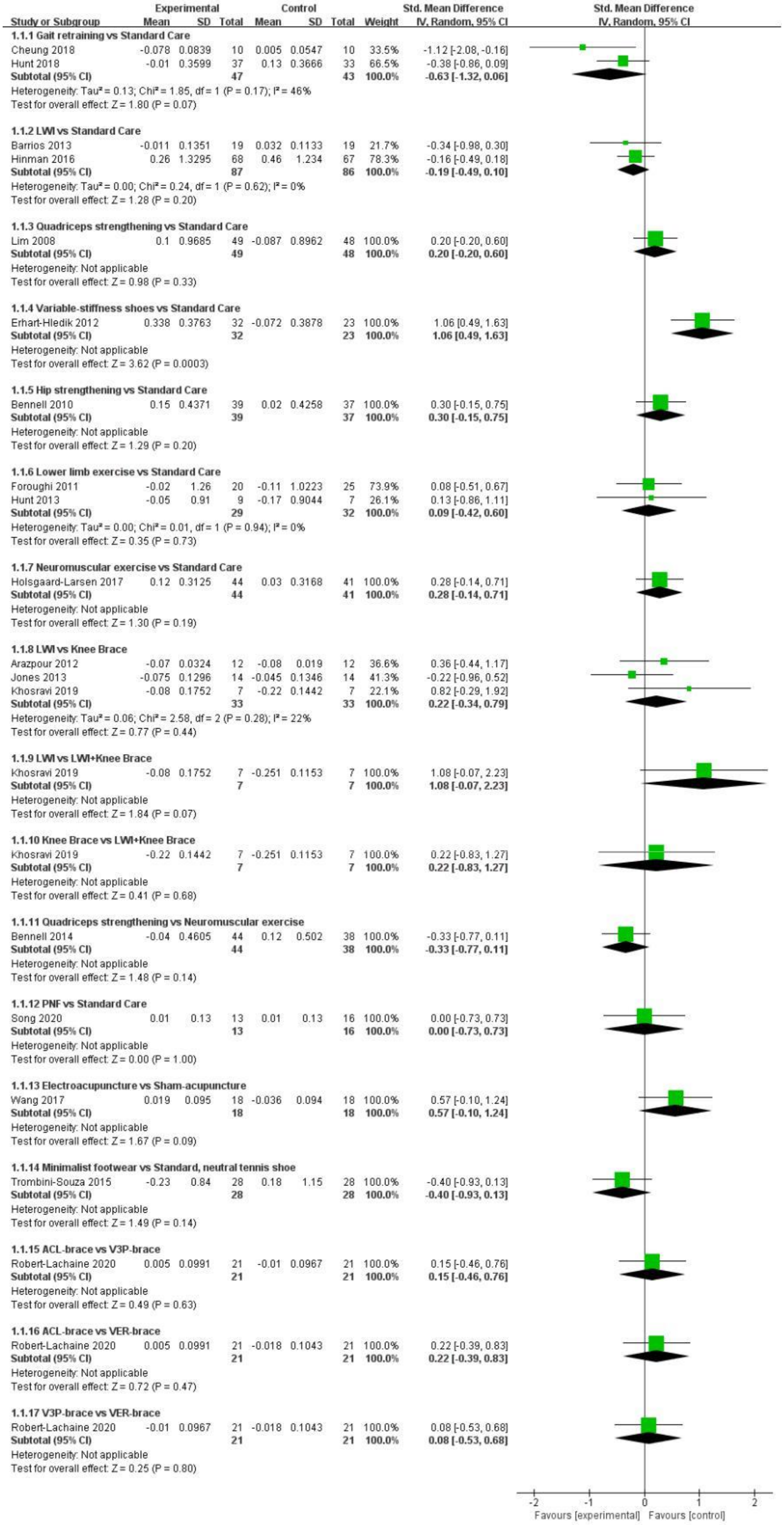
eFigure 2. Rankings for effects on First peak KAM (re-analysis). Graph displays distribution of probabilities for each treatment. X-axis represents the possible rank of each treatment (from the best to worst according to the outcomes), Y-axis represents the cumulative probability for each treatment to be the best option, among the best two options, among the best three options, and so on. A= Control condition; B= Lateral Wedge Insole; C= Knee Brace; D= Lateral Wedge Insole+ Knee Brace; E= Gait retraining; F= Quadriceps strengthening; G= Variable-stiffness shoe; H= Hip strengthening; I= Lower limb exercise; J= Neuromuscular exercise.

