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## 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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 2 **Factors Related to Knee Osteoarthritis: A systematic review and Bayesian**  
 3 **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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65

66 **ABSTRACT**

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

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

71 *Participants:* People with KOA.

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

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

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

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

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

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3  
4 87 intervention as it could reduce the values for KAM and KAAI at the same time based  
5  
6 88 on cumulative ranking and relative effect estimates.  
7  
8

9 89 *Registration*. INPLASY202090054; Doi:10.37766/inplasy2020.9.0054.  
10

## 11 90 **Significance and Innovations**

12  
13  
14 91 ① This Bayesian network meta-analysis is the first review on effect of physical  
15  
16 92 therapy and orthopedic equipment on the biomechanical parameters (KAM &  
17  
18 93 KAAI) of the knee OA.  
19

20  
21  
22 94 ② This review observes a null statistical reduction in KAM and KAAI for most  
23  
24 95 physical therapies and orthopedic equipment, using these non-surgical treatments  
25  
26 96 clinically could improve symptoms and physical activity level without increasing  
27  
28 97 the biomechanical magnitude; thus, improving the quality of life of patients with  
29  
30 98 KOA.  
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33  
34  
35 99 ③ This review suggests that further studies should require more research articles in  
36  
37 100 these areas to further explore the impact of various non-surgical therapies on OA  
38  
39 101 patients.  
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## 48 104 **1. INTRODUCTION**

49  
50 105 Knee osteoarthritis (KOA), a chronic progressive disease, affects approximately 3.8%  
51  
52 106 of people worldwide, mainly middle-aged and older adults. It is more prevalent in  
53  
54 107 women than in men<sup>1,2</sup>. The main clinical manifestation of KOA is knee pain and is  
55  
56 108 often accompanied by radiographic degeneration of the intra-articular cartilage  
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1  
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3  
4 109 associated with hypertrophic bone changes <sup>3</sup>. With the development of KOA,  
5  
6 110 patients may also report stiffness, locking, instability and function loss. Though it  
7  
8  
9 111 is not fatal, the persistent pain and movement difficulties associated with this  
10  
11  
12 112 condition negatively impact the physical and mental health of the patients; thus,  
13  
14 113 reducing their quality of life <sup>4</sup>.

15  
16  
17 114 These pathological changes of knee joint structure are the result of the break of  
18  
19  
20 115 biomechanical balance and the progression of the disease is now believed to be  
21  
22 116 associated with malalignment of the lower limb <sup>5</sup>. Of the three compartments of a  
23  
24  
25 117 knee joint, KOA mostly occurs in the medial tibiofemoral compartment as it bears  
26  
27 118 60-91% of the total body load, higher than the lateral one <sup>6</sup>. The external knee  
28  
29  
30 119 adduction moment (KAM) results from the unequal distribution of the transmitted  
31  
32  
33 120 load on both sides in the normal gait of humans. It is defined as the cross product  
34  
35 121 of the ground reaction force and the distance between the knee joint and the force  
36  
37  
38 122 line <sup>7</sup>. Individuals with obesity or other risk factors tend to have frontal plane knee  
39  
40  
41 123 malalignment, which alters the normal force line, forcing the medial knee joint to  
42  
43 124 bear more load and increased KAM <sup>8,9</sup>. The accumulation effect of the moment is  
44  
45  
46 125 determined by calculating the integral of the moment to time, which is also termed  
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48  
49 126 as Knee adduction angular impulse (KAAI). It reflects the change in knee joint  
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51  
52 127 rotation state during a stance period of gait <sup>10</sup>. Previous studies have revealed a  
53  
54  
55 128 strong correlation between the peak levels of KAM and KAAI and the severity and  
56  
57  
58 129 progression of the disease, which was reflected and calculated by the loss of medial  
59  
60 130 tibial cartilage<sup>11,12</sup>. Both these biomechanical parameters (KAM and KAAI) are

1  
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3  
4 131 commonly used to evaluate the medial knee load and predict the long-term  
5  
6 132 structural deterioration.  
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8  
9 133 Recent advancements in healthcare have resulted in the development of several  
10  
11 134 protocols for the intervention and treatment of KOA. KOA patients are primarily  
12  
13  
14 135 recommended non-surgical treatments with the intention of correcting the deviated  
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16  
17 136 force line and delaying the progressive pathological damage inside the knee joint <sup>7</sup>.  
18  
19 137 Several non-surgical treatments, such as exercise therapies and noninvasive orthotic  
20  
21  
22 138 devices, have been introduced in orthopedic clinics. Both these modalities focus on  
23  
24  
25 139 relieving pain and improving patients' symptoms by changing the biomechanical  
26  
27  
28 140 state of the knee joint. The exercise therapies mainly include muscular  
29  
30  
31 141 strengthening and gait modification, while orthotic devices include customized  
32  
33  
34 142 shoes/footwear, wedged insoles, and knee braces.  
35  
36 143 Previous studies have shown the positive impact of exercise therapy in KOA. The  
37  
38 144 strengthening of related lower limb muscles, which play a vital role in disease  
39  
40  
41 145 progression, are known to reduce pain and improve motor functions and are often  
42  
43 146 recommended to KOA patients <sup>13</sup>. Additionally, gait training presents a viable way  
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45  
46 147 to correct the patients' underlying gait pattern, which could also reduce their knee  
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48  
49 148 load and pain <sup>14,15</sup>. Further, several kinds of orthotic devices have been introduced  
50  
51  
52 149 for the treatment of KOA. The clinical use of lateral wedge insoles (LWI) has  
53  
54 150 gained immense popularity since its origin in 1987 <sup>16,17</sup>. The insoles work by  
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56  
57 151 shifting the lateral part of the foot more than the medial part by a slope. Thus, a  
58  
59 152 slope is created to increase the valgus tendency of lower extremities. The center of  
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1  
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4 153 the ground reaction force is shifted laterally, which induces a reduction in force  
5  
6 154 lever arm length and magnitude. Also, the valgus knee brace is a commonly used  
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9 155 device. It applies an external valgus force around the knee joint to reduce the medial  
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11  
12 156 knee load.

13  
14 157 In the past, several systematic reviews and meta-analysis have been published  
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16  
17 158 featuring the medical effects of a single KOA treatment. However, only a few of  
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20 159 them have focused on multifaceted interventions. Also, only a few reviews have  
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23 160 reported the effects of these changes on the biomechanical parameters. The  
24  
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26 161 mechanical changes in the body were not sufficiently investigated. Current reviews  
27  
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29 162 on KAM and KAAI have also not compared these changes. Thus, we performed a  
30  
31  
32 163 network meta-analysis (NMA) to appraise the benefits of physical treatments in  
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35 164 reducing the biomechanical risk factors in KOA patients to overcome these  
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38 165 shortcomings, and to help achieve the goal of reducing pain and improving function.  
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40  
41 166 Therefore the research questions for this systematic review were:

- 42  
43 167 1. Do physical therapy and orthopedic equipment efficiency in reducing the  
44  
45 168 biomechanical risk factors in people with knee osteoarthritis (KOA)?  
46  
47 169 2. Is one therapy better than the others for improving these outcomes?

## 48 170 2. METHODS

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50  
51 171 The protocol was registered on the INPLASY (registration number:  
52  
53 172 INPLASY202090054; Doi:10.37766/inplasy2020.9.0054). All pooled analyses  
54  
55  
56 173 were derived from previous studies and, therefore, did not require ethical approval  
57  
58  
59 174 and informed consent.  
60

## 175 **2.1 Identification and selection of studies.**

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

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

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

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4 197 the condition of bare foot.

5  
6 198 The exclusion criteria included: (1) studies that were not consistent with the  
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9 199 eligibility criteria; (2) studies that were in the form of the non-trial papers, including  
10  
11  
12 200 abstracts, comments, letters, or reviews; (3) studies including participants who had  
13  
14 201 received surgical treatment in the past; (4) studies that did not report suitable data.

## 17 202 **2.2 Data Collection and Quality assessment.**

18  
19 203 KAM and KAAI were the preferred biomechanical measures used in this meta-  
20  
21  
22 204 analysis. The biomechanical indicators of the included studies were measured on  
23  
24  
25 205 flat ground or treadmills. The number of trials that focused on the second peak of  
26  
27 206 KAM was insufficient to conduct an independent network meta-analysis.

28  
29  
30 207 Two authors (HXM, YZX) extracted data independently and then cross-checked the  
31  
32  
33 208 data. A predefined information sheet was used to extract the data, which included  
34  
35 209 the details of the first author (name), country, year of publication, population  
36  
37  
38 210 characteristics, intervention, and the time point. The authors of the original study  
39  
40 211 were contacted if more data was required.

## 43 212 **2.3 Assessment of characteristics of studies.**

### 45 213 *Risk of bias*

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47  
48 214 In this network meta-analysis, we used the Cochrane risk bias tool to assess the risk  
49  
50  
51 215 of bias in randomized controlled trials using the following evaluation indicators:  
52  
53 216 sequence generation, allocation concealment, blinding, incomplete outcome data  
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56 217 addressed, selective outcome reporting, and other biases<sup>18</sup>. The judgment of the bias  
57  
58 218 risk of this item was presented as "low," "high," and "unclear." Two authors



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4 219 independently evaluated the risk of bias of the included studies. The authors  
5  
6 220 discussed or referred to the opinion of a senior author to resolve any disagreements.  
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8  
9 221 Additionally, we evaluated the certainty of evidence which contributed to network  
10  
11 222 estimates of the main outcomes with the Grading of Recommendations Assessment,  
12  
13  
14 223 Development and Evaluation (GRADE) framework.

#### 17 224 *Intervention*

18  
19 225 In order to describe the experimental intervention, we extracted the following  
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21  
22 226 information: the method of training with relevant further details, the details and  
23  
24  
25 227 characteristics of orthopedic equipment, the frequency and total duration of training  
26  
27 228 or wearing.

#### 30 229 *Outcome measures*

31  
32 230 Biomechanical risk factors were extracted from barefoot walking test, including the  
33  
34  
35 231 first peak KAM, the second peak KAM and KAAI. KAM was normalized as %body  
36  
37  
38 232 weight times height, with conversion to Nm/kg where necessary. KAAI was the  
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40 233 accumulation effect of the moment which was determined by calculating the  
41  
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43 234 integral of the moment to time.

### 45 235 **2.4 Statistical Analysis.**

46  
47  
48 236 We conducted a network meta-analysis to compare multiple interventions,  
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51 237 including both direct evidences (where treatments were compared directly) and  
52  
53 238 indirect evidences (where treatments were compared with a common control),  
54  
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56 239 maintaining randomization in each independent study. Interventions and  
57  
58 240 demographic characteristics were either consistent or comparable across the  
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4 241 included studies<sup>19-24</sup>.  
5  
6 242 Due to different units, the continuous data used the standard mean difference (SMD)  
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9 243 as the statistical indicator of the effect, and the Frequentist 95% confidence interval  
10  
11 244 (CI) of each effect was calculated. Additionally, the  $I^2$  statistic was used to analyze  
12  
13  
14 245 the overall heterogeneity of the two-arm study and the network. The fixed-effect  
15  
16 246 model was used in case no statistical heterogeneity was found between the studies  
17  
18 247 ( $p > 0.05$ ,  $I^2 < 50\%$ ); else, the random effect model was used, and the source of  
19  
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21 248 heterogeneity was analyzed. The Node-Split Model was used for testing  
22  
23 249 consistency. If  $p > 0.05$ , then the consistency model was used for analysis; else, the  
24  
25 250 inconsistency model was used for analysis. Normal likelihood distributions were  
26  
27 251 assumed, non-informative prior distributions were set, and three Markov chains  
28  
29 252 were run simultaneously. The number of update iterations was 50,000, a total of  
30  
31 253 5000 simulations were used for annealing, and the subsequent 45,000 iterations  
32  
33 254 were examined. The mean rank and surface under the cumulative ranking curve  
34  
35 255 (SUCRA) were used for reporting the probability values. A SUCRA value of 100%  
36  
37 256 was considered best, whereas 0% indicated the worst treatment.  
38  
39 257 The data from eligible studies were combined using the Review Manager (RevMan)  
40  
41 258 software v5.3. The contribution of the effect sizes was dependent on the sample size  
42  
43 259 and their estimation accuracy. We performed the Bayesian analyses using  
44  
45 260 WinBUGs v1.4.3. Stata (StataCorp. 2015. Stata Statistical Software: Release 15.  
46  
47 261 College Station, TX: StataCorp LP) was used to conduct the frequentist NMA.

### 262 3. RESULTS

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

### 263 3.1 Flow of studies through the review

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

### 272 3.2 Characteristics of included studies

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

1  
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3  
4 285 analysis<sup>18</sup>. Tables 1 and 2 summarize the characteristics of the included studies and  
5  
6 286 participants.

### 7 8 9 287 **3.3 KAM.**

10  
11 288 A study reported that the VER-brace offers additional advantages on first peak  
12  
13 289 KAM compared to V3P-brace and ACL-brace<sup>42</sup>. No first peak KAM reduction was  
14  
15 290 observed between proprioceptive neuromuscular facilitation group and control  
16  
17 291 group<sup>40</sup>, and the result of the study of minimal footwear was the same<sup>39</sup>. Table 3  
18  
19 292 shows the NMA results of a comparative analysis of the reduction of the first peak  
20  
21 293 KAM. We found insignificant differences in most of the treatment modalities;  
22  
23 294 however, several interventions (Standard care (A) -1.06, 95% CI -1.63 to -0.49;  
24  
25 295 LWI (B) -1.26, 95% CI -1.90 to -0.61; Knee Brace (C) -1.47, 95% CI -2.29 to -0.66;  
26  
27 296 LWI + Knee Brace (D) -1.98, 95% CI -3.15 to -0.81; Gait retraining (E) -1.59, 95%  
28  
29 297 CI -2.30 to -0.87; Quadriceps strengthening (F) -0.93, 95% CI -1.60 to -0.27; Hip  
30  
31 298 strengthening (H) -0.76, 95% CI -1.49 to -0.03; Lower limb exercise (I) -0.97, 95%  
32  
33 299 CI -1.73 to -0.21; and Neuromuscular exercises (J) -0.69, 95% CI -1.36 to -0.02)  
34  
35 300 showed a statistically significant reduction in the first peak KAM over variable-  
36  
37 301 stiffness shoes (G). The overall difference in first peak KAM (v standard care(A))  
38  
39 302 was -0.53 (95% CI -0.95 to -0.10) for gait retraining (E), 1.06 (95% CI 0.49 to 1.63)  
40  
41 303 for variable-stiffness shoes (G), and 0.37 (95% CI 0.02 to 0.71) for neuromuscular  
42  
43 304 exercises (J). Based on the collective probability of being the overall best therapy  
44  
45 305 for reducing the first peak KAM, LWI plus knee brace (D) (93.4%) was closely  
46  
47 306 followed by gait retraining (E) (85.7%), and knee brace only(C) (79.3%) (Figure  
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Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

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4 307 2). On the other hand, after the electroacupuncture treatment, compared with the  
5  
6 308 control group, the second peak KAM significantly increased immediately when the  
7  
8  
9 309 patient ascended stairs<sup>41</sup>.

### 11 310 **3.4 KAAI.**

14 311 KAAI was reported in ten studies<sup>25,27,31,34-39,42</sup>. After wearing the three kinds of  
15  
16  
17 312 brace separately, the KAAI measured under barefoot conditions did not decrease  
18  
19 313 significantly, and there was no significant difference between the groups<sup>42</sup>. Table 3  
20  
21  
22 314 shows the NMA results of the reduction of KAAI. Most treatments were not  
23  
24  
25 315 statistically different from each other, consistent with the results of the first peak  
26  
27 316 KAM. Only gait retraining (E) has a statistical reduction compared with the  
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29  
30 317 standard care treatment (A) (-0.48, 95% CI -0.96 to -0.01). Based on the collective  
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32  
33 318 probability of being the overall best therapy for reducing KAAI, gait retraining (E)  
34  
35 319 (90.7%) was followed by LWI only (B) (74.1%), and lower limb exercise (I) (53.8%)  
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38 320 (Figure 3).

### 40 321 **3.5 Risk of bias.**

43 322 Figure 4 presents a summary of the quality of methods used in this analysis. Nine  
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45 323 studies presented a clear description of generating a randomization sequence<sup>29-</sup>  
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48 324 <sup>31,33,36-39,41</sup>. The study by Hinman et al. was the only double-blinded study, while  
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51 325 other studies were either single-blinded or did not clearly describe their blind design.  
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53 326 All trials provided follow-up data on their outcomes. Six studies did not report the  
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56 327 number or the reason for lost visits due to the length of follow-up <sup>25,29,30,32,33,36</sup>.  
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59 328 Consequently, all studies were included in the synthesis evaluation and qualified  
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4 329 for literature assessment. And we prepared comparison-adjusted funnel plots that  
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6 330 represented different comparisons with different colors. The funnel plots were  
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9 331 symmetrically distributed based on a visual inspection, which suggested the  
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12 332 absence of small-sample effects for our outcomes (see Appendix 5).

#### 13 14 333 4. DISCUSSION

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17 334 Our results did not show significant differences regarding the superiority of  
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19 335 intervention among different types of non-surgical therapies. This lack of difference  
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22 336 was attributed to the fact that the number of studies for several pairwise  
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25 337 comparisons was small. However, some of these therapies were still worth  
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27 338 recommending. Due to the small number of studies studying the outcome of the  
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29  
30 339 KAAI , We found gait retraining to be the relatively more convincing intervention  
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33 340 as it could reduce the values for KAM and KAAI at the same time based on  
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35 341 cumulative ranking and relative effect estimates. Due to the lack of significant  
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38 342 differences among the exercise interventions, we were not able to conclusively  
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40 343 accept the cumulative ranking obtained by the network meta-analysis. For example,  
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43 344 gait retraining, which occupied the first rank position (90.7%) for reducing the  
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45 345 KAAI, was only superior to the neuromuscular exercise interventions.

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48 346 This study had several strengths and limitations. Eligible RCT studies were  
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51 347 identified by conducting a comprehensive search on several databases and resources.  
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53 348 Additionally, two independent reviewers scanned through the search output,  
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56 349 extracted data, classified interventions, and evaluated the methodological quality of  
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59 350 each trial to minimize potential bias.

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4 351 This network meta-analysis is the first report on the effects of physical therapy and  
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6 352 orthopedic equipment on the parameters of knee load (KAM, KAAI). Since non-  
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9 353 surgical therapy is a complex intervention with a small number of trials comparing  
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11 354 the different types of interventions, network meta-analysis appeared to be the most  
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14 355 relevant form of analysis. The results of this meta-analysis would be more useful  
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17 356 for the decision-makers, service specialists, and caregivers to choose among the  
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19 357 various available options, compared with multiple separate pairwise meta-analyses  
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21  
22 358 <sup>43</sup>. Additionally, this network meta-analysis conducted each comparison separately  
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24  
25 359 with both direct and indirect statistical effects, deriving statistical power from all  
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27 360 included data <sup>43</sup>. Also, the Bayesian method provided the probability estimates  
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29 361 regarding the superior efficacy of specific exercise interventions, even though the  
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31 362 standard methods described the absence of a significant difference between them.  
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34 363 In addition, we calculated alternative rankings (second, third best, etc), because in  
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36 364 some cases the best exercise intervention might be unavailable, more costly, or  
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38 365 contraindicated in some patients.  
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41 366 As with most meta-analyses on non-surgical therapies for osteoarthritis, one of the  
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43 367 limitations of this network meta-analysis includes the inclusion of trials that had  
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46 368 variable periods of follow-up, which could have introduced heterogeneity into the  
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49 369 study analysis. Although there was no study that exclusively reported the immediate  
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51 370 effect, the span in follow-up periods cannot be ignored. There exist several methods  
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54 371 of analyzing and comparing trials with multiple durations of follow-up, as  
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57 372 recommended by the Cochrane handbook, such as performing individual patient  
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4 373 data meta-analysis and evaluating at a particular time point. However, methods are  
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6 374 being developed that would include all time points in a network meta-analysis<sup>18</sup>.  
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9 375 We removed a study which had a short follow-up time and might cause  
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11 376 heterogeneity<sup>25</sup>, and performed another network meta-analysis. There is no  
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13  
14 377 difference between the results of the reanalysis and the current ranking (see  
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17 378 Appendix 7). We were not able to evaluate the influence of population  
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19 379 characteristics (such as mean age, the severity of osteoarthritis), as the number of  
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22 380 the included studies was not large enough<sup>45-47</sup>. Additionally, other parameters, such  
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24  
25 381 as the external knee flexion moment to joint load, should have been studied.  
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27 382 However, due to the small number of related articles, we were temporarily unable  
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29  
30 383 to include them. By the way, according to the GRADE framework (see Appendix  
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33 384 6), the quality of the most comparisons was assessed as low or very low, which  
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35 385 might affect the reliability of the evidence.  
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38 386 A previous review showed that LWIs were able to reduce the KAM at baseline<sup>48</sup>;  
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40 387 however, the effect was no longer observed after a period of time. One study  
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43 388 showed that a 1-month wear-in period was the longest time period studied where  
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45 389 no reduction in biochemical risk factors was observed despite continued wear<sup>49</sup>.  
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48 390 Besides, several systematic reviews had concluded that exercise and gait retraining  
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51 391 could reduce pain and improve motor functioning in people with KOA<sup>50-52</sup>, it was  
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53 392 possible that any clinical changes in previous studies may due to the increased  
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56 393 physical activity levels, and not have been the results of altered loading environment  
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59 394 within the knee joint. Furthermore, another study revealed that an increase in the  
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4 395 amount of reduction in peak KAM in LWIs plus knee brace group was observed  
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6 396 after 4 weeks<sup>53</sup>.

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9 397 On the other hand, physical therapies and orthopedic equipment also need to be  
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11 398 considered for relieving patients' pain, which has been the focus of several reviews  
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14 399 in the past. As an important factor in kinetics and kinematics of gait, the joint pain  
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17 400 can affect the kinetics and kinematics of walking<sup>54</sup>. A meta-analysis reported that  
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19 401 exercise therapy had a positive impact on knee pain and kinematic function, though  
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22 402 this relief of pain subsided with time. After initiation, the efficiency of physical  
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25 403 exercise over placebo reached maxima at 2 months<sup>55</sup>.

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27 404 Cumulative loading is another significant parameter regarding knee load exposure  
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30 405 in OA<sup>56</sup>. KAAI has been proposed as another indicator to evaluate the duration and  
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33 406 intensity of KOA load, despite the association between KAM and disease  
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36 407 progression. According to a 12-month study, the loss of medial tibiofemoral  
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39 408 cartilage was not directly related to KAM but was related to KAAI<sup>57</sup>. Although the  
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42 409 effect of physical therapy and orthopedic equipment on KAM may gradually  
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45 410 disappears, it may have a huge cumulative effect on the knee during the early stages  
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48 411 of treatment. This should be considered while interpreting the results of this network  
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51 412 meta-analysis.

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54 413 The results presented in this study are both scientifically and clinically instructive.  
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57 414 Despite observing a null statistical reduction in KAM and KAAI for most non-  
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60 415 surgical therapies, using these treatments clinically could improve symptoms and  
416 physical activity level without increasing the biomechanical magnitude; thus,

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4 417 improving the quality of life of patients with KOA. Since the studies included in  
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6 418 this network meta-analysis mainly involves patients with medial knee osteoarthritis,  
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9 419 the results would be more useful for these patients.

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11 420 On the other hand, previous study reported that the increase in KAAI can explain  
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13 421 the significant variation in the uCTX-II levels and the uCTX-II:sCPII ratio in  
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15 422 patients with medial tibiofemoral KOA when additional variables are controlled<sup>58</sup>.

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17 423 This showed that intervention in the biomechanical structure of the knee joint in  
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19 424 patients with KOA is a potential beneficial role on cartilage structure. Mazzoli et  
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21 425 al. pointed out that adopting a modified gait that reduces the KAM can decrease the  
22  
23 426 pain in the medial compartment in KOA more than walking alone<sup>59</sup>, which suggests  
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25 427 that the KAM and KAAI of patients under non-surgical treatment can be restricted  
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27 428 to help reduce pain and improve joint function. More research is needed to further  
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29 429 illustrate the impact of changes in knee biomechanics on the prognosis of patients.

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31 430 Additionally, some other therapies have been reported, such as Taiji, ultrasound,  
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33 431 acoustic exercise, etc. However, due to the lack of RCT study design or the report  
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35 432 of their biomechanical outcomes, we were not able to include these therapies in our  
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37 433 review. Therefore, further studies would require more research articles in these  
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39 434 areas to further explore the impact of various non-surgical therapies on OA patients.

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41 435 After accumulating evidence regarding the role of non-surgical therapy in KOA, we  
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43 436 could conduct a similar network meta-analysis to understand the relative  
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45 437 effectiveness of various types of these interventions in relevant patients.

## 438 5. Conclusion

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4 439 This network meta-analysis provides valuable insight regarding the alterations in  
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6 440 KAM and KAAI of OA patients after non-surgical treatment. The results indicate  
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9 441 that lateral wedge insoles plus knee brace was the best therapy for reducing the first  
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11 442 peak KAM and gait retraining had the best effect on reducing the KAAI. On the  
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14 443 contrary, variable-stiffness shoe and neuromuscular exercise exhibited an increase  
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17 444 in the first peak KAM compared to the standard care group. Taken together, these  
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19 445 findings suggest that clinicians should choose carefully when treating OA.

## 22 446 **6. Authors' Contributions**

23  
24 447 HXM and YFZ conceived of the study, and participated in its design and  
25  
26  
27 448 coordination and helped to draft the manuscript; YZX, HY and CRY contributed  
28  
29  
30 449 significantly to analysis and manuscript preparation; YJK and LL helped perform  
31  
32 450 the analysis with constructive discussions and revised it critically for important  
33  
34  
35 451 intellectual content.

## 37 452 **7. Competing interests**

38  
39  
40 453 There were no conflicts of interest.

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43  
44  
45 455 This work was supported by the National Key R&D Program of China  
46  
47  
48 456 (No.2017YFB1303000).

## 49 457 **9. Ethics approval**

50  
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52 458 Not required.

## 53 459 **10. Patient and public involvement**

54  
55  
56 460 Patients and/or the public were not involved in the design, or conduct, or reporting,

461 or dissemination plans of this research.

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**Table 1. Characteristics of included studies (1) \***

Authors	Country	Clinical criteria†	Radiographic features	Intervention	Comparisons	Follow up
Barrios 2013 <sup>34</sup>	US	Medial compartment knee OA; Pain VAS ( $\geq 3$ of 10 upon walking)	K/L grade $\geq 2$ , medial tibiofemoral compartment	bespoke full-length LWI	Placebo	12 months
Hinman 2016 <sup>35</sup>	Australia	Medial compartment knee OA; Pain NRS ( $> 4$ of 11 upon walking) over the previous week	K/L grade $\geq 2$ , medial tibiofemoral compartment	5° full-length LWI	Placebo	6 months
Arazpour 2012 <sup>28</sup>	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 <sup>25</sup>	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 <sup>26</sup>	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**

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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 <sup>27</sup>	US	Medial compartment knee OA; Pain ( $\geq 3$ of 10) longer than 6 months	K/L grade $\geq 2$ , medial tibiofemoral compartment	Toe-out gait modification	Walking without any guidance	4 months
Lim 2008 <sup>29</sup>	Australia	Medial compartment knee OA; Medial knee pain	K/L grade $\geq 2$ , medial JSN	Quadriceps strengthening	No intervention	12 weeks
Erhart-Hledik 2012 <sup>30</sup>	US	Medial compartment knee OA; Medial knee pain	K/L grade $\geq 1$	Variable-stiffness shoe with stiffer soles on the lateral side	Constant-stiffness control shoe	12 months
Bennell 2010 <sup>31</sup>	Australia	Medial compartment knee OA; Varus malalignment; Pain ( $> 3$ of 11 upon walking)	K/L grade $\geq 2$ , medial JSN	Hip strengthening	No intervention	13 weeks
Cheung 2018 <sup>32</sup>	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 (3) \***

Authors	Country	Clinical criteria†	Radiographic features	Intervention	Comparisons	Follow up
Foroughi 2011 <sup>33</sup>	Australia	Primary knee OA	K/L grade $\geq 1$	Lower limb exercise	Sham-exercise	6 months
Bennell 2014 <sup>36</sup>	Australia	Medial compartment knee OA; Pain VAS ( $\geq 25$ of 100) over the past week	K/L grade $\geq 2$ , medial tibiofemoral compartment	Neuromuscular exercise	Quadriceps strengthening	12 weeks
Hunt 2013 <sup>37</sup>	Canada	Medial compartment knee OA; Knee pain $> 3/10$ on most days of the previous month	K/L grade $\geq 2$ , medial tibiofemoral compartment	Lower limb exercise	No intervention	11 weeks
Holsgaard-Larsen 2017 <sup>38</sup>	Denmark	Primary knee OA  Pain KOOS ( $< 80$ of 100, at least mild pain)	K/L grade $\leq 3$	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 <sup>40</sup>	China	Medial compartment knee OA in one or both legs.	K/L grade $\leq 3$	PNF (one-hour sessions three times a week)	Watch television or read magazines at the same time	12 weeks
Wang 2017 <sup>41</sup>	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 <sup>42</sup>	Canada	Medial compartment knee OA; Pain > 31/100 on WOMAC; Varus knee alignment $\geq 2^\circ$	K/L grade 2 and 3	V3P-brace; VER-brace; ACL-brace (wear the brace as often as possible)	/	3 months
Trombini-Souza 2015 <sup>39</sup>	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/m <sup>2</sup>	Bilateral knee OA included	K/L grade, no.				Main outcomes
								1	2	3	4	
Barrios 2013 <sup>34</sup>	38	NR	61.90±8.37	NR	NR	32.00±7.43	NR	0	17	14	7	1 <sup>st</sup> KAM; KAAI
Hinman 2016 <sup>35</sup>	164	20:21	64.30±7.45	1.67 ± 0.10	82.95±14.76	29.70±3.64	NR	0	49	52	63	1 <sup>st</sup> KAM; KAAI
Arazpour 2012 <sup>28</sup>	24	3:4	59.29±2.37	NR	NR	27.01±1.71	Yes	9	15	0	0	1 <sup>st</sup> KAM
Jones 2013 <sup>25</sup>	28	4:3	66.30±8.20	1.75±0.13	88.7±15.10	NR	No	0	10	18	0	1 <sup>st</sup> and 2 <sup>nd</sup> KAM; KAAI
Khosravi 2019 <sup>26</sup>	21	13:8	58.97±6.80	1.62±0.11	79.11±9.35	NR	NR	0	9	12	0	1 <sup>st</sup> 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 <sup>2</sup>	Bilateral knee OA included	K/L grade, no.				Main outcomes
								1	2	3	4	
Hunt 2018 <sup>27</sup>	79	24:55	64.99±8.60	1.65±0.10	74.59±13.15	27.35±3.48	Yes	0	37	31	11	1 <sup>st</sup> and 2 <sup>nd</sup> KAM; KAAI
Lim 2008 <sup>29</sup>	107	48:59	64.60±8.51	1.65±0.10	79.41±15.32	28.96±4.85	Yes	0	34	29	44	1 <sup>st</sup> KAM
Erhart-Hledik 2012 <sup>30</sup>	79	41:38	61.70±9.43	1.69±0.08	79.50±15.07	27.51±4.87	Yes	NR	NR	NR	NR	1 <sup>st</sup> KAM
Bennell 2010 <sup>31</sup>	89	46:43	64.55±8.34	NR	NR	27.94±4.41	Yes	0	30	29	30	1 <sup>st</sup> KAM; KAAI
Cheung 2018 <sup>32</sup>	20	1:1	61.95±6.11	1.63±0.09	65.85±6.64	27.35±3.48	NR	5	15	0	0	1 <sup>st</sup> 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 <sup>2</sup>	Bilateral knee OA included	K/L grade, no.				Main outcomes
									1	2	3	4	
1 2 3 4 5	Foroughi 2011 <sup>33</sup>	54	0:54	65.48±7.44	NR	82.87±18.43	32.07±7.08	Yes	20	7	20	1	1 <sup>st</sup> and 2 <sup>nd</sup>  KAM
6 7 8 9 10 11 12 13 14 15 16	Bennell 2014 <sup>36</sup>	100	48:52	62.45±7.32	1.67±0.10	82.70±14.29	29.65±4.08	Yes	0	22	43	35	1 <sup>st</sup> KAM;  KAAI
17 18 19 20 21	Hunt 2013 <sup>37</sup>	17	8:9	66.10±11.3	NR	NR	27.00±4.50	Yes	0	10	5	2	1 <sup>st</sup> KAM;  KAAI
22 23 24 25 26	Holsgaard-Larsen 2017 <sup>38</sup>	93	39:54	58.10±7.96	NR	79.64±12.49	26.90±3.09	NR	45	31	17	0	1 <sup>st</sup> 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 <sup>2</sup>	Bilateral knee OA included	K/L grade, no.				Main outcomes
								1	2	3	4	
Song 2020 <sup>40</sup>	36	1:1	68.01±3.91	1.62±0.07	68.16±6.77	NR	Yes	9	20	7	0	1 <sup>st</sup> KAM
Wang 2017 <sup>41</sup>	36	1:5	63.50±7.95	NR	NR	23.75±2.66	Yes	0	19	17	0	1 <sup>st</sup> and 2 <sup>nd</sup> KAM
Robert-Lachaine 2020 <sup>42</sup>	24	7:5	57.20±8.60	1.68±0.09	89.30±18.70	31.40±5.00	NR	0	15	8	0	1 <sup>st</sup> and 2 <sup>nd</sup> KAM; KAAI
Trombini-Souza 2015 <sup>39</sup>	56	NR	66.00±5.00	1.60±0.10	73.40±13.10	NR	NR	0	NR	NR	0	1 <sup>st</sup> 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.

