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.

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

1.REVIEWER COMMENT

- It is stated (and cited) that greater knee abduction angle is significantly greater 2 years after injury compared to baseline. I agree that it may be an increased risk for second injury, but I think it is important to state that the same potential ‘lack’ of motor control that existed with the primary injury is likely to persist and cause further risk for secondary injury.

Thus, what was an injury threshold initially, may be an even more pronounced threshold later as the motor control has not been adequately addressed.
AUTHORS RESPONSE AND ACTION

We agree with the reviewer regarding this and the sentence “Thus, it may be that knee abduction is more important for the risk of sustaining a second ACL injury than the risk of sustaining the primary ACL injury.” has been changed and now reads: “Thus, it is possible that persistent deficiencies in motor control after injury cause further risk of sustaining also a second ACL injury” (Lines 66-268)

2.REVIEWER COMMENT

- Further, a recent systematic review is cited [57] about bone bruising from MRI imaging to support a non-valgus positioning at the time of ACL injury. I somewhat disagree with the conclusions of this study and these details should be considered in the Discussion. Review of the data reported in this meta-analysis demonstrates that 66% (471/713) of the bruising occurred on the lateral tibial compartment and 72% (266/371) on the lateral femoral compartment. Clearly, if the majority of bruising is on the lateral compartment, this would indicate a prevalence of valgus position of the knee at impact with a force strong enough to cause bone bruising. If the valgus occurred after the ACL ruptured, the force would likely not be strong enough to bruise the bone with the knee 'buckling' into valgus afterward.

As I have mentioned earlier (and as is demonstrated in recent cadaveric studies), higher levels of ACL strain (and thus higher likelihood of ACL rupture) occur with both internal rotation and abduction of the tibia. These combined motions would account for the bone bruises on the lateral compartments and with shifts in the 'antero-posterior' aspects of the compartments demonstrated in the data. Once again, not all non-contact injuries are the same. Some will occur with hyperextension of the knee. Some will occur with internal rotation. Some will occur with knee abduction. Most will be multifactorial. However, there is a plethora of objective data that continues to point to a few key kinetics / kinematics that account for the majority of these injuries (thus, risk factors). These risk factors include: knee abduction, internal rotation, and lower knee flexion.

Thus, even though this citation concludes that the knee abduction occurs after the ACL rupture event, I would argue that the data clearly demonstrates that a knee abduction IS present at the time of ACL rupture.
AUTHORS RESPONSE AND ACTION

We appreciate the reviewer’s insight here. In order to present a balanced view of the different interpretations of the data, we have added the following sentence to this paragraph of the discussion: “It should, however, be noted that in the same systematic review a high number (approx. 70%) of bone bruises were located on the lateral side, which could indicate presence of knee abduction at the time of injury.” (Lines 259 – 262)

Reviewer 2

No comments

Reviewer 3

1.REVIEWER COMMENT

Table 1. missed important details about demographics such as weight, height, and BMI. The authors mentioned, "The results of individual studies are commonly not reported on Tables including studies [2-4]." I strongly disagree with the comment since a main goal of the systematic review is to provide a great overview of previous findings and thus the tables should involve main findings of each study with sufficient details [1-6]. It is very critical for readers to understand the previous studies related to this topic.

AUTHORS RESPONSE AND ACTION

Weight, height and BMI are now added to Table 1. Although all results from each individual study are clearly reported in the figures, a brief summary of the result of each study is now also added to Table 1.

2.REVIEWER COMMENT

Although the different measures (2D and 3D) were not used to pool data, the authors did interpret the results of different measures for the same aspect of the risk of ACL injury, which came from the assumption that these methods would not result in any differences in injury mechanisms. Thus, this study is not inconclusive due to the heterogeneous variables.
AUTHORS RESPONSE AND ACTION

Unfortunately, we have difficulties following this comment, but have made an attempt to respond. If one of these measures, e.g., 3D abduction would have been a risk factor and not the other, e.g., 2D abduction, a more extensive discussion regarding the differences in these variables would have been warranted. However, since none of the investigated variables (2D, 3D, MKD) during any time point (IC, peak, excursion) were found to be related to future injury we believe that this has little importance for the results of this review. A paragraph regarding this, however, is added to the limitations and reads:

“We included studies that employed differing methodologies to quantify knee joint mechanics. Of note, knee abduction angles were obtained with both 2D and 3D motion analysis systems; knee abduction moments were exclusively obtained with 3D motion analysis. While there is evidence that knee abduction angles measured in 2D are strongly correlated with knee abduction measured in 3D [1-3], the 2D measure also incorporates components of sagittal and transverse plane rotation and thus our findings with regard to 2D knee abduction kinematics are likely, to a small extent, to reflect the underlying sagittal and transverse plane knee kinematics. In light of these differences we did not pool the results from 2D and 3D studies. Yet, given the strong relationship between 2D and 3D knee abduction, taken together these results both support the absence of a predictive effect of baseline knee abduction on ACL injury development.” (Lines 303-314)