Appendix 3 Results of Inconsistency

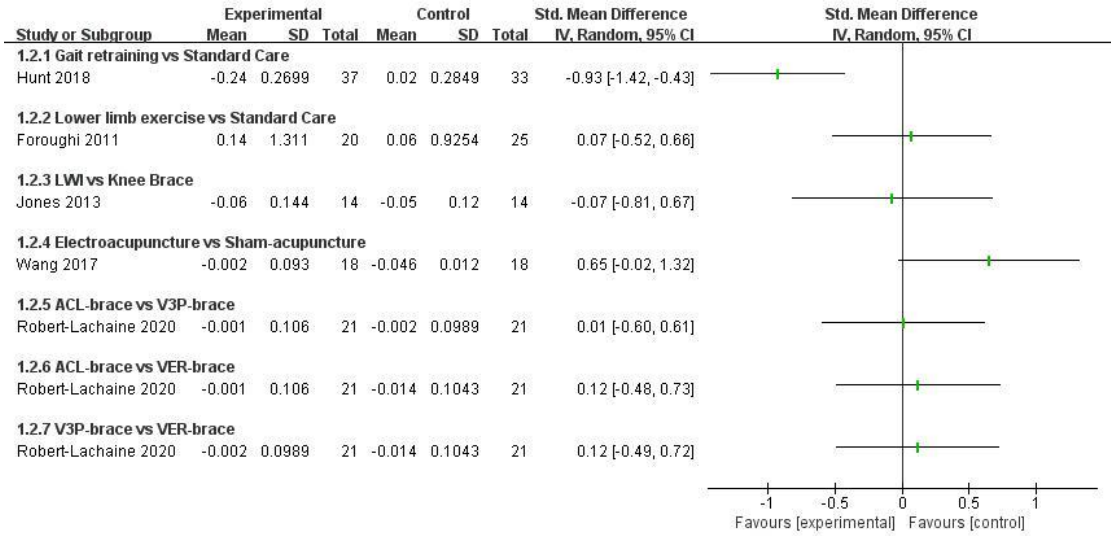


eFigure 1. Inconsistency for triangular loops in First peak KAM.

