Author’s response to reviews

Title: Do knee abduction kinematics and kinetics predict future anterior cruciate ligament injury risk? A systematic review and meta-analysis of prospective studies

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Author's response to reviews:

Dear Editor,

Thank you for your response and for the reviewers’ comments and suggestions. Changes have been made in order to meet the points raised, and in the few cases where we have not made the suggested changes, our reasons for not doing so are given.

We hereby submit the revised version of the paper, with marked changes, along with response to each of the specific comments provided by the reviewers.

On behalf of the authors,

Anna Cronström, PhD

Reviewer 1

Nathan Schilaty: In this manuscript, the authors performed a systematic review and meta-analysis of knee abduction kinematics and kinetics of ACL injury risk. The manuscript is well written and was a pleasure to read and critique. I thank the authors for their diligent efforts on this work and feel that it will contribute well to the literature pending revision. Although this manuscript is timely and an important step in the progress of research in this arena, my overall evaluation is that 1) the current title is misleading, 2) the current scope of the literature causes this study to be underpowered, and 3) the conclusions are too strong for what the data demonstrates.
I hope that the authors will consider the following revisions for improvement of this manuscript and to support current research prerogatives:

1. REVIEWER COMMENT
Page 5, Line 91 - Alignment has a misplaced capital

AUTHORS RESPONSE AND ACTION
We thank the reviewer for the thorough read of our manuscript. The misplaced capital is now corrected (Line 91)

2. REVIEWER COMMENT
Page 7, Line 126 - Be sure to remain consistent in terminology throughout the manuscript. 'Sex' was allocated, not gender. Sex is binomial and determined by genetics - gender is self-selected and is a large spectrum. In Line 129, the term 'sex' is appropriately utilized. Need to change on line 205.

AUTHORS RESPONSE AND ACTION
Thank you for highlighting this. We agree and “gender” is now replaced with “sex” on line 210

3. REVIEWER COMMENT
Page 7, Line 143 - Change to, "Of those, 10 articles…"

AUTHORS RESPONSE AND ACTION
A comma is inserted so that it now reads: “Of those,… ” (line 146)

4. REVIEWER COMMENT
The title needs to include 'risk' as only injury risk can be predicted… not actual injury.
AUTHORS RESPONSE AND ACTION

Changes have been made and the title now reads; “Do knee abduction kinematics and kinetics predict future anterior cruciate ligament injury risk? A systematic review and meta-analysis of prospective studies”

5.REVIEWER COMMENT

Line 236 - it needs to be made clear that a non-linear relationship may exist. It is alluded to with mention of a "linear relationship," but it could be more clearly stated.

AUTHORS RESPONSE AND ACTION

This is now clarified on line 245 and the sentence reads; “An alternative explanation for our findings could be that instead of a linear relationship between knee abduction and ACL injury risk there may be a non-linear relationship with a certain cut-point beyond which knee abduction is associated with ACL injury risk.”

6.REVIEWER COMMENT

Although it may be construed as promoting my own work, I think that the authors need to consider recent cadaveric publications that are highly controlled, randomized loading laboratory studies that clearly demonstrate knee abduction as a major contributing factor to ACL strain and rupture. Thus, there is not just clinical evidence to support the concept of knee abduction (as is the goal of this meta-analysis), but there is also basic and translational science that support knee abduction as a key contributor to ACL injury. ACL injury prediction is difficult as it is likely non-linear and will likely be multifactorial, but we cannot discount the high degree of evidence that continues to support that knee abduction angle and moment are key in loading the ACL, especially in a meta-analysis that will drive future research and funding. As a reviewer on this study, I am passionate about these topics and need to speak to the research that has been performed here. These articles could potentially be discussed (at the discretion of the authors) near line 257 and further in the Discussion near line 301. Also, this information should be considered when addressing the conclusion of 312-314.