<b>J</b>	0.41 (-0.66,1.49)	0.16 (-0.46,0.79)	-	0.20 (-0.23,0.64)	<b>0.81</b> <b>(0.17,1.45)</b>	-	0.30 (-0.61,1.21)	<b>0.54</b> <b>(0.02,1.07)</b>	0.32 (-0.10,0.75)
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Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)



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

**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)

1 **Figure 1. Flow chart of the study selection**

2 **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**  
3 **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**  
4 **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=**  
5 **Variable-stiffness shoe; H= Hip strengthening; I= Lower limb exercise; J= Neuromuscular exercise.**

6 **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**  
7 **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**  
8 **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**  
9 **exercise.**

10 **Figure 4. Risk of bias summary**

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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)**

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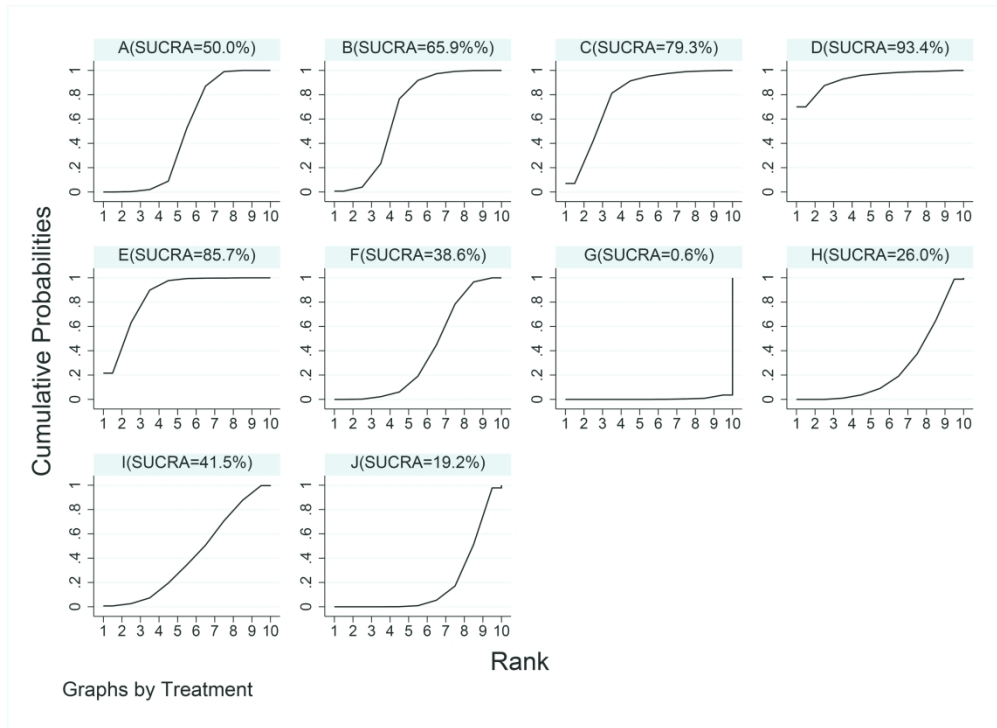


Figure 2

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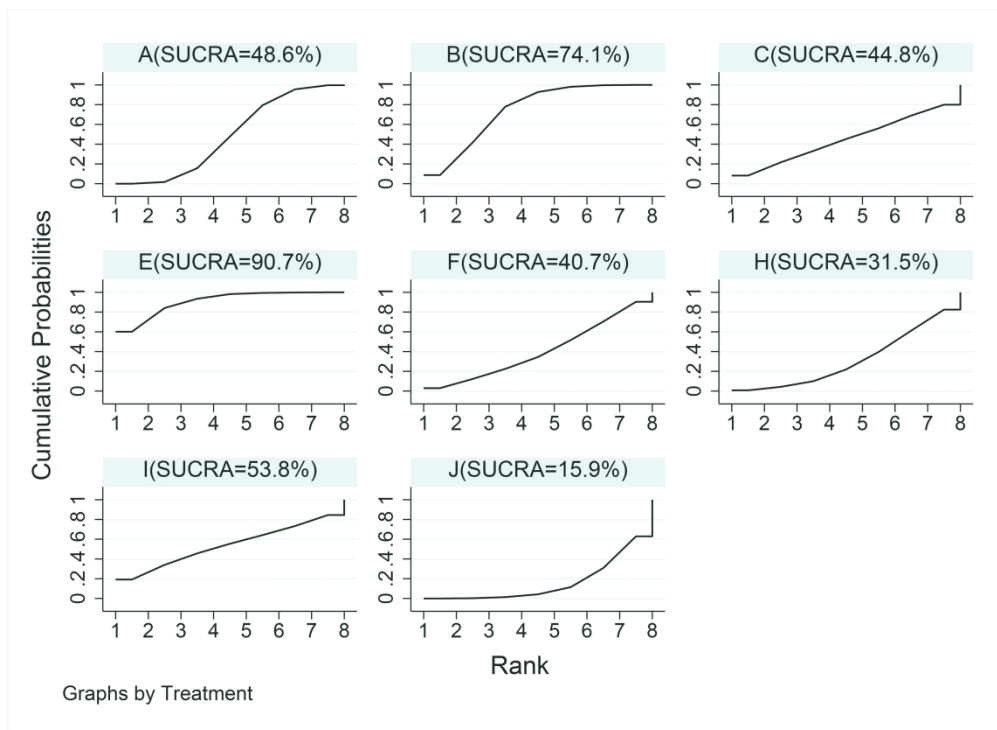


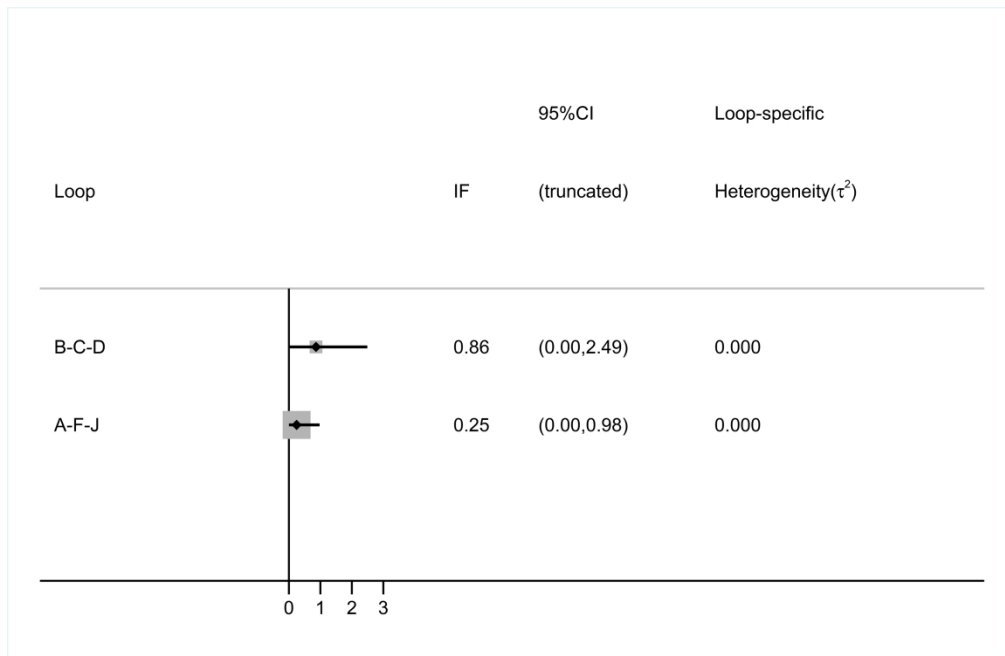
Figure 3

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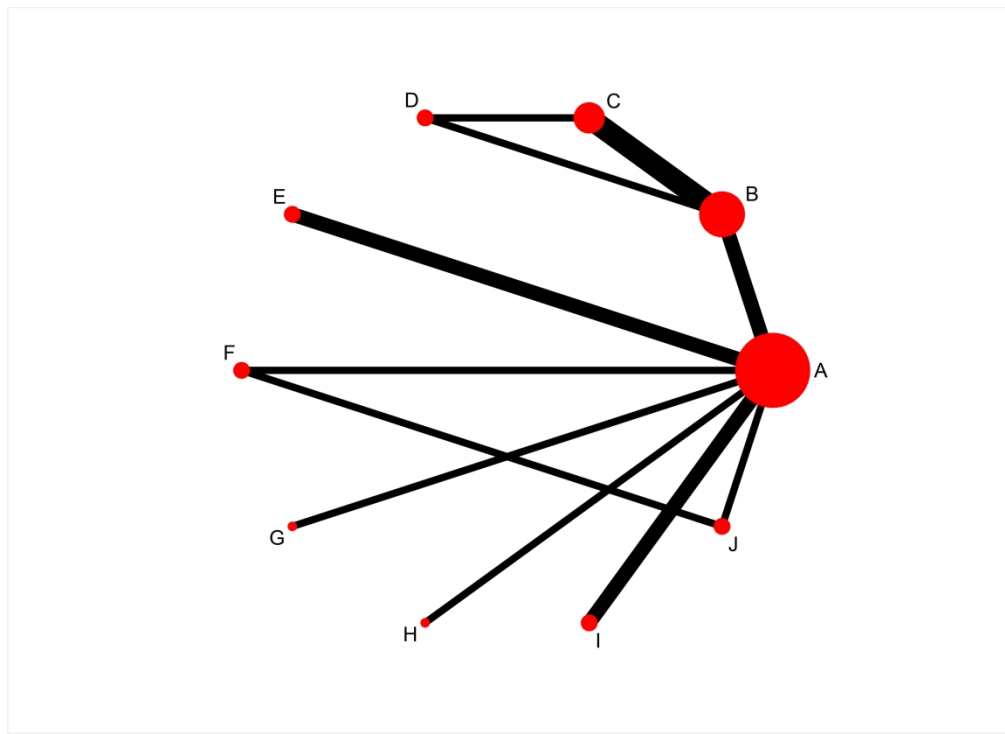


eFigure 1

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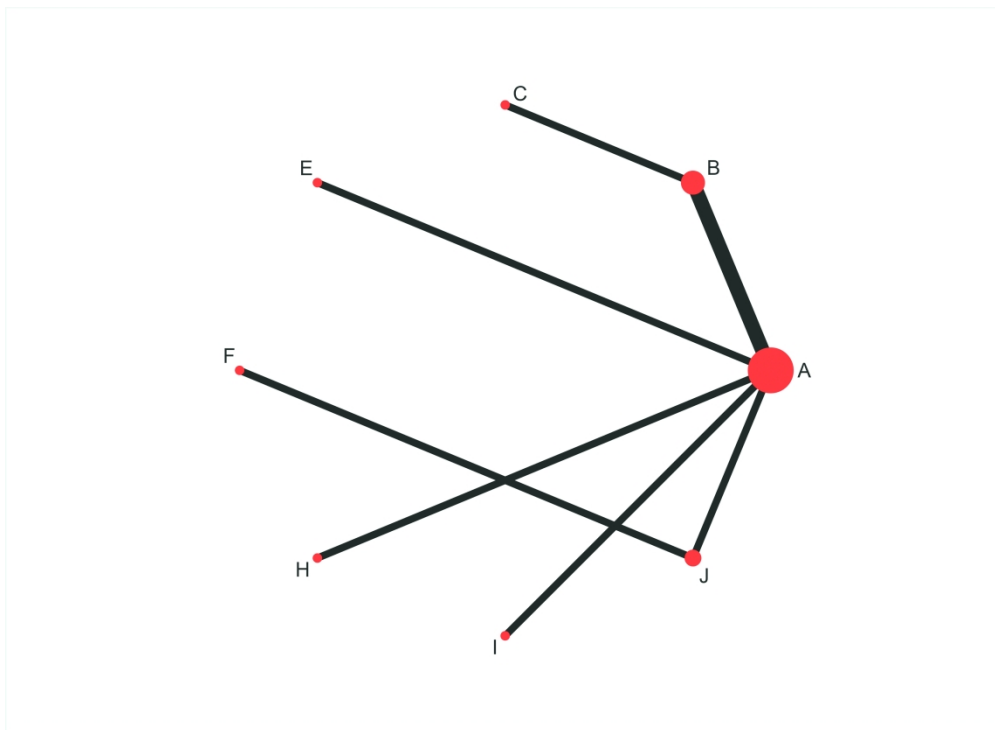
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eFigure 2a

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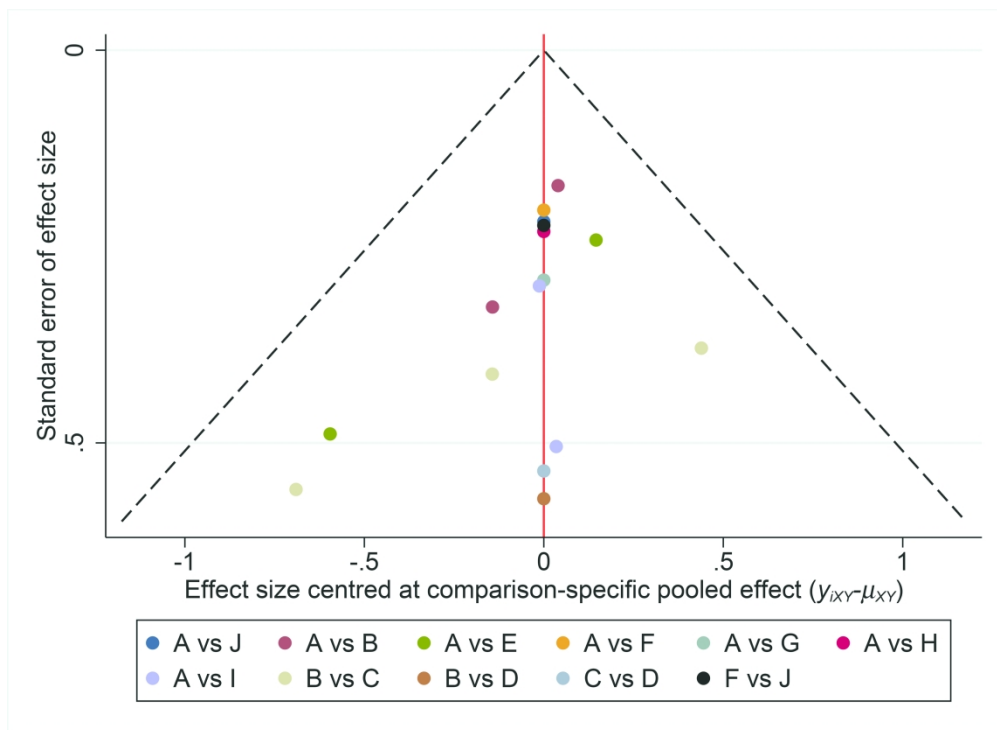
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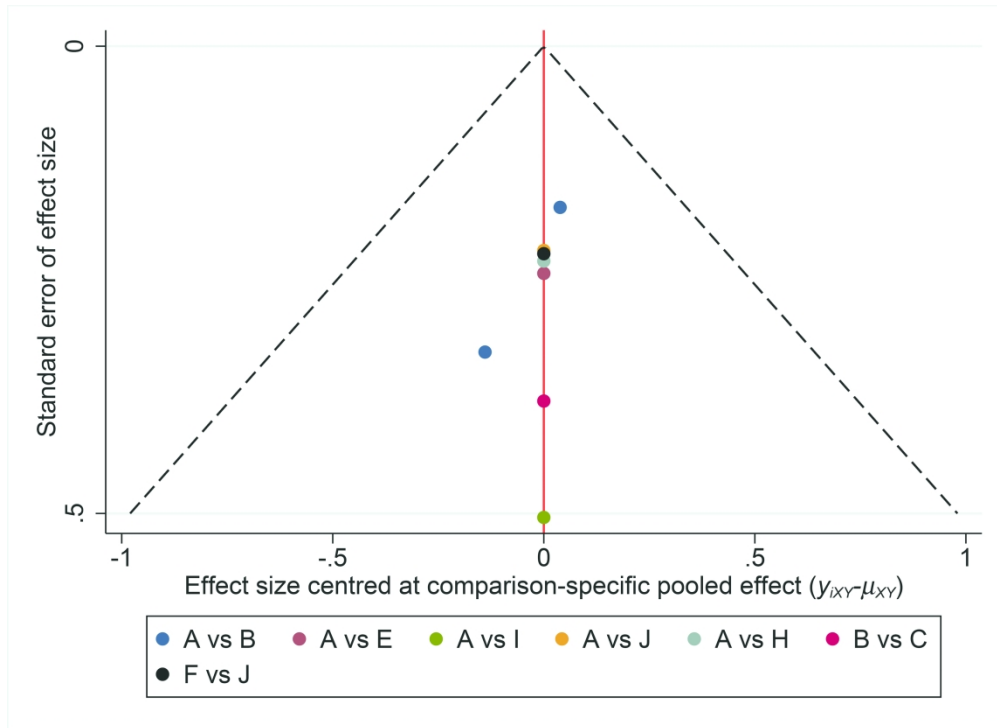
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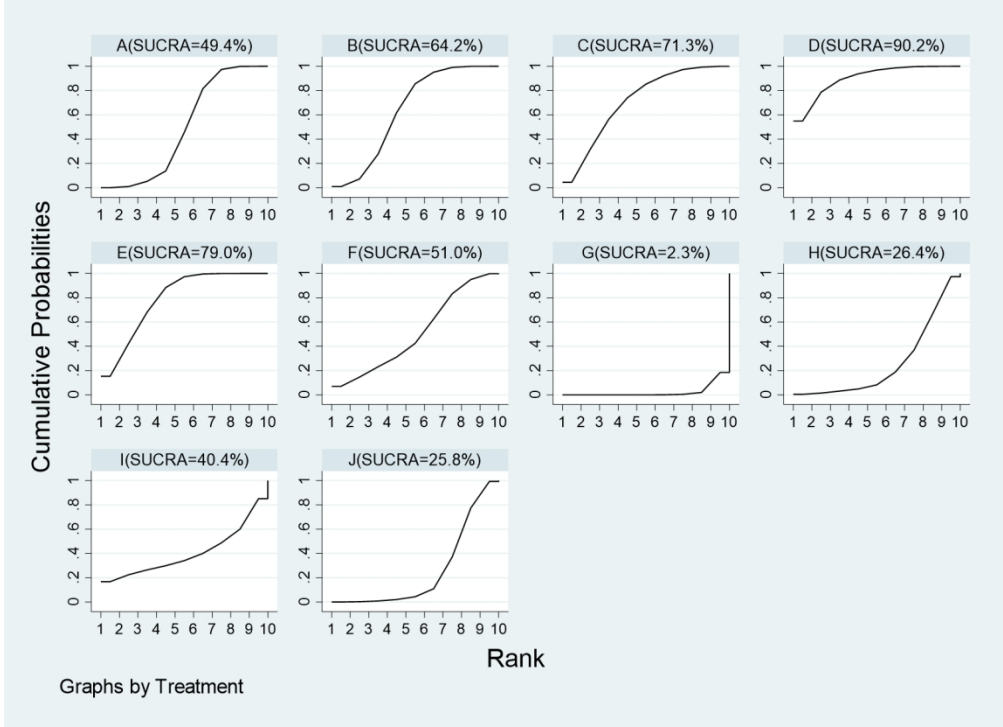
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eFigure 6

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## Appendix

Appendix 1 Search strategies.....	2
Appendix 2 Results of Inconsistency.....	4
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## 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-arthritis':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 'orthoepadic 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-arthritis':ab,ti OR 'knee

osteoarthritis':ab,ti OR 'osteoarthritis, knee':ab,ti OR 'osteoarthritis, 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 orthosis OR orthoses OR orthopedic support device OR orthotic device)
4. TI=(orthosis OR device OR orthosis OR orthoses OR orthopedic 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 osteoarthritis OR osteoarthritis)
7. TI=(knee osteoarthritis OR femorotibial arthrosis OR gonarthrosis OR knee arthrosis OR knee osteo-arthritis OR knee osteoarthritis OR osteoarthritis)
8. #6 OR #7
9. #8 AND #5

### Cochrane Library

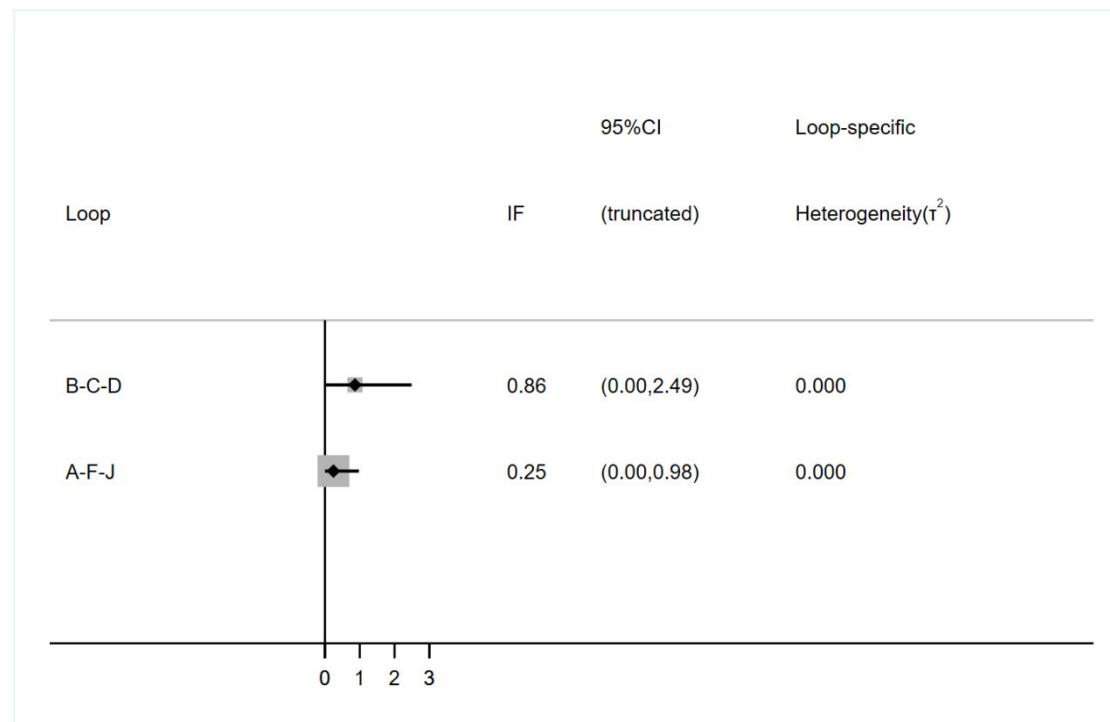
1. (MeSH descriptor: [Physical Therapy Modalities] explode all trees OR (Neurological Physiotherapy):ti,ab,kw OR (Physiotherapy, Neurological):ti,ab,kw OR (Neurophysiotherapy):ti,ab,kw OR (Techniques, Physical Therapy):ti,ab,kw OR (Physiotherapies (Techniques)):ti,ab,kw OR (Physical Therapy Techniques):ti,ab,kw 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 Osteoarthritis):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 Osteoarthritis):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 osteoarthritis) OR (osteoarthritis)
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 (orthosis)

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3 OR (orthoses) OR (orthopaedic support device)  
4 4. #2 OR #3  
5 5. #1 AND #4  
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## Appendix 2 Results of Inconsistency



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

## Appendix 3 Network Diagram

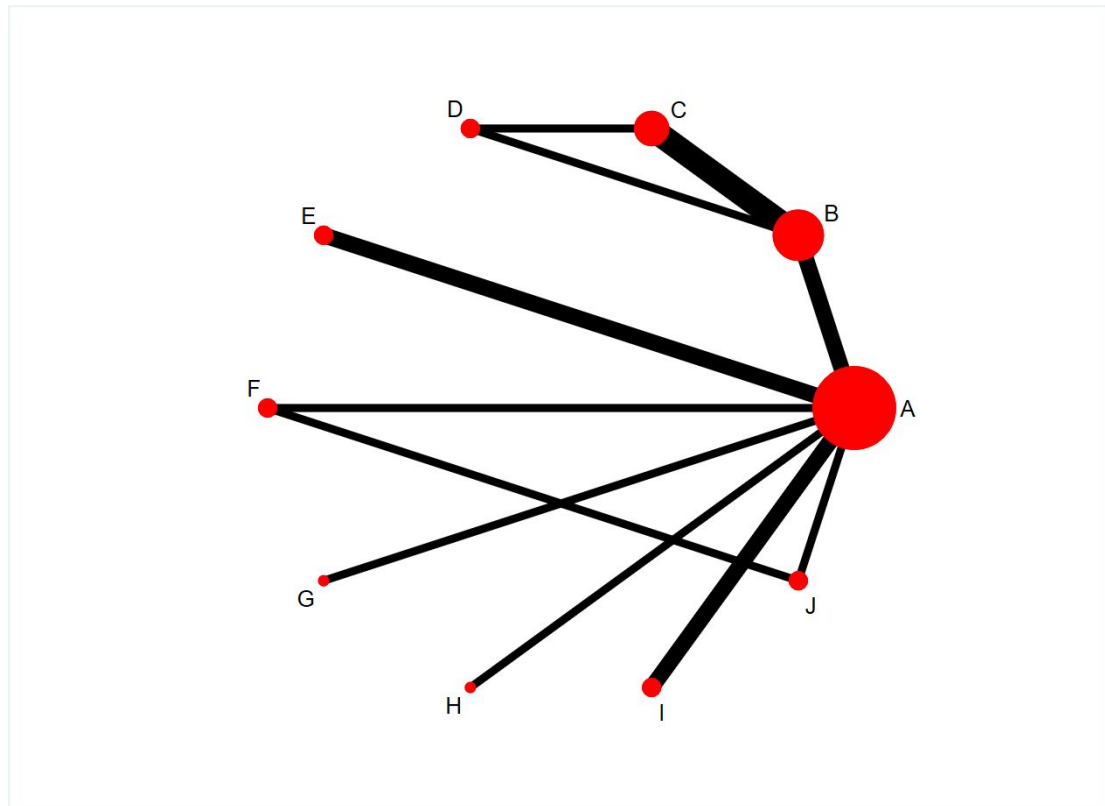
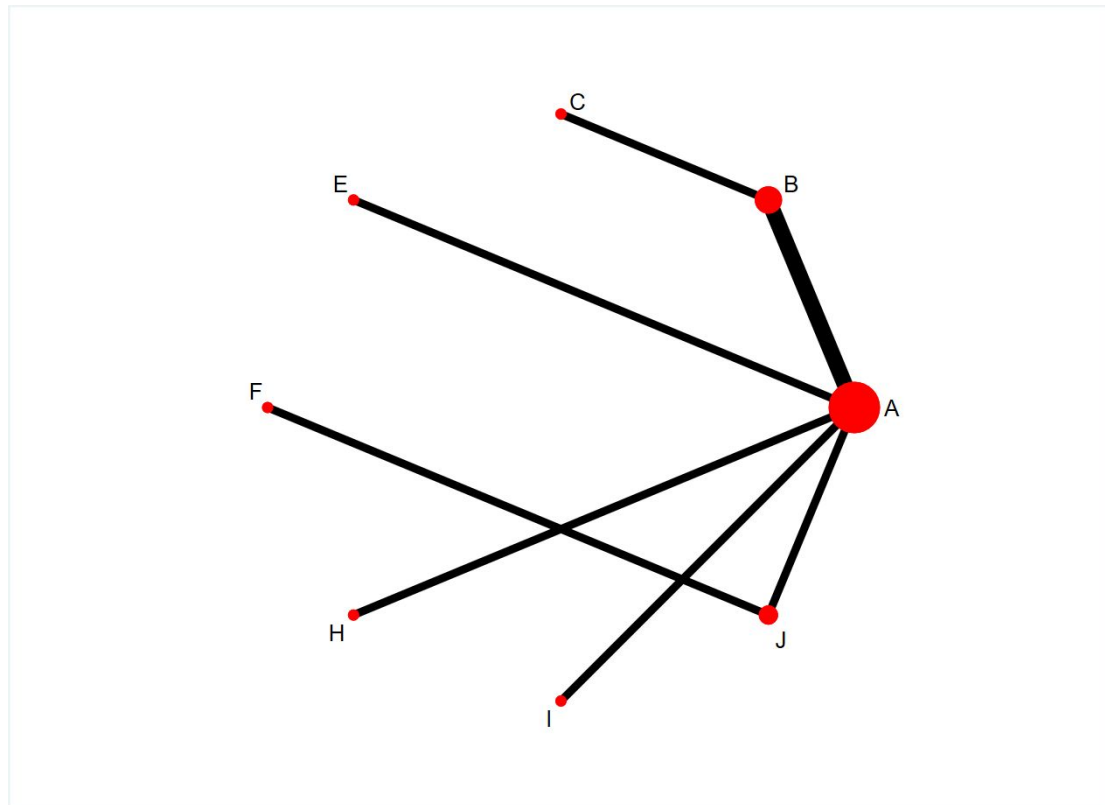


Figure 2a. Structure of network formed by interventions and their direct comparisons (First peak KAM). A= Standard care; B= Lateral Wedge Insole; C= Knee Brace; D= Lateral Wedge Insole+ Knee Brace; E= Gait retraining; F= Quadriceps strengthening; G= Variable-stiffness shoe; H= Hip strengthening; I= Lower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

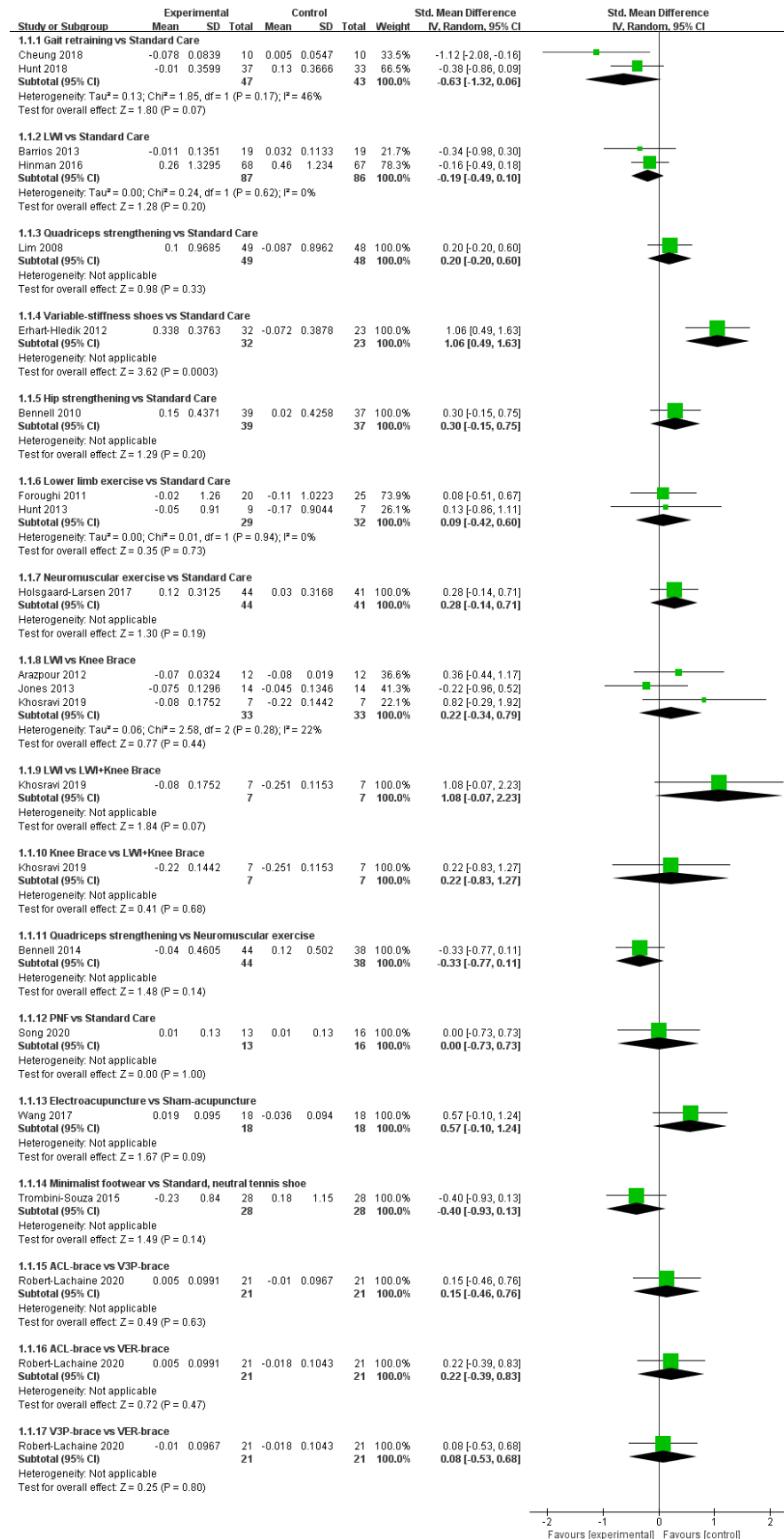
**Footnote:** Width of the lines is proportional to the number of trials comparing every pair of treatments. Size of every circle is proportional to the number of randomly assigned participants (ie, sample size).



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.

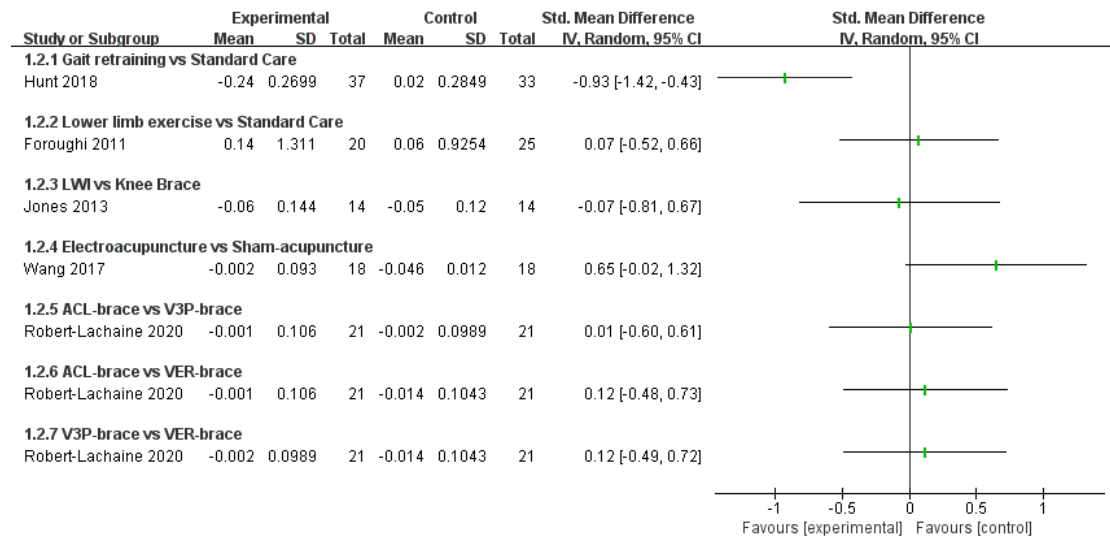
**Footnote:** Width of the lines is proportional to the number of trials comparing every pair of treatments. Size of every circle is proportional to the number of randomly assigned participants (ie, sample size).