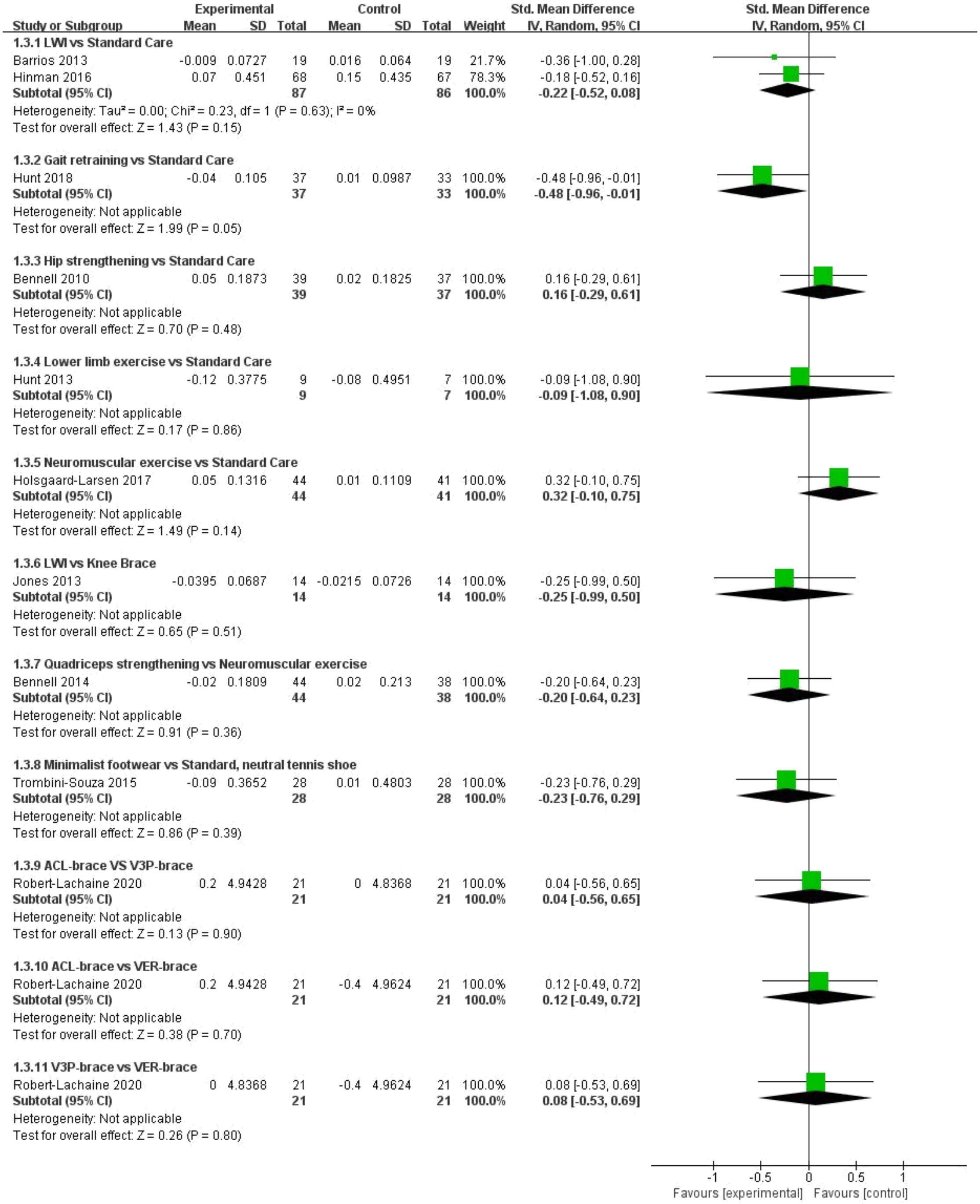
Appendix 4 Conventional meta-analyses results



eFigure 1a. Conventional meta-analysis of treatment effects on First peak KAM.

