


BMJ Open Physical therapy and orthopaedic equipment-induced reduction in the biomechanical risk factors related to knee osteoarthritis: a systematic review and Bayesian network meta-analysis of randomised controlled trials

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To cite: Huang X-M, Yuan F-Z, Chen Y-R, *et al.* Physical therapy and orthopaedic equipment-induced reduction in the biomechanical risk factors related to knee osteoarthritis: a systematic review and Bayesian network meta-analysis of randomised controlled trials. *BMJ Open* 2022;**12**:e051608. doi:10.1136/bmjopen-2021-051608

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2021-051608>).

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Received 24 March 2021
Accepted 14 January 2022



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ABSTRACT

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

Design Systematic review with network meta-analysis (NMA) 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 or orthopaedic equipment in reducing the biomechanical risk factors which included knee adduction moment (KAM) and knee adduction angular impulse (KAAl) in individuals with tibiofemoral OA.

Data extraction and synthesis Two authors extracted data independently and assessed risk of bias. We conducted an NMA to compare multiple interventions, including both direct and indirect evidences. Heterogeneity was assessed (sensitivity analysis) and quantified (I^2 statistic). Grading of Recommendations Assessment, Development and Evaluation assessed the certainty of the evidence.

Results Eighteen randomised 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 with the control condition group. And based on the collective probability of being the overall best therapy for reducing KAAl, 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

Strengths and limitations of this study

- The Bayesian method provided the probability estimates regarding the relative efficacy of specific interventions, even though standard methods found no significant differences among them.
- Physical therapies and orthopaedic equipment are complex interventions with a small number of trials comparing the different types of interventions.
- Besides knee adduction moment and knee adduction angular impulse, 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 network meta-analysis (NMA).
- Heterogeneity in NMA may reduce the validity of the results.

and KAAl and therefore it was the most recommended therapy for reducing the biomechanical risk factors.

INTRODUCTION

Knee osteoarthritis (KOA), a 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 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 loads¹⁰ 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 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 of the knee.

Recent advancements in healthcare have resulted in the development of several protocols for the intervention and treatment of KOA. Patients with KOA are primarily recommended physical therapy or orthopaedic 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 programmes, 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 orthopaedic equipment mainly incorporates customised shoes/footwear, wedged insoles and knee braces.

Several literary insights have shown the positive impact of physical therapy or orthopaedic equipment in patients with KOA.^{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} 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 centre 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 orthopaedic equipment in reducing biomechanical risk factors in patients with KOA.

Therefore, the research questions for this systematic review were:

1. Are physical therapies or orthopaedic 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?

METHODS

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

Identification and selection of studies

The following databases were searched for listed randomised 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 orthopaedic 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 online supplemental appendix 1). Additionally, we performed manual analyses of the published references regarding the use of physical therapy or orthopaedic equipment for treating KOA.

The eligibility of searched publications was independently reviewed by X-MH and Z-XY following the Cochrane manual directives.²⁸ Any additional inconsistencies were resolved either by deliberation or by a senior expert (YH). First, 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

Box 1 Inclusion criteria

Design

- ▶ Randomised controlled trial.

Participants

- ▶ People with radiologically confirmed knee osteoarthritis.

Intervention

- ▶ Manual therapy.
- ▶ Aerobic exercise.
- ▶ Pulsed electrical stimulation.
- ▶ Acupuncture.
- ▶ Knee braces.
- ▶ Ice/cooling treatment.
- ▶ Pulsed electromagnetic fields.
- ▶ Balneotherapy.
- ▶ Interferential therapy.
- ▶ Transcutaneous electrical nerve stimulation.
- ▶ Heat treatment.
- ▶ Foot orthoses.
- ▶ Laser/light therapy.
- ▶ Muscle-strengthening exercise.
- ▶ Static magnets.
- ▶ Tai Chi.
- ▶ Athletic tape.
- ▶ Neuromuscular electrical stimulation.

Comparator

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

Outcome measures

- ▶ Knee adduction moment and knee adduction angular impulse.