## Appendix 4 Conventional meta-analyses results





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



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

Peer review only

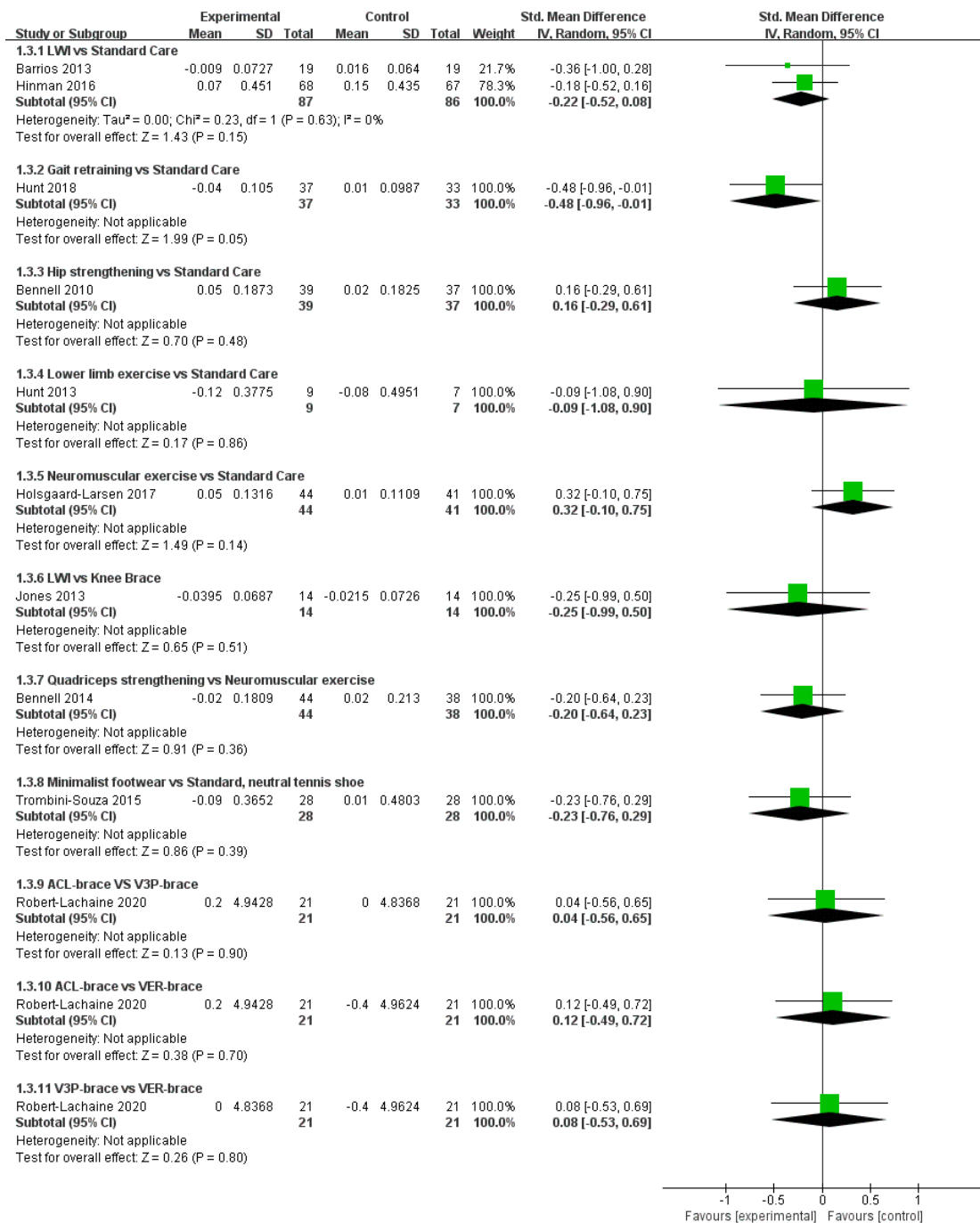
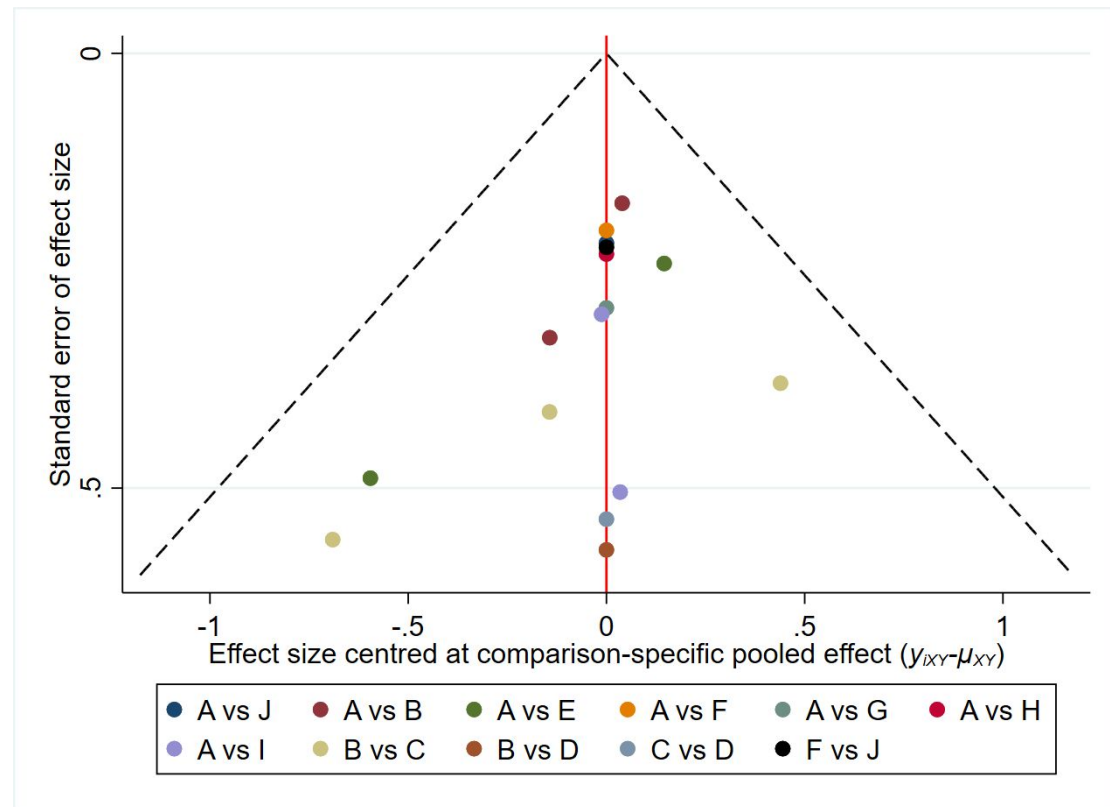


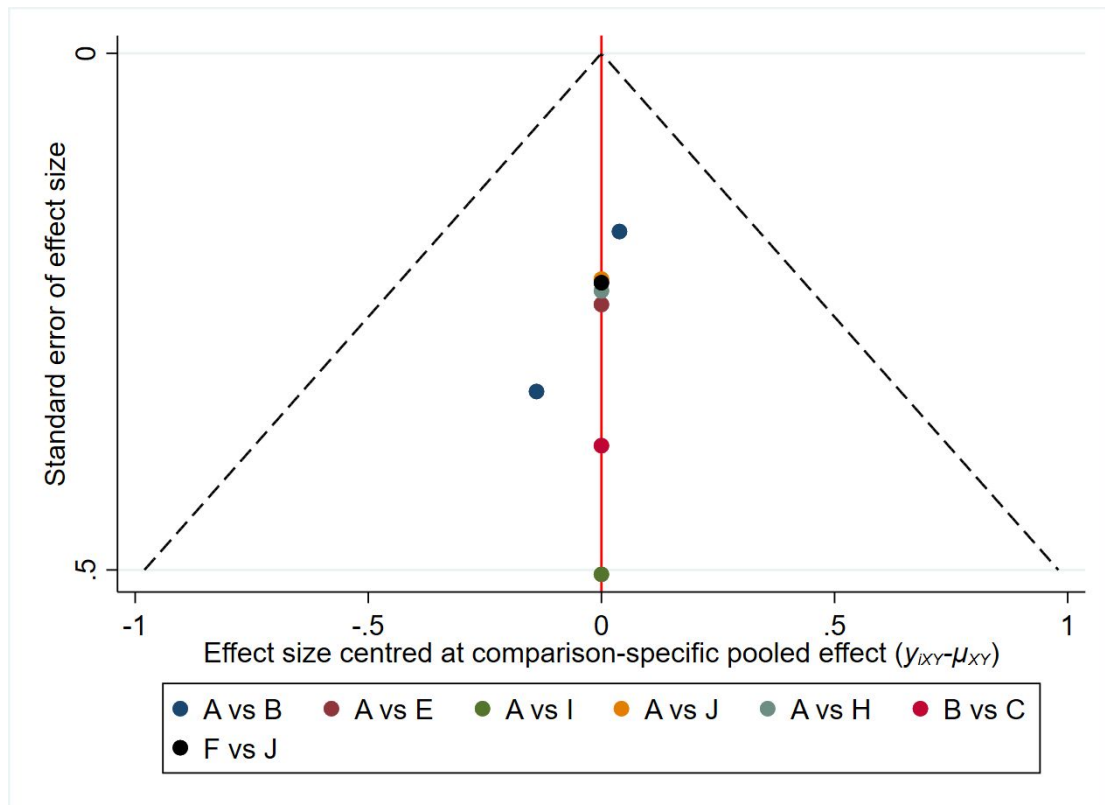
Figure 3c. Conventional meta-analysis of treatment effects on KAAI.

## 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	Downgrading due to
<b>AB:</b> Placebo vs LWI	Mixed	LOW	Study limitations; Imprecision
<b>AC:</b> Placebo vs Knee Brace	Indirect	LOW	Study limitations; Imprecision
<b>AD:</b> Placebo vs LWI+Knee Brace	Indirect	LOW	Study limitations; Imprecision
<b>AE:</b> Placebo vs Gait Retraining	Mixed	VERY LOW	Study limitations; Indirectness
<b>AF:</b> Placebo vs Quadriceps Strengthening	Mixed	VERY LOW	Study limitations; Imprecision
<b>AG:</b> Placebo vs Variable-Stiffness Shoes	Mixed	VERY LOW	Study limitations; Indirectness; Imprecision
<b>AH:</b> Placebo vs Hip Strengthening	Mixed	VERY LOW	Study limitations; Indirectness; Imprecision
<b>AI:</b> Placebo vs Lower Limb Exercise	Mixed	VERY LOW	Study limitations; Indirectness; Imprecision
<b>AJ:</b> Placebo vs Neuromuscular Exercise	Mixed	MODERATE	Study limitations
<b>BC:</b> LWI vs Knee Brace	Mixed	VERY LOW	Study limitations; Imprecision
<b>BD:</b> LWI vs LWI+Knee Brace	Mixed	VERY LOW	Study limitations; Imprecision

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

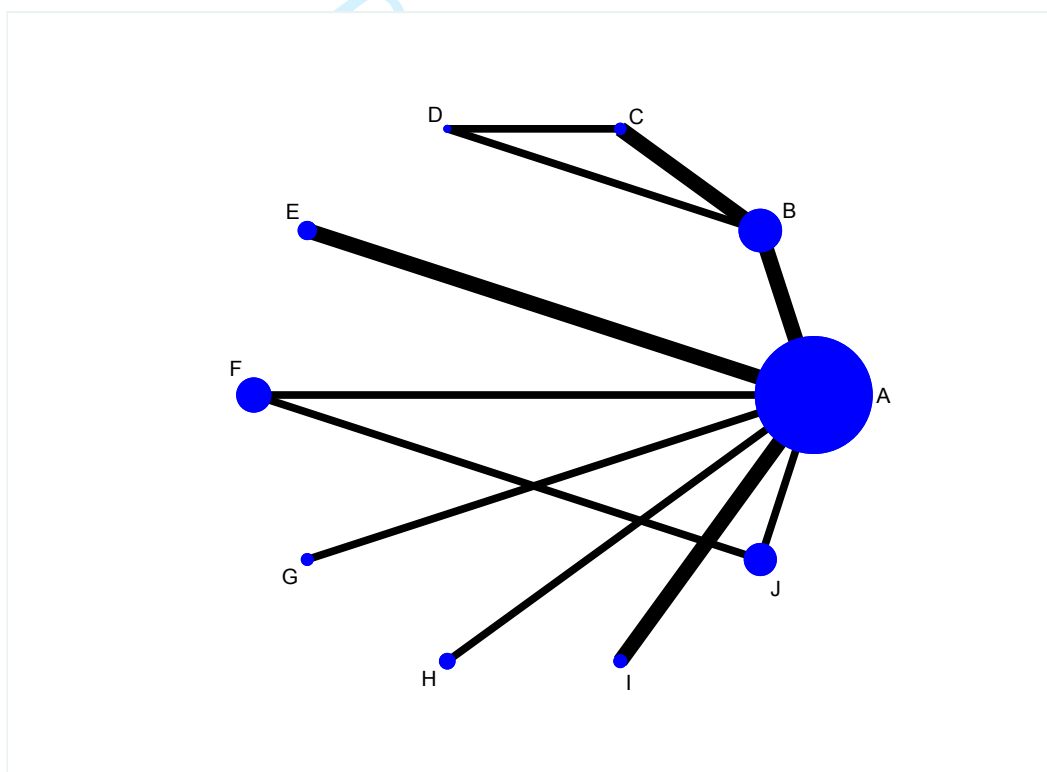
**GH:** Variable-Stiffness Shoes vs Hip Strengthening Indirect LOW Study limitations; Indirectness

**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

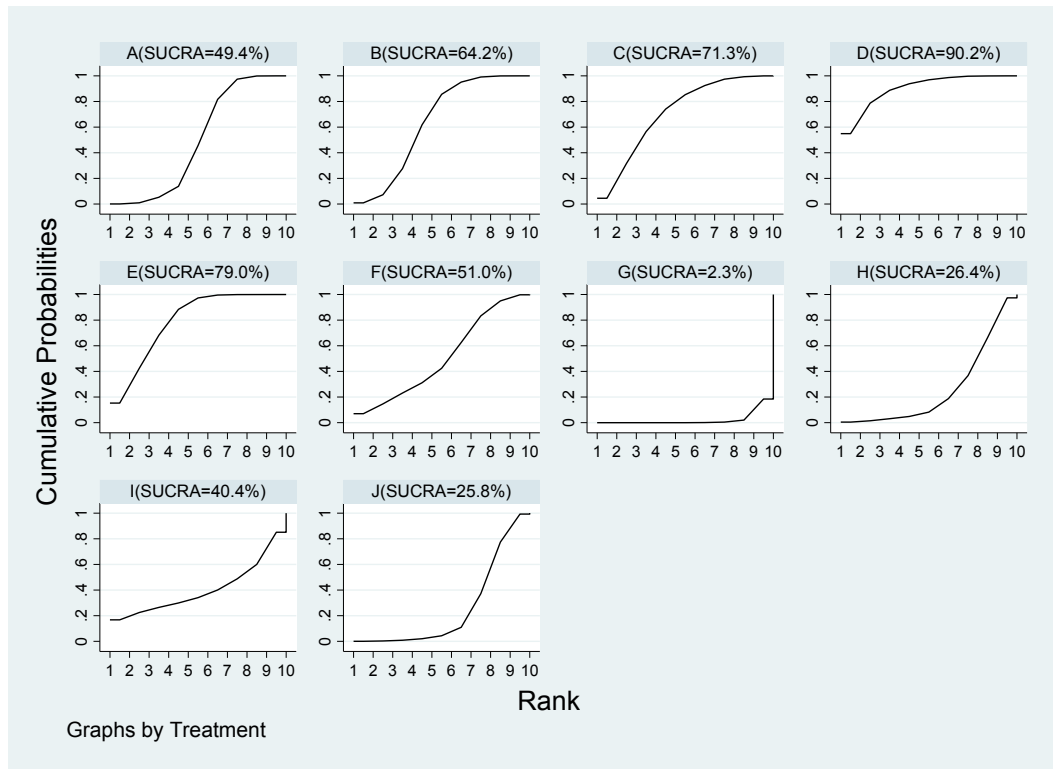
<b>HI:</b> Hip Strengthening vs Lower Limb Exercise	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
<b>HJ:</b> Hip Strengthening vs Neuromuscular Exercise	Indirect	VERY LOW	Study limitations; Indirectness; Imprecision
<b>IJ:</b> Lower Limb Exercise vs Neuromuscular Exercise	Indirect	VERY 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 #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
<b>ABSTRACT</b>			
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
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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, paragraph 1
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 <sup>2</sup> ) 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. <small><a href="http://bmjopen.bmj.com/site/about/guidelines.xhtml">http://bmjopen.bmj.com/site/about/guidelines.xhtml</a></small>	METHODS, Statistical



# PRISMA 2009 Checklist

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			Analysis
<b>RESULTS</b>			
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
<b>DISCUSSION</b>			
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). For peer review only - <a href="http://bmjopen.bmj.com/site/about/guidelines.xhtml">http://bmjopen.bmj.com/site/about/guidelines.xhtml</a>	Discussion, paragraph 1 & Conclusion



# PRISMA 2009 Checklist

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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
<b>FUNDING</b>			
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

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

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16  
17 No conflict of interest exists in the submission of this manuscript, and manuscript is  
18  
19 approved by all authors for publication. All authors contributed to the creation of this  
20  
21 manuscript for important intellectual content. I would like to declare on behalf of my  
22  
23 co-authors that the work described was original research that has not been published  
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25 previously, and not under consideration for publication elsewhere, in whole or in part.  
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29 All the authors listed have approved the manuscript that is enclosed.  
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32 This study aims to evaluate the effects of non-surgical treatment in reducing the  
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34 biomechanical risk factors related to knee osteoarthritis (KOA) and this Bayesian  
35  
36 network meta-analysis is the first review on effect of physical therapy on the  
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38 biomechanical parameters (KAM & KAAI) of the knee OA. The review observes a null  
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40 statistical reduction in KAM and KAAI for most therapies, using these non-surgical  
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42 treatments clinically could improve symptoms and physical activity level without  
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44 increasing the biomechanical magnitude; thus, improving the quality of life of patients  
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46 with KOA. I hope this paper is suitable for “*BMJ Open*”.  
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53 We deeply appreciate your consideration of our manuscript, and we look forward to  
54  
55 receiving comments from the reviewers. If you have any queries, please don't hesitate  
56  
57 to contact me at the address below.  
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4 Thank you and best regards.  
5

6 Jia-Kuo Yu, MD&PhD, is the corresponding author and his address and other  
7  
8 information is as follows,  
9

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14 Address: Institute of Sports Medicine, Peking University Third Hospital, Beijing Key  
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17 Laboratory of Sports Injuries, Beijing, 100191, China  
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19  
20 Yours sincerely,  
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22 Dr. Huang  
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# 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

Journal:	<i>BMJ Open</i>
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<b>Primary Subject Heading</b>:	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

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1 **Title: Physical Therapy and Orthopedic Equipment-induced Reduction in the**  
 2 **Biomechanical Risk Factors Related to Knee Osteoarthritis: A systematic review**  
 3 **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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23 **Abbreviated title:** Biomechanical Phenomena, Osteoarthritis, Knee, Physical and  
24 Rehabilitation Medicine

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

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30 **Tables:** 3

31 **Figures:** 4

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8 66 **ABSTRACT**

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10 67 *Objective:* Are physical therapy and orthopedic equipment efficacious in reducing the  
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12 68 biomechanical risk factors in people with tibiofemoral OA? Is there a better treatment  
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15 69 than others to improve these outcomes?

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18 70 *Design:* Systematic review with network meta-analysis of randomised trials.

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21 71 *Data sources:* PubMed, Web of Science, Cochrane Library, Embase, and MEDLINE  
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23 72 were searched through January 2021.

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26 73 *Eligibility criteria for selecting studies:* We included randomised controlled trials  
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28 74 exploring the benefits of using physical therapy and orthopedic equipment in reducing  
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31 75 the biomechanical risk factors which included the KAM and the KAAI in patients with  
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33 76 tibiofemoral OA.

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36 77 *Data extraction and synthesis:* Two authors extracted data independently and assessed  
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38 78 risk of bias. We conducted a network meta-analysis to compare multiple interventions,  
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41 79 including both direct evidences and indirect evidences. Heterogeneity was assessed  
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44 80 (sensitivity analysis) and quantified ( $I^2$  statistic). GRADE assessed the certainty of the  
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47 81 evidence.

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49 82 *Results:* Eighteen randomized controlled trials, including 944 participants, met the  
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52 83 inclusion criteria. Based on the collective probability of being the overall best therapy  
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55 84 for reducing the first peak KAM, lateral wedge insoles (LWI) plus knee brace was  
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57 85 closely followed by gait retraining, and knee brace only. Although no significant  
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60 86 difference was observed among the eight interventions, variable-stiffness shoe and  
Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

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4 87 neuromuscular exercise exhibited an increase in the first peak KAM compared to the  
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6 88 standard care group. And based on the collective probability of being the overall best  
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9 89 therapy for reducing KAAI, gait retraining was followed by LWI only, and lower limb  
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12 90 exercise.

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14 91 *Conclusion:* The ranking statistics like surface under the cumulative ranking curve  
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17 92 values of our Bayesian network meta-analysis support the use of LWI plus knee brace  
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20 93 for reducing the first peak KAM. We found gait retraining to be the most efficacious  
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23 94 intervention as it could reduce the values for KAM and KAAI at the same time based  
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25 95 on cumulative ranking and relative effect estimates.

## 26 27 96 **Strengths and limitations**

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30 97 ① This Bayesian network meta-analysis is the first review on efficacy of physical  
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32 98 therapy and orthopedic equipment on the biomechanical parameters (KAM &  
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35 99 KAAI) of the knee OA.
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38 100 ② the Bayesian method provided the probability estimates regarding the superior  
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40 101 efficacy of specific interventions, even though the standard methods described the  
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43 102 absence of a significant difference between them.
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46 103 ③ Physical therapies and orthopedic equipment are complex interventions with a  
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48 104 small number of trials comparing the different types of interventions.
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51 105 ④ Besides KAM and KAAI, we were temporarily unable to include other  
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53 106 biomechanical risk factors, such as the external knee flexion moment to joint load.

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## 109 1. INTRODUCTION

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

118 These pathological changes of knee joint structure are the result of the break of  
119 biomechanical balance and the progression of the disease is now believed to be  
120 associated with malalignment of the lower limb.<sup>5</sup> Of the three compartments of a  
121 knee joint, KOA mostly occurs in the medial tibiofemoral compartment as it bears  
122 60-91% of the total body load, higher than the lateral one.<sup>6</sup> The external knee  
123 adduction moment (KAM) results from the unequal distribution of the transmitted  
124 load on both sides in the normal gait of humans. It is defined as the cross product  
125 of the ground reaction force and the distance between the knee joint and the force  
126 line.<sup>7</sup> Individuals with obesity,<sup>8</sup> meniscal lesions,<sup>9</sup> occupational load<sup>10</sup> or other risk  
127 factors tend to have frontal plane knee malalignment, which alters the normal force  
128 line, forcing the medial knee joint to bear more load and increased KAM.<sup>11,12</sup> The  
129 accumulation effect of the moment is determined by calculating the integral of the  
130 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)

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4 131 It reflects the change in knee joint rotation state during a stance period of gait.<sup>13</sup>  
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6 132 Previous studies have revealed a strong correlation between the peak levels of KAM  
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9 133 and KAAI and the severity and progression of the disease, which was reflected and  
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11 134 calculated by the loss of medial tibial cartilage.<sup>14,15</sup> Both these biomechanical  
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14 135 parameters (KAM and KAAI) are commonly used to evaluate the medial knee load  
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17 136 and predict the long-term structural deterioration.  
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19 137 Recent advancements in healthcare have resulted in the development of several  
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22 138 protocols for the intervention and treatment of KOA. KOA patients are primarily  
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25 139 recommended physical therapy and orthopedic equipment with the intention of  
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28 140 correcting the deviated force line and delaying the progressive pathological damage  
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31 141 inside the knee joint.<sup>7</sup> Both these modalities focus on relieving pain and improving  
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34 142 patients' symptoms by changing the biomechanical state of the knee joint. The  
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37 143 physical therapy mainly includes muscular strengthening, exercise therapy, electric  
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40 144 stimulation therapy, extracorporeal shockwave therapy and gait modification, while  
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43 145 orthopedic equipment mainly includes customized shoes/footwear, wedged insoles,  
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46 146 and knee braces.  
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48 147 Previous studies have shown the positive impact of physical therapy and orthopedic  
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51 148 equipment in KOA. The strengthening of related lower limb muscles, which play a  
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54 149 vital role in disease progression, are known to reduce instability and abnormal  
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57 150 stresses across the joint. Previous studies have shown that a lower knee joint loading  
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60 151 rate in patients with stronger quadriceps and hamstring.<sup>16</sup> Additionally, gait training  
152 presents a viable way to correct the patients' underlying gait pattern, which could

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4 153 also reduce their knee load and pain.<sup>17,18</sup> Further, several kinds of orthotic devices  
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6 154 have been introduced for the treatment of KOA. The clinical use of lateral wedge  
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9 155 insoles (LWI) has gained immense popularity since its origin in 1987.<sup>19,20</sup> The  
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12 156 insoles work by shifting the lateral part of the foot more than the medial part by a  
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15 157 slope. Thus, a slope is created to increase the valgus tendency of lower extremities.  
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17 158 The center of the ground reaction force is shifted laterally, which induces a  
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20 159 reduction in force lever arm length and magnitude. Also, the valgus knee brace is a  
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23 160 commonly used device. It applies an external valgus force around the knee joint to  
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26 161 reduce the medial knee load.

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28 162 In the past, several systematic reviews and meta-analysis have been published  
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31 163 featuring the medical effects of a single KOA treatment. However, only a few of  
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34 164 them have focused on multifaceted interventions. Also, only a few reviews have  
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37 165 reported the effects of these changes on the biomechanical parameters. The  
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40 166 mechanical changes in the body were not sufficiently investigated. Current reviews  
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43 167 on KAM and KAAI have also not compared these changes. Thus, we performed a  
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46 168 network meta-analysis (NMA) to appraise the benefits of physical treatments and  
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49 169 orthopedic equipment in reducing the biomechanical risk factors in KOA patients  
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52 170 to overcome these shortcomings, and to help achieve the goal of reducing pain and  
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55 171 improving function.

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57 172 Therefore the research questions for this systematic review were:

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59 173 1. Are physical therapy and orthopedic equipment efficacious in reducing the  
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174 biomechanical risk factors in people with KOA?



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4 175 2. Is there a better treatment than others to improve these outcomes?  
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6 176 **2. METHODS**  
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9 177 All pooled analyses were derived from previous studies and, therefore, did not  
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11 178 require ethical approval and informed consent.  
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14 179 **2.1 Identification and selection of studies.**  
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17 180 We searched the following databases for randomized controlled trials that were  
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19 181 published before January 2021, which explored the benefits of using physical  
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21 182 therapy and orthopedic equipment in reducing the biomechanical risk factors which  
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23 183 included the KAM and the KAAI in patients with tibiofemoral OA: PubMed, Web  
24  
25 184 of Science, Cochrane Library, Embase, and MEDLINE. The search was not  
26  
27 185 restricted by date, publication type, or publication status (see Appendix 1).  
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29 186 Additionally, we performed manual analyses of the published references regarding  
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31 187 the use of physical therapy and orthopedic equipment for treating KOA.  
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38 188 The eligibility of searched publications was independently reviewed by HXM, YZX  
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40 189 following the Cochrane manual.<sup>21</sup> Any additional inconsistencies were resolved  
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42 190 either by deliberation or by a senior expert (HY). First, the study titles and abstracts,  
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44 191 published in the English language, were screened. Next, complete articles were  
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46 192 reviewed against the following criteria in Box 1.  
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50 193 Eligible comparison subjects, including standard/conventional care or waiting list  
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52 194 control (analgesic advice and education), were defined as “standard care.” Standard  
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54 195 care treatment also included placebo intervention, no intervention, and sham-  
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56 196 exercise. In this network meta-analysis, lower limb exercise was defined as the  
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4 197 simultaneous exercise of multiple groups of muscles (including hip abductors,  
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6 198 quadriceps, and hamstrings). Since our research needed to maintain clinical and  
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9 199 statistical homogeneity and also focus on the left-over biomechanical effects after  
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11 200 intervention, we selected articles whose measurements were strictly obtained under  
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14 201 the condition of bare foot.

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17 202 The exclusion criteria included: (1) studies that were not consistent with the  
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19 203 eligibility criteria; (2) studies that were in the form of the non-experimental papers,  
20  
21 204 including abstracts, comments, letters, or reviews; (3) studies including participants  
22  
23 205 who had received surgical treatment in the past; (4) studies that did not report  
24  
25 206 suitable data which included the KAM or the KAAI.

## 207 **2.2 Data Collection and Quality assessment.**

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

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

## 218 **2.3 Assessment of characteristics of studies.**

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

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4 219 *Risk of bias*

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6 220 In this network meta-analysis, we used the Cochrane Risk of Bias tool 2 (RoB2) to  
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9 221 assess the risk of bias in randomized controlled trials using the following evaluation  
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11 222 indicators: randomization process, deviations from intended interventions, missing  
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14 223 outcome data, measurement of the outcome, and selection of the reported result.<sup>21</sup>  
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17 224 The judgment of the bias risk of this item was presented as "low," "high," and "  
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19 225 some concerns." Two authors independently evaluated the risk of bias of the  
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21  
22 226 included studies. The authors discussed or referred to the opinion of a senior author  
23  
24  
25 227 to resolve any disagreements. Additionally, we evaluated the certainty of evidence  
26  
27 228 which contributed to network estimates of the main outcomes with the Grading of  
28  
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30 229 Recommendations Assessment, Development and Evaluation (GRADE)  
31  
32 230 framework.

33  
34  
35 231 *Intervention*

36  
37  
38 232 In order to describe the experimental intervention, we extracted the following  
39  
40 233 information: the method of training with relevant further details, the details and  
41  
42  
43 234 characteristics of orthopedic equipment, the frequency and total duration of training  
44  
45  
46 235 or wearing.

47  
48 236 *Outcome measures*

49  
50  
51 237 Baseline biomechanical risk factors were extracted from walking test without any  
52  
53 238 orthopedic equipment before intervention, and post-intervention biomechanical risk  
54  
55  
56 239 factors were extracted from walking test with orthopedic equipment. Biomechanical  
57  
58 240 risk factors included the first peak KAM, the second peak KAM and KAAI. KAM

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3  
4 241 was normalized as %body weight times height, with conversion to Nm/kg where  
5  
6 242 necessary. KAAI was the accumulation effect of the moment which was determined  
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8  
9 243 by calculating the integral of the moment to time.  
10

#### 11 244 **2.4 Statistical Analysis.**

12  
13  
14 245 We conducted a network meta-analysis to compare multiple interventions,  
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16  
17 246 including both direct evidences (where treatments were compared directly) and  
18  
19  
20 247 indirect evidences (where treatments were compared with a common control),  
21  
22  
23 248 maintaining randomization in each independent study.<sup>22-24</sup> Interventions and  
24  
25 249 demographic characteristics were either consistent or comparable across the  
26  
27  
28 250 included studies.<sup>25-30</sup> At the same time, we did not include the studies that only  
29  
30 251 reported the immediate effect into meta-analysis.  
31

32 252 Due to different units, the continuous data used the standard mean difference (SMD)  
33  
34  
35 253 as the statistical indicator of the effect, and the Frequentist 95% confidence interval  
36  
37  
38 254 (CI) of each effect was calculated. Additionally, the  $I^2$  statistic was used to analyze  
39  
40  
41 255 the overall heterogeneity of the two-arm study and the network. The fixed-effect  
42  
43  
44 256 model was used in case no statistical heterogeneity was found between the studies  
45  
46  
47 257 ( $p > 0.05$ ,  $I^2 < 50\%$ ); given the heterogeneity between studies, a random-effects  
48  
49  
50 258 model for meta-analysis was used.<sup>31</sup> A sensitivity analysis (see Appendix 2, eFigure  
51  
52  
53 259 1 and 2) was conducted by omitting one study and investigating the influence of a  
54  
55  
56 260 single study on the overall pooled estimate to evaluate the source of heterogeneity.  
57  
58  
59 261 The Node-Split Model was used for testing consistency (see Appendix 3, eFigure  
60  
262 3). If  $p > 0.05$ , then the consistency model was used for analysis; else, the

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4 263 inconsistency model was used for analysis.<sup>32</sup> Normal likelihood distributions were  
5  
6 264 assumed, non-informative prior distributions were set, and three Markov chains  
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9 265 were run simultaneously. The number of update iterations was 50,000, a total of  
10  
11 266 5000 simulations were used for annealing, and the subsequent 45,000 iterations  
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13  
14 267 were examined. The mean rank and surface under the cumulative ranking curve  
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16  
17 268 (SUCRA) were used for reporting the probability values. A SUCRA value of 100%  
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19 269 was considered best, whereas 0% indicated the worst treatment.<sup>33</sup> Besides, we also  
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21  
22 270 made a conventional meta-analysis (see Appendix 4, eFigure 4a, 4b and 4c).  
23  
24  
25 271 The data from eligible studies were combined using the Review Manager (RevMan)  
26  
27 272 software v5.3. The contribution of the effect sizes was dependent on the sample size  
28  
29  
30 273 and their estimation accuracy. We performed the Bayesian analyses using  
31  
32  
33 274 WinBUGs v1.4.3. Stata (StataCorp. 2015. Stata Statistical Software: Release 15.  
34  
35 275 College Station, TX: StataCorp LP) was used to conduct the frequentist NMA.

### 276 3. RESULTS

#### 277 3.1 Flow of studies through the review

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

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4 285 trials (792 participants) were included.  
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6  
7 **286 3.2 Characteristics of included studies**  
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9 287 All studies included the radiologically confirmed tibiofemoral OA. The duration of  
10  
11 288 treatment ranged from 2 weeks to 12 months, although most intervention times were  
12  
13  
14 289 administered over an 8-13-week period. The number of exercises varied from 2-5  
15  
16  
17 290 times per week, depending on the preparation.<sup>40,42,45,46</sup> Both studies of gait training  
18  
19 291 used the faded feedback paradigm, which meant gradual removal of the real-time  
20  
21  
22 292 biofeedback.<sup>36,41</sup> Of the fourteen studies that were included in NMA, nine were  
23  
24  
25 293 classified as Kellgren/Lawrence grade 2 and above. All studies reported either the  
26  
27 294 BMI or the values for height and weight, and in some studies recruiting a general  
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29  
30 295 population, the mean BMI was classified as overweight or obese. One study  
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32  
33 296 included in NMA had a randomized crossover design.<sup>34</sup> After referring to the  
34  
35 297 manual and consulting a professional statistician, the mean and standard deviation  
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37  
38 298 of the experimental and the control groups were analyzed in this network meta-  
39  
40  
41 299 analysis.<sup>21</sup> Tables 1 and 2 summarize the characteristics of the included studies and  
42  
43 300 participants.  
44

45 **301 3.3 KAM.**  
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47  
48 302 A study reported that the VER-brace offers additional advantages on first peak  
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50  
51 303 KAM compared to V3P-brace and ACL-brace.<sup>51</sup> No first peak KAM reduction was  
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53  
54 304 observed between proprioceptive neuromuscular facilitation group and control  
55  
56 305 group,<sup>49</sup> and the result of the study of minimal footwear was the same.<sup>48</sup> On the  
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58  
59 306 other hand, after the electroacupuncture treatment, compared with the control group,  
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4 307 the second peak KAM significantly increased immediately when the patient  
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6 308 ascended stairs.<sup>50</sup> Table 3 shows the NMA results of a comparative analysis of the  
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9 309 reduction of the first peak KAM. We found insignificant differences in most of the  
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11 310 treatment modalities; however, variable-stiffness shoes showed a statistically  
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13  
14 311 significant increase in the first peak KAM over the rest of the included interventions.  
15  
16  
17 312 Neuromuscular exercise was better than variable-stiffness shoes, but was still  
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19 313 inferior to most other interventions. At the same time, lateral wedge insole plus knee  
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21  
22 314 brace and gait retraining performed relatively well in reducing the first peak KAM  
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24  
25 315 compared with standard care and other treatments. Based on the collective  
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27 316 probability of being the overall best therapy for reducing the first peak KAM, LWI  
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29  
30 317 plus knee brace (93.4%) was closely followed by gait retraining (85.7%), and knee  
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32  
33 318 brace only (79.3%) (Figure 2).

### 319 3.4 KAAI.

37 320 KAAI was reported in ten studies.<sup>34,36,40,43-48,51</sup> After wearing the three kinds of  
38  
39  
40 321 brace separately, the KAAI measured without brace did not decrease significantly,  
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42  
43 322 and there was no significant difference between the groups.<sup>51</sup> Table 3 shows the  
44  
45 323 NMA results of the reduction of KAAI. Most treatments were not statistically  
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47  
48 324 different from each other, consistent with the results of the first peak KAM. Only  
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51 325 gait retraining has a statistical reduction compared with the standard care treatment.  
52  
53 326 The aggregated results suggested that gait retraining is efficient in reducing the  
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56 327 KAAI, while neuromuscular exercise will relatively increase the KAAI compared  
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59 328 with some treatment. Based on the collective probability of being the overall best  
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4 329 therapy for reducing KAAI, gait retraining (90.7%) was followed by LWI only  
5  
6 330 (74.1%), and lower limb exercise (53.8%) (Figure 3).  
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8

### 9 331 **3.5 Heterogeneity.**

10  
11 332 We removed a study which had a short follow-up time and might cause  
12  
13 333 heterogeneity,<sup>34</sup> and performed another network meta-analysis. There is no  
14  
15 334 difference between the results of the reanalysis and the current ranking (see  
16  
17 335 Appendix 2, eFigure 1 and 2).  
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### 22 336 **3.6 GRADE assessment**

23  
24 337 According to the GRADE framework (see Appendix 6), the quality of the most  
25  
26 338 comparisons was assessed as low or very low. Only neuromuscular exercise  
27  
28 339 compared with standard care, neuromuscular exercise compared with LWI,  
29  
30 340 neuromuscular exercise compared with knee brace, and neuromuscular exercise  
31  
32 341 compared with LWI plus knee brace were evaluated as a moderate-grade  
33  
34 342 comparison.  
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### 40 343 **3.7 Risk of bias.**

41  
42 344 Figure 4 depicts a summary of the risk-of-bias scores for the included RCTs in this  
43  
44 345 analysis. Nine studies presented a clear description of generating a randomization  
45  
46 346 sequence.<sup>38-40,42,45-48,50</sup> The study by Hinman et al. was the only double-blinded  
47  
48 347 study, while other studies were either single-blinded or did not clearly describe their  
49  
50 348 blind design. All trials provided follow-up data on their outcomes. Six studies did  
51  
52 349 not report the number or the reason for lost visits due to the length of follow-  
53  
54 350 up.<sup>34,38,39,41,42,45</sup> Consequently, all studies were included in the synthesis evaluation  
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4 351 and qualified for literature assessment. And we prepared comparison-adjusted  
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6 352 funnel plots that represented different comparisons with different colors. The funnel  
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9 353 plots were symmetrically distributed based on a visual inspection, which suggested  
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11 354 the absence of small-sample effects for our outcomes (see Appendix 7, eFigure 6a  
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13  
14 355 and 6b).