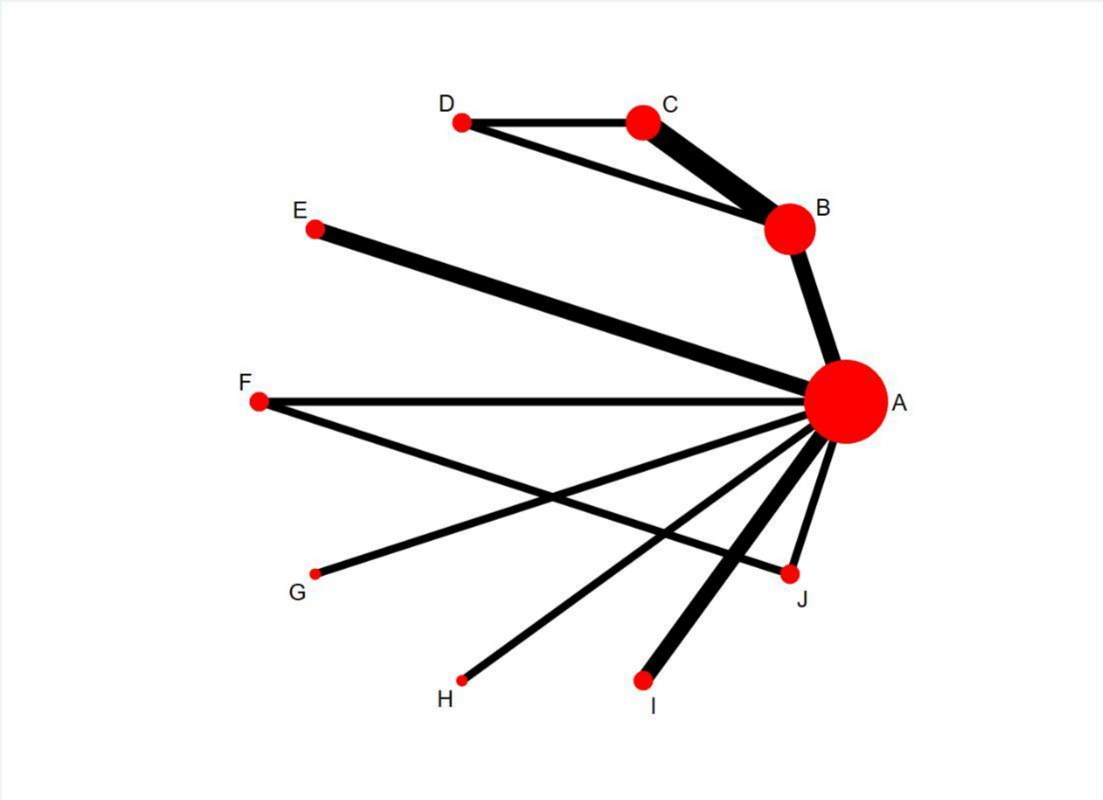


eFigure 1b. Conventional meta-analysis of treatment effects on Second peak KAM.



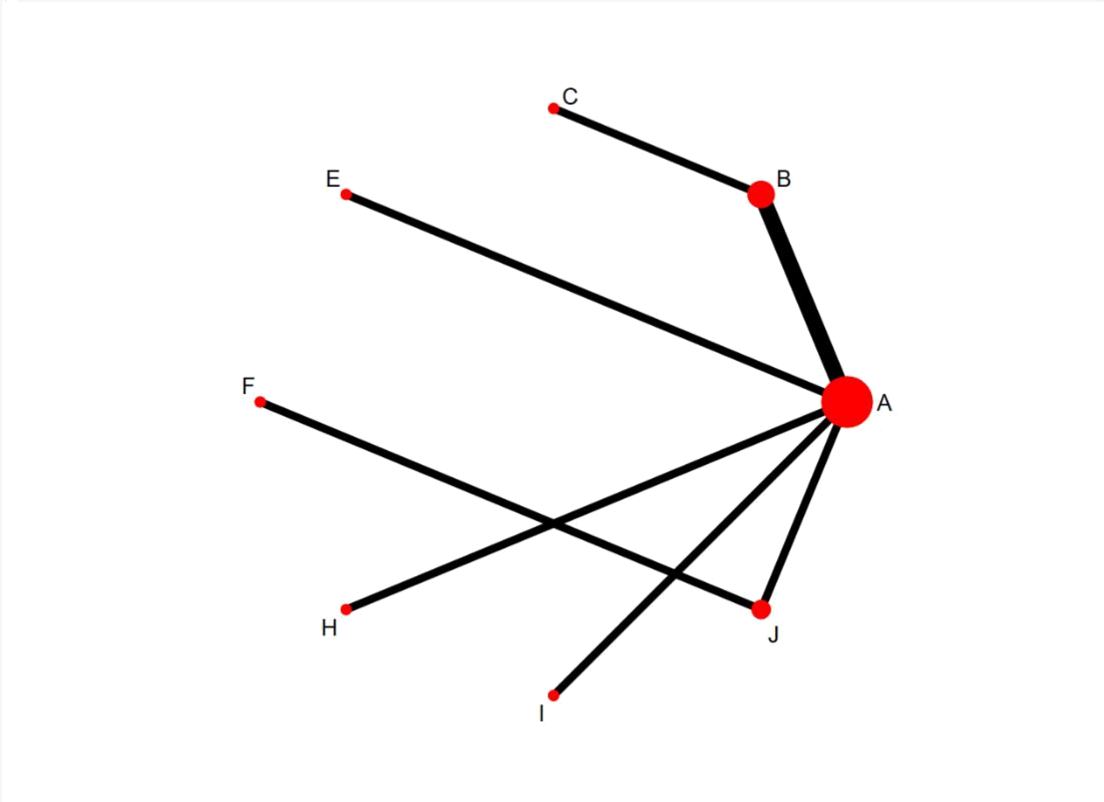
eFigure 1c. Conventional meta-analysis of treatment effects on KAAI.