See Figure 5 and 6


AUTHORS RESPONSE AND ACTION

Thank you for these suggestions. That knee abduction is a major contributor to ACL strain is described in the background on lines 56-57 “Several in vitro studies have also shown that the knee abduction moment is a major contributor to ACL strain…” and in the discussion on lines 228-229 “Conceivably, the findings of Hewett and colleagues, in combination with earlier evidence from cadaver knees…”. We have now also added a sentence regarding this in the discussion on lines 272-275 and the following references are added as suggested; Ueno et.al 2020 and Schilaty et.al. 2019. The sentence reads; “Although some recent cadaveric studies report an association between increased knee abduction moment and ACL failure (ref), in support of the latter, a recent systematic review on bone bruises assessed with MRI after ACL injury (ref) concludes that knee abduction occurs after the ACL is ruptured, not before.”
We have also clarified that we referred to both kinematics and kinetics for several planes on line 321 and the suggested references were added (Ueno et.al., Navacchia et.al. (Bates et.al., AJSM was already cited here)). The sentence now reads;

“Several studies highlight that the mechanisms of ACL injury are in fact multifactorial and that several combined factors, such as knee abduction and internal rotation kinematics and kinetics, but also neuromuscular control of the hip and trunk may contribute to the injury mechanism (ref). Even though knee abduction kinematics and kinetics alone cannot predict injury risk, future studies will reveal if knee abduction may contribute to knee injury when combined with other risk factors, such as those described above.” (Lines 321-325)

7.REVIEWER COMMENT
Table 1 - Smeets et al. 2019 Quality Score is incorrect. It should be 11/19.

AUTHORS RESPONSE AND ACTION
Thank you for pointing this out. This quality score is now corrected accordingly

8.REVIEWER COMMENT
It is not clear if the Forest plot was adequately weighted based on the numerical values of the studies. This should be made clear.

AUTHORS RESPONSE AND ACTION
Thank you for pointing this out. The meta-analyses were all weighted according to the random effect model analysis. This is now added to the methods on lines 126-128 “All meta-analysis and corresponding forest plots were weighted under the random effect model, taking both within study variance and between study variance (Tau2) into account”

9.REVIEWER COMMENT
I have concerns for the Goerger et al. study data as presented in the manuscript (Forest plot). It really is the only study that is an outlier of the other 3D studies that trend in favor of 'increased knee abduction' as a ACL injury risk predictor. This is the study that disagrees with all of the other studies on the Forest Plot. However, Figure 3D of this study and the conclusions counteract what has been summarized by the authors of this current manuscript. In fact, Figure 3D demonstrates a baseline IC abduction angle of 11 +/- 4 deg. I would advise the authors to revisit their data extraction and ensure that it is accurate in their analyses.

AUTHORS RESPONSE AND ACTION

We have revisited the data, and the data is correct. In Table 3 in the study by Goerger et.al., the authors report baseline knee abduction at IC to be 2.61 for individuals that sustained an ACLR and 0.96 for controls (negative values = abduction, indicating that ACLR individuals had more adduction) resulting in a mean diff of 1.65 degrees, as reported in figure 3 (not 11 degrees). We are not sure where the 11 degrees that the reviewer refer to is coming from. In Table 4, in the study by Goerger et.al., a mean diff of 1.33 in baseline peak knee abduction is reported between controls and ACLR, as in our figure 3. The individuals with ACLR did, however present with 11 degrees peak knee abduction at follow-up (after ACL injury) in that study; this appears to be the data that the reviewer is referring to in their comment. Since we base our analysis on prospective data, we only use baseline values of knee abduction to predict future ACL injury. In addition, the forest plots represent the baseline mean differences in knee abduction between those who sustained a future ACL injury and those who did not, and thus, not absolute values. The study by Goerger et.al., is the only study in the analyses on 3D knee abduction that includes both men and women, which may be one explanation for the contradicting results between this and the other studies in the meta-analyses. We did, however, perform a sensitivity analysis excluding this study, as reported in online resource B and there was still no association between 3D knee abduction (peak and IC) and future ACL injury.