#### 17 356 4. DISCUSSION

18  
19 357 Our results did not show significant differences regarding the superiority of  
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21  
22 358 intervention among different types of physical therapies and orthopedic equipment.  
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24 359 This lack of difference was attributed to the fact that the number of studies for  
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26  
27 360 several pairwise comparisons was small. However, some of these therapies were  
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29  
30 361 still worth recommending. Due to the small number of studies studying the outcome  
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33 362 of the KAAI, we found gait retraining to be the relatively more convincing  
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35 363 intervention as it could reduce the values for KAM and KAAI at the same time  
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37  
38 364 based on cumulative ranking and relative effect estimates. Due to the lack of  
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41 365 significant differences among the interventions, we were not able to conclusively  
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43 366 accept the cumulative ranking obtained by the network meta-analysis. For example,  
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45 367 gait retraining, which occupied the first rank position (90.7%) for reducing the  
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47  
48 368 KAAI, was only superior to the neuromuscular exercise interventions.

49  
50 369 This study had several strengths and limitations. This network meta-analysis is the  
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52  
53 370 first report on the effects of physical therapy and orthopedic equipment on the  
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56 371 parameters of knee load (KAM, KAAI). Since physical therapies and orthopedic  
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59 372 equipment are complex interventions with a small number of trials comparing the  
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4 373 different types of interventions, network meta-analysis appeared to be the most  
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6 374 relevant form of analysis. The results of this meta-analysis would be more useful  
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9 375 for the decision-makers, service specialists, and caregivers to choose among the  
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11 376 various available options, compared with multiple separate pairwise meta-  
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13  
14 377 analyses.<sup>52</sup> Additionally, this network meta-analysis conducted each comparison  
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17 378 separately with both direct and indirect statistical effects, deriving statistical power  
18  
19 379 from all included data.<sup>52</sup> Also, the Bayesian method provided the probability  
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21 380 estimates regarding the superior efficacy of specific interventions, even though the  
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23 381 standard methods described the absence of a significant difference between them.  
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25  
26  
27 382 In addition, we calculated alternative rankings (second, third best, etc), because in  
28  
29 383 some cases the best intervention might be unavailable, more costly, or  
30  
31 384 contraindicated in some patients. As with most meta-analyses on non-surgical  
32  
33 385 therapies for osteoarthritis, one of the limitations of this network meta-analysis  
34  
35 386 includes the inclusion of trials that had variable periods of follow-up, which could  
36  
37 387 have introduced heterogeneity into the study analysis. There exist several methods  
38  
39 388 of analyzing and comparing trials with multiple durations of follow-up, as  
40  
41 389 recommended by the Cochrane handbook, such as performing individual patient  
42  
43 390 data meta-analysis and evaluating at a particular time point. However, methods are  
44  
45 391 being developed that would include all time points in a network meta-analysis.<sup>21</sup>  
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47  
48 392 We were not able to evaluate the influence of population characteristics (such as  
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50 393 mean age, the severity of osteoarthritis), as the number of the included studies was  
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52  
53 394 not large enough.<sup>53-55</sup> Additionally, other parameters, such as the external knee  
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4 395 flexion moment to joint load, should have been studied. However, due to the small  
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7 396 number of related articles, we were temporarily unable to include them.  
8  
9 397 A previous review showed that LWIs were able to reduce the KAM at baseline;<sup>56</sup>  
10  
11 398 however, the effect was no longer observed after a period. One study showed that a  
12  
13  
14 399 1-month wear-in period was the longest time period studied where no reduction in  
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16  
17 400 biochemical risk factors was observed despite continued wear.<sup>57</sup> Besides, several  
18  
19 401 systematic reviews had concluded that exercise and gait retraining could reduce  
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21  
22 402 pain and improve motor functioning in people with KOA,<sup>58-60</sup> it was possible that  
23  
24  
25 403 any clinical changes in previous studies may due to the increased physical activity  
26  
27 404 levels, and not have been the results of altered loading environment within the knee  
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29  
30 405 joint. Furthermore, another study revealed that an increase in the amount of  
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32  
33 406 reduction in peak KAM in LWIs plus knee brace group was observed after 4  
34  
35 407 weeks.<sup>61</sup> In this network meta-analysis, we focused on the studies of non-immediate  
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37  
38 408 effect, removed the research with a follow-up time of less than one month in the  
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40  
41 409 sensitivity analysis, and made the final rank. The results showed that only gait  
42  
43 410 training produces a significant reduction in KAM and KAAI, indicating that the  
44  
45 411 biomechanical reduction effect of orthopedic equipment cannot be maintained for  
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47  
48 412 a long time when they are donned. Once the time of the treatment was extended,  
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50  
51 413 the biomechanical reduction effect might lessen. The reason may be that orthopedic  
52  
53 414 equipment deform and render them less effective mechanically, although typically  
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56 415 made of high density materials.  
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58  
59 416 On the other hand, physical therapies and orthopedic equipment also need to be  
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4 417 considered for relieving patients' pain, which has been the focus of several reviews  
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6 418 in the past. As an important factor in kinetics and kinematics of gait, the joint pain  
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9 419 can affect the kinetics and kinematics of walking.<sup>62</sup> A meta-analysis reported that  
10  
11 420 exercise therapy had a positive impact on knee pain and kinematic function, though  
12  
13  
14 421 this relief of pain subsided with time. After initiation, the efficiency of physical  
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16  
17 422 exercise over placebo reached maxima at 2 months.<sup>63</sup>  
18  
19 423 Cumulative loading is another significant parameter regarding knee load exposure  
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21  
22 424 in OA.<sup>64</sup> KAAI has been proposed as another indicator to evaluate the duration and  
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24  
25 425 intensity of KOA load, despite the association between KAM and disease  
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27  
28 426 progression. According to a 12-month study, the loss of medial tibiofemoral  
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31 427 cartilage was not directly related to KAM but was related to KAAI.<sup>65</sup> Although the  
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33  
34 428 effect of physical therapy and orthopedic equipment on KAM may gradually  
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37 429 disappears, it may have a huge cumulative effect on the knee during the early stages  
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39  
40 430 of treatment. This should be considered while interpreting the results of this network  
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42  
43 431 meta-analysis.  
44  
45 432 The results presented in this study are both scientifically and clinically instructive.  
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47  
48 433 Despite observing a null statistical reduction in KAM and KAAI for most therapies,  
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51 434 using these treatments clinically could improve symptoms and physical activity  
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53  
54 435 level without increasing the biomechanical magnitude; thus, improving the quality  
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56  
57 436 of life of patients with KOA. Although the results of this study suggested that  
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59  
60 437 wearing variable-stiffness shoes is not a good choice for long-term reduction of  
438 KAM, current study have pointed out that variable-stiffness shoe will have greater

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4 439 benefits in reducing KAM for patients with increasing walking speed.<sup>66</sup> At the same  
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6 440 time, variable-stiffness shoes had relatively weaker discomfort than equipment such  
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9 441 as LWI. Since the studies included in this network meta-analysis mainly involves  
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11 442 patients with medial knee osteoarthritis, the results would be more useful for these  
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14 443 patients.

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16  
17 444 On the other hand, previous study reported that the increase in KAAI can explain  
18  
19 445 the significant variation in the uCTX-II levels and the uCTX-II:sCPII ratio in  
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21  
22 446 patients with medial tibiofemoral KOA when additional variables are controlled.<sup>67</sup>

23  
24  
25 447 This showed that intervention in the biomechanical structure of the knee joint in  
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27 448 patients with KOA is a potential beneficial role on cartilage structure. Maleki et al.  
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29  
30 449 pointed out that adopting a modified gait that reduces the KAM can decrease the  
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32  
33 450 pain in the medial compartment in KOA more than walking alone,<sup>68</sup> which suggests  
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35 451 that the KAM and KAAI of patients under non-surgical treatment can be restricted  
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37  
38 452 to help reduce pain and improve joint function. More research is needed to further  
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40 453 illustrate the impact of changes in knee biomechanics on the prognosis of patients.

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42  
43 454 Additionally, some other therapies have been reported, such as Taiji, ultrasound,  
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45 455 acoustic exercise, etc. However, due to the lack of RCT study design or the report  
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47  
48 456 of their biomechanical outcomes, we were not able to include these therapies in our  
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50  
51 457 review. Therefore, further studies would require more research articles in these  
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53 458 areas to further explore the impact of various non-surgical therapies on OA patients.

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56 459 After accumulating evidence regarding the role of non-surgical therapy in KOA, we  
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58  
59 460 could conduct a similar network meta-analysis to understand the relative  
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4 461 effectiveness of various types of these interventions in relevant patients.  
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6  
7 462 **5. Conclusion**  
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9 463 This network meta-analysis provides valuable insight regarding the alterations in  
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11 464 KAM and KAAI of OA patients after physical therapy and orthopedic equipment.  
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14 465 After integrating cumulative ranking and relative effect estimates, gait retraining  
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17 466 was the most recommended therapy for reducing the biomechanical risk factors. On  
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19 467 the contrary, variable-stiffness shoe and neuromuscular exercise needed to be used  
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21  
22 468 with caution in clinical treatment. Taken together, these findings suggest that  
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25 469 clinicians should choose carefully when treating OA.  
26

27 470 **6. Authors' Contributions**  
28

29  
30 471 HXM and YFZ conceived of the study, and participated in its design and  
31  
32 472 coordination and helped to draft the manuscript; YZX, HY and CRY contributed  
33  
34  
35 473 significantly to analysis and manuscript preparation; YJK and LL helped perform  
36  
37  
38 474 the analysis with constructive discussions and revised it critically for important  
39  
40  
41 475 intellectual content.  
42

43 476 **7. Competing interests**  
44

45 477 There were no conflicts of interest.  
46  
47

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49

50  
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57  
58 482 EMTC-02-00897).  
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4 483 **9. Ethics approval**

5  
6 484 Not required.

7  
8  
9 485 **10. Data availability statement**

10  
11 486 No data are available.

12  
13  
14 487 **11. Patient and public involvement**

15  
16  
17 488 Patients and/or the public were not involved in the design, or conduct, or reporting, or  
18  
19 489 dissemination plans of this research.

20  
21  
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Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)



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



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

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

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**Table 1. Characteristics of included studies (1) \***

Authors	Country	Clinical criteria†	Radiographic features	Intervention	Comparisons	Follow up
Barrios 2013 <sup>43</sup>	US	Medial compartment knee OA; Pain VAS ( $\geq 3$ of 10 upon walking)	K/L grade $\geq 2$ , medial tibiofemoral compartment	bespoke full-length LWI	Placebo	12 months
Hinman 2016 <sup>44</sup>	Australia	Medial compartment knee OA; Pain NRS ( $> 4$ of 11 upon walking) over the previous week	K/L grade $\geq 2$ , medial tibiofemoral compartment	5° full-length LWI	Placebo	6 months
Arazpour 2012 <sup>37</sup>	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 <sup>34</sup>	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 <sup>35</sup>	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)

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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;

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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 <sup>36</sup>	US	Medial compartment knee OA; Pain ( $\geq 3$ of 10) longer than 6 months	K/L grade $\geq 2$ , medial tibiofemoral compartment	Toe-out gait modification	Walking without any guidance	4 months
Lim 2008 <sup>38</sup>	Australia	Medial compartment knee OA; Medial knee pain	K/L grade $\geq 2$ , medial JSN	Quadriceps strengthening	No intervention	12 weeks
Erhart-Hledik 2012 <sup>39</sup>	US	Medial compartment knee OA; Medial knee pain	K/L grade $\geq 1$	Variable-stiffness shoe with stiffer soles on the lateral side	Constant-stiffness control shoe	12 months
Bennell 2010 <sup>40</sup>	Australia	Medial compartment knee OA; Varus malalignment; Pain ( $> 3$ of 11 upon walking)	K/L grade $\geq 2$ , medial JSN	Hip strengthening	No intervention	13 weeks
Cheung 2018 <sup>41</sup>	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 (3) \***

Authors	Country	Clinical criteria†	Radiographic features	Intervention	Comparisons	Follow up
Foroughi 2011 <sup>42</sup>	Australia	Primary knee OA	K/L grade $\geq 1$	Lower limb exercise	Sham-exercise	6 months
Bennell 2014 <sup>45</sup>	Australia	Medial compartment knee OA; Pain VAS ( $\geq 25$ of 100) over the past week	K/L grade $\geq 2$ , medial tibiofemoral compartment	Neuromuscular exercise	Quadriceps strengthening	12 weeks
Hunt 2013 <sup>46</sup>	Canada	Medial compartment knee OA; Knee pain $> 3/10$ on most days of the previous month	K/L grade $\geq 2$ , medial tibiofemoral compartment	Lower limb exercise	No intervention	11 weeks
Holsgaard-Larsen 2017 <sup>47</sup>	Denmark	Primary knee OA  Pain KOOS ( $< 80$ of 100, at least mild pain)	K/L grade $\leq 3$	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 <sup>49</sup>	China	Medial compartment knee OA in one or both legs.	K/L grade $\leq 3$	PNF (one-hour sessions three times a week)	Watch television or read magazines at the same time	12 weeks
Wang 2017 <sup>50</sup>	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 <sup>51</sup>	Canada	Medial compartment knee OA; Pain > 31/100 on WOMAC; Varus knee alignment $\geq 2^\circ$	K/L grade 2 and 3	V3P-brace; VER-brace; ACL-brace (wear the brace as often as possible)	/	3 months
Trombini-Souza 2015 <sup>48</sup>	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/m <sup>2</sup>	Bilateral knee OA included	K/L grade, no.				Main outcomes
								1	2	3	4	
Barrios 2013 <sup>43</sup>	38	NR	61.90±8.37	NR	NR	32.00±7.43	NR	0	17	14	7	1 <sup>st</sup> KAM; KAAI
Hinman 2016 <sup>44</sup>	164	20:21	64.30±7.45	1.67 ± 0.10	82.95±14.76	29.70±3.64	NR	0	49	52	63	1 <sup>st</sup> KAM; KAAI
Arazpour 2012 <sup>37</sup>	24	3:4	59.29±2.37	NR	NR	27.01±1.71	Yes	9	15	0	0	1 <sup>st</sup> KAM
Jones 2013 <sup>34</sup>	28	4:3	66.30±8.20	1.75±0.13	88.7±15.10	NR	No	0	10	18	0	1 <sup>st</sup> and 2 <sup>nd</sup> KAM; KAAI
Khosravi 2019 <sup>35</sup>	21	13:8	58.97±6.80	1.62±0.11	79.11±9.35	NR	NR	0	9	12	0	1 <sup>st</sup> 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 <sup>2</sup>	Bilateral knee OA included	K/L grade, no.				Main outcomes
								1	2	3	4	
Hunt 2018 <sup>36</sup>	79	24:55	64.99±8.60	1.65±0.10	74.59±13.15	27.35±3.48	Yes	0	37	31	11	1 <sup>st</sup> and 2 <sup>nd</sup> KAM; KAAI
Lim 2008 <sup>38</sup>	107	48:59	64.60±8.51	1.65±0.10	79.41±15.32	28.96±4.85	Yes	0	34	29	44	1 <sup>st</sup> KAM
Erhart-Hledik 2012 <sup>39</sup>	79	41:38	61.70±9.43	1.69±0.08	79.50±15.07	27.51±4.87	Yes	NR	NR	NR	NR	1 <sup>st</sup> KAM
Bennell 2010 <sup>40</sup>	89	46:43	64.55±8.34	NR	NR	27.94±4.41	Yes	0	30	29	30	1 <sup>st</sup> KAM; KAAI
Cheung 2018 <sup>41</sup>	20	1:1	61.95±6.11	1.63±0.09	65.85±6.64	27.35±3.48	NR	5	15	0	0	1 <sup>st</sup> 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 <sup>2</sup>	Bilateral knee OA included	K/L grade, no.				Main outcomes
								1	2	3	4	
Foroughi 2011 <sup>42</sup>	54	0:54	65.48±7.44	NR	82.87±18.43	32.07±7.08	Yes	20	7	20	1	1 <sup>st</sup> and 2 <sup>nd</sup> KAM
Bennell 2014 <sup>45</sup>	100	48:52	62.45±7.32	1.67±0.10	82.70±14.29	29.65±4.08	Yes	0	22	43	35	1 <sup>st</sup> KAM; KAAI
Hunt 2013 <sup>46</sup>	17	8:9	66.10±11.3	NR	NR	27.00±4.50	Yes	0	10	5	2	1 <sup>st</sup> KAM; KAAI
Holsgaard-Larsen 2017 <sup>47</sup>	93	39:54	58.10±7.96	NR	79.64±12.49	26.90±3.09	NR	45	31	17	0	1 <sup>st</sup> 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 <sup>2</sup>	Bilateral knee OA included	K/L grade, no.				Main outcomes
								1	2	3	4	
Song 2020 <sup>49</sup>	36	1:1	68.01±3.91	1.62±0.07	68.16±6.77	NR	Yes	9	20	7	0	1 <sup>st</sup> KAM
Wang 2017 <sup>50</sup>	36	1:5	63.50±7.95	NR	NR	23.75±2.66	Yes	0	19	17	0	1 <sup>st</sup> and 2 <sup>nd</sup> KAM
Robert-Lachaine 2020 <sup>51</sup>	24	7:5	57.20±8.60	1.68±0.09	89.30±18.70	31.40±5.00	NR	0	15	8	0	1 <sup>st</sup> and 2 <sup>nd</sup> KAM; KAAI
Trombini-Souza 2015 <sup>48</sup>	56	NR	66.00±5.00	1.60±0.10	73.40±13.10	NR	NR	0	NR	NR	0	1 <sup>st</sup> 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.

<b>J</b>	0.41 (-0.66,1.49)	0.16 (-0.46,0.79)	-	0.20 (-0.23,0.64)	<b>0.81</b> <b>(0.17,1.45)</b>	-	0.30 (-0.61,1.21)	<b>0.54</b> <b>(0.02,1.07)</b>	0.32 (-0.10,0.75)
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Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

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

**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**

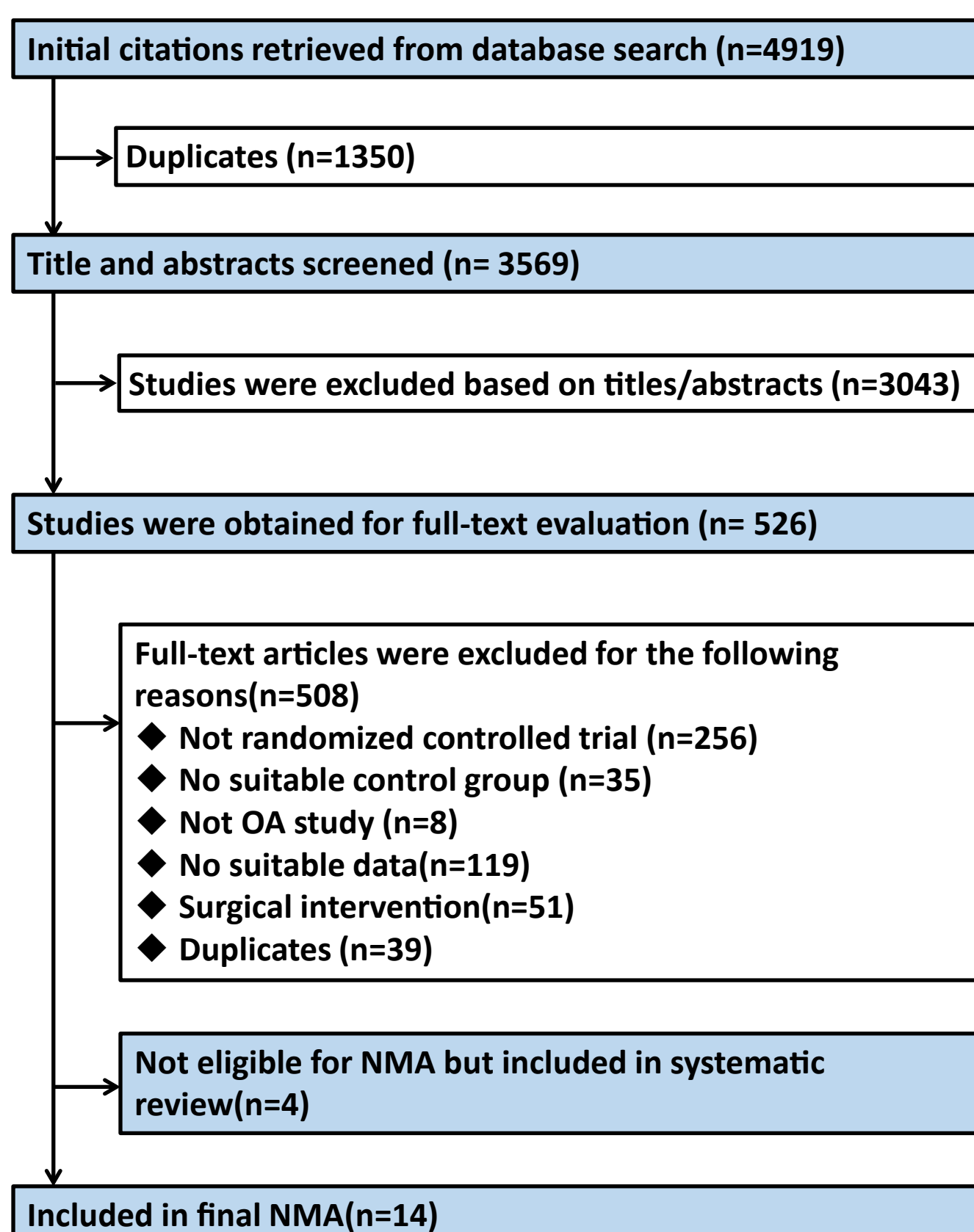
**Figure 2. Rankings for effects on First peak KAM. Graph displays distribution of probabilities for each treatment. X-axis represents the possible rank of each treatment (from the best to worst according to the outcomes), Y-axis represents the cumulative probability for each treatment to be the best 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**

For peer review only

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



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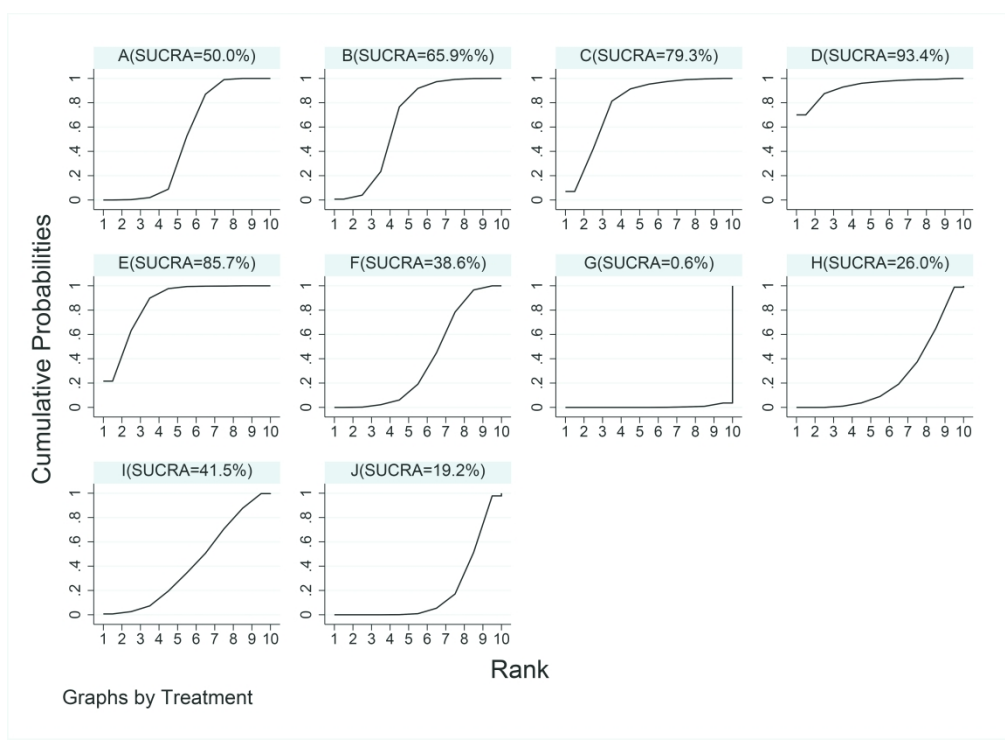


Figure 2

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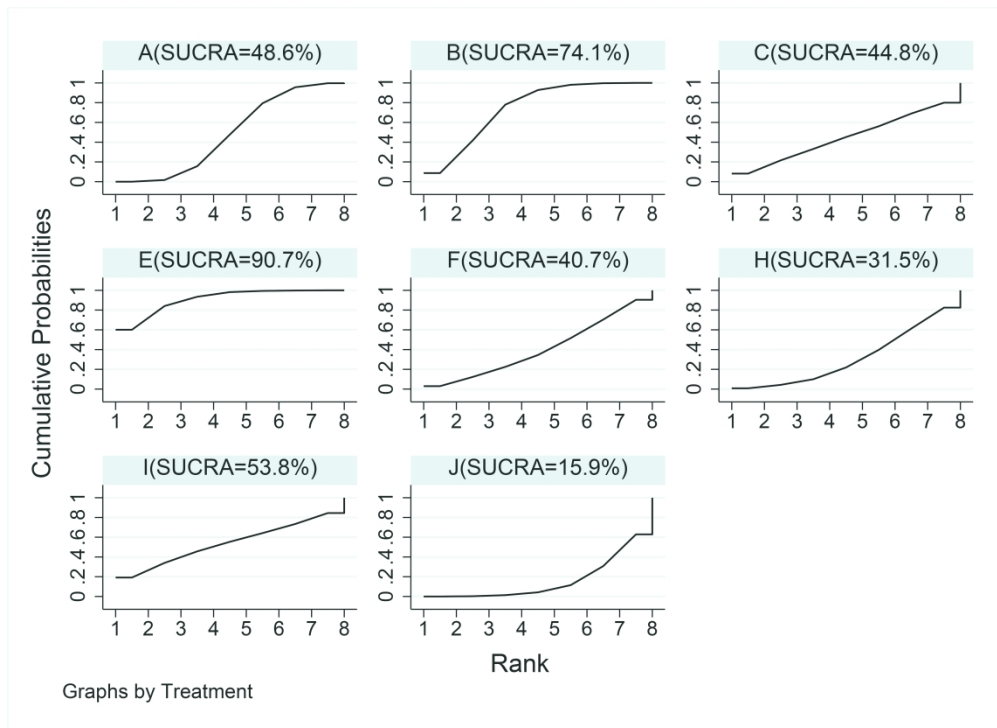
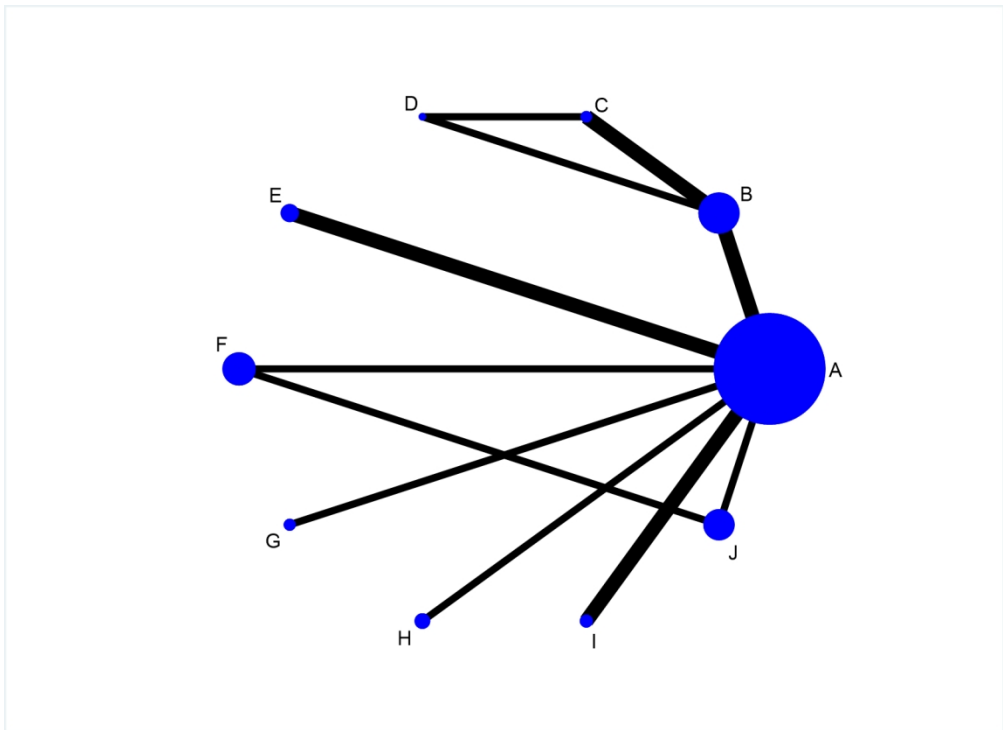


Figure 3

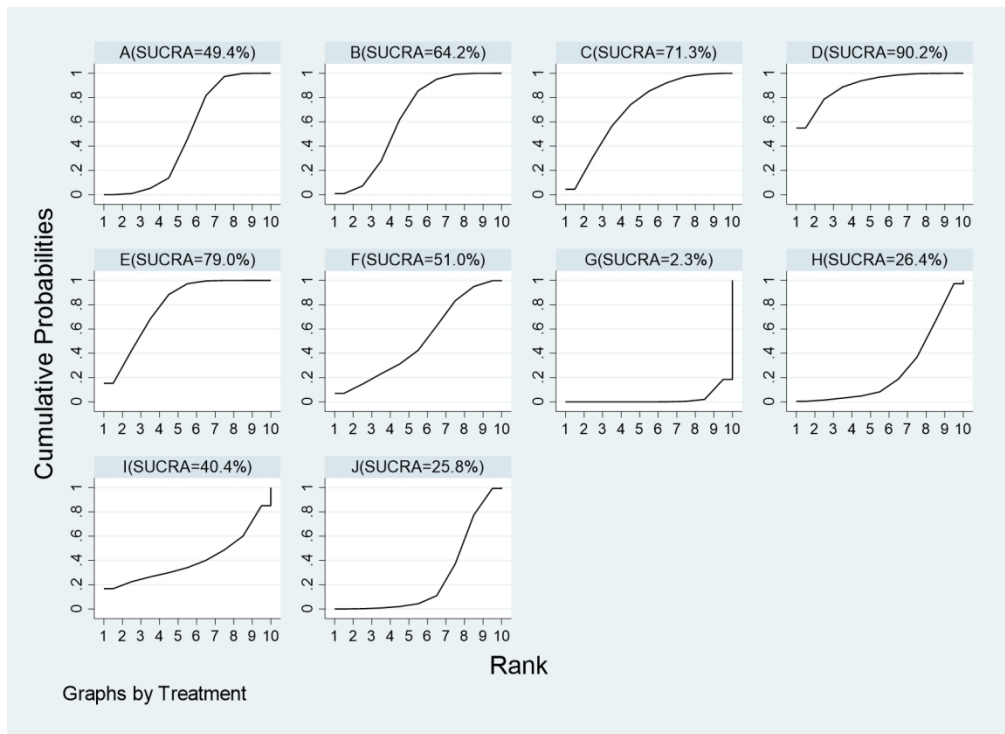
Study ID	Randomization process	Deviations from intended i	Missing outcome data	Measurement of the outcome	Selection of the reported	Overall
Arazpour 2012	?	?	?	+	+	!
Barrios 2013	?	+	+	+	+	!
Bennell 2010	+	+	+	+	+	+
Bennell 2014	+	+	?	+	+	?
Cheung 2018	?	?	?	+	?	?
Erhart-Hledik 2012	?	+	?	+	?	?
Foroughi 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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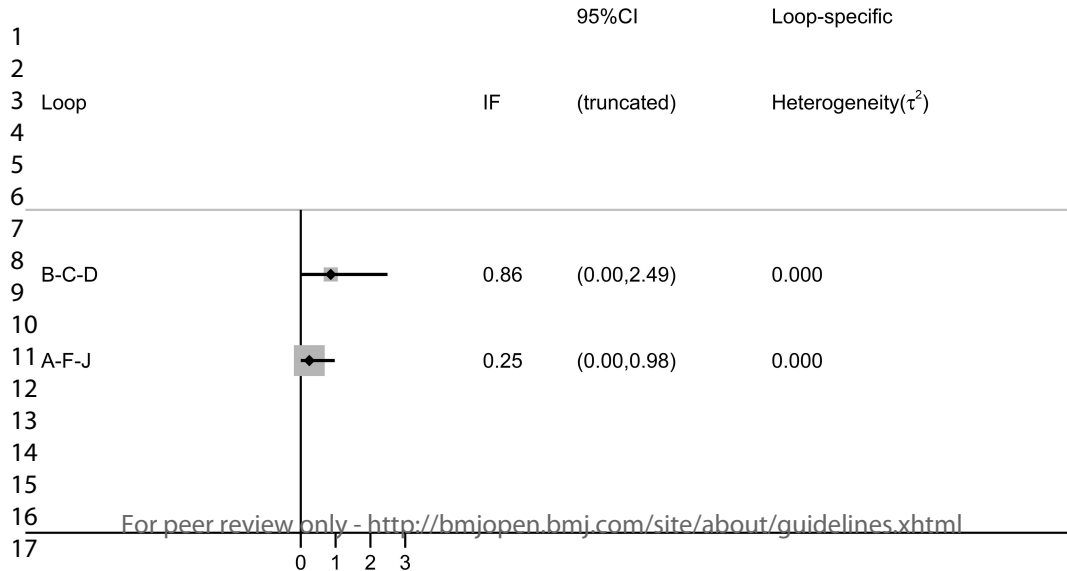