Comparisons

- ▶ All interventions compared with the comparator and to each other.

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 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; and (4) studies that did not report KAM or KAAI.

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 NMA 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 (X-MH and Z-XY) 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.

Assessment of characteristics of studies

Risk of bias

This NMA used the Cochrane Risk of Bias 2 to assess the risk of bias in randomised controlled trials using the following evaluation indicators: randomisation process, deviations from the intended interventions, missing outcome data, outcome measurement and selection of the reported results.²¹ The judgement 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 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 orthopaedic 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 orthopaedic equipment before the intervention, while post-intervention biomechanical risk factors were extracted from walking trials that incorporated orthopaedic equipment. Biomechanical risk factors included in the study were the first peak KAM, the second peak KAM and KAAI. KAM was normalised 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.

Statistical analysis

An NMA 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 randomisation 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 as the statistical indicator of the effect, and the frequentist 95% CI of each effect was calculated. Additionally, the I^2 statistic was used to analyse 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 online supplemental appendix 2, eFigures 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 online supplemental appendix 3, eFigure 3). If $p > 0.05$, then the consistency model was used for analysis; otherwise, the inconsistency model was used.³⁹ Normal likelihood distributions were assumed, non-informative prior distributions were set and three Markov chains were run simultaneously. Since 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.⁴⁰ Besides, a conventional meta-analysis was also carried out (see online supplemental appendix 4, eFigure 4A–C). Comparison-adjusted funnel plots were prepared that represented different comparisons with different colours.

The data from the eligible studies were combined using the Review Manager (RevMan) software V.5.3. The contribution of the effect sizes was dependent on the sample size and their estimation accuracy. The Bayesian analyses were carried out using WinBUGS V.1.4.3. Stata (StataCorp. 2015. Stata Statistical Software: Release 15) was employed to conduct the frequentist NMA.

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.

RESULTS

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 evaluated their full text. **Figure 1** presents the study selection flow chart. Eighteen randomised 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 online supplemental appendix 5, eFigure 5A,B), only 14 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}

Characteristics of included studies

All studies included tibiofemoral OA cases, which were radiologically confirmed. Although most interventions

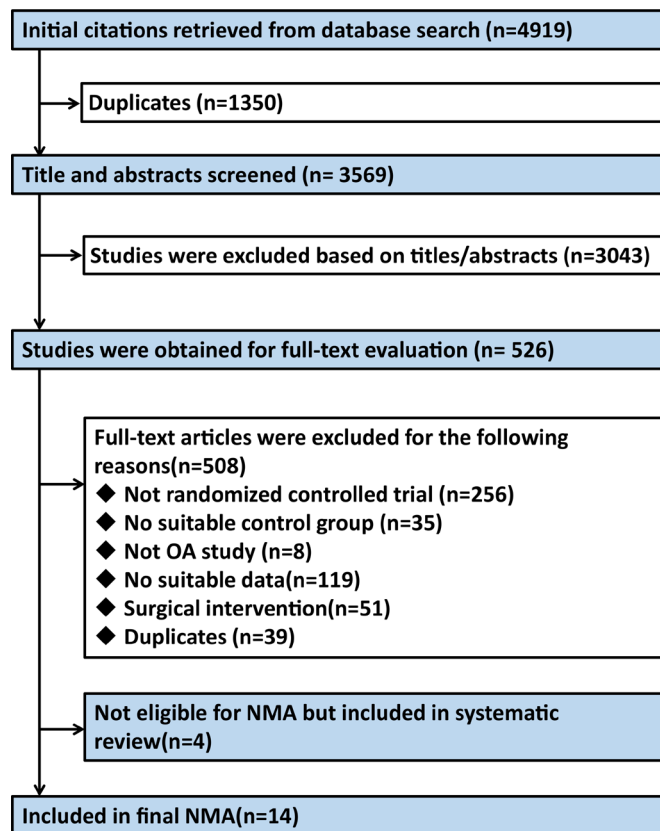


Figure 1 Flow chart of the study selection. NMA, network meta-analysis; OA, osteoarthritis.

were administered over an 8–13 week period, the treatment duration ranged from 2 weeks to 12 months. The number of exercises varied from 2 to 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 14 studies, 9 were classified as Kellgren/Lawrence grade 2 and above. All studies reported either the values for body mass index (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 randomised crossover design.⁵⁰ After consulting a reference manual along with a professional statistician, the mean and SD of the experimental and the control groups were analysed in this NMA.²⁸ **Tables 1 and 2** summarise the characteristics of the included studies and their participants.