10.REVIEWER COMMENT

Supplemental Data (mentioned with Funnel plots in the abstract): The Funnel plots only have 3-4 data points and clearly are not adequately powered to determine publication bias. However, observation of the Forest plot from the current manuscript demonstrates that knee abduction is clearly factor in ACL injury risk prediction. This needs to be specifically mentioned in the limitations of the study as it is currently overlooked with being supplemental material.

AUTHORS RESPONSE AND ACTION
We do not refer to the Funnel plot in the abstract. We do, however, agree with the reviewer that the number of studies in each analysis are too few to be able to assess publication bias using Funnel plots. This is now updated in the methods, results and limitations as follows;

In methods;

“Publication bias was explored using Funnel plots with trim and fill if ten or more studies were included in the meta-analysis (ref)” (lines 140-141)

In the results;

“There were too few studies in each meta-analysis to explore publication bias using Funnel plots with trim and fill imputations (ref)” (lines 199-200). The Funnel plots are also removed from Online resource C.

And in the limitations;

“Also, there were too few studies included to be able to explore publication bias. However, since it is more likely that studies reporting no significant results are the studies that are not being published, this is unlikely to have an influence on our result.” (Lines 316-318)

11.REVIEWER COMMENT

Line 245 - I think that there needs to be caution with the term 'normal range.' This needs to be carefully defined as there is a spectrum of knee motion that could be considered 'normal', yet there can be high risk in the 'normal' motion. For example, people present with disease even when their biometrics are in the 'normal' range. Usually, there are multifactorial presentations that amount to the disease / risk even though one could be within 'normal' range.

AUTHORS RESPONSE AND ACTION

This is a good point and we agree with the reviewer regarding this and a sentence has been added to the discussion.
“Given the lack of an injury risk threshold, it is also not clear if there is an elevated risk of knee injury in individuals presenting with knee abduction at the higher end of the normal range that has been postulated.” (Lines 255-257)

12.REVIEWER COMMENT

In the opinion of the reviewer, the conclusion (in abstract and text) is currently too strong for the data presented. Although this current publication is warranted, the conclusion and title are quite misleading to the current amount of data present in the literature. There is a definitive clinically relevant trend (Figure 1 - Forest plot), although there is currently not statistical significance. The lack of statistical significance may not show as the limited literature causes the study to be 'underpowered,' but the trends are clearly favoring that knee abduction does predict ACL injury risk based on the Forest plot provided.

AUTHORS RESPONSE AND ACTION

We do not agree with the reviewer regarding this. The only study that show a clear result in the direction of knee abduction being a risk factor for ACL injury is the 15 years old study by Hewett et.al. By pooling data across all eligible studies, we have by definition substantially increased statistical power compared with any individual study included in our analysis [1]. To account for the uncertainty that will always exist in the inferential statistical analysis of applied data we have modified our study title and conclusions.

The title now reads; “Do knee abduction kinematics and kinetics predict future anterior cruciate ligament injury risk? A systematic review and meta-analysis of prospective studies”

In the conclusion in the abstract and the main manuscript we have added “may not be risk factors” instead of our previous statement that said “are not risk factors” (Lines 39 and 329)


Reviewer 2

Sandra Shultz, PhD (Reviewer 2): This is a very well written and crafted manuscript that makes every effort to provide an unbiased and critical appraisal of the available literature on this topic.
I really did not identify any major concerns, but do provide the following suggestions to the authors

1. REVIEWER COMMENT

Line 110-114 - follow up period should be added here

AUTHORS RESPONSE AND ACTION

Thank you for pointing this out. Follow-up period is now added to line 114

2. REVIEWER COMMENT

Line 129 - should a sensitivity analysis also be performed on follow up period given the large range?

AUTHORS RESPONSE AND ACTION

This is a good point and follow-up period is now added to the sensitivity analysis in online resource B. In addition, follow-up period is added on line 131 in the methods, on line 193 in the results and on line 306 in the limitations. Since a short follow-up period may underestimate the number of ACL injuries, we chose to exclude studies that had a follow-up period of ≤ 1 year in the sensitivity analysis.

