Author’s response to reviews

Title: Cross-sectional associations between variations in ankle shape by statistical shape modeling, injury history, and race: the Johnston County Osteoarthritis Project

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Author’s response to reviews:

RESPONSE TO REVIEWERS

(Please see attached pdf version for included figures)

Reviewer #1: The paper is well written and organized. The methods are clearly stated and the discussion of the results are detailed and denote a clear perspective on the topic and the impact of this research. There are however some points that should be assessed in the reviewer's opinion.

Author response: Thank you very much for your comments and suggestions.

1 - It is not proper to speak of ankle shape: this terminology should be better explained or modified. While a bone as a shape, a joint is described by the relative position and orientation, or briefly configuration, of all the bones that participate to the articulation. The articular configuration may change according to the joint mobility. As a result, the bones relative geometry and thus the shape of the ankle is not uniquely defined.
Author response: Thank you for this comment. We agree that the terminology is not precise, but also want to use something brief in the title and abstract. We have further defined our use of the term “ankle shape” for the purposes of this manuscript as soon as possible in the introduction.

Changes made: Added to Introduction, top of page 4: “For the purposes of this manuscript, “ankle shape” refers to the radiographic two dimensional shapes and relationships (alignment) between shapes, of the distal tibia, talus, calcaneus, and navicular in the lateral view (see also Figure 1).”

2 - How is it granted that the joint configurations of the considered participants are comparable?

When assessing differences in the articular geometry among individuals, a reference configuration must be established and kept during the acquisition of all the data, in order to exclude the effect of joint mobility from the analysis. In this work it seems that the scanning ankle configuration is defined simply as the standing position. Is opinion of the reviewer that this is not sufficient to define uniquely the joint configuration. It is in fact possible to stand with different flexion of the ankle. In this condition, the result of the analysis cannot completely separate postural from geometrical correlation with ankle injury. Indeed, differences associated with mode 1 could reflect postural variation.

Author response: We agree that standardization of positioning is a limitation in this large cohort, although every reasonable attempt is made to achieve this goal. Proper positioning is assessed by the consistent projection of the talar dome as a single cortical surface on the lateral image and by the symmetric tibiotalofibular mortise width on the mortise oblique image. It is of course possible that some of the “ankle shape” variation is due to differences in weight bearing or postural variation.

Changes made: 1) Added detail to methods regarding radiograph acquisition on page 5: “Lateral views of each ankle were obtained separately with equal weight-bearing on each limb, the foot parallel to the cassette, and the x-ray tube angled at 90 degrees and centered at the base of the first metatarsal (distance=1 meter).” ; 2) Added to limitations on page 9: “…we selected and modeled the shape of the ankle from lateral radiographs…differences in positioning could contribute to the observed variation.”

3 - How is the scanning plane defined? Similarly to the definition of the joint configuration, also the choice of the scanning plane may affect the measure, determining how the three-dimensional shape of the bones is projected on a two dimensional space. It should thus be clarified how the subjects are placed with the X-ray scanner.

Author response: Please see above response and changes to the description of x-ray acquisition.

4 - What is the impact of the inter/intra-reader reproducibility on the proposed measure?

With respect to the dimension of the ankle, having 40% of the points defining the bones shape differing of more than 1 mm between two observers can considerably change how the bones shape is reconstructed. The impact of these differences in term of mode variation should be
assessed. In particular, two points showing a distance of 1mm in the projecting plane can be much more apart in the 3D space.

Author response: We agree that we are not able to capture the 3 dimensional variability here, so are only attempting to quantify the 2D variation from landmark point placement. We carefully positioned subjects as noted above to reduce variability due to positioning. Again, we are not “reconstructing” any 3D shape, only the 2D shape as shown in Figure 1 and clarified above in R1 Q1. The mean difference between points between readers was 1mm, and for one reader at 2 times was <1mm; these small differences would not be anticipated to greatly affect the mode scores. While one way to address this would be to generate mode scores for the different readers for the n=20 reproducibility films, these models would likely show more variability due to the small numbers (as the shape model would be based on only 20 films in each case, vs. n=213 for the main analysis). However, it is possible to compare Mode 1 between readers as this mode alone explains more than 30% of the shape variance for the reproducibility set, as shown in the table below.

Table. Intra-class correlation coefficients for mode 1

<table>
<thead>
<tr>
<th></th>
<th>Reader 1 vs. Reader 2</th>
<th>Reader 2 vs. Reader 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inter-reader</td>
<td>Intra-reader</td>
</tr>
<tr>
<td>ICC (95% CI)</td>
<td>0.97 (0.93, 0.99)</td>
<td>0.99 (0.98, 0.99)</td>
</tr>
</tbody>
</table>

Changes made: Bottom of page 5, added: “Twenty randomly selected films were read by the same reader (SL) or two readers (SL and AEN) one week apart to establish intra- and inter-reader repeatability, as well as intraclass correlation coefficients (ICC) for mode 1.” Bottom of page 6-top of page 7, edited as: “Inter-reader reproducibility was shown as 53% of points placed within 1mm, 88% within 1.5mm, and 100% within 2mm by two independent readers (mean difference 1mm). For intra-reader repeatability, 63% of points were placed within 1mm, 90% within 1.5mm, and 96% within 2mm by one reader (mean difference <1mm). For mode 1, which explained >30% of the total variance for these 20 radiographic shapes, both the inter-reader and intra-reader ICCs were greater than 0.97.