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 (unloader brace with valgus and external rotation functions) offers additional advantages on first peak KAM compared with V3P-brace (three-point bending system valgus knee brace) and ACL-brace (functional medial-lateral stabilisation brace used after ligament injuries).⁵⁴ No first peak KAM reduction

Table 1 Characteristics of included studies

Authors	Country	Clinical criteria	Radiographic features	Intervention	Comparisons	Follow-up
Barrios <i>et al</i> ⁴²	USA	Medial compartment knee OA; pain VAS (≥ 3 of 10 on walking)	K/L grade ≥ 2 , medial tibiofemoral compartment	bespoke full-length LWI	Placebo	12 months
Hinman <i>et al</i> ⁵³	Australia	Medial compartment knee OA; pain NRS (> 4 of 11 on walking) over the previous week	K/L grade ≥ 2 , medial tibiofemoral compartment	5° full-length LWI	Placebo	6 months
Arazpour <i>et al</i> ⁴¹	Iran	Medial compartment knee OA	K/L grades 1 and 2, medial tibiofemoral compartment	6° full-length LWI	bespoke unloader knee braces	6 weeks
Jones <i>et al</i> ⁵⁰	UK	Medial compartment knee OA	K/L grades 2 and 3, medial JSN	LWI: The heel was inclined at 5° with the inclination reduced to 0° at the fifth metatarsal head with a contoured arch profile	6° valgus knee brace	2 weeks
Khosravi <i>et al</i> 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
Hunt <i>et al</i> ⁴⁸	USA	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 <i>et al</i> ⁵²	Australia	Medial compartment knee OA; medial knee pain	K/L grade ≥ 2 , medial JSN	Quadriceps strengthening	No intervention	12 weeks
Erhart-Hledik <i>et al</i> ⁴⁵	USA	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 <i>et al</i> ⁴³	Australia	Medial compartment knee OA; varus malalignment; pain (> 3 of 11 on walking)	K/L grade ≥ 2 , medial JSN	Hip strengthening	No intervention	13 weeks
Cheung <i>et al</i> ²³	China	Medial compartment knee OA; knee pain occurred at least 1 day a week during each of the 8 weeks prior	K/L grades 1 and 2	Gait retraining for KAM reduction	Walking without any guidance	6 weeks
Foroughi <i>et al</i> ⁴⁶	Australia	Primary knee OA	K/L grade ≥ 1	Lower limb exercise	Sham-exercise	6 months
Bennell <i>et al</i> 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 <i>et al</i> 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 <i>et al</i> ⁴⁷	Denmark	Primary knee OA; pain KOOS (< 80 of 100, at least mild pain)	K/L grade ≤ 3	Neuromuscular exercise	Analgesic advice	8 weeks
Song <i>et al</i> ⁵⁵	China	Medial compartment knee OA in one or both legs.	K/L grade ≤ 3	PNF (1 hour sessions three times a week)	Watch television or read magazines at the same time	12 weeks

Continued

Table 1 Continued

Authors	Country	Clinical criteria	Radiographic features	Intervention	Comparisons	Follow-up
Wang <i>et al</i> ⁵⁷	China	Medial compartment knee OA	K/L grades 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 <i>et al</i> ⁵⁴	Canada	Medial compartment knee OA; pain >31/100 on WOMAC; varus knee alignment $\geq 2^\circ$	K/L grades 2 and 3	V3P-brace; VER-brace; ACL-brace (wear the brace as often as possible)	/	3 months
Trombini-Souza <i>et al</i> ⁵⁶	Brazil	Medial compartment knee OA; knee pain between 3 and 8 on VAS	K/L grades 2 and 3	Minimalist footwear (Moleca)	Standard, neutral tennis shoe	6 months

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.