3. REVIEWER COMMENT

Line 136-138 - this was already stated earlier

AUTHORS RESPONSE AND ACTION

The statement on line 107 referred to the screening and data extraction procedures and the statement on line 136 to the quality assessment. However, to avoid confusion this statement is now deleted on line 138
4. REVIEWER COMMENT
Line 151 - This paragraph is a bit hard to digest - consider making a table grid so that one can easily see commonalities between the different studies.

AUTHORS RESPONSE
Thank you for this suggestion. However, this information is already included in Table 1, as referred to on Line 161.

5. REVIEWER COMMENT
Line 166-173 - This text largely repeats Figures 2 and 3 - the only thing missing from the figures is the N of ACL injury vs controls. I would suggest adding that data to the figures and remove the text - figures are much easier to decipher.

AUTHORS RESPONSE AND ACTION
The numerical results are now removed from the text and “n” is added to the figures 2 and 3 as suggested by the reviewer. (Lines 169-176)

6. REVIEWER COMMENT
Line 175-186 - I find these paragraphs a bit difficult to follow. Perhaps these could be placed in a separate table with their relevant findings - in text, just note 3 studies that were not included in MA = in the table provide study, reason for not included in MA, and finding. At minimum, please break up 175-181 (currently one sentence) into 2 or more sentences, and speak about each study individually (it gets confusing toggling back and forth between the two).

AUTHORS RESPONSE AND ACTION
Thank you for this suggestion. The two paragraphs are now replaced with one sentence and Table 2 is added.
“Two articles (ref) included factors not eligible for meta-analysis and the results for these articles are reported in Table 2” (lines 178-179)

7.REVIEWER COMMENT

Discussion - Overall, the authors have done a very good job of fairly interpreting the data. A few suggestions:

Line 214 to end of paragraph - while I think the author raise a valid point here (particularly since the other studies follow 10 years later), consider comparing this change in values over time to change in injury rates. I don't believe we have seen a similar decrease in ACL injury rates over this time - which would suggest that although females may be displaying less valgus as a result of these programs, we are not seeing an overall change or decrease in injury rates.

AUTHORS RESPONSE AND ACTION

This is an interesting point and a sentence regarding this is added to the end of this paragraph.

“On the other hand, although injury prevention programs may have decreased the amount of knee abduction exhibited during activities, there seem to be no decrease in the incidence of ACL injury during the same time period (ref), indicating that knee abduction may play a minor role in ACL injury.” (Lines 239-242)

8.REVIEWER COMMENT

Line 236-238 - This is a great point - we do not know at what point this may become problematic, and why it makes it challenging to simply compare mean values.

AUTHORS RESPONSE

Thank you for this comment

9.REVIEWER COMMENT
Another factor that the authors might consider highlighting is the task that has been traditionally used in these studies - a drop vertical jump (particularly Double leg) off a box while fully attending to the task really does not challenge the LE in the same way as sport - so is this task simply too controlled to adequately expose tendencies towards valgus when in more unconstrained tasks (again, a threshold concern). Is this also a direction to be considered for future research?

AUTHORS RESPONSE AND ACTION

This is another great point. A few sentences regarding this is added to the end of this paragraph:

“Furthermore, most studies investigating knee abduction as a risk factor for ACL injury assess knee abduction during a drop vertical jump. The vertical drop jump is a bilateral task and may not reflect movements when injury occurs and does not seem to detect sex differences in knee abduction compared to other tasks (ref). Thus, it is possible that this task is not challenging enough to capture the amount of knee abduction that may be associated with injury. Other more challenging tasks, such as cutting tasks, should, therefore, be considered when evaluating knee abduction as a risk factor for ACL injury in future studies.” (lines 258-264)

A slight change was also made to the conclusion; “Future studies are warranted to investigate whether knee abduction during more demanding tasks, in combination with other risk factors and/or in other cohorts, such as recreational athletes, is associated with future primary as well as second ACL injury.” (Lines 334)

10.REVIEWER COMMENT

Line 278 - The limitations section is very thorough, critical and reasonable. I applaud the authors for their objectivity in this review.