3.REVIEWER COMMENT

I understand that involved studies are valuable and followed participants for the potential ACL injuries, and thus it might be inevitable to have unbalanced samples. However, I don't think it is not a reason for pooling data to get better generalizability. First, the author insisted that an increase in the post-ACL subjects by pooling data is a strength of this study. However, I don't think merely increasing samples could strengthen the current study. Thorlund et al [7] have warned that if meta-analyses are performed too early, before enough studies are available, there is a danger that incorrect conclusions may be drawn. Thus, it is recommended that we be careful when interpreting the results from underpowered meta-analysis, and thus extremely underpowered meta-analysis should not be performed.
Also, I found critical errors in the results of I2. For example, the I2 value for Figure 3 (peak knee abduction moment) was wrong as compared to my calculation (I2 = about 90%, extremely heterogeneous). The I2 cannot be < 0.001% when seeing the forest plot of Figure 3 so now I am suspecting all I2 values across the results. Again, the substantial heterogeneity (I2 = 90%) may indicate that pooling studies would not strengthen the study.

AUTHORS RESPONSE AND ACTION

We have added sentences in the limitation regarding sample size and overestimation of the results along with the suggested reference.

The sentence reads; “Moreover, some of the meta-analysis included a relatively low number of individuals with ACL injury, e.g., the analysis on 2D peak knee abduction (n=8). Performing meta-analysis with a low number of events may increase the risk of overestimating the effect [4].” (Lines 315-317)

Regarding I2 values: We thank the reviewer for highlighting this. We have revisited the data and have also been in contact with our statistical advisor and the meta-analysis software support. It turns out that the I2 value the software report (and consequently the values we reported) under the random effect model is representing the I2 when Q is re-calculated after the between study variance has been taken into account. The reviewer’s calculation is, thus, correct and we have corrected all the I2 values in our analysis and we truly apologize for this misconception. Q is always computed under the fixed effect model and represents the dispersion that is not explained by the model, which makes sense for fixed effect. However, as the reviewer points out, some heterogeneity between the included studies are expected. Thus, we used a random effect model in our analysis. This is clearly described on lines 126-129; “A random effect model was used due to expected heterogeneity between studies, such as task, follow-up duration, gender, age, sport, and activity level. 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 [5]”. In contrast to the fixed effect model, under the random effect model, the between study variance (as explained by the I2 statistics) is incorporated in the model and is, thus, taken into account in the presented effect measure.
We have now added a sentence in the limitations; “Furthermore, our heterogeneity analysis using I2 statistics revealed mostly low to moderate heterogeneity between studies. The analysis for peak knee abduction moment was, however, associated with high heterogeneity. To account for expected heterogeneity, we have performed all analysis under the random effect model that incorporates both within study and between study variance in the analysis. It has also been suggested that the I2 statistics may be subject to bias when only a small amount of studies are included in the analysis [6]. Thus, the I2 statistics presented in this review should be interpreted with caution.” (Lines 317-323)

4.REVIEWER COMMENT

As mentioned before, the data pooled from 2-3 underpowered studies would not improve generalizability because the data synthesis showed substantial heterogeneity across the studies. Also, I am wondering how meaningful the results of the sensitivity analysis are when considering underpowered results and biased samples.

AUTHORS RESPONSE AND ACTION

As per answer to comment 3, we have now added a paragraph in the Discussion acknowledging this potential limitation: “Moreover, some of the meta-analysis included a relatively low number of individuals with ACL injury, e.g., the analysis on 2D peak knee abduction (n=8). Performing meta-analysis with a low number of events may increase the risk of overestimating the effect [4]. Furthermore, our heterogeneity analysis using I2 statistics revealed mostly low to moderate heterogeneity between studies. The analysis for peak knee abduction moment was, however, associated with high heterogeneity. To account for expected heterogeneity, we have performed all analysis under the random effect model that incorporates both within study and between study variance in the analysis. It has also been suggested that the I2 statistics may be subject to bias when only a small amount of studies are included in the analysis [6]. Thus, the I2 statistics presented in this review should be interpreted with caution.” (Lines 314-323)

5.REVIEWER COMMENT

The mean difference is not the effect size. Please clarify why the authors used the mean difference for the meta-analysis instead of the effect size.
AUTHORS RESPONSE AND ACTION

Although the word “effect size” is commonly used for describing different effect measures in meta-analysis [5], to avoid confusion, we have replaced the word “effect size” with “effect measure” throughout the manuscript. The use of the raw mean difference and associated confidence interval, as opposed to the standardized difference in mean (as we believe the reviewer refers to as effect size), is preferable when the outcome is measured on a familiar scale, such as degrees of knee abduction at baseline, and will as such make more sense and be much easier to interpret. Had the outcome been assessed on an unfamiliar or arbitrary scale, we agree that the standardized difference in mean would be a better fit. There are also no differences in the results if standardized difference in mean was used instead of the raw mean difference.


6. von Hippel PT. The heterogeneity statistic I(2) can be biased in small meta-analyses. BMC medical research methodology. 2015 Apr 14;15:35.