ACL-brace, Functional medial-lateral stabilisation brace used after ligament injuries; JSN, Joint space narrowing; K/L, Kellgren/Lawrence; KOOS, Knee injury and Osteoarthritis Outcome Score; LWI, Lateral wedged insoles; NR, Not reported; NRS, Numerical rating scale; OA, Osteoarthritis; PNF, Proprioceptive neuromuscular facilitation; VAS, Visual analogue scale; VER-brace, Unloader brace with valgus and external rotation functions; V3P-brace, Three-point bending system valgus knee brace; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

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.

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 10 studies.^{42-44 47-50 53 54 56} 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.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.

Heterogeneity

We removed a study which had a short follow-up time and might cause heterogeneity,⁵⁰ and performed another NMA. There was no difference between the results of the reanalysis and the current ranking (see online supplemental appendix 2, eFigures 1 and 2).

GRADE assessment

According to the GRADE framework (see online supplemental 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.

Risk of bias

Figure 4 depicts a summary of the risk-of-bias scores for the included randomised controlled trials (RCTs) in this analysis. Nine studies presented a clear description of generating a randomisation sequence.^{43-47 49 52 56 57} The study by Hinman *et al* was the only double-blinded study,

Table 2 Characteristics of participants in included studies*

Authors	No.	Sex, M:F	Age, years	Height, metres	Body mass, kg	BMI, kg/m ²	Bilateral knee OA included	K/L grade, no.				Main outcomes
								1	2	3	4	
Barrios <i>et al</i> ⁴²	38	NR	61.90±8.37	NR	NR	32.00±7.43	NR	0	17	14	7	First KAM; KAAI
Hinman <i>et al</i> ⁶³	164	20:21	64.30±7.45	1.67±0.10	82.95±14.76	29.70±3.64	NR	0	49	52	63	First KAM; KAAI
Arazpour <i>et al</i> ⁴¹	24	3:4	59.29±2.37	NR	NR	27.01±1.71	Yes	9	15	0	0	First KAM
Jones <i>et al</i> ⁶⁰	28	4:3	66.30±8.20	1.75±0.13	88.7±15.10	NR	No	0	10	18	0	First and second KAM; KAAI
Khosravi <i>et al</i> ⁵¹	21	13:8	58.97±6.80	1.62±0.11	79.11±9.35	NR	NR	0	9	12	0	First KAM
Hunt <i>et al</i> ⁴⁸	79	24:55:00	64.99±8.60	1.65±0.10	74.59±13.15	27.35±3.48	Yes	0	37	31	11	First and second KAM; KAAI
Lim <i>et al</i> ⁶²	107	48:59:00	64.60±8.51	1.65±0.10	79.41±15.32	28.96±4.85	Yes	0	34	29	44	First KAM
Erhart-Hledik <i>et al</i> ⁴⁵	79	41:38:00	61.70±9.43	1.69±0.08	79.50±15.07	27.51±4.87	Yes	NR	NR	NR	NR	First KAM
Bennell <i>et al</i> ⁴³	89	46:43:00	64.55±8.34	NR	NR	27.94±4.41	Yes	0	30	29	30	First KAM; KAAI
Cheung <i>et al</i> 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	First KAM
Foroughi <i>et al</i> ⁴⁶	54	0:54	65.48±7.44	NR	82.87±18.43	32.07±7.08	Yes	20	7	20	1	First and second KAM
Bennell <i>et al</i> ⁴⁴	100	48:52:00	62.45±7.32	1.67±0.10	82.70±14.29	29.65±4.08	Yes	0	22	43	35	First KAM; KAAI
Hunt <i>et al</i> ⁴⁹	17	8:9	66.10±11.3	NR	NR	27.00±4.50	Yes	0	10	5	2	First KAM; KAAI
Holsgaard-Larsen <i>et al</i> ⁴⁷	93	39:54:00	58.10±7.96	NR	79.64±12.49	26.90±3.09	NR	45	31	17	0	First KAM; KAAI
Song <i>et al</i> ⁵⁵	36	1:1	68.01±3.91	1.62±0.07	68.16±6.77	NR	Yes	9	20	7	0	First KAM
Wang <i>et al</i> ⁵⁷	36	1:5	63.50±7.95	NR	NR	23.75±2.66	Yes	0	19	17	0	First and second KAM
Robert-Lachaine <i>et al</i> 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	First and second KAM; KAAI
Trombini-Souza <i>et al</i> ⁵⁶	56	NR	66.00±5.00	1.60±0.10	73.40±13.10	NR	NR	0	NR	NR	0	First KAM; KAAI