AUTHORS RESPONSE

Again, thank you for your positive comments
Reviewer 3

Junsig Wang, PhD: The authors performed a systematic review and meta-analysis to determine whether knee abduction kinematics and kinetics were associated with risks of ACL injury. However, there are several major flaws in data synthesis that discourage me from accepting it from publication. Also, the manuscript needs a better rationale and story in the introduction with firm connections.

1.REVIEWER COMMENT

For table 1, more comprehensive and detailed results (e.g. demographic information and main findings) are needed for a better understanding of the previous findings.

AUTHORS RESPONSE AND ACTION

We are not sure of which demographic variables the reviewer wants us to add in Table 1. We have included year of publication, sample size, number of ACL injuries, age, sex, activity level, sports played, the task used to assess knee abduction, method to assess knee abduction, follow-up period and methodological quality of each individual study. The results of individual studies are commonly not reported in Tables including study characteristics when meta-analysis is applied and the results are reported across all studies [2-4]. We have, however, added Table 2, including the results of the 2 studies that included factors that were not eligible for meta-analysis.


2.REVIEWER COMMENT
This study included heterogeneous measures (2D and 3D motion analysis, visual observation), I did not see why these various measures were chosen and why the 2D motion analysis and visual observation have the same quality as 3D motion analysis. I don't think that the frontal kinematics from the 2D and visual observation are appropriate.

AUTHORS RESPONSE

Although 3D motion analysis is considered gold standard in assessing kinematics, this equipment is expensive and time consuming and is not always available in all research, sporting and clinical settings. We wanted to also include measures of knee abduction that may be more likely to be used in the clinics or as a screening measure in the sport setting. We agree that these measures may not assess exactly the same thing, although a systematic review and meta-analysis indicates that visual assessment of knee abduction is valid in both 3D and 2D [5]. We did, however, not find any studies that used visual observation to investigate if knee abduction is a risk factor for ACL injury and consequently no such studies are included in the present review. Most importantly, we did not pool studies using different methods to assess knee abduction (3D, 2D, visual) in our analysis. We do not think that including both 2D and 3D measures of knee abduction is a flaw of this review but rather a strength as this reflects current literature. Also, since we did not pool 2D and 3D measures and all results point in the same direction, i.e., knee abduction (assessed both with 2D and 3D) is not related to ACL injury, we do not believe that excluding 2D analysis from this review would make any difference for the result.


3. REVIEWER COMMENT

In the discussion, the author mentioned "Our conclusions are based on a large sample (1979 participants across 8 studies)". However, the study included extremely unbalanced samples between ACL and control groups. For example, the result of peak knee abduction moments was based on 54 ACLs vs. 1330 controls. Thus, this study did not show any better picture and still limits its generalizability. In addition, most studies (Smeets et al 2019; Dingenen et.al 2015; Räisänen et al. 2018; Nilstad et al. 2014) only included 4 female subjects for ACL (vs. up to 125 controls).
AUTHORS RESPONSE

We agree with the reviewer that the samples are not evenly distributed in the groups of ACL injury and controls. However, in this review we only included longitudinal, prospective studies on risk factors for ACL injury. Thus, it is not possible to have, or expect, equal samples of ACL injuries and controls, since the samples in these studies represent the real-life incidence of ACL injury in cohorts of athletes in different sports/activity level over time. We do believe that including longitudinal, prospective studies is a strength of this review, compared to also including cross-sectional studies where a more even distribution would be possible, but no causal relationship could be reported. As the reviewer points out, some of the individual studies report a small number of ACL injuries, but by pooling the studies this number rise to up to 72 in the separate analysis which may be compared to the 9 ACL injuries reported in the study by Hewett et.al that gave rise to the thesis that knee abduction was a major risk factor for ACL injury. Also, the sensitivity analysis revealed that the result in our review was generalizable across sexes, tasks, age and follow-up period (Online resource B). By pooling data across multiple studies (that may be subject to individual biases), our data are far more generalizable than any other published studies to date. This is part of the inherent design and purpose of meta-analyses and why they are the top of the evidence pyramid [6].