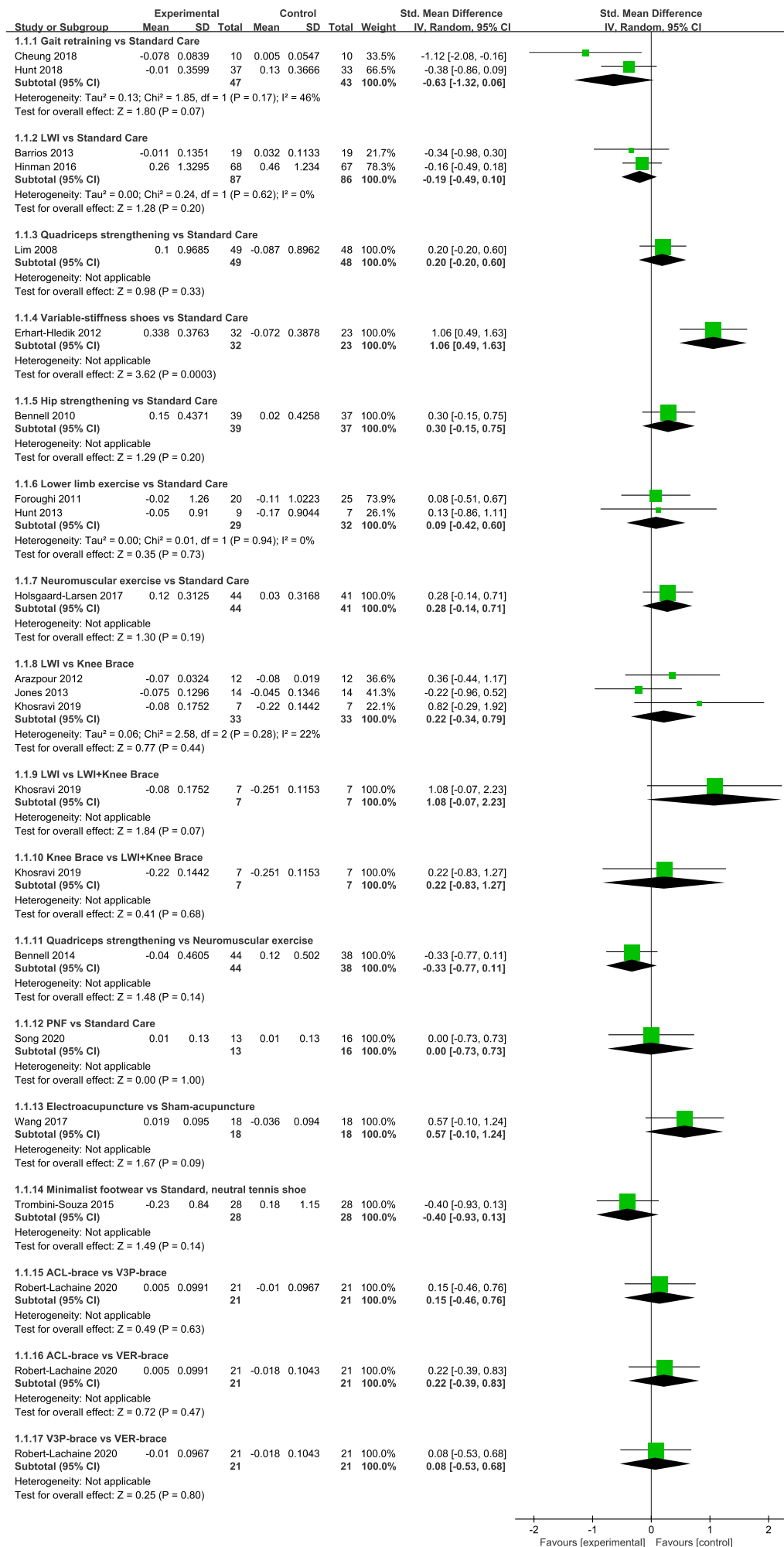
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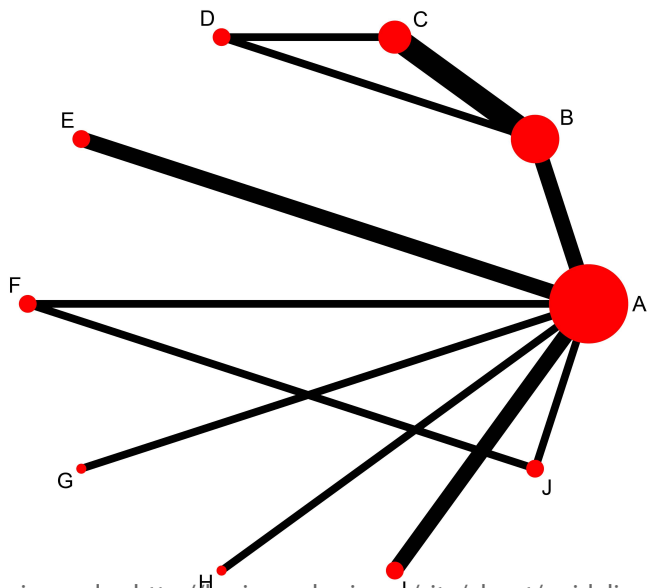
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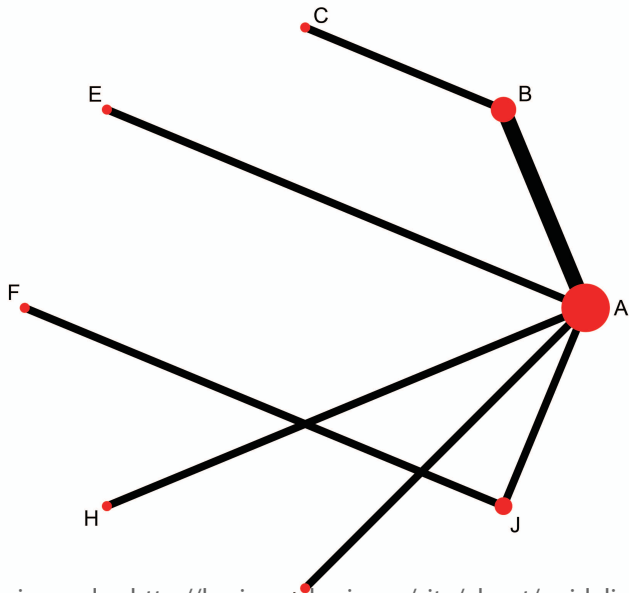
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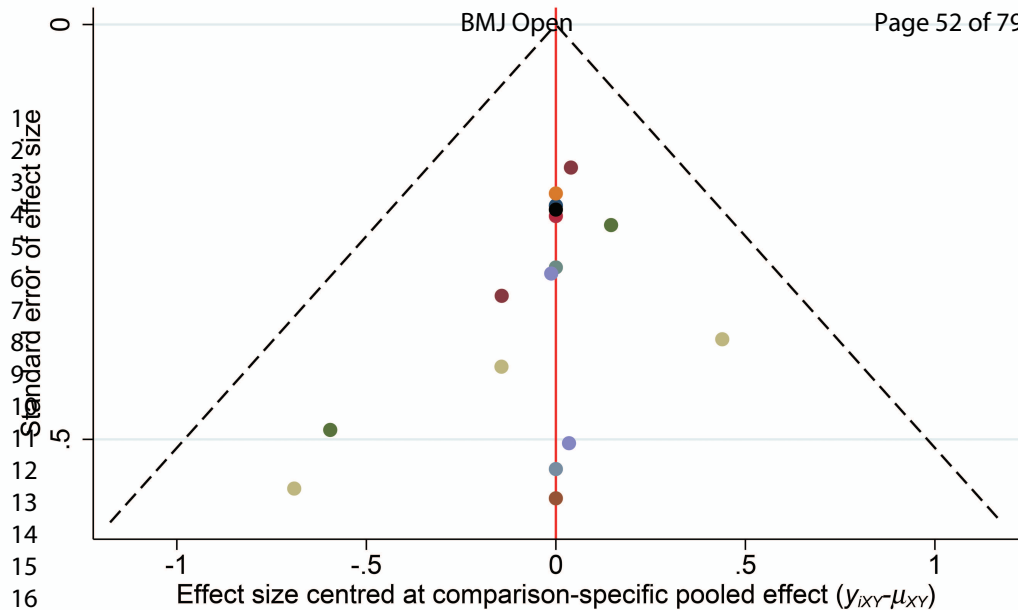
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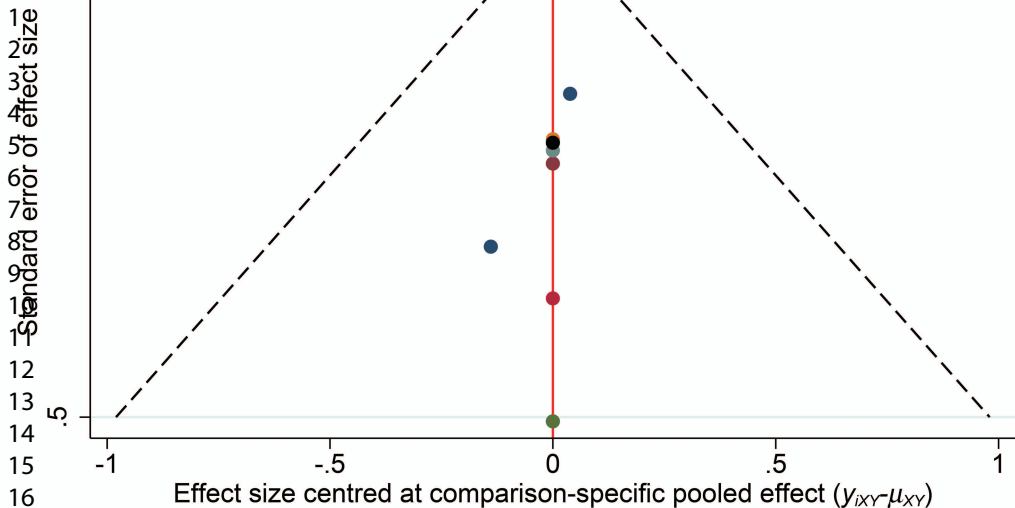


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## Appendix

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## Appendix 1 Search strategies

### Search strategies for randomized controlled trials

#### Pubmed

1. (((((((("Osteoarthritis, Knee"[Mesh]) OR Knee Osteoarthritis[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 Osteoarthritis[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-arthritis':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 'orthoepadic 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-arthritis':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 orthosis OR orthoses OR orthopaedic support device OR orthotic device)
4. TI=(orthosis OR device OR orthosis OR orthoses OR orthopaedic 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 osteoarthritis OR osteoarthritis)
7. TI=(knee osteoarthritis OR femorotibial arthrosis OR gonarthrosis OR knee arthrosis OR knee osteo-arthritis OR knee osteoarthritis OR osteoarthritis)
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 Osteoarthritis):ti,ab,kw OR (Knee Osteoarthritis):ti,ab,kw OR (Knee 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 Osteoarthritis):ti,ab,kw OR (Knee Osteoarthritis):ti,ab,kw OR (Knee Osteoarthritis of the Knee):ti,ab,kw) OR MeSH descriptor: [Osteoarthritis, Knee] explode all trees)

#### **MEDLINE**

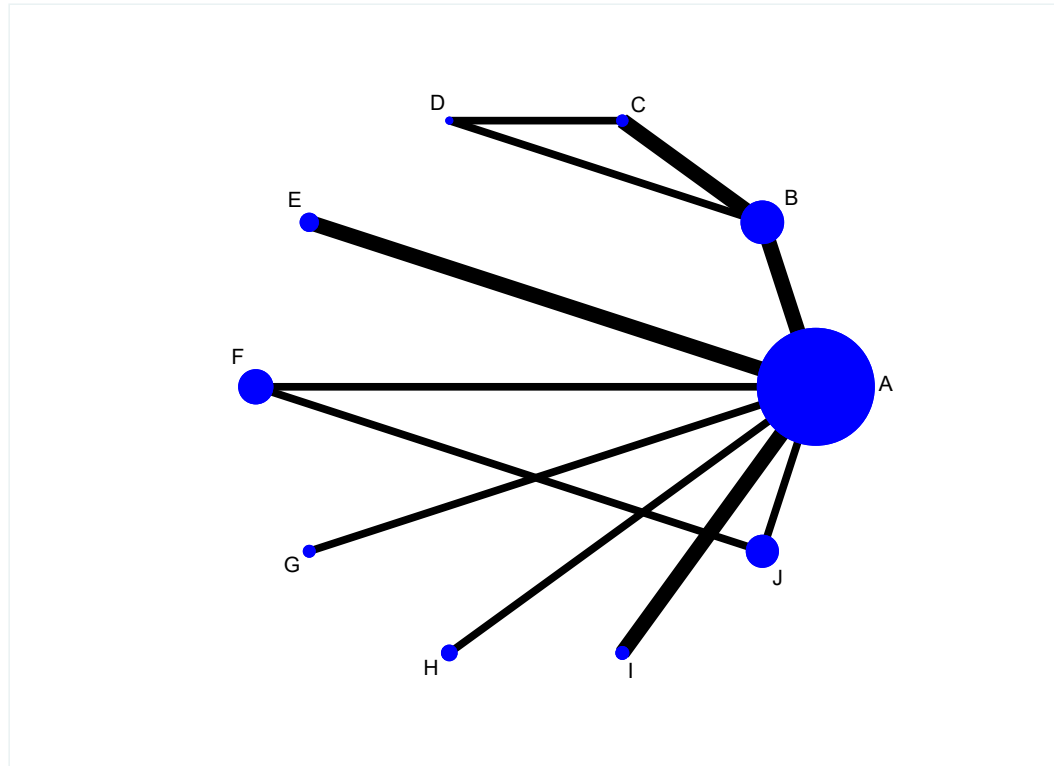
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5. #1 AND #4

## 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.

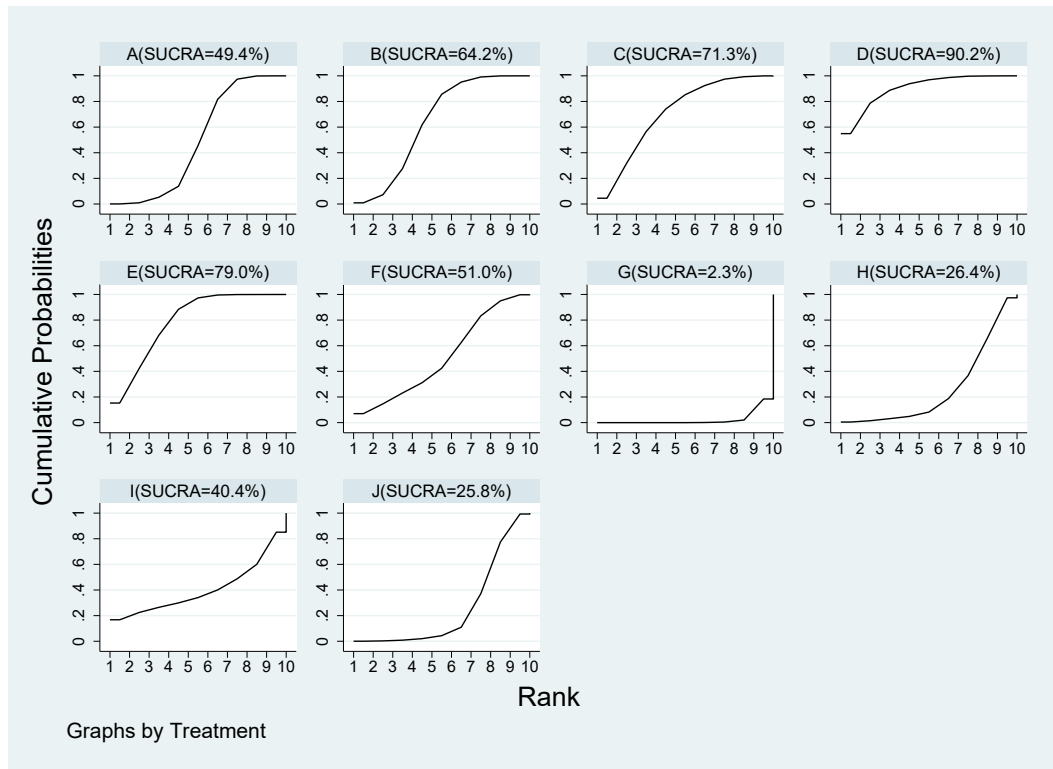
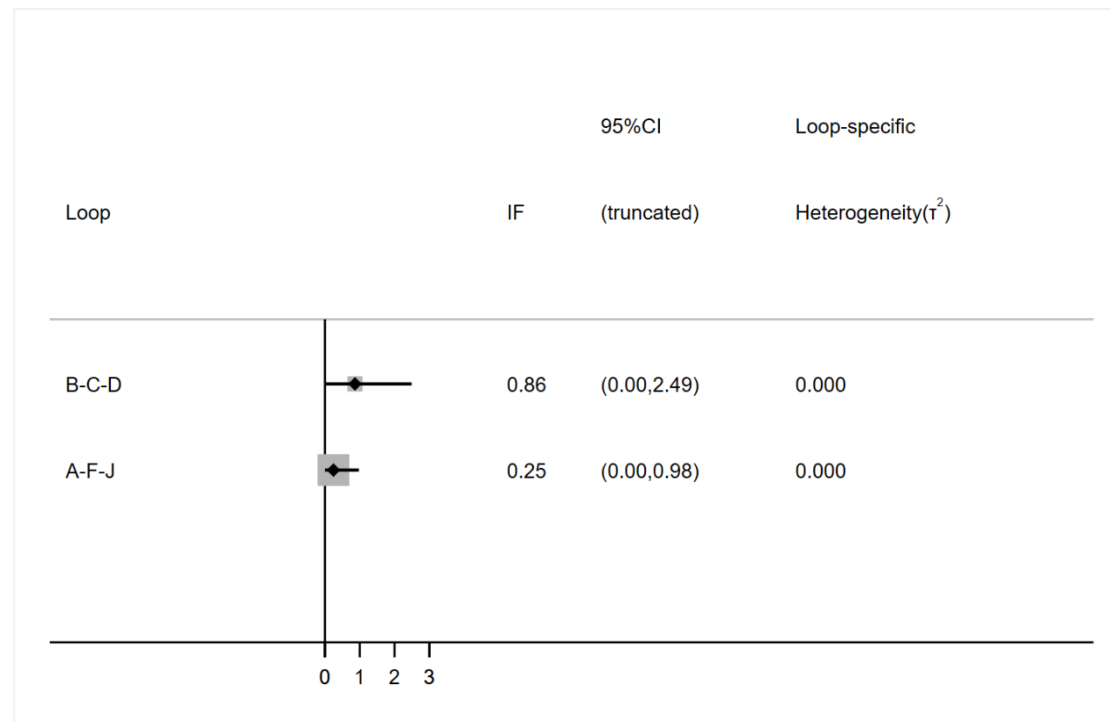


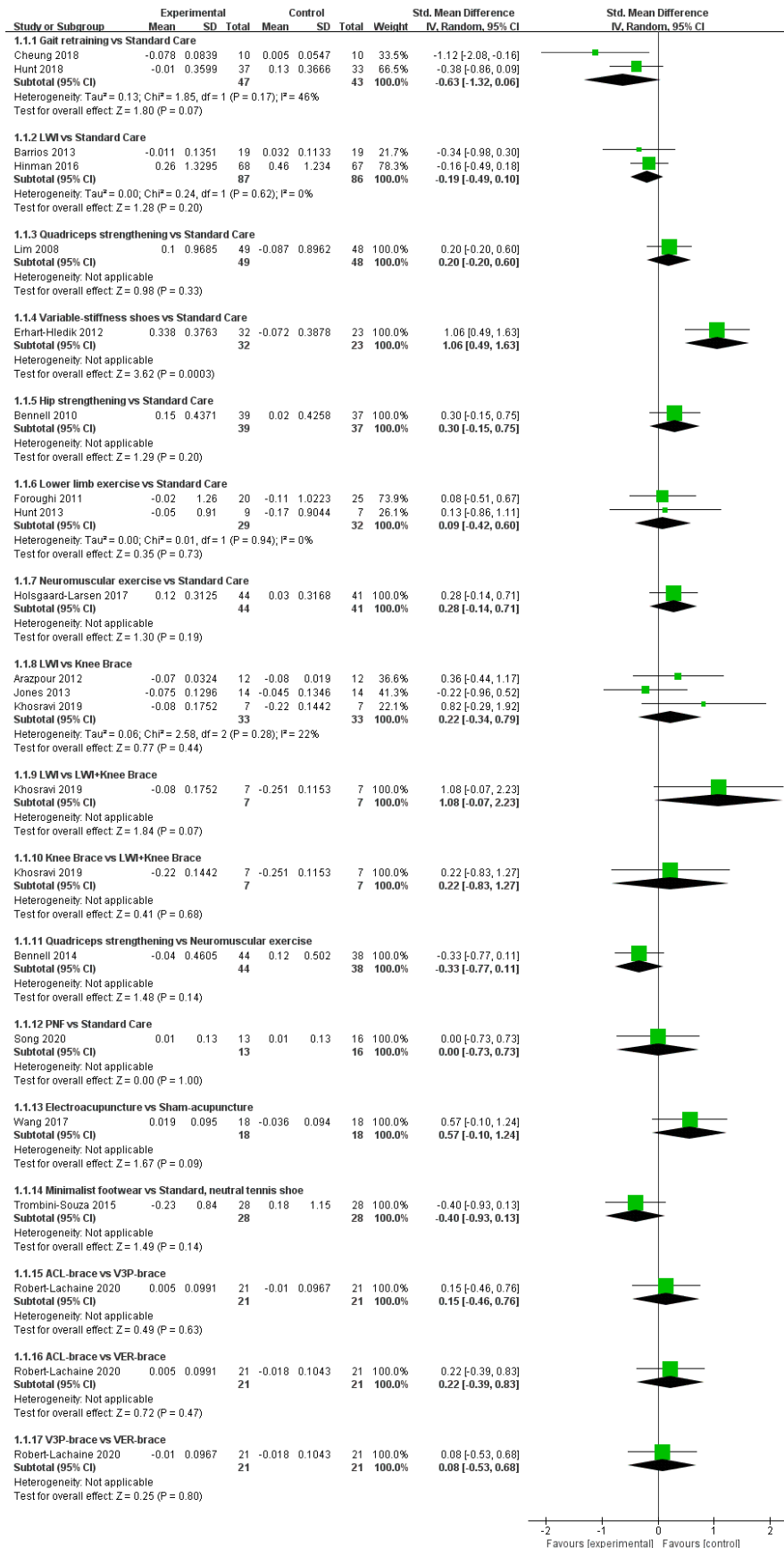
Figure 2. Rankings for effects on First peak KAM (re-analysis). Graph displays distribution of probabilities for each treatment. X-axis represents the possible rank of each treatment (from the best to worst according to the outcomes), Y-axis represents the cumulative probability for each treatment to 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

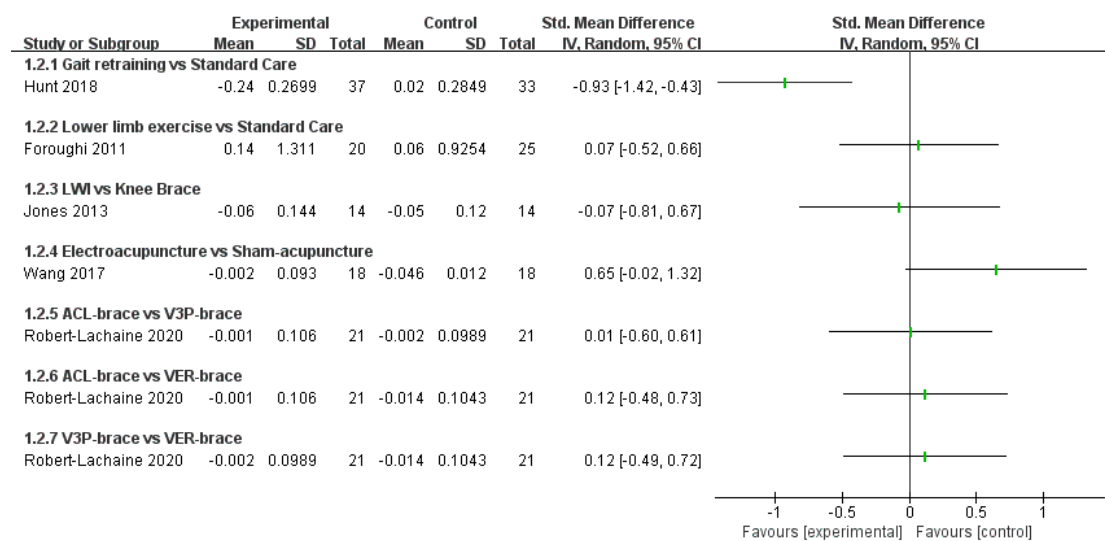


eFigure 3. Inconsistency for triangular loops in First peak KAM.

## Appendix 4 Conventional meta-analyses results



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



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

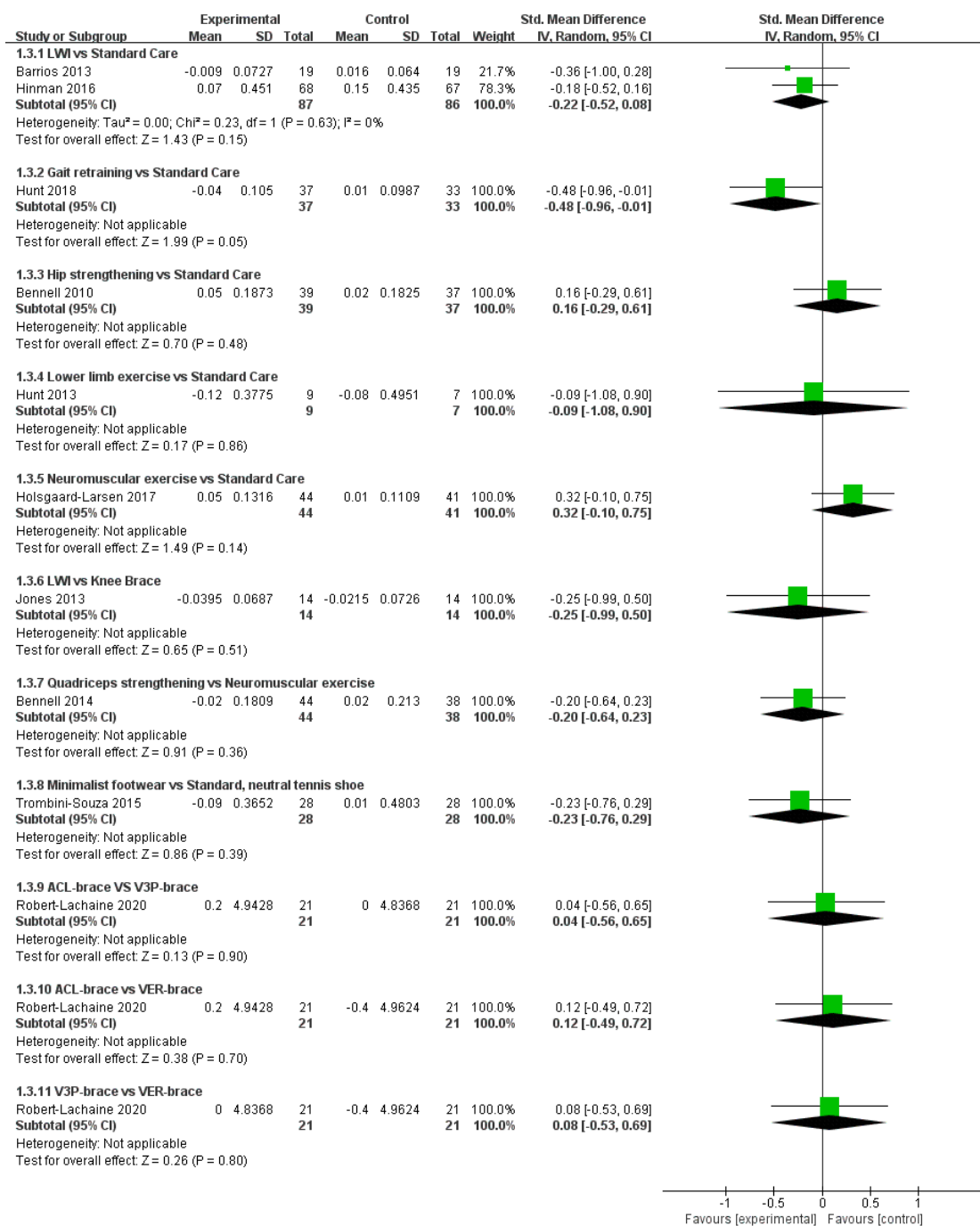


Figure 4c. Conventional meta-analysis of treatment effects on KAAI.

## Appendix 5 Network Diagram

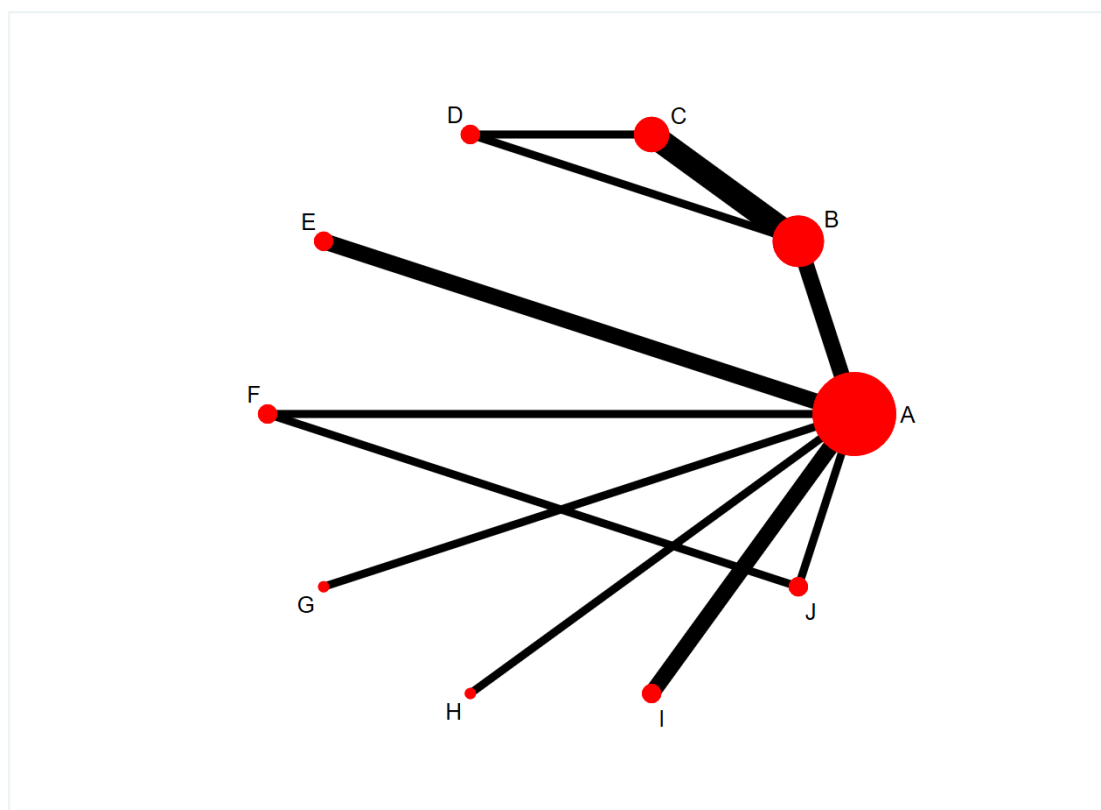
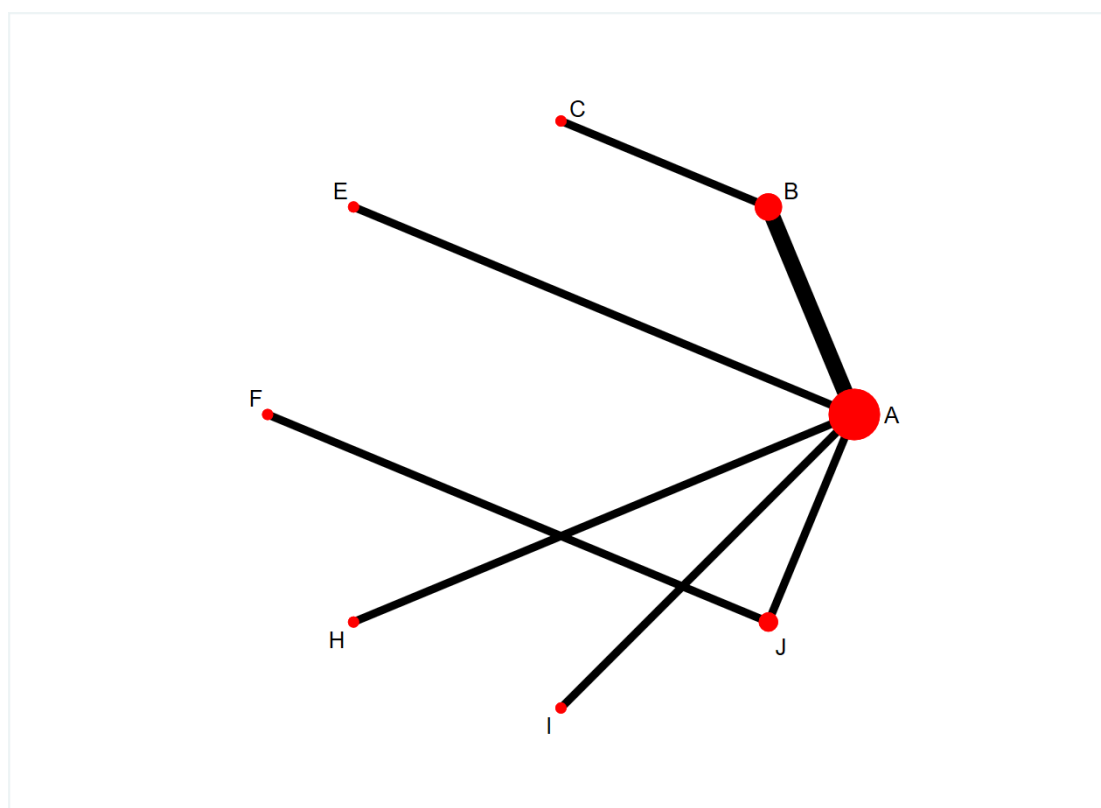


Figure 5a. Structure of network formed by interventions and their direct comparisons (First peak KAM). A= Standard care; B= Lateral Wedge Insole; C= Knee Brace; D= Lateral Wedge Insole+ Knee Brace; E= Gait retraining; F= Quadriceps strengthening; G= Variable-stiffness shoe; H= Hip strengthening; I= Lower 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	Downgrading due to
<b>AB:</b> Standard Care vs LWI	Mixed	LOW	Study limitations; Imprecision
<b>AC:</b> Standard Care vs Knee Brace	Indirect	LOW	Study limitations; Imprecision
<b>AD:</b> Standard Care vs LWI+Knee Brace	Indirect	LOW	Study limitations; Imprecision
<b>AE:</b> Standard Care vs Gait Retraining	Mixed	VERY LOW	Study limitations; Indirectness
<b>AF:</b> Standard Care vs Quadriceps Strengthening	Mixed	VERY LOW	Study limitations; Imprecision
<b>AG:</b> Standard Care vs Variable-Stiffness Shoes	Mixed	VERY LOW	Study limitations; Indirectness;
<b>AH:</b> Standard Care vs Hip Strengthening	Mixed	VERY LOW	Study limitations; Indirectness; Imprecision
<b>AI:</b> Standard Care vs Lower Limb	Mixed	VERY LOW	Study limitations; Indirectness;

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

1				
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3				
4	<b>DF: LWI+Knee Brace vs Quadriceps</b>	Indirect	LOW	Study limitations; Imprecision
5	Strengthening			
6				
7	<b>DG: LWI+Knee Brace vs Variable-</b>	Indirect	VERY LOW	Study limitations; Indirectness
8	Stiffness Shoes			
9				
10				
11	<b>DH: LWI+Knee Brace vs Hip</b>	Indirect	LOW	Study limitations; Indirectness
12	Strengthening			
13				
14				
15	<b>DI: LWI+Knee Brace vs Lower Limb</b>	Indirect	VERY LOW	Study limitations; Indirectness;
16	Exercise			Imprecision
17				
18				
19	<b>DJ: LWI+Knee Brace vs</b>	Indirect	MODERATE	Study limitations
20	Neuromuscular Exercise			
21				
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23	<b>EF: Gait Retraining vs Quadriceps</b>	Indirect	VERY LOW	Study limitations; Indirectness
24	Strengthening			
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27	<b>EG: Gait Retraining vs Variable-</b>	Indirect	VERY LOW	Study limitations; Indirectness
28	Stiffness Shoes			
29				
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31	<b>EH: Gait Retraining vs Hip</b>	Indirect	LOW	Study limitations; Indirectness
32	Strengthening			
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35	<b>EI: Gait Retraining vs Lower limb</b>	Indirect	VERY LOW	Study limitations; Indirectness;
36	Exercise			Imprecision
37				
38				
39	<b>EJ: Gait Retraining vs Neuromuscular</b>	Indirect	LOW	Study limitations; Indirectness
40	Exercise			
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42				
43	<b>FG: Quadriceps Strengthening vs</b>	Indirect	VERY LOW	Study limitations; Indirectness
44	Variable-Stiffness Shoes			
45				
46	<b>FH: Quadriceps Strengthening vs Hip</b>	Indirect	VERY LOW	Study limitations; Indirectness;
47	Strengthening			Imprecision
48				
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50	<b>FI: Quadriceps Strengthening vs</b>	Indirect	VERY LOW	Study limitations; Indirectness;
51	Lower Limb Exercise			Imprecision
52				
53				
54	<b>FJ: Quadriceps Strengthening vs</b>	Mixed	LOW	Study limitations; Imprecision
55	Neuromuscular Exercise			
56				
57				
58	<b>GH: Variable-Stiffness Shoes vs Hip</b>	Indirect	LOW	Study limitations; Indirectness
59				
60				