*Values are the mean±SD unless indicated otherwise.

BMI, body mass index; JSN, joint space narrowing; KAAI, knee adduction angular impulse; KAM, knee adduction moment; K/L, Kellgren/Lawrence; NR, not reported.

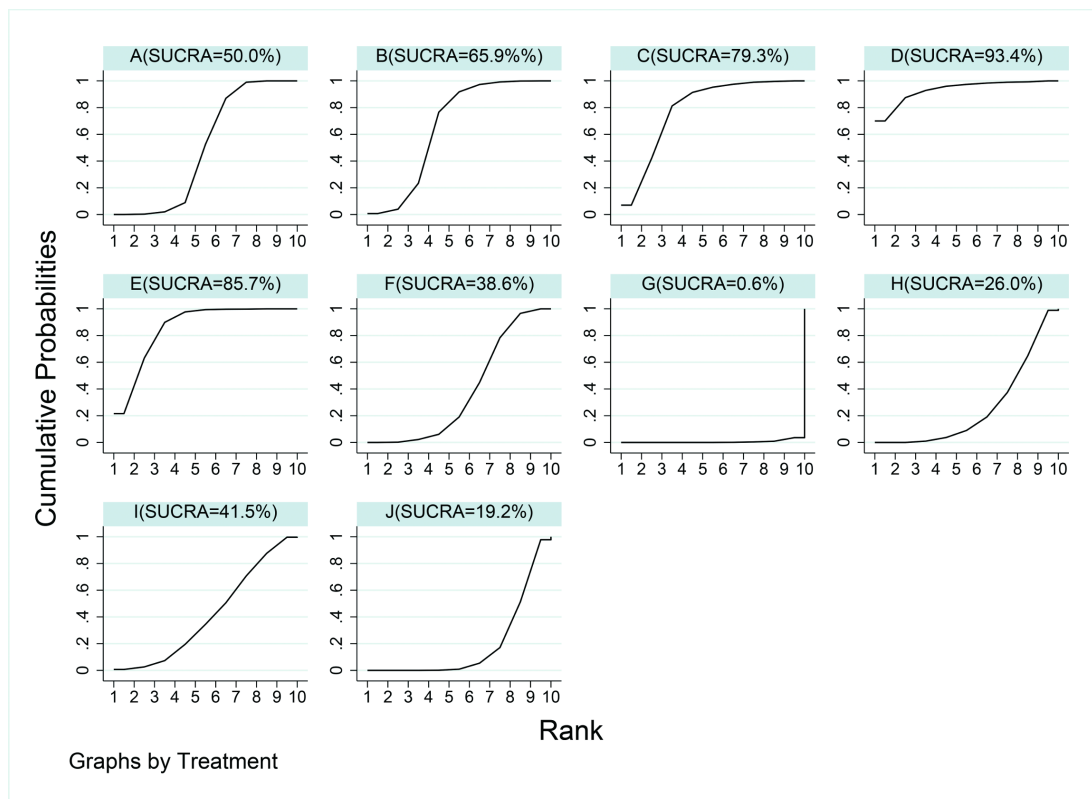


Figure 2 Rankings for effects on first peak knee adduction moment. The graph displays the distribution of probabilities for each treatment. The X-axis represents the possible rank of each treatment (from the best to worst according to the outcomes), Y-axis represents the cumulative probability for each 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; SUCRA, surface under the cumulative ranking curve.