4.REVIEWER COMMENT

Due to a higher risk of ACL injury in women, this study should've focused on females, but it seems that some individual studies that did not consider the gender effect were included. Also, "the higher risk in females" was mentioned in the introduction, but this manuscript did not consider the gender differences.

AUTHORS RESPONSE AND ACTION

We agree with the reviewer that females have a higher proportional risk of sustaining an ACL injury. However, in absolute numbers, there are more males that sustain an ACL injury than females [7]. It is our opinion that male risk factors for ACL injury is largely overlooked. Thus, we chose to include articles on both men and women in this review. We found, however, only 1
article that included male participants. We did perform a sensitivity analysis excluding this study which did not alter the results. Consequently, focusing on females only will not have any impact on the result of this review. We would, therefore, prefer to keep the review as is. We do, however, have a sentence in the limitation regarding this;

“This review has some limitations. We pooled studies on females alone and those that included both men and women, had different follow-up periods as well as different weight-bearing tasks in some of our analyses. While these primary analyses may have masked associations between knee abduction and injury risk, our sensitivity analyses demonstrate that this is unlikely to be the case.” (lines xx)


5. REVIEWER COMMENT
In the figure 2, the medial knee displacements were from double-leg and single leg jump but I can't believe that the results during single and double leg vertical jump are comparable.

AUTHORS RESPONSE AND ACTION
We agree with the reviewer that there may be a difference between these two tests and that a single-leg drop may be more demanding than a double leg drop. The study on single-leg drop also reported a slightly greater difference (1 degree) between ACL-injured and controls than the articles on double leg drop, although not significant. Yet, our sensitivity analysis did not show any difference if the study on single leg drop was excluded (Online resource B). We have also added a paragraph regarding that double leg tests may not be demanding enough in the discussion.

“Furthermore, most studies investigating knee abduction as a risk factor for ACL injury assess knee abduction during a drop vertical jump. The vertical drop jump is a bilateral task and may not reflect movements when injury occurs and does not seem to detect sex differences in knee abduction compared to other tasks (ref). Thus, it is possible that this task is not challenging enough to capture the amount of knee abduction that may be associated with injury. Other more
challenging tasks, such as cutting tasks, should, therefore, be considered when evaluating knee abduction as a risk factor for ACL injury in future studies.” (Lines 258-264)

6.REVIEWER COMMENT

Overall, the data pooled from 2 and 3 studies were included in the meta-analysis for most variables, but the number of individual studies was also limited. As with ACL sample size, the pooled results were not generalizable

AUTHORS RESPONSE AND ACTION

As per answer to comment 3, in this systematic review with meta-analysis, we only included longitudinal, prospective studies on risk factors for ACL injury. Thus, it is not possible, or expected, to have equal samples of ACL injuries and controls, since the samples in these studies represent the real-life incidence of ACL injury in cohorts of athletes in different sports/activity level. We do think that this is a strength of this review compared to also including cross-sectional studies where a more even distribution would be possible, but no causal relationship could be reported. Moreover, the sensitivity analysis revealed that the result was generalizable across sexes, tasks, age and follow-up period (Online resource B). We systematically searched and screened the relevant literature according to internationally recognized guidelines [8]. Therefore, we argue that our findings (based on the synthesis of peer-reviewed prospective studies) are scientifically rigorous. By pooling data across multiple studies (that may be subject to individual biases), our data are far more generalizable than any other published studies to date. This is part of the inherent design and purpose of meta-analyses and why they are the top of the evidence pyramid [6].