Appendix 5 Network Diagram



eFigure 1a. Structure of network formed by interventions and their direct comparisons (First peak KAM). A= Control condition; B= Lateral Wedge Insole; C= Knee Brace; D= Lateral Wedge Insole+ Knee Brace; E= Gait retraining; F= Quadriceps strengthening; G= Variable-stiffness shoe; H= Hip strengthening; I= Lower limb exercise; J= Neuromuscular exercise.

Footnote: Width of the lines is proportional to the number of trials comparing every pair of treatments. Size of every circle is proportional to the number of randomly assigned participants (ie, sample size).



eFigure 1b. Structure of network formed by interventions and their direct comparisons (KAAI). A= Control condition; B= Lateral Wedge Insole; C= Knee Brace; E= Gait retraining; F= Quadriceps strengthening; H= Hip strengthening; I= Lower limb exercise; J= Neuromuscular exercise.

Footnote: Width of the lines is proportional to the number of trials comparing every pair of treatments. Size of every circle is proportional to the number of randomly assigned participants (ie, sample size).

Appendix 6 Table of GRADE

Based on all the above information, we GRADEd each network estimate according to the following criteria:

1) Study limitations: We downgraded by one level when the contributions from low RoB comparisons were less than 30% and contributions from moderate RoB comparisons were 70% or greater. And we downgraded by two level when the contributions from low RoB comparisons were more than 30%.
2) Imprecision: We considered a clinically meaningful threshold for CI to be 0 and did not

downgrade the estimate if the upper limit is below 0; or if the lower limit is above 0.

3) Inconsistency: We rated two concepts, heterogeneity and incoherence (inconsistency), in this domain. For heterogeneity, we did not downgrade any network estimate for heterogeneity, because we looked at the common tau and found that it is low. For inconsistency, we looked at the results of inconsistency (Appendix 2), where we have not downgraded for imprecision.

4) Indirectness: We have assured transitivity in our network by limiting the included studies to patients with knee osteoarthritis. Evaluation of transitivity for singly-connected nodes is unclear, so we downgraded such nodes for indirectness.

5) Publication bias: The comparison-adjusted funnel plot (Appendix 5) did not suggest presence of overall publication bias. We managed to retrieve supplementary and unpublished information included in the available systematic reviews and network meta-analyses, and we are confident that we have all available information that is possible to capture from clinical trial registries. Although we cannot completely rule out the possibility that some research is still missing, we still believe that the project does not need to be downgraded.