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 online supplemental appendix 7, eFigure 6A,B).

DISCUSSION

Our study results did not show any significant difference regarding the relative efficacy of intervention among different types of physical therapies or orthopaedic 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 NMA 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.

This study had several strengths and limitations. This NMA is the first report on the effects of physical therapy or orthopaedic equipment on the parameters of knee load (KAM and KAAI). Since physical therapies and orthopaedic equipment are complex interventions with a small number of trials comparing the different types of interventions, NMA 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 with 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

Table 3 Detailed results of network meta-analysis for the first peak knee adduction moment (grey) and knee adduction angular impulse (white)

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

Data are standard mean differences (SMDs) (from the top left to the bottom right, higher comparator vs 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.

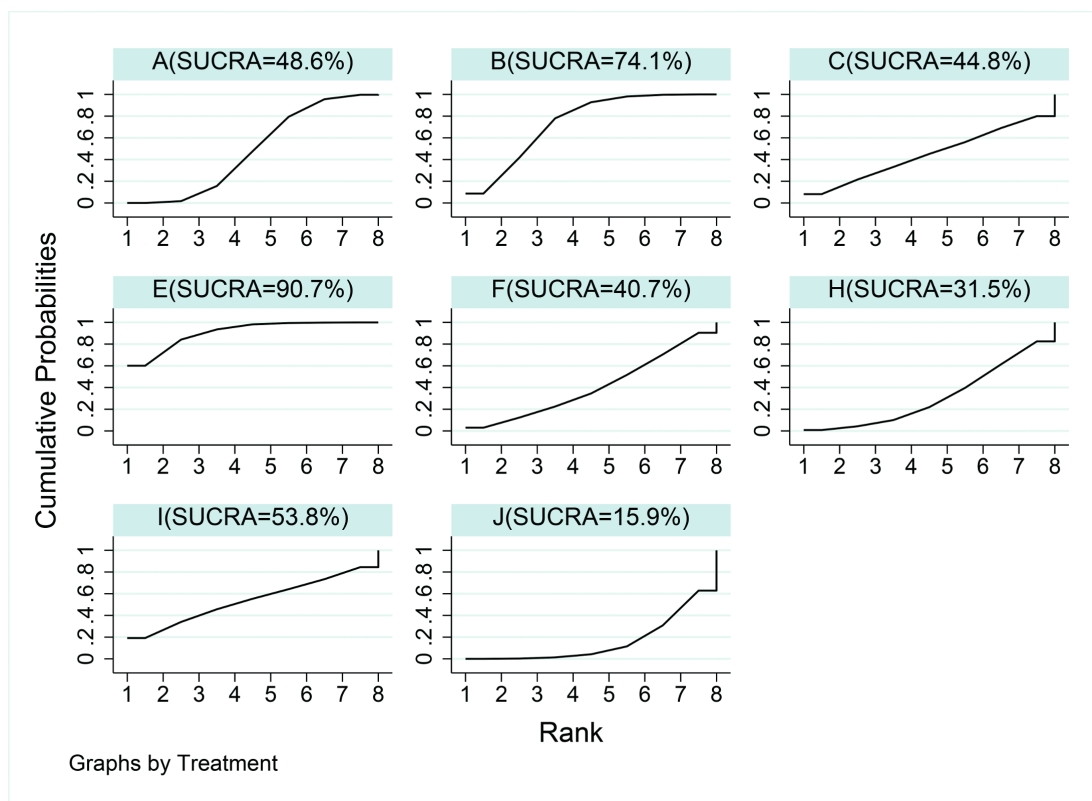


Figure 3 Rankings for effects on knee adduction angular impulse. The graph displays the distribution of probabilities for each treatment. The X-axis represents the possible rank of each treatment (from the best to worst according to the outcomes), Y-axis represents the cumulative probability for each 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; E, gait retraining; F, quadriceps strengthening; H, hip strengthening; I, lower limb exercise; J, neuromuscular exercise; SUCRA, surface under the cumulative ranking curve.