Strengthening

**GI:** Variable-Stiffness Shoes vs Lower Limb Exercise Indirect VERY LOW Study limitations; Indirectness

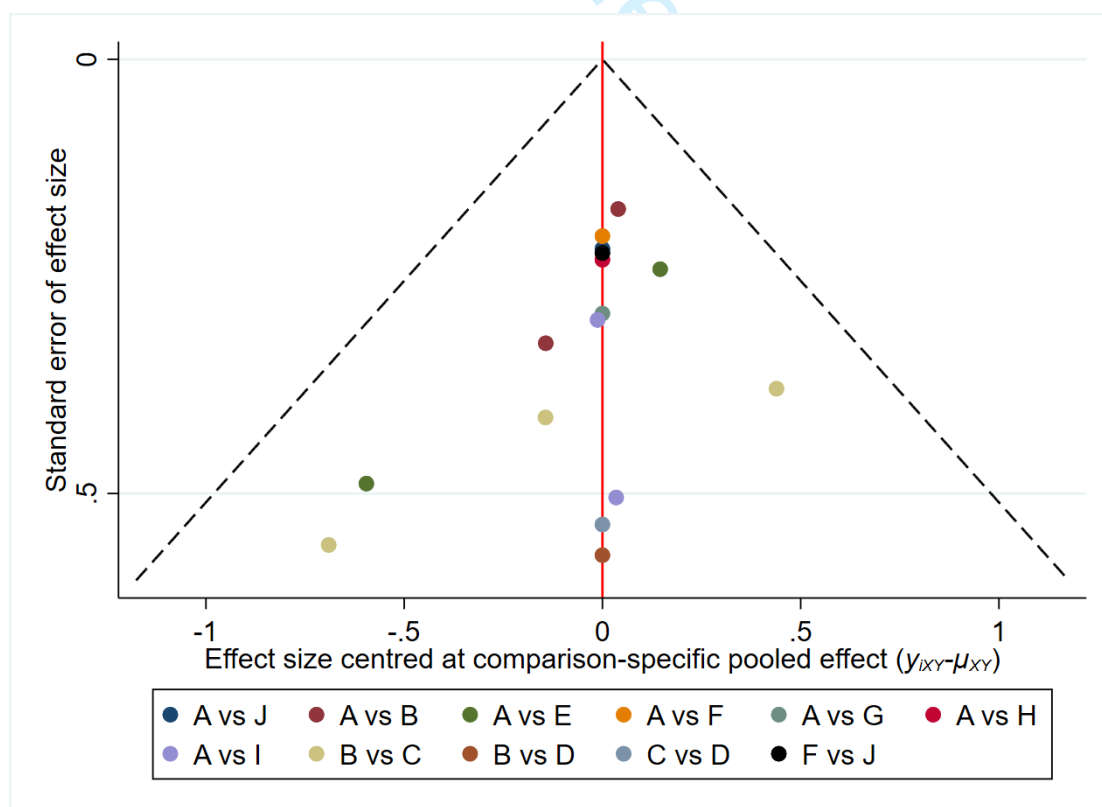
**GJ:** Variable-Stiffness Shoes vs Neuromuscular Exercise Indirect LOW Study limitations; Indirectness

**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

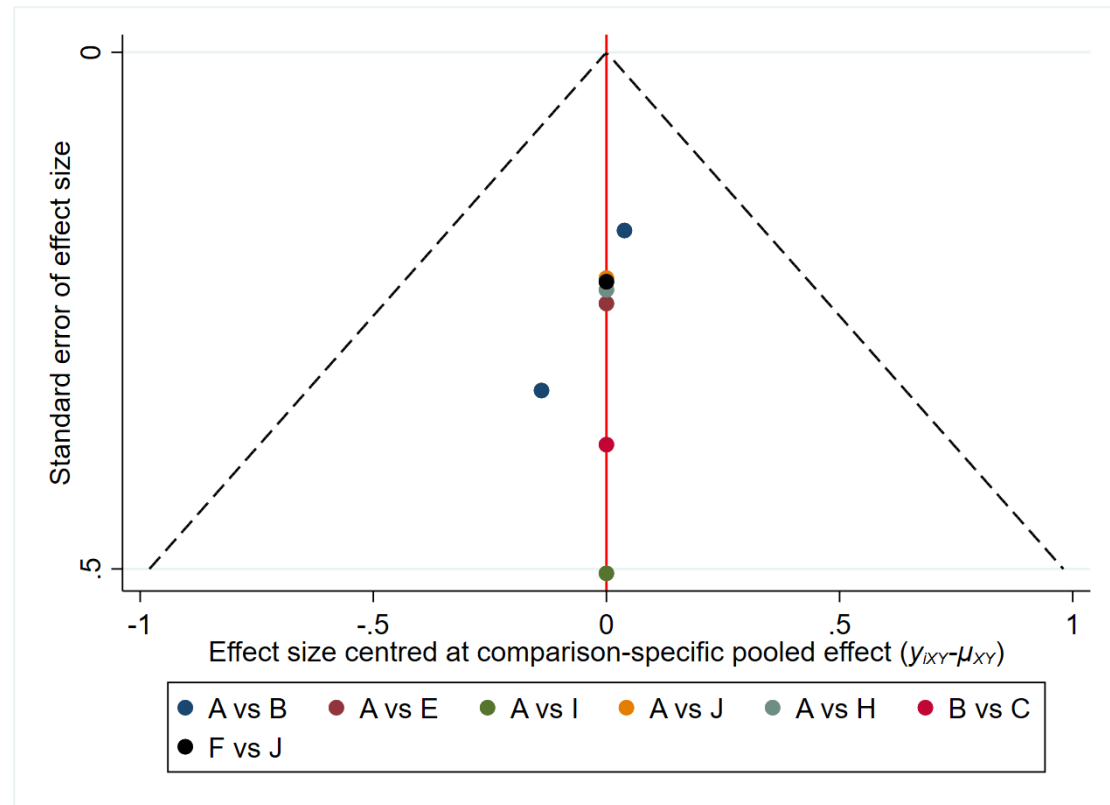
**IJ:** Lower Limb Exercise vs Neuromuscular Exercise Indirect VERY LOW Study limitations; Indirectness; Imprecision

**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 #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
<b>ABSTRACT</b>			
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
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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, paragraph 1
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

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For peer review only

			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
<b>RESULTS</b>			
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
<b>DISCUSSION</b>			
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

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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
<b>FUNDING</b>			
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](http://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 KAI 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 KAI). 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. Bayesian 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<sup>4</sup> (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<sup>2</sup>. These modalities such as ultrasound and Taiji had a certain effect on pain relief<sup>5</sup>, 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

1  
2  
3 labelled as such. Box 1 is worded in a way that suggests that actual standard care was not included.  
4 Please reword and clarify.

5  
6 Response 10: We thank the reviewer for pointing out this issue. In fact, we named standard care as  
7 a summative name for a variety of control interventions with high homogeneity such as placebo, no  
8 intervention, sham, standard / conventional care or waiting list control (analytical advice and  
9 education). We also considered whether this word fully fit each treatment it contains. Although these  
10 treatments were roughly the same, there were still some differences. Using standard care to  
11 summarize these treatments may not completely and accurately describe each included intervention,  
12 but we consider that it is a more appropriate description and a more understandable description. At  
13 the same time, we also replaced the description in box 1 with a more comprehensive description.

14  
15  
16 Line 199. “non-trial papers” – do the authors mean papers that were not peer-reviewed? Please  
17 clarify.

18  
19 Response 11: We replaced this word with " non-experimental".

20  
21 Line 201. What constitutes “studies that did not report suitable data”. Please be concrete about what  
22 this means.

23  
24 Response 12: The “studies that did not report suitable data” corresponds to “studies that did not  
25 report KAM or KAAI” (this is now clarified in the text) (Line 205).

26  
27 Line 214. Please justify why Cochrane ROB version 1 was used, or consider updating to use the  
28 current ROB version 2 which is currently recommended by Cochrane.

29  
30 Response 13: We agree, and we have used ROB version 2 to replace the previous version.

31  
32 Line 229. Please be specific about the conditions and time of assessments of the outcomes. Some  
33 RCTs only measure biomechanics as immediate effects with and without the knee brace on, for  
34 example, and they do so prior to the actual clinical trial. For all studies in which devices were worn  
35 (braces, insoles, etc), be sure to report whether the outcomes were measured before or after treatment,  
36 and whether the device was worn or not at the time of evaluation.

37  
38 Response 14: We apologize for our carelessness. We have already described the conditions and time  
39 of assessments of the outcomes in more detail. “ Baseline biomechanical risk factors were extracted  
40 from walking test without any orthopedic equipment before intervention, and biomechanical risk  
41 factors after intervention were extracted from walking test with orthopedic equipment.” (Line 236-  
42 238).

43  
44 Statistical analyses.

45  
46 Please include references for all statistical tests and methods employed.

47  
48 Response 15: Revised.

49  
50 Line 247. What methods were employed to evaluate the source of heterogeneity? Also, remember  
51 to report in the results with a result was based on FE or RE, and the results of these additional  
52 analyses to evaluate source of heterogeneity.

53  
54 Response 16: We used a random-effects model for meta-analysis, and a sensitivity analysis to  
55 evaluate the source of heterogeneity (this is now added in the text). (Line 254-259). At the same  
56 time, we added heterogeneity evaluation to the results (Line 328-332).

57  
58 Figure 1. Using the PRISMA guidelines, it is not required to report reasons for exclusion at the  
59 title/abstract screen. Please update Figure 1 to adhere to PRISMA guidelines.

60  
61 Response 17: We agree with the reviewer’s assessment and have implemented their suggestion.

62  
63 Results.

64  
65 For orthopaedic interventions, please remember to discuss whether biomechanical effects were pre-

1  
2  
3 and post-intervention, or if they were done at a single time point with orthopaedic device off and  
4 then on.

5  
6 [Response 18: We have added a detailed description of this \(Line 236-238\).](#)

7  
8 Section 3.3 KAM, 3.4 KAI

9  
10 Please rewrite this section to provide a narrative synthesis/summary of the results in a way that is  
11 understandable to the reader. Effect sizes do not need to be repeated in the text since they are already  
12 in Table 3, so use this space to help the reader understand the results. Please make sure to emphasize  
13 that despite the rankings at the end of each section, they are not significant and therefore not  
14 clinically relevant. For any results that are statistically significant, be sure to also consider their  
15 clinical interpretation – are any of the results clinically important?

16  
17 [Response 19: We have made correction according to the Reviewer's comments. We have re-written](#)  
18 [the result section to help readers understand the final clinical significance of our study. At the](#)  
19 [same time, we have increased the clinical interpretation of the results \(Line 403-411\).](#)

20  
21 Line 307. This sentence should be removed regarding stair ambulation. Stairs was not included in  
22 the eligibility criteria of this analysis.

23  
24 [Response 20: We are very sorry for the misunderstanding of our previous description. This article](#)  
25 [met our eligibility criteria. However, considering that its inclusion in meta-analysis will lead to](#)  
26 [excessive heterogeneity, we excluded it from the network meta-analysis. Our intention is that the](#)  
27 [biomechanical indicators of the studies included in the Bayesian network meta-analysis were](#)  
28 [measured on flat ground or treadmills. Other studies that cannot be included in the network meta-](#)  
29 [analysis were included in the systematic review. We have corrected this imprecise sentence \(Line](#)  
30 [208-209\).](#)

31  
32 Risk of Bias.

33  
34 Figure 4 seems to be missing – the only Figure 4 I can see is the funnel plot, not the ROB table.  
35 ROB is not the same thing as quality. Be sure to use accurate and consistent language.

36  
37 [Response 21: We apologize for our carelessness. We uploaded the Figure 4 according to ROB 2.0.](#)  
38 [At the same time, we have refined the language \(Line 341-342\).](#)

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

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.

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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<sup>1</sup>. 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<sup>3</sup>. 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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For peer review only



# 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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<b>Primary Subject Heading</b>:	Sports and exercise medicine
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Keywords:	Biophysics < NATURAL SCIENCE DISCIPLINES, Adult orthopaedics < ORTHOPAEDIC & TRAUMA SURGERY, Knee < ORTHOPAEDIC & TRAUMA SURGERY, REHABILITATION MEDICINE

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1 **Title: Physical Therapy and Orthopedic Equipment-induced Reduction in the**  
 2 **Biomechanical Risk Factors Related to Knee Osteoarthritis: A systematic review**  
 3 **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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5 23 **Abbreviated title:** Biomechanical Phenomena, Osteoarthritis, Knee, Physical and  
6 24 Rehabilitation Medicine  
7 25 **Key words:** Physical Therapy; Orthopedic Equipment; Knee Osteoarthritis;  
8 26 KAM; KAAI; Bayesian Network Meta-analysis.  
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Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

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4 66 **ABSTRACT**  
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6 67 *Objective:* Are physical therapy or orthopedic equipment efficacious in reducing the  
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9 68 biomechanical risk factors in people with tibiofemoral OA? Is there a better therapeutic  
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12 69 intervention than others to improve these outcomes?  
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14 70 *Design:* Systematic review with network meta-analysis of randomized trials.  
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17 71 *Data sources:* PubMed, Web of Science, Cochrane Library, Embase, and MEDLINE  
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19 72 were searched through January 2021.  
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22 73 *Eligibility criteria for selecting studies:* We included randomized controlled trials  
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24 74 exploring the benefits of using physical therapy or orthopedic equipment in reducing  
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27 75 the biomechanical risk factors which included KAM and KAAI in individuals with  
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30 76 tibiofemoral OA.  
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32 77 *Data extraction and synthesis:* Two authors extracted data independently and assessed  
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35 78 risk of bias. We conducted a network meta-analysis to compare multiple interventions,  
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38 79 including both direct and indirect evidences. Heterogeneity was assessed (sensitivity  
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40 80 analysis) and quantified ( $I^2$  statistic). GRADE assessed the certainty of the evidence.  
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43 81 *Results:* Eighteen randomized controlled trials, including 944 participants, met the  
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45 82 inclusion criteria, of which 14 trials could be included in the NMA. Based on the  
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48 83 collective probability of being the overall best therapy for reducing the first peak KAM,  
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51 84 lateral wedge insoles (LWI) plus knee brace was closely followed by gait retraining,  
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53 85 and knee brace only. Although no significant difference was observed among the eight  
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56 86 interventions, variable-stiffness shoes and neuromuscular exercise exhibited an  
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58 87 increase in the first peak KAM compared to the control condition group. And based on  
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Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

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4 88 the collective probability of being the overall best therapy for reducing KAAI, gait  
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6 89 retraining was followed by LWI only, and lower limb exercise.  
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9 90 *Conclusion:* The results of our study support the use of LWI plus knee brace for  
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11 91 reducing the first peak KAM. Gait retraining did not rank highest but it influenced both  
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14 92 KAM and KAAI and therefore it was the most recommended therapy for reducing the  
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17 93 biomechanical risk factors.  
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#### 19 94 **Strengths and limitations**

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22 95 ① The Bayesian method provided the probability estimates regarding the relative  
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24 96 efficacy of specific interventions, even though standard methods found no  
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27 97 significant differences among them.  
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30 98 ② Physical therapies and orthopedic equipment are complex interventions with a  
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32 99 small number of trials comparing the different types of interventions.  
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35 100 ③ Besides KAM and KAAI, we were unable to include other biomechanical risk  
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37 101 factors, such as the external knee flexion moment to joint load, because the number  
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40 102 of these studies was not enough to form a complete NMA.  
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43 103 ④ Heterogeneity in NMA may reduce the validity of the results.  
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## 50 106 **1. INTRODUCTION**

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53 107 Knee osteoarthritis (KOA), an chronic progressive disease, affects approximately  
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55 108 3.8% of people worldwide and frequently occurs in the middle-aged and the elderly  
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58 109 population.<sup>1</sup> The main clinical manifestation of KOA is knee pain and is often  
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4 110 accompanied by radiographic degeneration of the intra-articular cartilage associated  
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6 111 with hypertrophic bone changes.<sup>2</sup> Furthermore, the KOA development often leads  
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9 112 to knee stiffness, joint locking, and instability, along with functional loss. Though  
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12 113 it is not fatal, the persistent pain and movement restrictions associated with this  
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14 114 condition negatively impact the physical and mental health of the patients, thus,  
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17 115 reducing their quality of life.<sup>3</sup>  
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19 116 These pathological changes in knee joints are a cumulative result of various  
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22 117 biomechanical imbalances leading to the progression of the disease and are now  
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24 118 believed to be associated with malalignment of the lower limb.<sup>4</sup> Tibiofemoral OA  
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27 119 most commonly occurs in the medial compartment, since several studies have stated  
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30 120 that patellofemoral compartment is as prevalent as medial tibiofemoral joint.<sup>5,6</sup> The  
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33 121 external knee adduction moment (KAM) results from the unequal distribution of  
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36 122 the transmitted load on both sides in the normal gait of humans. It is defined as the  
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39 123 cross product of the ground reaction force and the distance between the knee joint  
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42 124 and the force line.<sup>7</sup> Individuals with obesity,<sup>8</sup> meniscal lesions,<sup>9</sup> occupational  
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45 125 loads,<sup>10</sup> or other associated risk factors tend to have a frontal plane knee  
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48 126 malalignment, which alters the normal force line and forces the medial knee joint  
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51 127 to bear more load and thus, leads to increased KAM.<sup>11,12</sup> The accumulation effect  
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54 128 of the moment is determined by calculating the integral of the moment to time,  
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57 129 which is also called knee adduction angular impulse (KAAI). It reflects the change  
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60 130 in knee joint rotation state during a stance period of gait.<sup>13</sup> Previous studies have  
131 revealed a strong correlation between the peak levels of KAM and KAAI and the

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

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4 132 severity and progression of the disease, which was reflected and calculated by the  
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6 133 loss of medial tibial cartilage.<sup>14,15</sup> Both these biomechanical parameters (KAM and  
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9 134 KAAI) are commonly utilized to evaluate the medial knee load and predict the long-  
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12 135 term structural deterioration of the knee.

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14 136 Recent advancements in healthcare have resulted in the development of several  
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17 137 protocols for the intervention and treatment of KOA. KOA patients are primarily  
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19 138 recommended physical therapy or orthopedic equipment with the intention of  
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22 139 correcting the deviated force line and delaying the progressive pathological damage  
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25 140 inside the knee joint.<sup>7</sup> Some other modalities, such as ultrasound and Taiji programs,  
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27 141 primarily focus on relieving the pain, and therefore, this might improve the  
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30 142 biomechanical state of the knee joint.<sup>16,17</sup> The physical therapy mainly includes  
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33 143 muscular strengthening, exercise therapy, electric stimulation therapy,  
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35 144 extracorporeal shockwave therapy and gait modification, while orthopedic  
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38 145 equipment mainly incorporates customized shoes/footwear, wedged insoles, and  
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41 146 knee braces.

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43 147 Several literary insights have shown the positive impact of physical therapy or  
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46 148 orthopedic equipment in KOA patients.<sup>13,18,19</sup> The strengthening of related lower  
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49 149 limb muscles, which play a vital role in disease progression, are known to reduce  
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52 150 instability and abnormal stresses across the joint.<sup>20,21</sup> Another study displayed a  
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55 151 lower knee joint loading rate in patients with stronger quadriceps and hamstrings.<sup>22</sup>  
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58 152 Additionally, gait training presents a viable way for correcting the patients'  
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60 153 underlying gait pattern, thus, further reducing their knee load and pain.<sup>23,24</sup>



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4 154 Furthermore, various kinds of orthotic devices have been introduced for the  
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6 155 treatment of KOA. The clinical use of lateral wedge insoles (LWI) has gained  
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9 156 immense popularity since its origin in 1987.<sup>25,26</sup> The insoles tends to shift the lateral  
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12 157 part of the foot more than the medial part by a slope that increases the valgus  
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14 158 tendency of lower extremities. The center of the ground reaction force is shifted  
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17 159 laterally, which induces a reduction in force lever arm length and magnitude.<sup>27</sup> Also,  
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19 160 the valgus knee brace is a commonly used device. It applies an external valgus force  
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22 161 around the knee joint to reduce the medial knee load.

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24 162 In the past, several systematic reviews and meta-analyses have been published  
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27 163 featuring the medical effects of a single KOA treatment. However, only a few of  
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30 164 them have focused on multifaceted interventions. Also, only a few reviews have  
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33 165 reported the effects on biomechanical parameters. The mechanical changes in the  
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35 166 body were not sufficiently investigated. Current reviews on KAM and KAAI have  
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38 167 also not compared these changes. Thus, a network meta-analysis (NMA) was  
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41 168 performed to appraise the benefits of physical treatments or orthopedic equipment  
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43 169 in reducing biomechanical risk factors in KOA patients.

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45 170 Therefore, the research questions for this systematic review were:

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48 171 1. Are physical therapies or orthopedic equipment efficacious in reducing the  
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51 172 biomechanical risk factors in people with KOA?  
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53 173 2. Is there a better therapeutic intervention than others to improve these outcomes?  
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## 56 174 2. METHODS

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58 175 All pooled analyses were derived from previous studies and, therefore, did not  
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4 176 require ethical approval and informed consent.  
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7 177 **2.1 Identification and selection of studies.**  
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9 178 The following databases were searched for listed randomized controlled trials that  
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11 179 were published before January 2021: PubMed, Web of Science, Cochrane Library,  
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14 180 Embase, and MEDLINE. These studies explored the benefits of using physical  
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17 181 therapy or orthopedic equipment in reducing the biomechanical risk factors  
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19 182 including KAM and KAAI in patients with tibiofemoral OA. The search was not  
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22 183 restricted by date, publication type, or status (see Appendix 1). Additionally, we  
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25 184 performed manual analyses of the published references regarding the use of  
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27 185 physical therapy or orthopedic equipment for treating KOA.

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30 186 The eligibility of searched publications was independently reviewed by HXM and  
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32 187 YZX following the Cochrane manual directives.<sup>28</sup> Any additional inconsistencies  
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35 188 were resolved either by deliberation or by a senior expert (HY). Firstly, the study  
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38 189 titles and abstracts, published in English literature, were screened. Next, the  
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41 190 complete articles were reviewed against the directed criteria described in box 1.  
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43 191 Eligible comparison subjects, including standard/conventional care or waiting list  
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45 192 control (analgesic advice and education), were defined as “control condition.”  
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48 193 Control condition also included placebo intervention, no intervention, and sham-  
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51 194 exercise. This NMA defined lower limb exercise as the simultaneous exercise of  
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53 195 multiple muscle groups that included hip abductors, quadriceps, and hamstrings.  
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56 196 Since our research needed to maintain clinical and statistical homogeneity and focus  
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58 197 on the residual biomechanical effects after the intervention, only those articles were  
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4 198 selected whose measurements were strictly obtained under the condition of going  
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6 199 barefoot.

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9 200 The exclusion criteria included: (1) studies that were not consistent with the  
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11 201 eligibility criteria; (2) experimental peer-reviewed studies; (3) studies that included  
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14 202 participants who had received surgical treatment in the past; (4) studies that did not  
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17 203 report KAM or KAAI.

## 18 19 20 204 **2.2 Data Collection and Quality assessment.**

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22 205 KAM and KAAI were the preferred biomechanical measures used in this meta-  
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24 206 analysis. The biomechanical outcomes of the studies included in the Bayesian  
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27 207 network meta-analysis were measured on flat ground or treadmills. Additionally,  
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30 208 the number of trials focusing on the second peak of KAM was insufficient to  
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33 209 conduct an independent NMA.

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35 210 The data were extracted independently by two authors (HXM, YZX) and were  
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38 211 cross-checked. A predefined information sheet was used for data extraction, which  
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41 212 included the details of the first author (name), country, the year of publication,  
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44 213 population characteristics, intervention, and the time points. The authors of the  
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47 214 original study were contacted in the cases requiring more data.

## 48 215 **2.3 Assessment of characteristics of studies.**

### 49 50 51 216 *Risk of bias*

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53 217 This NMA utilized the Cochrane Risk of Bias 2 (RoB2) to assess the risk of bias in  
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56 218 randomized controlled trials using the following evaluation indicators:  
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59 219 randomization process, deviations from the intended interventions, missing  
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4 220 outcome data, outcome measurement, and selection of the reported results.<sup>21</sup> The  
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6 221 judgment of the bias risk of this item was presented as "low," "high," and "some  
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9 222 concerns." Two authors independently evaluated the risk of bias in all the included  
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11 223 studies. The authors discussed or referred to the opinion of a senior author to resolve  
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14 224 any disagreements. Additionally, the certainty of evidence the evidence was also  
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17 225 evaluated, which contributed to network estimates of the main outcomes with the  
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19 226 Grading of Recommendations Assessment, Development and Evaluation (GRADE)  
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22 227 framework.<sup>29</sup>

### 228 *Intervention*

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

### 233 *Outcome measures*

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

## 242 2.4 Statistical Analysis.

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

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

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4 264 update iterations was 50,000, a total of 5000 simulations were used for annealing,  
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6 265 and the subsequent 45,000 iterations were examined. The mean rank and surface  
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8  
9 266 under the cumulative ranking curve (SUCRA) were used for reporting the  
10  
11 267 probability values. A SUCRA value of 100% was considered best, whereas 0%  
12  
13  
14 268 indicated the worst treatment.<sup>40</sup> Besides, a conventional meta-analysis was also  
15  
16  
17 269 carried out (see Appendix 4, eFigure 4a, b, and c). Comparison-adjusted funnel  
18  
19  
20 270 plots were prepared that represented different comparisons with different colors.  
21  
22 271 The data from the eligible studies were combined using the Review Manager  
23  
24 272 (RevMan) software v5.3. The contribution of the effect sizes was dependent on the  
25  
26  
27 273 sample size and their estimation accuracy. The Bayesian analyses were carried out  
28  
29  
30 274 using WinBUGs v1.4.3. Stata (StataCorp. 2015. Stata Statistical Software: Release  
31  
32 275 15. College Station, TX: StataCorp LP) was employed to conduct the frequentist  
33  
34  
35 276 NMA.

## 37 277 **2.5 Patient and Public Involvement.**

38  
39  
40 278 No patients were directly involved in the development of the study question,  
41  
42  
43 279 selection of the outcome measures, design and implementation of the study, or  
44  
45  
46 280 explanation of the results.

## 47 48 281 **3. RESULTS**

### 49 50 282 **3.1 Flow of studies through the review**

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52  
53 283 A comprehensive investigation of databases retrieved 4919 citations. After  
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56 284 screening articles by title and abstract, and deleting duplicate articles, we identified  
57  
58  
59 285 526 studies that might meet the criteria for inclusion, and then we searched and  
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4 286 evaluated their full text. Figure 1 presents the study selection flow chart. Eighteen  
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6 287 randomized controlled trials, including 944 participants, met the inclusion  
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8  
9 288 criteria.<sup>23,41-57</sup> Since the present NMA only considered trials comparing the nine  
10  
11 289 treatments with control condition or each other (see Appendix 5, eFigure 5a and b),  
12  
13  
14 290 only fourteen trials (792 participants) were included. Furthermore, four trials were  
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16  
17 291 excluded from the NMA considering their excessive heterogeneity and inability to  
18  
19 292 form NMA with other studies.<sup>54-57</sup>

### 22 293 **3.2 Characteristics of included studies**

24 294 All studies included tibiofemoral OA cases, which were radiologically confirmed.  
25  
26  
27 295 Although most interventions were administered over an 8–13week period, the  
28  
29  
30 296 treatment duration ranged from 2 weeks to 12 months. The number of exercises  
31  
32 297 varied from 2-5 times per week, depending on the initial preparation.<sup>43,44,46,49</sup> Both  
33  
34  
35 298 gait training studies used the faded feedback paradigm, which meant gradual  
36  
37  
38 299 removal of the real-time biofeedback.<sup>23,48</sup> As NMA included fourteen studies, nine  
39  
40 300 were classified as Kellgren/Lawrence grade 2 and above. All studies reported either  
41  
42  
43 301 the values for BMI or height and weight, while the studies recruiting a general  
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45  
46 302 population classified the mean BMI as overweight or obese. Additionally, one  
47  
48 303 NMA study had a randomized crossover design.<sup>50</sup> After consulting a reference  
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50  
51 304 manual along with a professional statistician, the mean and standard deviation of  
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53  
54 305 the experimental and the control groups were analyzed in this network meta-  
55  
56 306 analysis.<sup>28</sup> Tables 1 and 2 summarize the characteristics of the included studies and  
57  
58 307 their participants.  
59  
60

### 308 3.3 KAM.

309 According to the collective probability of being the overall best therapy for reducing  
310 the first peak KAM, LWI plus knee brace (93.4%) was closely followed by gait  
311 retraining (85.7%), and knee brace only (79.3%) (Figure 2). A study reported that  
312 the VER-brace offers additional advantages on first peak KAM compared to V3P-  
313 brace and ACL-brace.<sup>54</sup> No first peak KAM reduction was observed between  
314 proprioceptive neuromuscular facilitation group and controls,<sup>55</sup> and the result of the  
315 study of minimal footwear was the same.<sup>56</sup> On the other hand, after the  
316 electroacupuncture treatment, compared with the control group, the second peak  
317 KAM significantly increased immediately when the patient ascended stairs.<sup>57</sup> Table  
318 3 shows the NMA results of a comparative analysis of the reduction of the first peak  
319 KAM. We found no differences in most of the treatment modalities; however,  
320 variable-stiffness shoes showed a statistically significant increase in the first peak  
321 KAM over the rest of the included interventions. Neuromuscular exercise was better  
322 than variable-stiffness shoes, but was still inferior to most other interventions. At  
323 the same time, lateral wedge insole plus knee brace and gait retraining performed  
324 relatively well in reducing the first peak KAM compared with control condition and  
325 other treatments.

### 326 3.4 KAAI.

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



1  
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4 330 wearing the three kinds of brace separately, the KAAI measured without brace did  
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6 331 not decrease significantly, and there was no significant difference between the  
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8  
9 332 groups.<sup>54</sup> Table 3 shows the NMA results of the reduction of KAAI. Most  
10  
11 333 treatments were not statistically different from each other, consistent with the  
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13  
14 334 results of the first peak KAM. Only gait retraining had a statistical reduction  
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16  
17 335 compared with control condition. The aggregated results suggested that gait  
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19  
20 336 retraining is efficacious in reducing the KAAI, while neuromuscular exercise  
21  
22 337 increased the KAAI compared with gait retraining and knee brace.

### 23 24 25 338 **3.5 Heterogeneity.**

26  
27 339 We removed a study which had a short follow-up time and might cause  
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29  
30 340 heterogeneity,<sup>50</sup> and performed another network meta-analysis. There was no  
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32  
33 341 difference between the results of the reanalysis and the current ranking (see  
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35 342 Appendix 2, eFigure 1 and 2).

### 36 37 38 343 **3.6 GRADE assessment**

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40 344 According to the GRADE framework (see Appendix 6), the quality of most  
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42  
43 345 comparisons was assessed as low or very low. Only neuromuscular exercise  
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45  
46 346 compared with control condition, neuromuscular exercise compared with LWI,  
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48  
49 347 neuromuscular exercise compared with knee brace, and neuromuscular exercise  
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51 348 compared with LWI plus knee brace were evaluated as a moderate-grade  
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53 349 comparison.

### 54 55 56 350 **3.7 Risk of bias.**

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58 351 Figure 4 depicts a summary of the risk-of-bias scores for the included RCTs in this  
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4 352 analysis. Nine studies presented a clear description of generating a randomization  
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6 353 sequence.<sup>43-47,49,52,56,57</sup> The study by Hinman et al. was the only double-blinded  
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9 354 study, while other studies were either single-blinded or did not clearly describe their  
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11 355 blind design. All trials provided follow-up data on their outcomes. Six studies did  
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13  
14 356 not report the patient number or the reason for lost visits due to the length of follow-  
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16  
17 357 up.<sup>23,44-46,50,52</sup> All studies were included in the synthesis evaluation. The  
18  
19 358 comparison-adjusted funnel plots were symmetrically distributed based on a visual  
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21  
22 359 inspection, which suggested the absence of small-sample effects for our study  
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24  
25 360 outcomes (see Appendix 7, eFigure 6a and 6b).

#### 27 361 4. DISCUSSION

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30 362 Our study results did not show any significant difference regarding the relative  
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32 363 efficacy of intervention among different types of physical therapies or orthopedic  
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35 364 equipment. This lack of difference might be attributed to the fact that the number  
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38 365 of studies for several pairwise comparisons was small. However, some of these  
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41 366 therapies were still worth recommending. Due to a small number of studies studying  
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43 367 the outcome of the KAAI, we found gait retraining to be the relatively more  
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46 368 convincing intervention as it could simultaneously reduce the values for KAM and  
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49 369 KAAI values based on cumulative ranking and relative effect estimates. Due to the  
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51 370 lack of significant differences among the interventions, the cumulative ranking  
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54 371 obtained by the network meta-analysis could not be conclusively accepted. For  
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56 372 example, gait retraining, which was employed as the foremost intervention (90.7%)  
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59 373 for KAAI reduction, was only superior to the neuromuscular exercise interventions.  
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4 374 This study had several strengths and limitations. This NMA is the first report on the  
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6 375 effects of physical therapy or orthopedic equipment on the parameters of knee load  
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9 376 (KAM, KAAI). Since physical therapies and orthopedic equipment are complex  
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11 377 interventions with a small number of trials comparing the different types of  
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14 378 interventions, network meta-analysis was deemed as the most relevant form of  
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17 379 analysis. The results of this meta-analysis could be more useful for the decision-  
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19 380 makers and primary service providers for choosing wisely among the various  
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22 381 available options, as compared to the multiple separate pairwise meta-analyses.<sup>58</sup>  
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25 382 Additionally, this NMA conducted each comparison distinctly with both direct and  
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27 383 indirect statistical effects, deriving statistical power from all included data.<sup>58</sup> Also,  
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30 384 the Bayesian method provided the probability estimates regarding the relative  
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33 385 efficacy of specific interventions, even though the standard methods described the  
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35 386 absence of a significant difference between them. Furthermore, alternative rankings  
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38 387 (second, third best, etc.) were calculated to provide overall feasibility due to  
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41 388 unavailability of the best-suited interventions, more expensive therapies, or  
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43 389 contraindications in some cases. As with most meta-analyses based on non-surgical  
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46 390 therapies for osteoarthritis, one of the limitations of this NMA was the inclusion of  
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48 391 trials that had variable periods of follow-up, which might have introduced  
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51 392 heterogeneity into the study analyses. The Cochrane handbook recommends several  
52  
53 393 methods for analyzing and comparing trials with multiple durations of follow-up,  
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56 394 as recommended by the Cochrane handbook, such as performing individual patient  
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58 395 data meta-analysis and a precise evaluation at a particular time point. However,  
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Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)

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4 396 newer approaches are now being developed that would include all the time points  
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6 397 in a NMA.<sup>28</sup> Our study was unable to evaluate the influence of population  
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9 398 characteristics (such as mean age, the severity of osteoarthritis), as the number of  
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11 399 the included studies was not large enough.<sup>59-61</sup> Additionally, other parameters, such  
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14 400 as the external knee flexion moment to joint load, should have been studied in detail.  
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17 401 However, due to lesser available literature, our study was unable to include them.  
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19 402 Finally, standard/conventional care, placebo intervention, no intervention, sham-  
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22 403 exercise, analgesic advice and education were all considered as the same parameter  
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24  
25 404 in defining the 'control condition'. Therefore, the relative rankings in our study  
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27  
28 405 might not represent the true factual rankings as compared to actual standard care  
29  
30 406 due to lack of consideration of bias introduced by heterogeneity and lack of blinding.  
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32  
33 407 A previous review reported that LWIs were able to reduce the KAM at the  
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35 408 baseline;<sup>13</sup> however, the effect was no longer observed after a specific period.  
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38 409 Another study displayed that a month wear-in period was the longest study time in  
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41 410 which no reduction in biochemical risk factors was observed despite continued  
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43 411 wear.<sup>18</sup> Besides, several other systematic reviews stated that exercise and gait  
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46 412 retraining could further reduce pain and improve motor functioning in people with  
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48 413 KOA.<sup>62-64</sup> There is a high probability that any clinical changes occurring in previous  
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51 414 studies might be due to increased physical activity levels, and not owing to the  
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54 415 altered loading environment within the knee joint. Furthermore, another study  
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56 416 revealed that an increase in the amount of reduction in peak KAM in LWIs plus  
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59 417 knee brace group was observed after four weeks.<sup>65</sup> In our NMA, we focused on the  
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4 418 studies of non-immediate effect, removed the research with a follow-up time of less  
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6 419 than one month in the sensitivity analysis, and made the final rank. Our results  
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9 420 showed that only gait training produces a significant reduction in KAM and KAAI  
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11 421 when compared with control condition, indicating that the biomechanical reduction  
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14 422 effect of orthopedic equipment cannot be maintained for a long time when they are  
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16  
17 423 donned. It was evident that an extension of the treatment time led to a decrease in  
18  
19 424 the biomechanical reduction effect, which might be due to the gradual deformation  
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21  
22 425 of the orthopedic equipment that renders them ineffective, despite being made from  
23  
24  
25 426 high-density materials.