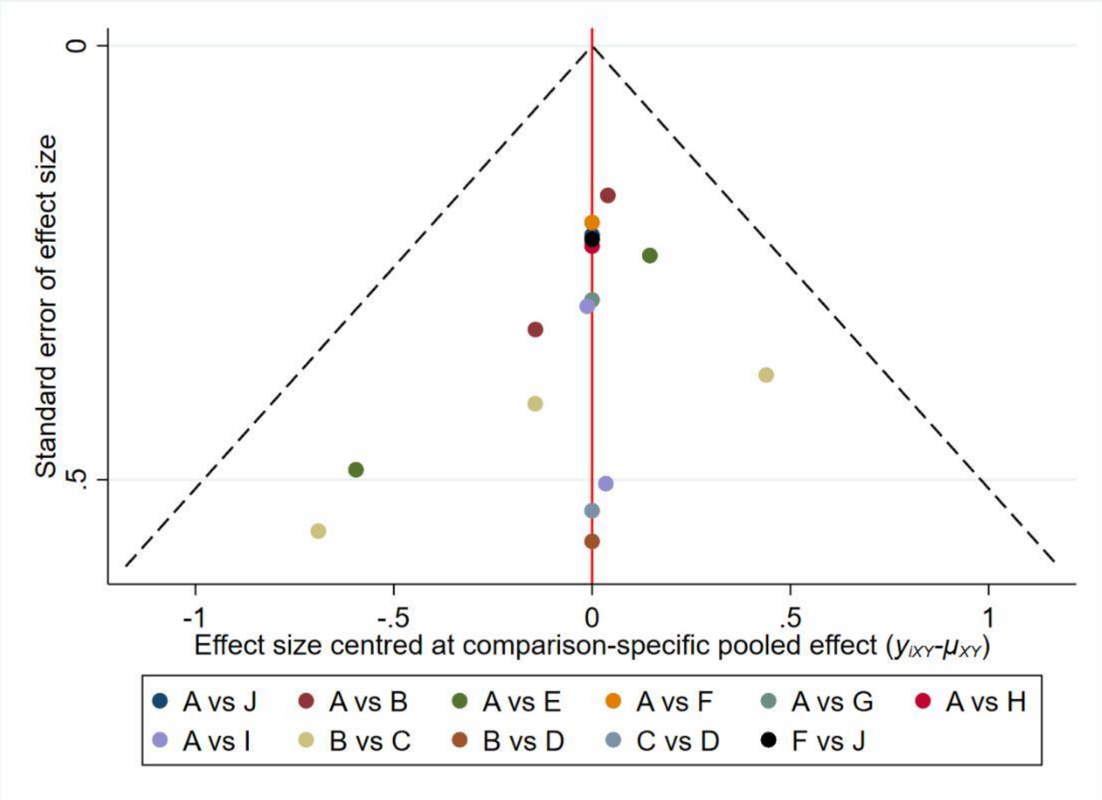
Comparison	Nature of the Evidence	GRADE	Downgarding due to
AB: Control Condition *vs* LWI	Mixed	LOW	Study limitations; Imprecision
AC: Control Condition *vs* Knee Brace	Indirect	LOW	Study limitations; Imprecision
AD: Control Condition *vs* LWI+Knee Brace	Indirect	LOW	Study limitations; Imprecision
AE: Control Condition *vs* Gait Retraining	Mixed	VERY LOW	Study limitations; Indirectness
AF: Control Condition *vs* Quadriceps Strengthening	Mixed	VERY LOW	Study limitations; Imprecision
AG: Control Condition *vs* Variable-Stiffness Shoes	Mixed	VERY LOW	Study limitations; Indirectness;
AH: Control Condition *vs* Hip Strengthening	Mixed	VERY LOW	Study limitations; Indirectness; Imprecision

AI: Control Condition *vs* Lower Limb Exercise	Mixed	VERY LOW	Study limitations; Indirectness; Imprecision
AJ: Control Condition *vs* Neuromuscular Exercise	Mixed	MODERATE	Study limitations
BC: LWI *vs* Knee Brace	Mixed	VERY LOW	Study limitations; Imprecision
BD: LWI *vs* LWI+Knee Brace	Mixed	VERY LOW	Study limitations; Imprecision
BE: LWI *vs* Gait Retraining	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
BF: LWI *vs* Quadriceps Strengthening	Indirect	LOW	Study limitations; Imprecision
BG: LWI *vs* Variable-Stiffness Shoes	Indirect	LOW	Study limitations; Indirectness
BH: LWI *vs* Hip Strengthening	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
BI: LWI *vs* Lower Limb Exercise	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
BJ: LWI *vs* Neuromuscular Exercise	Indirect	MODERATE	Study limitations
CD: Knee Brace *vs* LWI+Knee Brace	Mixed	VERY LOW	Study limitations; Imprecision
CE: Knee Brace *vs* Gait Retraining	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
CF: Knee Brace *vs* Quadriceps Strengthening	Indirect	LOW	Study limitations; Imprecision
CG: Knee Brace *vs* Variable-Stiffness Shoes	Indirect	LOW	Study limitations; Indirectness
CH: Knee Brace *vs* Hip Strengthening	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
CI: Knee Brace *vs* Lower Limb Exercise	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
CJ: Knee Brace *vs* Neuromuscular Exercise	Indirect	MODERATE	Study limitations
DE: LWI+Knee Brace *vs* Gait	Indirect	VERY LOW	Study limitations; Indirectness;