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 analysing 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, newer approaches are now being developed that would include all the time points in an NMA.²⁸ Our study was unable 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.^{59–61} Additionally, other parameters, such as the external knee flexion moment to joint load, should have been studied in detail. However, due to lesser available literature, our study was unable to include them. Finally, standard/conventional care, placebo intervention, no intervention, sham-exercise, analgesic advice and education were all considered as the same parameter in defining the ‘control condition’. Therefore, the relative rankings in our study might not represent the true factual rankings as compared with actual standard care due to

lack of consideration of bias introduced by heterogeneity and lack of blinding.

A previous review reported that LWIs were able to reduce the KAM at the baseline¹³; however, the effect was no longer observed after a specific period. Another study displayed that a month wear-in period was the longest study time in which no reduction in biochemical risk factors was observed despite continued wear.¹⁸ Besides, several other systematic reviews stated that exercise and gait retraining could further reduce pain and improve motor functioning in people with KOA.^{62–64} There is a high probability that any clinical changes occurring in previous studies might be due to increased physical activity levels, and not owing to the 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.⁶⁵ In our NMA, we focused on the studies of non-immediate effect, removed the research with a follow-up time of less than 1 month in the sensitivity analysis and made the final rank. Our results showed that only gait training produces a significant reduction in KAM and KAAI when compared with control condition, indicating that the biomechanical reduction effect of orthopaedic equipment cannot be maintained for a long time when they are donned. It was evident that an

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	+	?	+	+	?	?

Figure 4 Risk of bias summary.

extension of the treatment time led to a decrease in the biomechanical reduction effect, which might be due to the gradual deformation of the orthopaedic equipment that renders them ineffective, despite being made from high-density materials.

On the other hand, various physical therapies and orthopaedic equipment also should be considered for relieving patients' pain, which has been the focus of several past reviews. As an important gait parameter, the joint pain can affect the kinetics and kinematics of walking.¹⁹ 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 proper initiation, the efficiency of physical exercise over placebo reached a maximum level at 2 months.⁶⁶

Cumulative loading is another significant parameter regarding knee load exposure in OA.⁶⁷ KAAI has been proposed as another indicator for evaluating the

duration and intensity of KOA load, despite the association between KAM and disease progression. According to a study lasting for a year, the loss of medial tibiofemoral cartilage was not directly linked to KAM but was promptly related to KAAI.¹⁴ Although the effect of physical therapy or orthopaedic equipment on KAM are short-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 NMA 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 patients with medial tibiofemoral KOA after controlling additional variables.⁴⁹ It was evident that appropriate intervention in the biomechanical structure of the knee joint in patients with KOA 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 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.

Additionally, some other therapies have also been reported, such as Taiji, ultrasound, acoustic exercises. 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 patients with OA. After accumulating evidence regarding the role of non-surgical therapy in KOA, another similar NMA to understand the relative effectiveness of various treatment in the relevant patients.

CONCLUSION

To conclude, this NMA provides valuable insights regarding the KAM and KAAI alterations in patients with

OA after the usage of physical therapy or orthopaedic 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 patients with OA.

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Contributors X-MH and F-ZY conceived of the study, and participated in its design and coordination and helped to draft the manuscript; Z-XY, YH and Y-RC contributed significantly to analysis and manuscript preparation; J-KY and LL helped perform the analysis with constructive discussions and revised it critically for important intellectual content. J-KY is responsible for the overall content as the guarantor.

Funding This work was supported by the National Key R&D Program of China (No.2017YFB1303000) and the Construction of a Basic Public Service Platform for Industrial Technology in the Field of Advanced Medical Equipment (0714-EMTC-02-00897).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study does not involve human participants.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

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