

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Huang, XiMeng; Yuan, Fu-Zhen; Chen, You-Rong; Huang, Ying; Yang, Ze-Xi; Lin, Lin; Yu, Jia-Kuo

VERSION 1 – REVIEW

REVIEWER	Macri, Erin Erasmus MC
REVIEW RETURNED	24-May-2021

GENERAL COMMENTS	<p>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.</p> <p>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.</p> <p>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. Line 81 - please clarify that variable stiffness shoes made the KAM worse (lower rate of KAM reduction is misleading).</p> <p>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.</p> <p>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</p>
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	<p>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?</p> <p>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.</p> <p>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.</p> <p>Please reword research questions so that they are grammatically correct and accurate and specific to the present study.</p> <p>Methods Line 180 and 187: Please clarify if the eligible studies were in English language only or not and be consistent here.</p> <p>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.</p> <p>Line 189. Placebo, no intervention, and sham are not standard care and should therefore not be labelled as such. Box 1 is worded in a way that suggests that actual standard care was not included. Please reword and clarify.</p> <p>Line 199. "non-trial papers" – do the authors mean papers that were not peer-reviewed? Please clarify.</p> <p>Line 201. What constitutes "studies that did not report suitable data". Please be concrete about what this means.</p> <p>Line 214. Please justify why Cochrane ROB version 1 was used, or consider updating to use the current ROB version 2 which is currently recommended by Cochrane.</p> <p>Line 229. Please be specific about the conditions and time of assessments of the outcomes. Some RCTs only measure biomechanics as immediate effects with and without the knee brace on, for example, and they do so prior to the actual clinical trial. For all studies in which devices were worn (braces, insoles, etc), be sure to report whether the outcomes were measured before or after treatment, and whether the device was worn or not at the time of evaluation.</p> <p>Statistical analyses. Please include references for all statistical tests and methods employed.</p>
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	<p>Line 247. What methods were employed to evaluate the source of heterogeneity? Also, remember to report in the results with a result was based on FE or RE, and the results of these additional analyses to evaluate source of heterogeneity.</p> <p>Figure 1. Using the PRISMA guidelines, it is not required to report reasons for exclusion at the title/abstract screen. Please update Figure 1 to adhere to PRISMA guidelines.</p> <p>Results. For orthopaedic interventions, please remember to discuss whether biomechanical effects were pre- and post-intervention, or if they were done at a single time point with orthopaedic device off and then on.</p> <p>Section 3.3 KAM, 3.4 KAI Please rewrite this section to provide a narrative synthesis/summary of the results in a way that is understandable to the reader. Effect sizes do not need to be repeated in the text since they are already in Table 3, so use this space to help the reader understand the results. Please make sure to emphasize that despite the rankings at the end of each section, they are not significant and therefore not clinically relevant. For any results that are statistically significant, be sure to also consider their clinical interpretation – are any of the results clinically important?</p> <p>Line 307. This sentence should be removed regarding stair ambulation. Stairs was not included in the eligibility criteria of this analysis.</p> <p>Risk of Bias. Figure 4 seems to be missing – the only Figure 4 I can see if the funnel plot, not the ROB table. ROB is not the same thing as quality. Be sure to use accurate and consistent language.</p> <p>Be sure to include the GRADE results in the Results section.</p> <p>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.</p> <p>Line 369. “there was no study that reported the immediate effect” – what about Wang 2017? Table reports these were immediate effects.</p> <p>Line 375. Sensitivity analyses should be reported in the methods and results section, no in the Discussion section.</p> <p>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?</p> <p>Line 424. Mazzoli references is Maleki.</p>
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	<p>Line 430. Please justify why the authors think that Taiji, ultrasound and acoustic exercises might alter biomechanics. Are these studies really necessary?</p> <p>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?</p> <p>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.</p> <p>Thank you for the opportunity to review this work.</p>
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VERSION 1 – AUTHOR RESPONSE

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 KAll 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 KAll). 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 4 (Line 147-150). Although the effects of gait retraining and orthopedic devices on biomechanics are more direct than the effects of modalities such as ultrasound and Taiji, some studies have shown that the joint pain can affect the kinetics and kinematics of walking 2. These modalities such as ultrasound and Taiji had a certain effect on pain relief 5, so we didn't want to miss any treatment which can affect biomechanics when we set the topic. Besides, we introduce the concept of physical therapy and orthopedic equipment into the introduction (Line 141-145).

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

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

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

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

Methods

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Please include references for all statistical tests and methods employed.

Response 15: Revised.

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

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

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

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

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

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

Section 3.3 KAM, 3.4 KAAI

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

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

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

Response 20: We are very sorry for the misunderstanding of our previous description. This article met our eligibility criteria. However, considering that its inclusion in meta-analysis will lead to excessive heterogeneity, we excluded it from the network meta-analysis. Our intention is that the biomechanical indicators of the studies included in the Bayesian network meta-analysis were measured on flat

ground or treadmills. Other studies that cannot be included in the network meta-analysis were included in the systematic review. We have corrected this imprecise sentence (Line 208-209).

Risk of Bias.

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

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

Figure 4

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

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

Discussion.

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

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

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

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

Line 375. Sensitivity analyses should be reported in the methods and results section, not in the Discussion section.

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

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

Response 26: We have added this part to the discussion (Line 394-396, 403-411). The results of current study showed that there is no statistically significant reduction in biomechanics after taking off the LWI after one year of treatment, which is contrary to the results of donning it. 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 LWI3. 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.

VERSION 2 – REVIEW

REVIEWER	Macri, Erin Erasmus MC
REVIEW RETURNED	29-Nov-2021

GENERAL COMMENTS	This manuscript has improved substantially, thank you for addressing most of my previous comments and questions. I have made several comments now directly in the word document (see attached) for mostly minor suggestions for improvement, such as including more recent references or some grammatical suggestions. I continue to disagree with the authors that placebo, sham and no treatment are the same thing as unblinded 'standard care'. Blinding will very much influence individual study results, so I think authors should consider a different term than 'standard care' - control or comparison group is probably sufficient. Please acknowledge this is a limitation in the Discussion section. Finally, please consider having a native English speaker clean up the Discussion section so that it flows better and is easier to read. Thank you for the opportunity to review this revised manuscript.
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

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

Comments to the Author:

This manuscript has improved substantially, thank you for addressing most of my previous comments and questions. I have made several comments now directly in the word document (see attached) for mostly minor suggestions for improvement, such as including more recent references or some grammatical suggestions. I continue to disagree with the authors that placebo, sham and no treatment are the same thing as unblinded 'standard care'. Blinding will very much influence individual study results, so I think authors should consider a different term than 'standard care' - control or comparison group is probably sufficient. Please acknowledge this is a limitation in the Discussion section. Finally, please consider having a native English speaker clean up the Discussion section so that it flows better and is easier to read. Thank you for the opportunity to review this revised manuscript.

Response: We think your opinion is very constructive and have made point-to-point modifications according to your comments in the word document. We have renamed the term "standard care" in this

study as "control condition" to include these control treatments more unambiguously. At the same time, we have also added the limitation of this part in the discussion part (Line 405-410). Finally, we have invited a professional copyediting service to help us to polish the full text. Thank you very much for your rigorous modification and valuable comments, which greatly helped us to further improve this article.