Retraining			Imprecision
DF: LWI+Knee Brace *vs* Quadriceps Strengthening	Indirect	LOW	Study limitations; Imprecision
DG: LWI+Knee Brace *vs* Variable-Stiffness Shoes	Indirect	VERY LOW	Study limitations; Indirectness
DH: LWI+Knee Brace *vs* Hip Strengthening	Indirect	LOW	Study limitations; Indirectness
DI: LWI+Knee Brace *vs* Lower Limb Exercise	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
DJ: LWI+Knee Brace *vs* Neuromuscular Exercise	Indirect	MODERATE	Study limitations
EF: Gait Retraining *vs* Quadriceps Strengthening	Indirect	VERY LOW	Study limitations; Indirectness
EG: Gait Retraining *vs* Variable-Stiffness Shoes	Indirect	VERY LOW	Study limitations; Indirectness
EH: Gait Retraining *vs* Hip Strengthening	Indirect	LOW	Study limitations; Indirectness
EI: Gait Retraining *vs* Lower limb Exercise	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
EJ: Gait Retraining *vs* Neuromuscular Exercise	Indirect	LOW	Study limitations; Indirectness
FG: Quadriceps Strengthening *vs* Variable-Stiffness Shoes	Indirect	VERY LOW	Study limitations; Indirectness
FH: Quadriceps Strengthening *vs* Hip Strengthening	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
FI: Quadriceps Strengthening *vs* Lower Limb Exercise	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
FJ: Quadriceps Strengthening *vs* Neuromuscular Exercise	Mixed	LOW	Study limitations; Imprecision