26  
27 427 On the other hand, various physical therapies and orthopedic equipment also should  
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29  
30 428 be considered for relieving patients' pain, which has been the focus of several past  
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33 429 reviews. As an important gait parameter, the joint pain can affect the kinetics and  
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35 430 kinematics of walking.<sup>19</sup> A meta-analysis reported that exercise therapy had a  
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37  
38 431 positive impact on knee pain and kinematic function, though this relief of pain  
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41 432 subsided with time. After proper initiation, the efficiency of physical exercise over  
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43 433 placebo reached a maximum level at two months.<sup>66</sup>

44  
45 434 Cumulative loading is another significant parameter regarding knee load exposure  
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47  
48 435 in OA.<sup>67</sup> KAAI has been proposed as another indicator for evaluating the duration  
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50  
51 436 and intensity of KOA load, despite the association between KAM and disease  
52  
53  
54 437 progression. According to a study lasting for a year, the loss of medial tibiofemoral  
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56 438 cartilage was not directly linked to KAM but was promptly related to KAAI.<sup>14</sup>

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58  
59 439 Although the effect of physical therapy or orthopedic equipment on KAM are short-

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4 440 lived, it might have a huge cumulative effect on the knee during the early stages of  
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6 441 treatment and should be considered while interpreting our NMA results.  
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9 442 Our study results are both scientifically and clinically instructive. Despite a majority  
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11 443 of therapies displaying a null statistical KAM and KAAI reduction, the clinical  
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14 444 usage of these treatment modalities could significantly improve the presenting  
15  
16  
17 445 symptoms and physical activity level without increasing the biomechanical  
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19 446 magnitude; thus, improving the quality of life of patients with KOA. Although the  
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21  
22 447 results of this study suggested that wearing variable-stiffness shoes is not preferable  
23  
24 448 for long-term KAM reduction, our current study explained that variable-stiffness  
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26  
27 449 shoes displayed a major advantage in reducing KAM for patients with increasing  
28  
29  
30 450 walking speed.<sup>68</sup> At the same time, variable-stiffness shoes had relatively less  
31  
32 451 discomfort than equipment such as LWI. Since the studies included in this network  
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35 452 meta-analysis mainly involves patients with medial KOA, the consolidated results  
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38 453 would be more useful for such patients.

39  
40 454 On the other hand, a previous study reported that an increase in KAAI can explain  
41  
42 455 the significant variation in the uCTX-II levels as well as the uCTX-II:sCPII ratio in  
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44  
45 456 medial tibiofemoral KOA patients after controlling additional variables.<sup>49</sup> It was  
46  
47  
48 457 evident that appropriate intervention in the biomechanical structure of the knee joint  
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51 458 in KOA patients exert a potential beneficial role on cartilage structure. Maleki et al.  
52  
53 459 reported that adopting a modified gait for reducing the KAM can decrease the pain  
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55  
56 460 in the medial compartment in KOA more than walking alone,<sup>69</sup> which suggests that  
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58 461 the KAM and KAAI of patients undergoing non-surgical approaches could be  
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4 462 restricted to reduce pain and improve the joint function. More research is further  
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6 463 needed to promptly illustrate the impact of changes in knee biomechanics on the  
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9 464 prognosis of such patients.  
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11 465 Additionally, some other therapies have also been reported, such as Taiji,  
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14 466 ultrasound, acoustic exercises, etc. However, due to the lack of RCT study design  
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17 467 or the report of their biomechanical outcomes, these therapies were not included in  
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20 468 our review. Therefore, further studies would require more research articles in these  
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22 469 areas for exploring the impact of various non-surgical therapies on OA patients.  
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24  
25 470 After accumulating evidence regarding the role of non-surgical therapy in KOA,  
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27 471 another similar network meta-analysis to understand the relative effectiveness of  
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29  
30 472 various treatment in the relevant patients.  
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## 32 473 **5. Conclusion**

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35 474 To conclude, this network meta-analysis provides valuable insights regarding the  
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38 475 KAM and KAAI alterations in OA patients after the usage of physical therapy or  
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41 476 orthopedic equipment. After integrating cumulative ranking and relative effect  
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43 477 estimates, LWI plus knee brace was the highest-ranking intervention despite an  
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46 478 absence of statistical significance. Although gait retraining did not score a higher  
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48  
49 479 rank, it remarkably influenced both KAM and KAAI values and, therefore, was the  
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51 480 most recommended therapy for reducing the biomechanical risk factors. On the  
52  
53 481 contrary, variable-stiffness shoe and neuromuscular exercise should be used with  
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56 482 caution in clinical practice. Taken together, these findings suggest that clinicians  
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59 483 should carefully consider all appropriate treatment modalities when treating OA  
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4 484 patients.

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7 485 **6. Authors' Contributions**

8  
9 486 HXM and YFZ conceived of the study, and participated in its design and  
10  
11 487 coordination and helped to draft the manuscript; YZX, HY and CRY contributed  
12  
13  
14 488 significantly to analysis and manuscript preparation; YJK and LL helped perform  
15  
16  
17 489 the analysis with constructive discussions and revised it critically for important  
18  
19  
20 490 intellectual content.

21  
22 491 **7. Competing interests**

23  
24  
25 492 There were no conflicts of interest.

26  
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28  
29  
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31  
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34  
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36  
37  
38 497 EMTC-02-00897).

39  
40 498 **9. Ethics approval**

41  
42  
43 499 Not required.

44  
45 500 **10. Data availability statement**

46  
47  
48 501 No data are available.

49  
50 502 **11. Patient and public involvement**

51  
52  
53 503 Patients and/or the public were not involved in the design, or conduct, or reporting, or  
54  
55  
56 504 dissemination plans of this research.

57  
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Knee osteoarthritis (KOA); Knee adduction moment (KAM); Knee adduction angular impulse (KAAI)



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## Tables

**Table 1. Characteristics of included studies (1) \***

Authors	Country	Clinical criteria†	Radiographic features	Intervention	Comparisons	Follow up
Barrios 2013 <sup>42</sup>	US	Medial compartment knee OA; Pain VAS ( $\geq 3$ of 10 upon walking)	K/L grade $\geq 2$ , medial tibiofemoral compartment	bespoke full-length LWI	Placebo	12 months
Hinman 2016 <sup>53</sup>	Australia	Medial compartment knee OA; Pain NRS ( $> 4$ of 11 upon walking) over the previous week	K/L grade $\geq 2$ , medial tibiofemoral compartment	5° full-length LWI	Placebo	6 months
Arazpour 2012 <sup>41</sup>	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 <sup>50</sup>	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 <sup>51</sup>	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;

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 <sup>48</sup>	US	Medial compartment knee OA; Pain ( $\geq 3$ of 10) longer than 6 months	K/L grade $\geq 2$ , medial tibiofemoral compartment	Toe-out gait modification	Walking without any guidance	4 months
Lim 2008 <sup>52</sup>	Australia	Medial compartment knee OA; Medial knee pain	K/L grade $\geq 2$ , medial JSN	Quadriceps strengthening	No intervention	12 weeks
Erhart-Hledik 2012 <sup>45</sup>	US	Medial compartment knee OA; Medial knee pain	K/L grade $\geq 1$	Variable-stiffness shoe with stiffer soles on the lateral side	Constant-stiffness control shoe	12 months
Bennell 2010 <sup>43</sup>	Australia	Medial compartment knee OA; Varus malalignment; Pain ( $> 3$ of 11 upon walking)	K/L grade $\geq 2$ , medial JSN	Hip strengthening	No intervention	13 weeks
Cheung 2018 <sup>23</sup>	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 (3) \***

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



**Table 1. Characteristics of included studies (4) \***

Authors	Country	Clinical criteria†	Radiographic features	Intervention	Comparisons	Follow up
Song 2020 <sup>55</sup>	China	Medial compartment knee OA in one or both legs.	K/L grade $\leq 3$	PNF (one-hour sessions three times a week)	Watch television or read magazines at the same time	12 weeks
Wang 2017 <sup>57</sup>	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 <sup>54</sup>	Canada	Medial compartment knee OA; Pain > 31/100 on WOMAC; Varus knee alignment $\geq 2^\circ$	K/L grade 2 and 3	V3P-brace; VER-brace; ACL-brace (wear the brace as often as possible)	/	3 months
Trombini-Souza 2015 <sup>56</sup>	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/m <sup>2</sup>	Bilateral knee OA included	K/L grade, no.				Main outcomes
								1	2	3	4	
Barrios 2013 <sup>42</sup>	38	NR	61.90±8.37	NR	NR	32.00±7.43	NR	0	17	14	7	1 <sup>st</sup> KAM; KAAI
Hinman 2016 <sup>53</sup>	164	20:21	64.30±7.45	1.67 ± 0.10	82.95±14.76	29.70±3.64	NR	0	49	52	63	1 <sup>st</sup> KAM; KAAI
Arazpour 2012 <sup>41</sup>	24	3:4	59.29±2.37	NR	NR	27.01±1.71	Yes	9	15	0	0	1 <sup>st</sup> KAM
Jones 2013 <sup>50</sup>	28	4:3	66.30±8.20	1.75±0.13	88.7±15.10	NR	No	0	10	18	0	1 <sup>st</sup> and 2 <sup>nd</sup> KAM; KAAI
Khosravi 2019 <sup>51</sup>	21	13:8	58.97±6.80	1.62±0.11	79.11±9.35	NR	NR	0	9	12	0	1 <sup>st</sup> 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 <sup>2</sup>	Bilateral knee OA included	K/L grade, no.				Main outcomes
								1	2	3	4	
Hunt 2018 <sup>48</sup>	79	24:55	64.99±8.60	1.65±0.10	74.59±13.15	27.35±3.48	Yes	0	37	31	11	1 <sup>st</sup> and 2 <sup>nd</sup> KAM; KAAI
Lim 2008 <sup>52</sup>	107	48:59	64.60±8.51	1.65±0.10	79.41±15.32	28.96±4.85	Yes	0	34	29	44	1 <sup>st</sup> KAM
Erhart-Hledik 2012 <sup>45</sup>	79	41:38	61.70±9.43	1.69±0.08	79.50±15.07	27.51±4.87	Yes	NR	NR	NR	NR	1 <sup>st</sup> KAM
Bennell 2010 <sup>43</sup>	89	46:43	64.55±8.34	NR	NR	27.94±4.41	Yes	0	30	29	30	1 <sup>st</sup> KAM; KAAI
Cheung 2018 <sup>23</sup>	20	1:1	61.95±6.11	1.63±0.09	65.85±6.64	27.35±3.48	NR	5	15	0	0	1 <sup>st</sup> 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 <sup>2</sup>	Bilateral knee OA included	K/L grade, no.				Main outcomes
								1	2	3	4	
Foroughi 2011 <sup>46</sup>	54	0:54	65.48±7.44	NR	82.87±18.43	32.07±7.08	Yes	20	7	20	1	1 <sup>st</sup> and 2 <sup>nd</sup> KAM
Bennell 2014 <sup>44</sup>	100	48:52	62.45±7.32	1.67±0.10	82.70±14.29	29.65±4.08	Yes	0	22	43	35	1 <sup>st</sup> KAM; KAAI
Hunt 2013 <sup>49</sup>	17	8:9	66.10±11.3	NR	NR	27.00±4.50	Yes	0	10	5	2	1 <sup>st</sup> KAM; KAAI
Holsgaard-Larsen 2017 <sup>47</sup>	93	39:54	58.10±7.96	NR	79.64±12.49	26.90±3.09	NR	45	31	17	0	1 <sup>st</sup> 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 <sup>2</sup>	Bilateral knee OA included	K/L grade, no.				Main outcomes
								1	2	3	4	
Song 2020 <sup>55</sup>	36	1:1	68.01±3.91	1.62±0.07	68.16±6.77	NR	Yes	9	20	7	0	1 <sup>st</sup> KAM
Wang 2017 <sup>57</sup>	36	1:5	63.50±7.95	NR	NR	23.75±2.66	Yes	0	19	17	0	1 <sup>st</sup> and 2 <sup>nd</sup> KAM
Robert-Lachaine 2020 <sup>54</sup>	24	7:5	57.20±8.60	1.68±0.09	89.30±18.70	31.40±5.00	NR	0	15	8	0	1 <sup>st</sup> and 2 <sup>nd</sup> KAM; KAAI
Trombini-Souza 2015 <sup>56</sup>	56	NR	66.00±5.00	1.60±0.10	73.40±13.10	NR	NR	0	NR	NR	0	1 <sup>st</sup> 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)

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

**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 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.**

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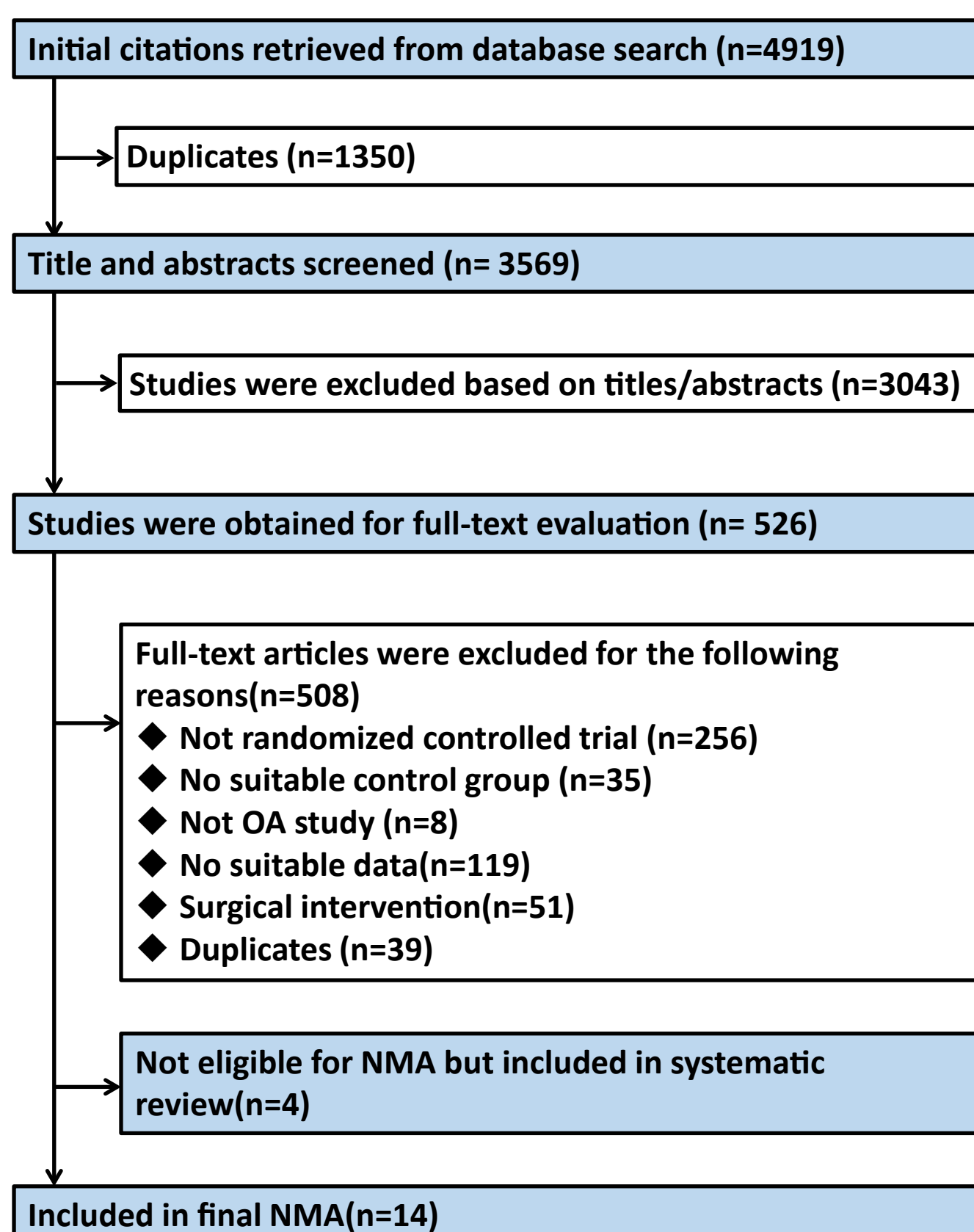
best to worst according to the outcomes), Y-axis represents the cumulative probability for each treatment to be the best option, among the best two options, among the best three options, and so on. A= Control condition; B= Lateral Wedge Insole; C= Knee Brace; E= Gait retraining; F= Quadriceps strengthening;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

**Figure 4. Risk of bias summary**

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





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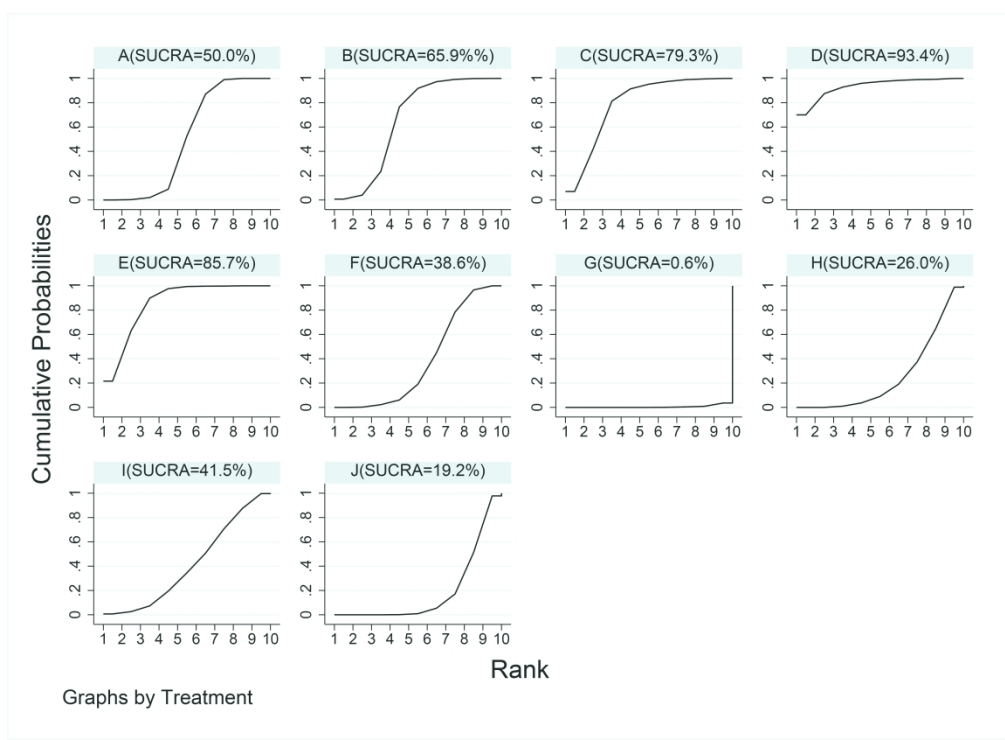


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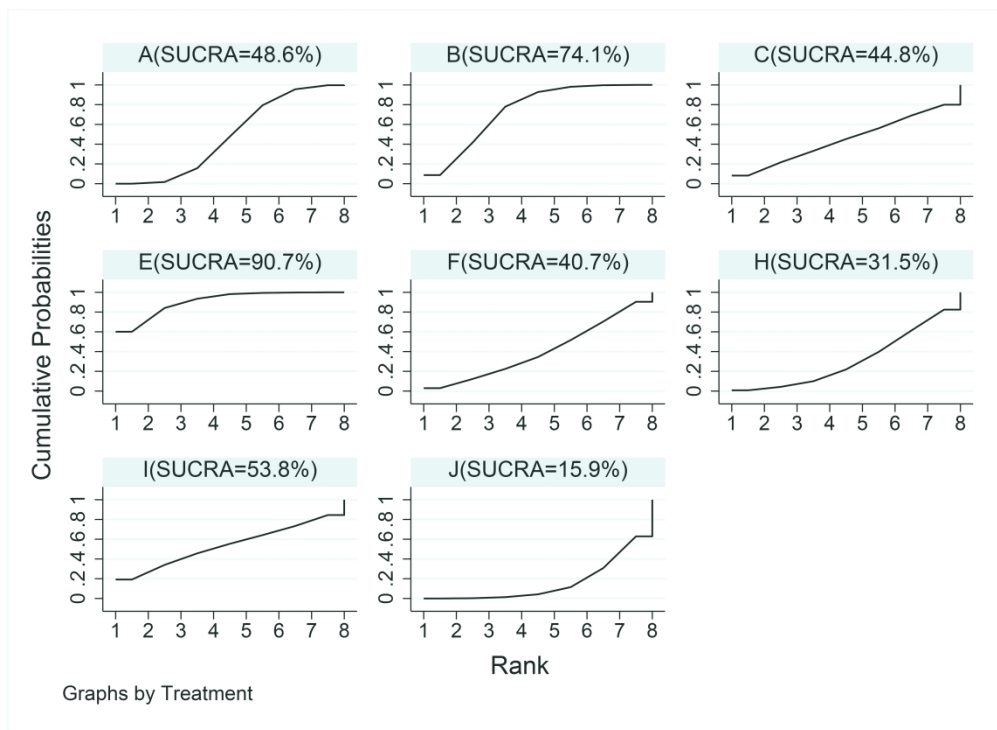
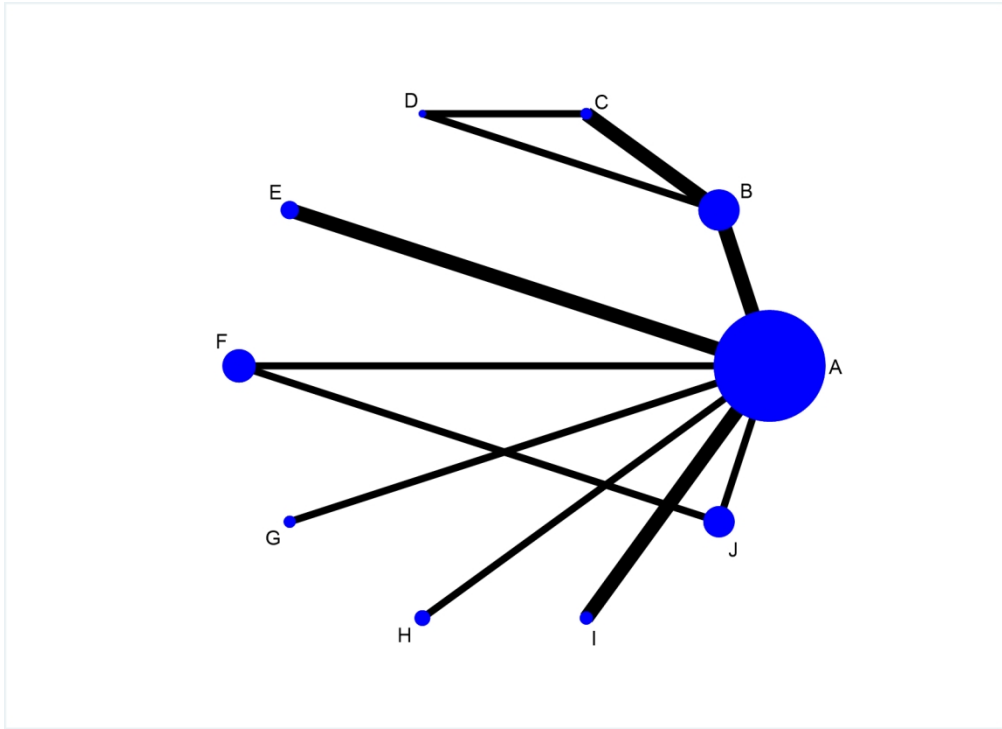


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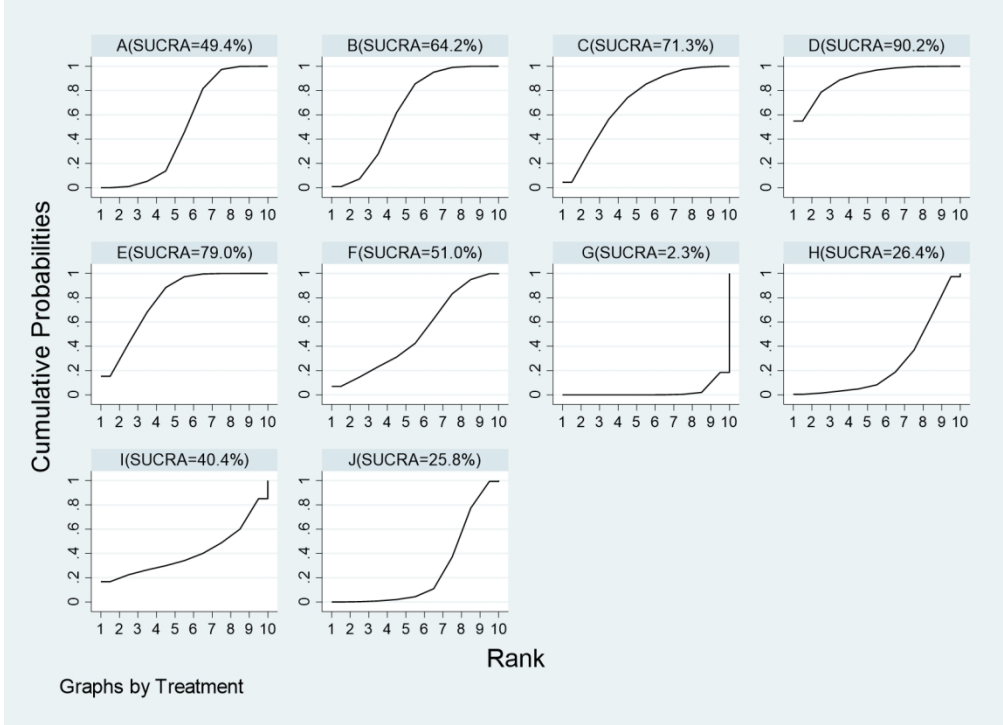
Study ID	Randomization process	Deviations from intended i	Missing outcome data	Measurement of the outcome	Selection of the reported	Overall
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Barrios 2013	?	+	+	+	+	!
Bennell 2010	+	+	+	+	+	+
Bennell 2014	+	+	?	+	+	?
Cheung 2018	?	?	?	+	?	?
Erhart-Hledik 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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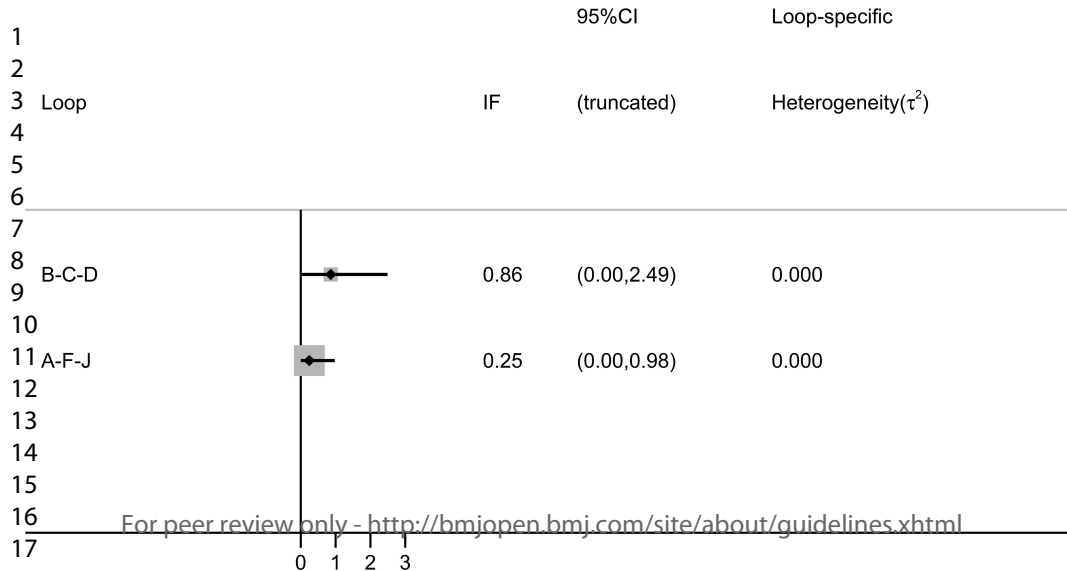


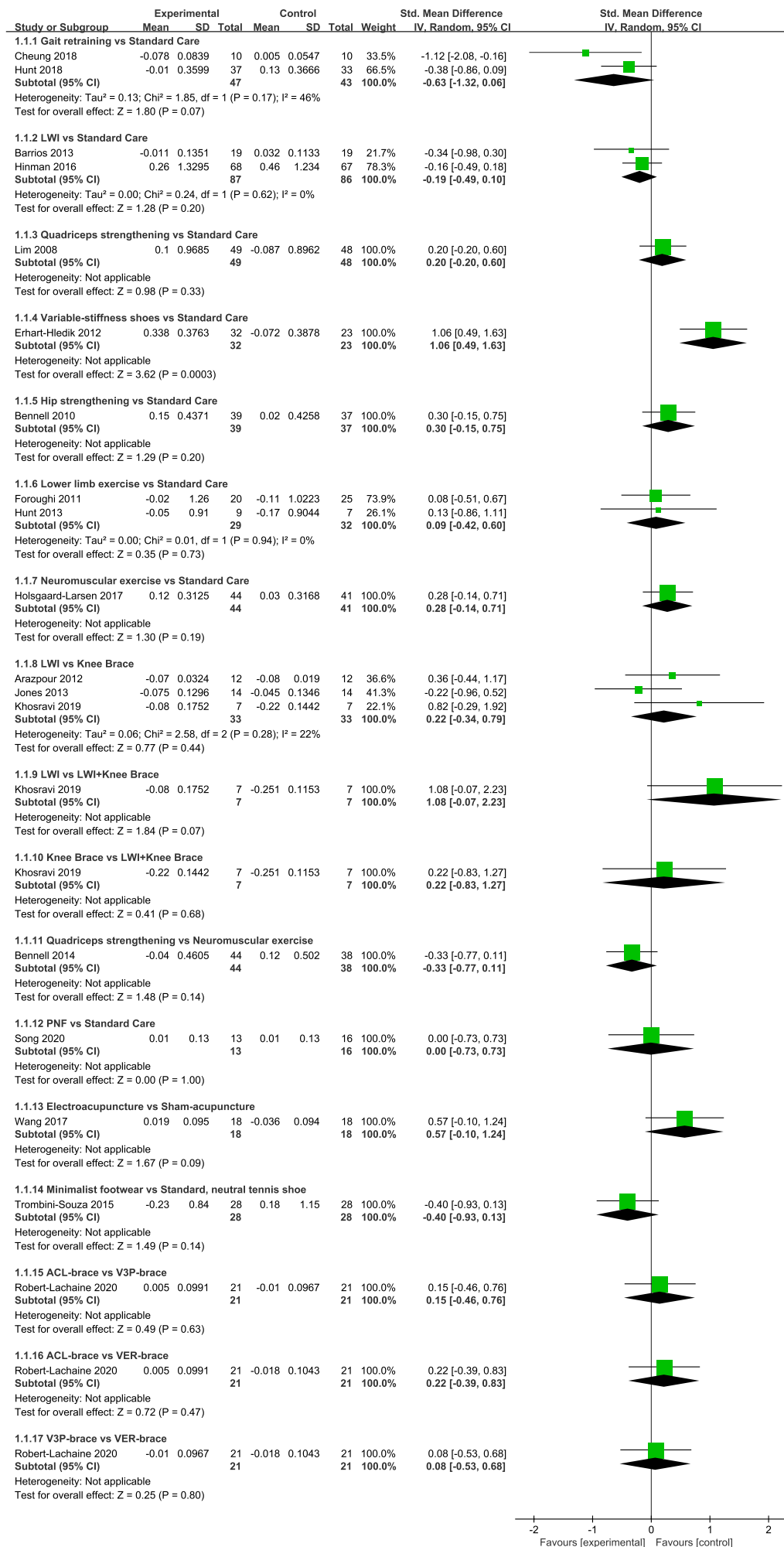
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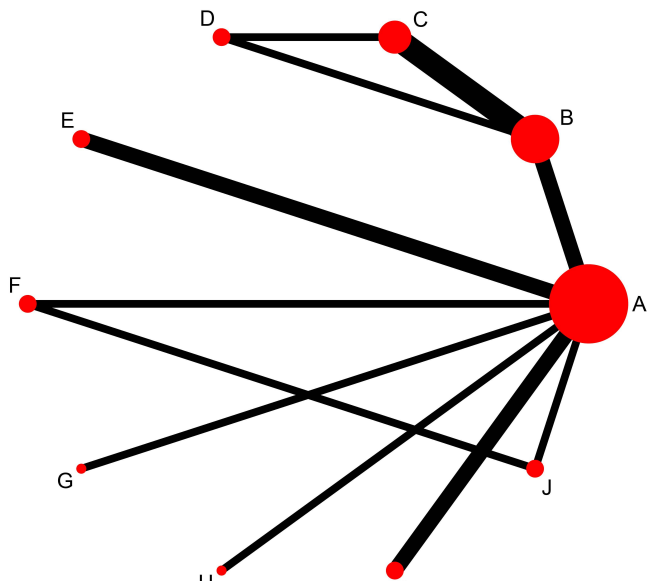