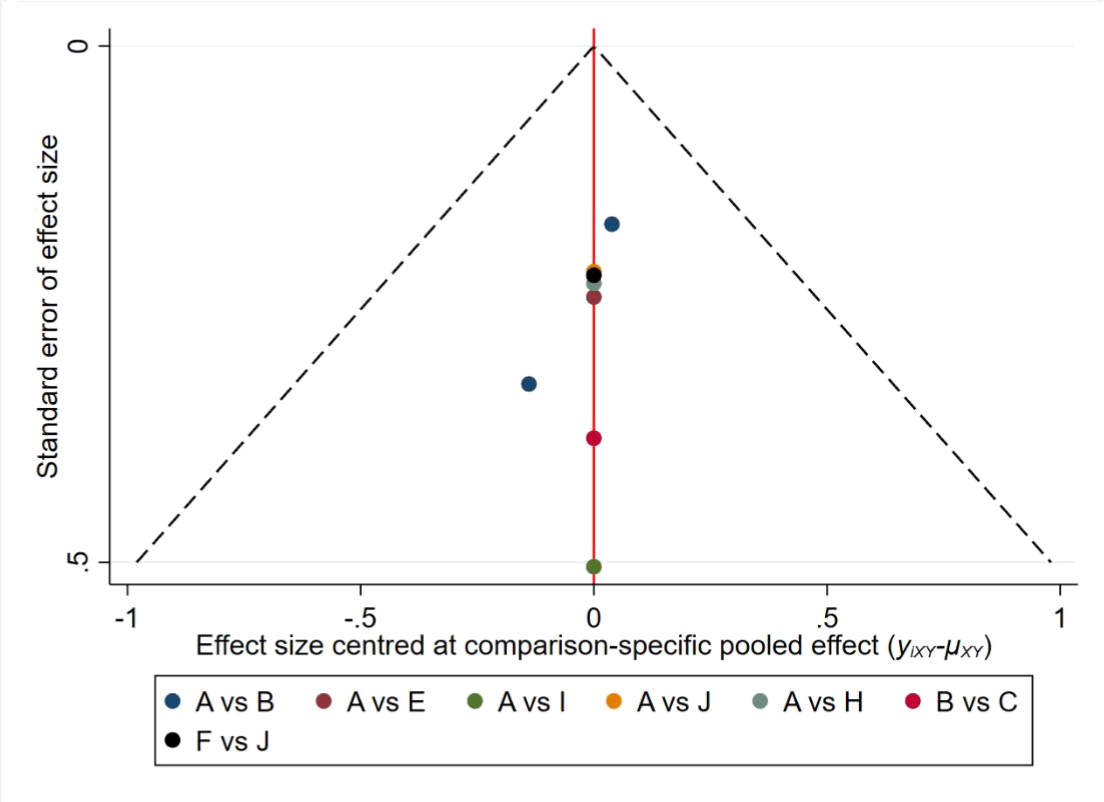
GH: Variable-Stiffness Shoes *vs* Hip Strengthening	Indirect	LOW	Study limitations; Indirectness
GI: Variable-Stiffness Shoes *vs* Lower Limb Exercise	Indirect	VERY LOW	Study limitations; Indirectness
GJ: Variable-Stiffness Shoes *vs* Neuromuscular Exercise	Indirect	LOW	Study limitations; Indirectness
HI: Hip Strengthening *vs* Lower Limb Exercise	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
HJ: Hip Strengthening *vs* Neuromuscular Exercise	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
IJ: Lower Limb Exercise *vs* Neuromuscular Exercise	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision

Appendix 7 Comparison-adjusted funnel plot for each outcome from the network meta-analysis



eFigure 1a. Comparison-adjusted funnel plot for First peak KAM.

A= Control condition; B= Lateral Wedge Insole; C= Knee Brace; D= Lateral Wedge Insole+ Knee Brace; E= Gait retraining; F= Quadriceps strengthening; G= Variable-stiffness shoe; H= Hip strengthening; I= Lower limb exercise; J= Neuromuscular exercise.



eFigure 1b. Comparison-adjusted funnel plot for KAAI.

A= Control condition; B= Lateral Wedge Insole; C= Knee Brace; E= Gait retraining; F= Quadriceps strengthening; H= Hip strengthening; I= Lower limb exercise; J= Neuromuscular exercise.

PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 3, Line 67-93
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 4-5, Line 107-169
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 7, Line 167-169
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	None
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 8, Line 179-186
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 8, Line 179-186
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1 Search strategies
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 8, Line 179-186 & Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 9, Line 206-215
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 8, Line 192-196
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 9-10, Line 217-242

PRISMA 2009 Checklist

			& Figure 4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 11-12, Line 244-272
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 11-12, Line 244-272

Section/Topic	#	Checklist Item	Reported on Page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 9-10, Line 217-228
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 12, Line 267-272
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 12-13, Line 285-294 & Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 13-14, Line 296-309 & Table 1, 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 16, Line 353-362 & Figure

PRISMA 2009 Checklist

			4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 14-15, Line 310-339 & Appendix 4
Synthesis of results	21	Present the main results of the review. If meta-analyses done, include for each, confidence intervals and measures of consistency.	Page 14-15, Line 310-339 &Table 3 & Figure 2, 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 16, Line 353-362 & Appendix 6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 15, Line 340-351 & Appendix 2 & 3 & 7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 16-17, Line 364-376
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 17-18,

PRISMA 2009 Checklist

			Line 392-410
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 19-22, Line 431-489
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 22, Line 499-502

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.