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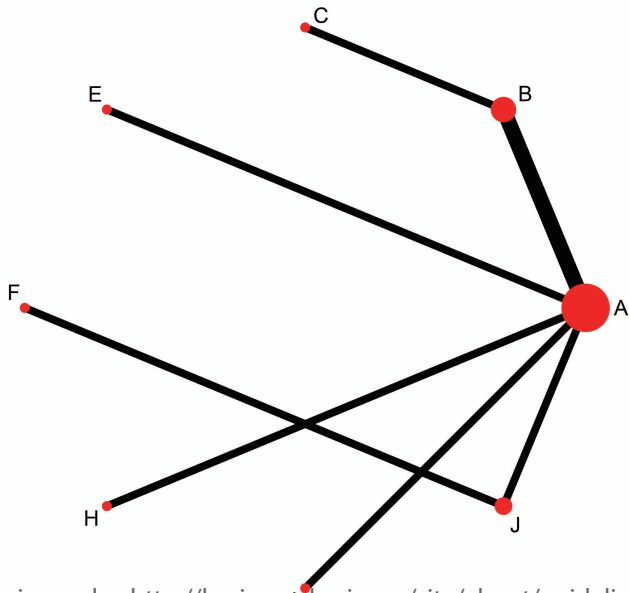
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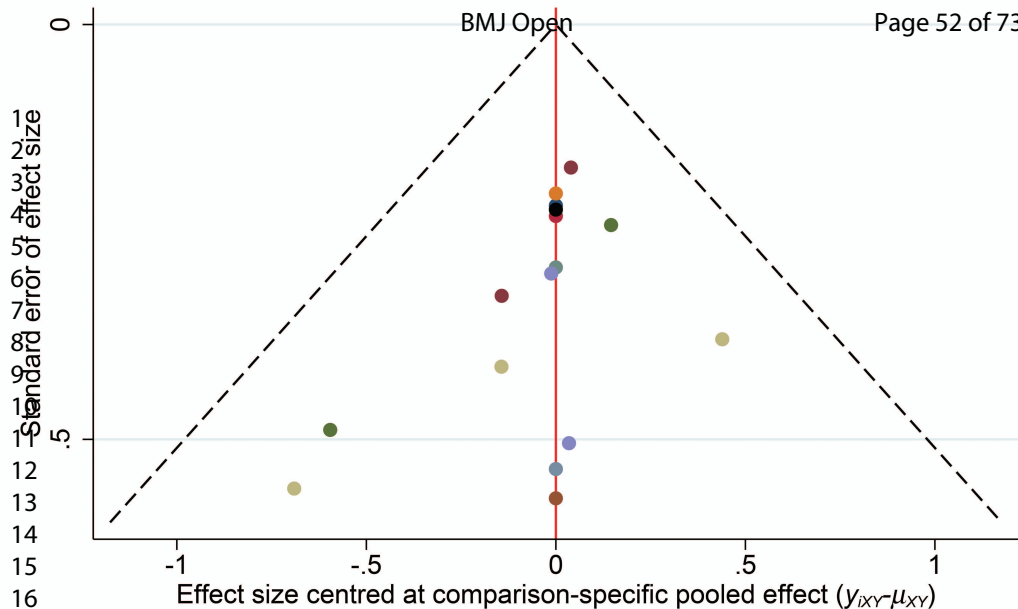


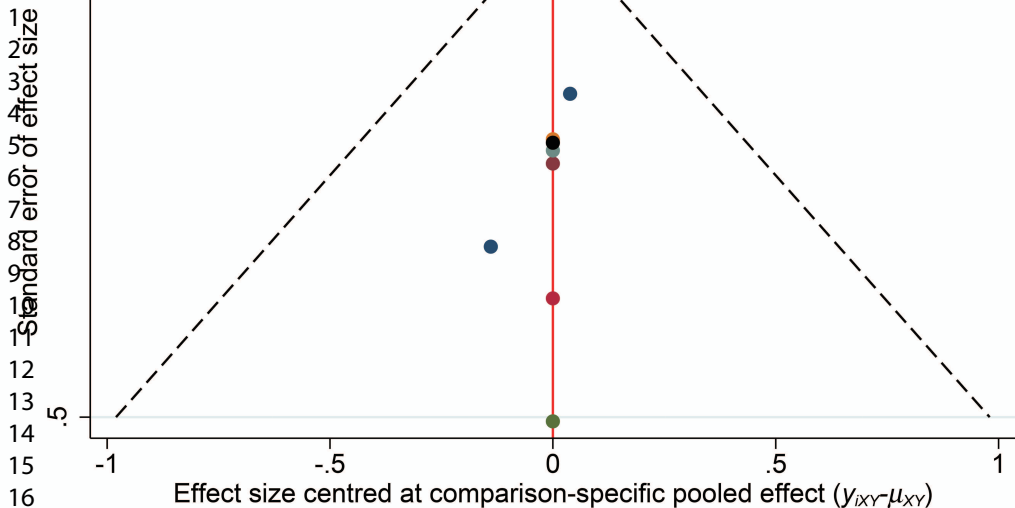
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## Appendix

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## Appendix 1 Search strategies

### Search strategies for randomized controlled trials Pubmed

1. (((((((("Osteoarthritis, Knee"[Mesh]) OR Knee Osteoarthritis[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 Osteoarthritis[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 osteoarthritis':ab,ti OR 'osteoarthritis, knee':ab,ti OR 'osteoarthrosis, knee':ab,ti)
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### Web of Science



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4. TI=(orthosis OR device OR orthosis OR orthoses OR orthopedic 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 osteoarthritis OR osteoarthritis)
7. TI=(knee osteoarthritis OR femorotibial arthrosis OR gonarthrosis OR knee arthrosis OR knee osteo-arthritis OR knee osteoarthritis OR osteoarthritis)
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 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 Osteoarthritis):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)

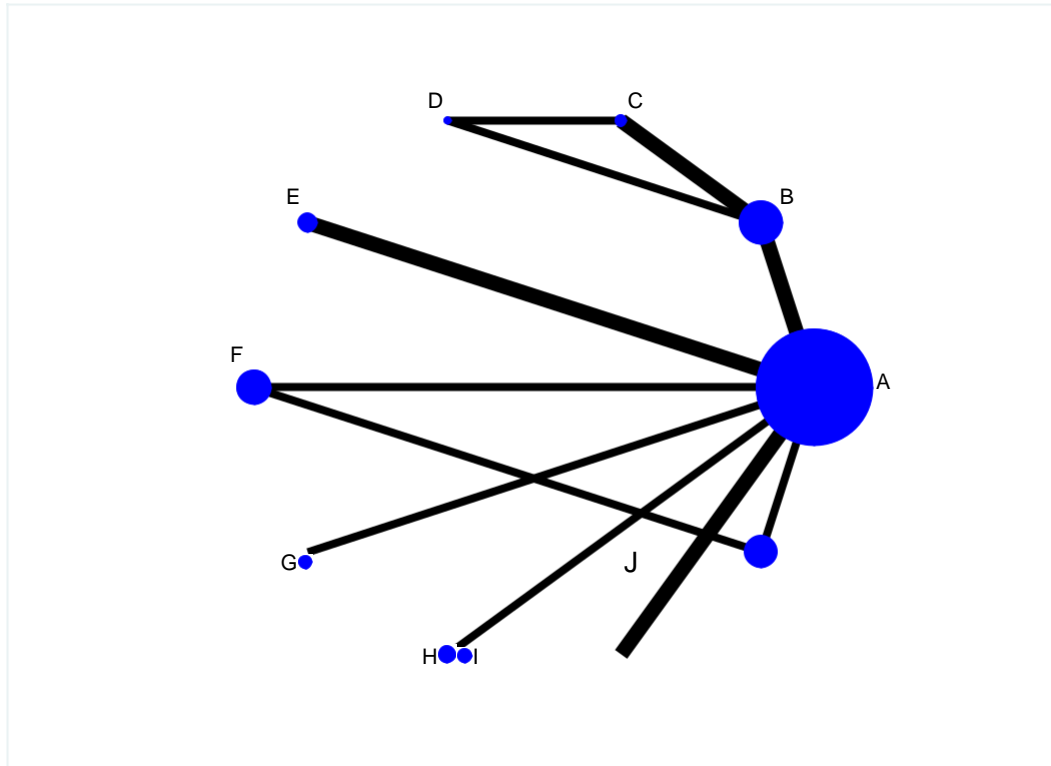
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## Appendix 2 Results of re-analysis

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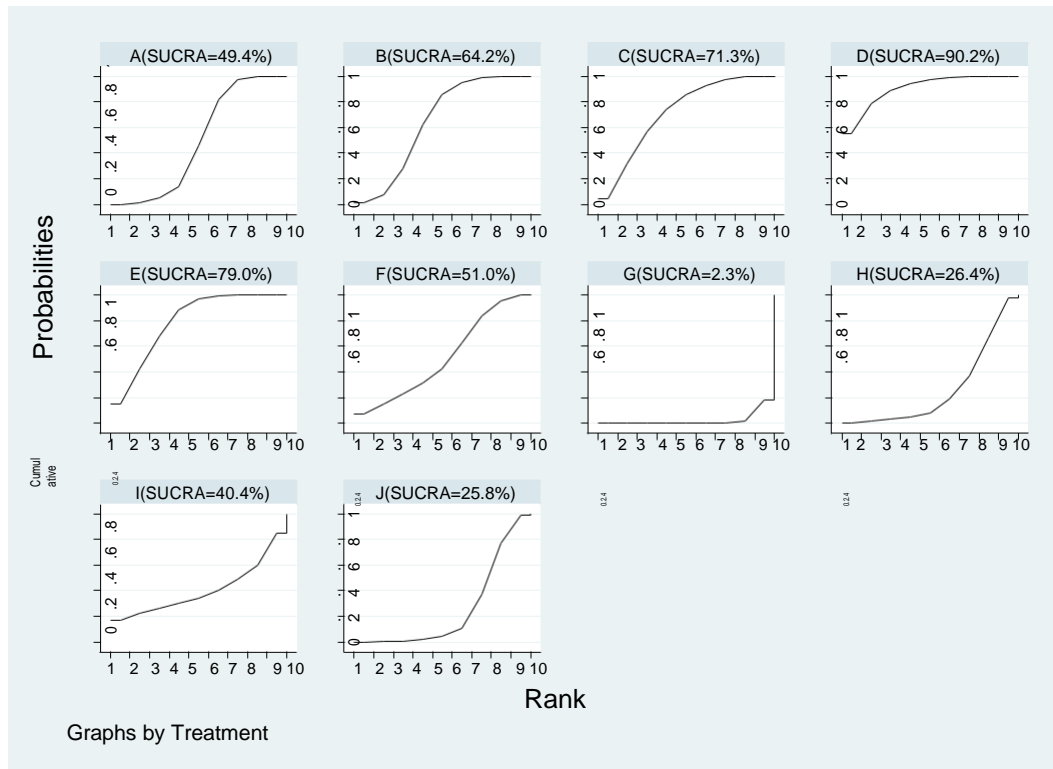
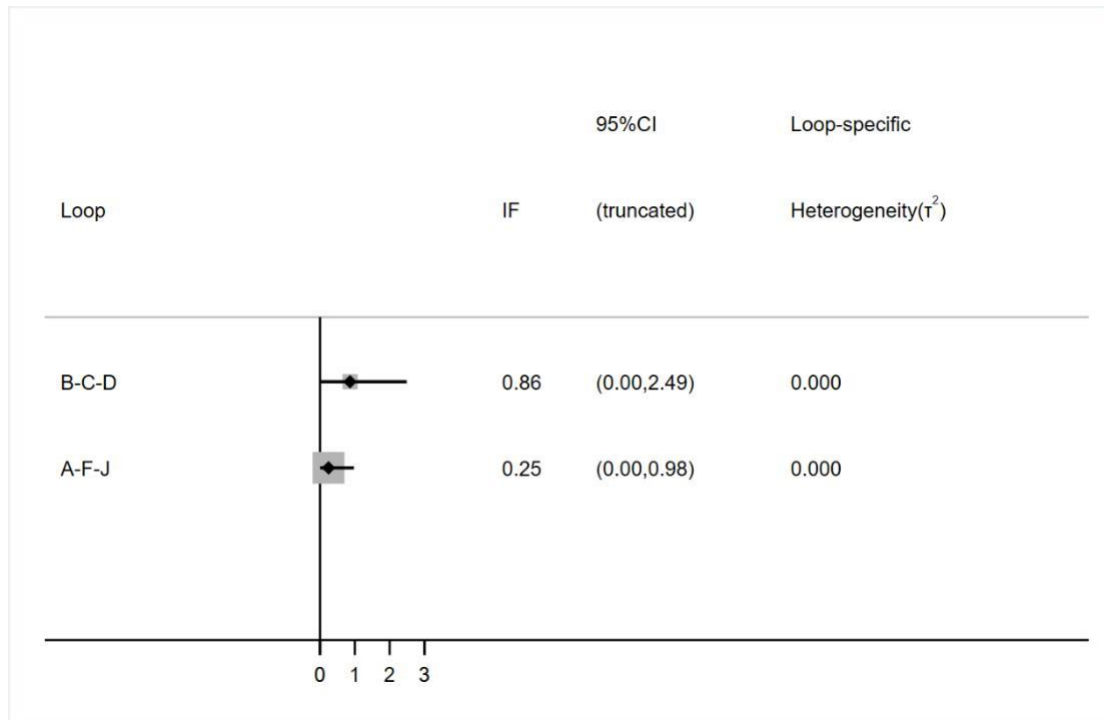


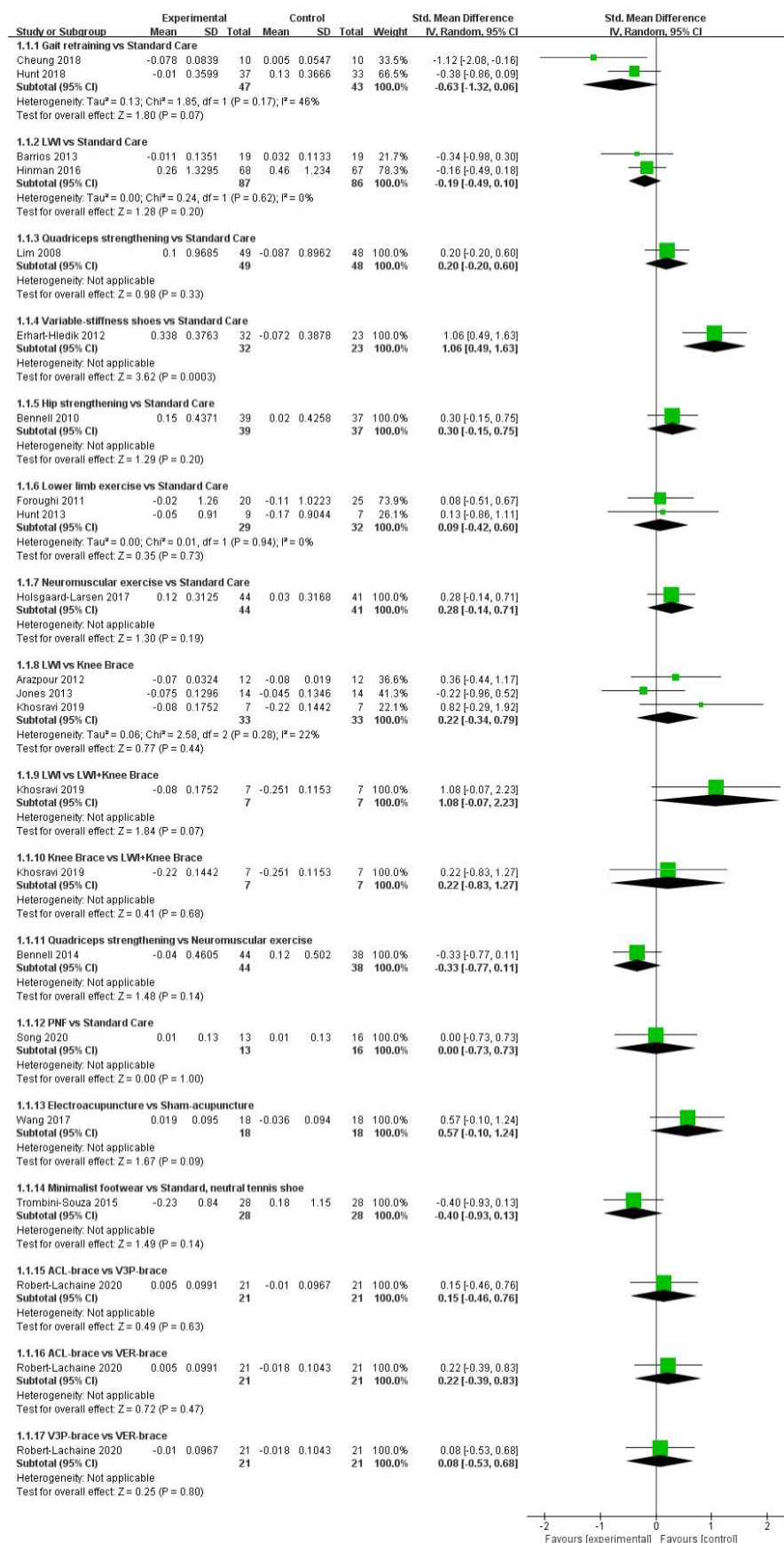
Figure 2. Rankings for effects on First peak KAM (re-analysis). Graph displays distribution of probabilities for each treatment. X-axis represents the possible rank of each treatment (from the best to worst according to the outcomes), Y-axis represents the cumulative probability for each treatment to 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

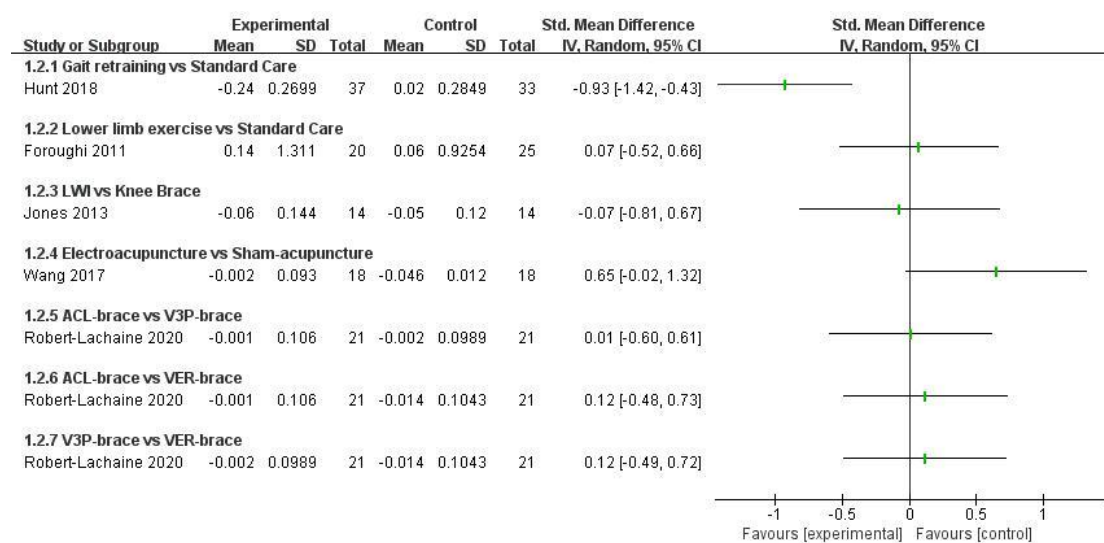


eFigure 1. Inconsistency for triangular loops in First peak KAM.

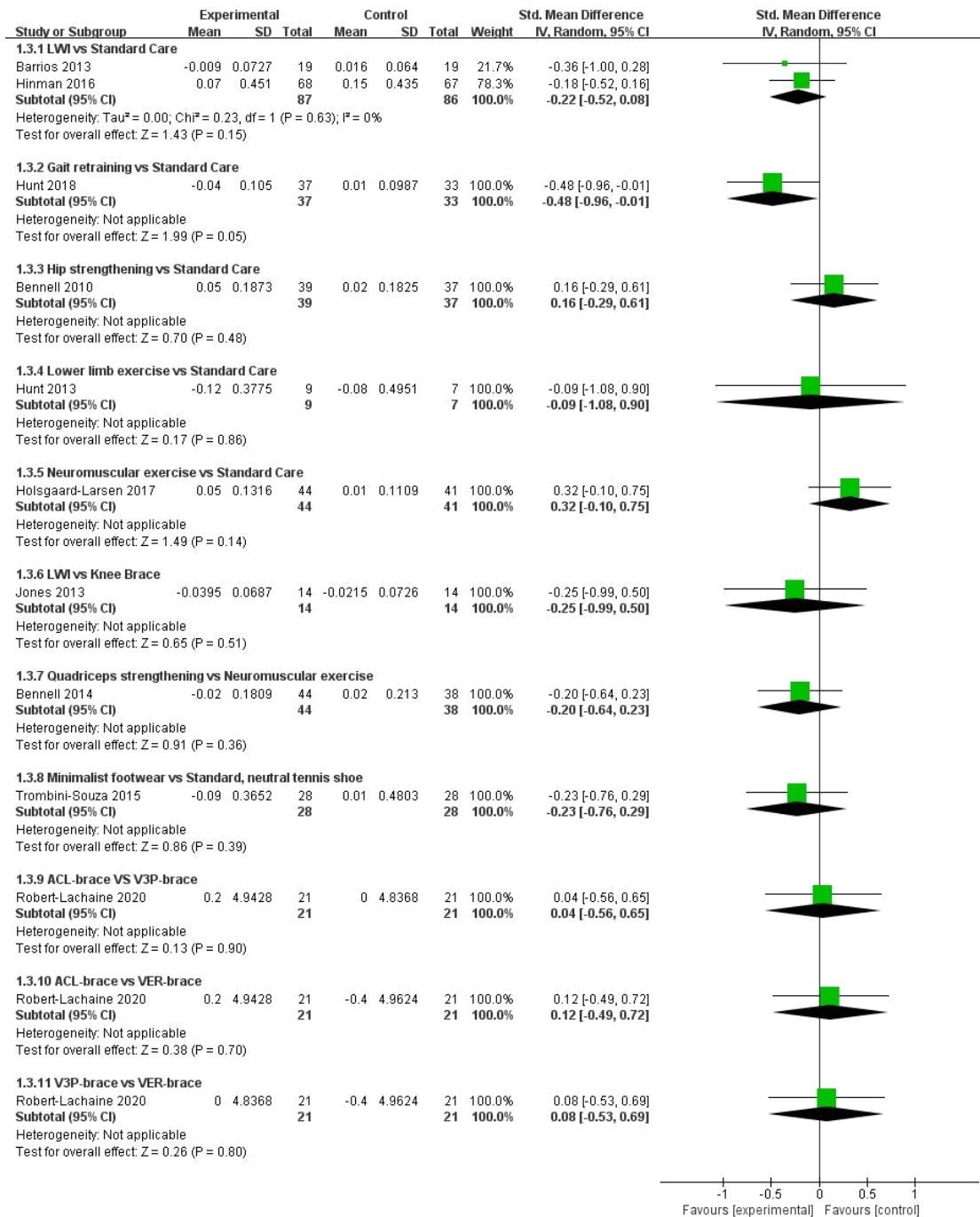
## Appendix 4 Conventional meta-analyses results



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

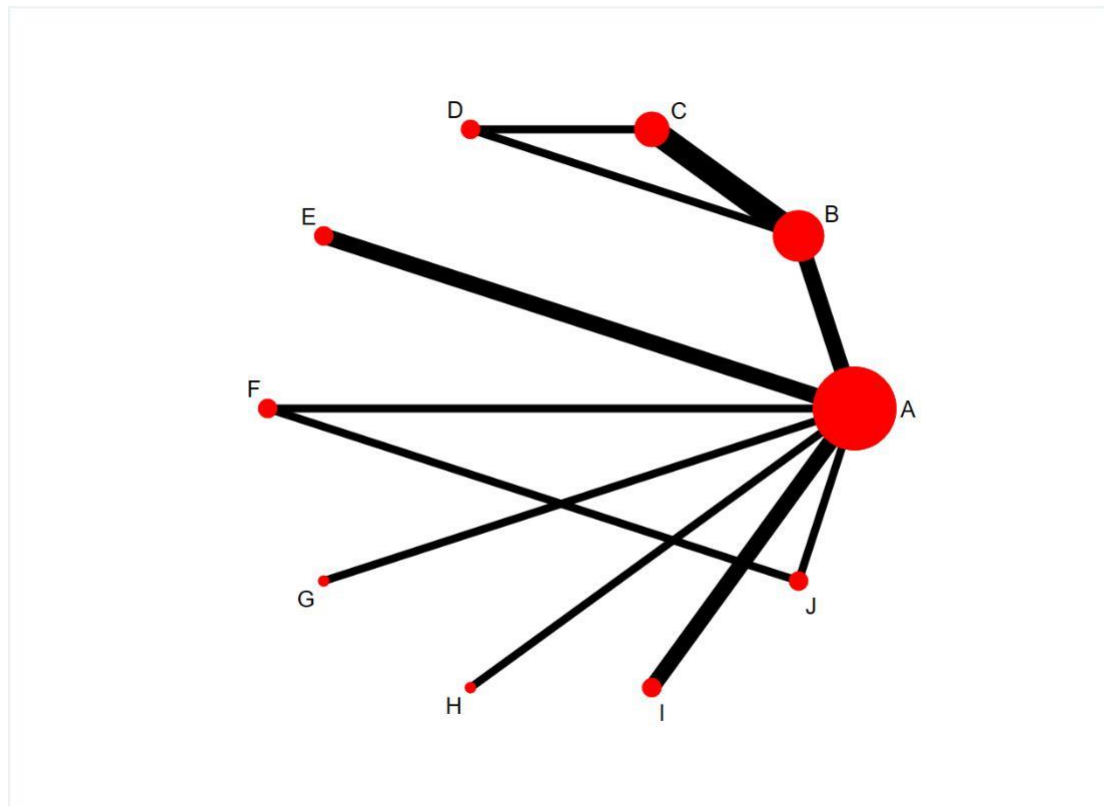
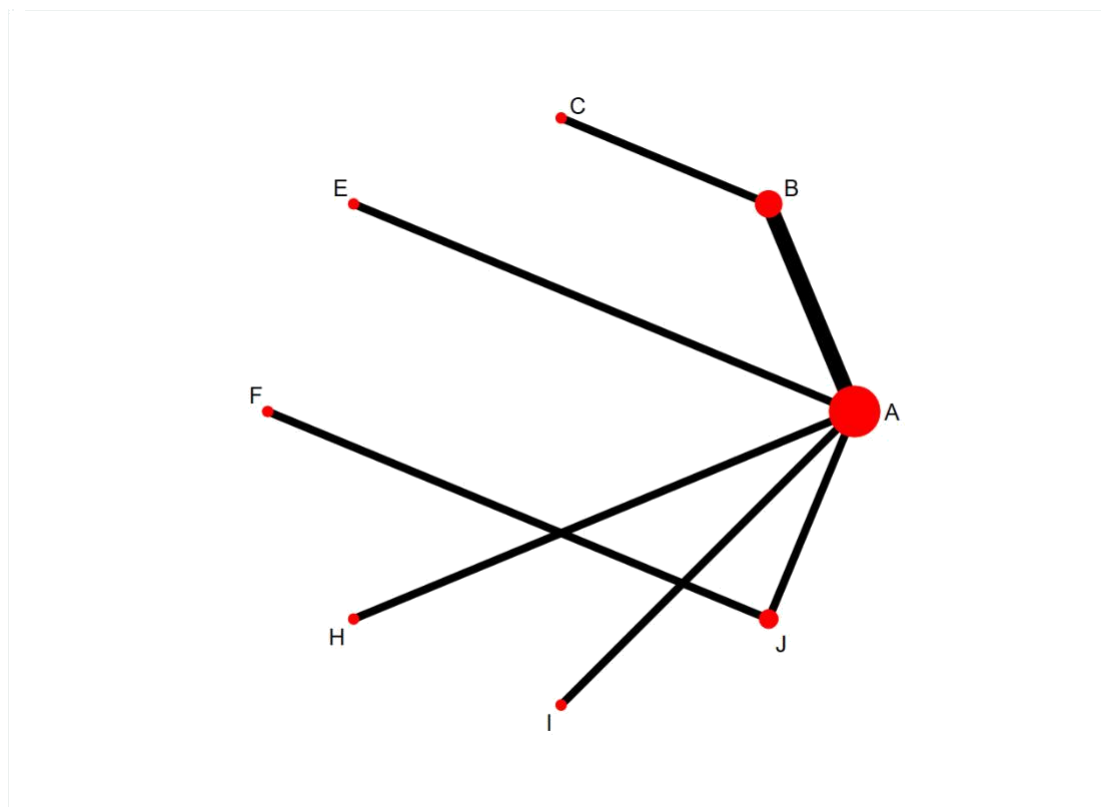


Figure 1a. Structure of network formed by interventions and their direct comparisons (First peak KAM). A= Control condition; B= Lateral Wedge Insole; C= Knee Brace; D= Lateral Wedge Insole+ Knee Brace; E= Gait retraining; F= Quadriceps strengthening; G= Variable-stiffness shoe; H= Hip strengthening;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

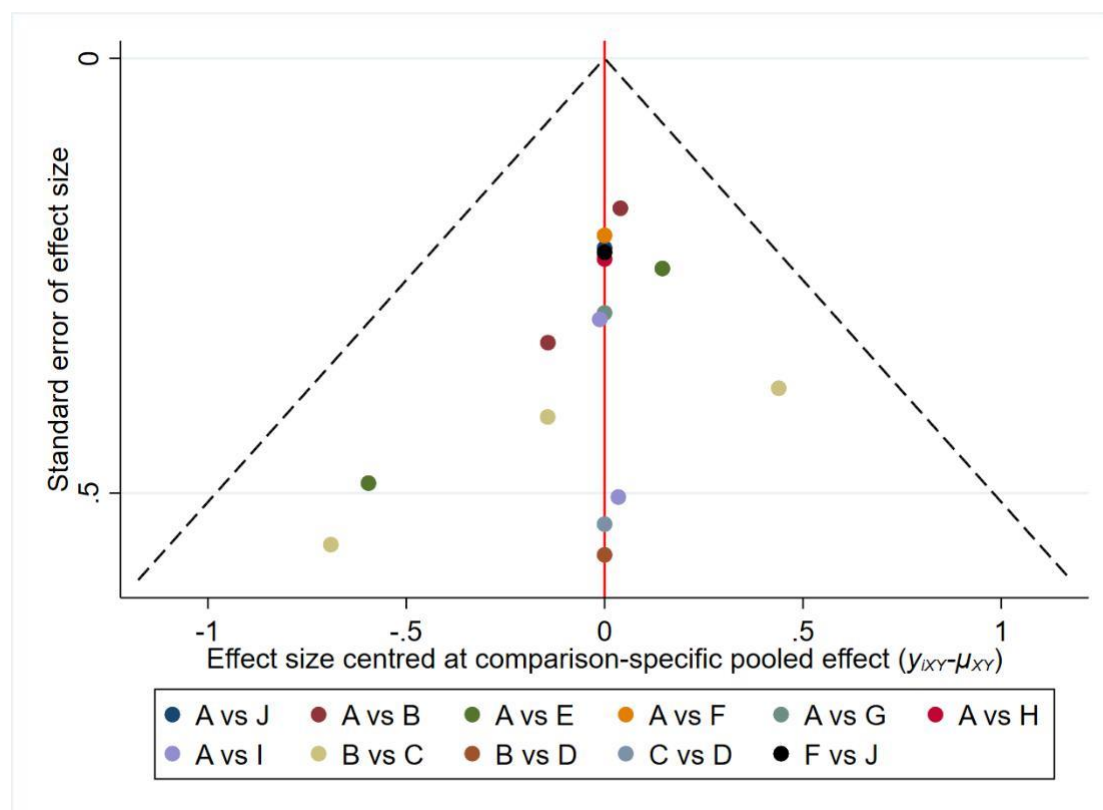
Comparison	Nature of the Evidence	GRADE	Downgrading due to
<b>AB:</b> Control Condition vs LWI	Mixed	LOW	Study limitations; Imprecision
<b>AC:</b> Control Condition vs Knee Brace	Indirect	LOW	Study limitations; Imprecision
<b>AD:</b> Control Condition vs LWI+Knee Brace	Indirect	LOW	Study limitations;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

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

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

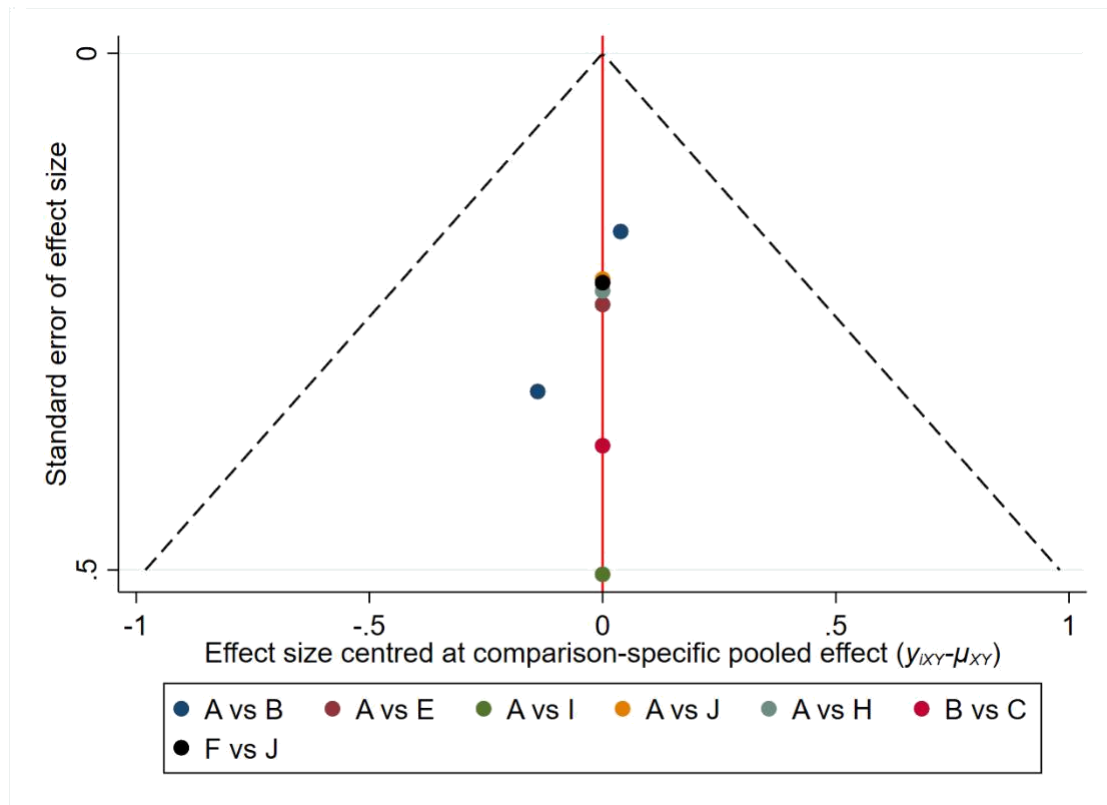
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4	<b>GH:</b> Variable-Stiffness Shoes vs Hip	Indirect	LOW	Study limitations; Indirectness
5	Strengthening			
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7	<b>GI:</b> Variable-Stiffness Shoes vs Lower	Indirect	VERY LOW	Study limitations; Indirectness
8	Limb Exercise			
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11	<b>GJ:</b> Variable-Stiffness Shoes vs	Indirect	LOW	Study limitations; Indirectness
12	Neuromuscular Exercise			
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15	<b>HI:</b> Hip Strengthening vs Lower Limb	Indirect	VERY LOW	Study limitations; Indirectness;
16	Exercise			Imprecision
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19	<b>HJ:</b> Hip Strengthening vs	Indirect	VERY LOW	Study limitations; Indirectness;
20	Neuromuscular Exercise			Imprecision
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23	<b>IJ:</b> Lower Limb Exercise vs	Indirect	VERY LOW	Study limitations; Indirectness;
24	Neuromuscular Exercise			Imprecision
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## 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 #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
<b>ABSTRACT</b>			
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
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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





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			& 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

Page 1 of 2

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



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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
<b>DISCUSSION</b>			
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,



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			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
<b>FUNDING</b>			
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

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