As a minor comment, it would be of interest to assess if there is correlation with activity/sedentary of the subjects.

Author response: Thank you for this comment. Unfortunately we do not have objective data such as accelerometry in this cohort, but we do have some self-reported PA data. We added an additional variable reflecting whether a participant met the weekly physical activity recommendations using the BRFSS (in this sample, 33 individuals, or 16%, met the recommended PA per week) and the results did not change substantially compared to OR2 in Table 2. For this output, q00_kl is the baseline KL grade, Sx=baseline symptoms, and RecPA is a binary variable indicating whether or not the participant was meeting PA recommendations. The OR for the PA variable was not significant, and the estimates for the mode scores did not change with its addition to the model.
Changes made: Page 5 methods, added: “).  In a sensitivity analysis, the contribution of physical activity was assessed using a binary variable, “0” if not meeting physical activity guidelines and “1” if meeting this level of physical activity [1].” Page 7, results added: “No differences were seen when additional adjustment was made for physical activity (data not shown).”

6 - As a final suggestion, there are several measure to evaluate quantitatively joint congruence. This quantification could improve the causality insight of this analysis. Among the many, the measure presented in [1] was explicitly developed for the analysis of the ankle joint. It can be applied also when cartilage information are missing [2] and with some modification could reasonably be adapted for the planar analysis.


Author response: Thank you for this insightful and interesting comment. The cited studies are based upon high accuracy 3D measurement systems, and therefore provide more accurate measures for assessment of congruence. While we agree that such a measure would be of interest in our work, as we have only standard clinical lateral foot x-rays, it is not immediately clear how this more detailed analysis could be adapted and applied in the context of the current work. We are excited to explore this, however, in ongoing research projects utilizing more advanced methodology.

Changes made: added to page 10 section on limitations and future directions: “and further studies using 3-dimensional assessments (incorporating elastic foundation or finite element based modeling [2, 3]) could provide insight into some of our preliminary observations.”

Reviewer #2:

This study presents a reasonably novel approach to evaluating the relationships between 2D ankle shape and injury/race. However, I suggest that it is difficult to draw conclusions from the results given the uncertainty in causation of joint shape variation and the period of time between injury and capture of joint shape.

Author response. Thank you very much for your comments. We certainly agree that no conclusion regarding causality can be made from this cross-sectional analysis, and have emphasized this in the limitations on page 10 (“Finally, this analysis is cross-sectional, so we are not able to address causality. That is, did the injury alter the shape (and potentially predispose the ankle to later OA), or was the shape already abnormal and predisposed the ankle to injury (and potentially later OA) in the first place?”), and by including the cross-sectional nature of our work in the title. This is the first attempt at 2D shape analysis in this setting and we hope to build upon this further with longitudinal data and other imaging modalities in the future.
Specific comments

1. Page 3, lines 12-14

The intended meaning of the phrase "changing the ability of joint tissues to control forces" is not clear. Please clarify.

Author response/Changes made: We are sorry for any confusion. For clarity, the sentence was changed to read “Injuries likely accelerate progression to OA in weight bearing joints by altering joint alignment and biomechanics, thereby changing the magnitudes and locations of peak joint forces during movements, resulting in abnormal loading of the cartilage, subchondral bone, and ligamentous structures.”

2. Page 3, lines 48-51

Are the authors referring to changes in the shape of the bones within the joint or in the relative alignment and orientation of the bones within the joint? It seems more likely that injury would lead to compensatory reactions, which would lead to variation in biomechanics, than change in joint shape. Please clarify.

Author response/Changes made: Thank you for noting this, please see our response to R1, Q1 above along with changes made for clarification.

3. Page 4, lines 4

It is not clear that Dr. Gregory pioneered statistical shape modeling, as Davies, Cootes, Twinning, Taylor, and others have published earlier studies. Please clarify.

Author response: Thank you for this observation. We meant to say that Dr. Gregory pioneered the use of this method for this purpose, and have tried to clarify this in the text.

Changes made: Sentence changed to read: “Statistical Shape Modeling (SSM) was developed by Cootes, et. al,[4] as a way of segmenting images. The application of SSM as a tool for quantifying bone shape was pioneered by Dr. Gregory,[5] to model variations in hip shape which are associated with risk of hip OA.[5-7]”

4. Page 4, lines 42

It seems likely that sprains and fracture would have very different effects on joint mechanics and a different relationship to mechanics and loading conditions. Please discuss.

Author response: We certainly agree with this important observation, and have tried to acknowledge this in the limitations section on page 9-10: “Participants were asked a fairly general question regarding prior ankle injury, so we do not have detailed data regarding the type and severity of that injury. Our definition of ankle injury may have captured milder injuries
along with those that were more severe, potentially attenuating the observed associations if only severe injuries are related to joint shape.”

Changes made: We have re-written the above sentence in the limitations section as follows: “Participants were asked a fairly general question regarding prior ankle injury, so we do not have detailed data about aspects of the injury that may be more or less likely to alter joint mechanics, such as type of injury (e.g., fracture vs. sprain), joint tissues involved, and severity of the injury. Our definition of ankle injury may have captured milder injuries along with those that were more severe, potentially attenuating the observed associations if only severe injuries are related to joint shape.”

5. Page 5, line 20

Were landmarks positions corresponding or adjusted to be corresponding, in the sense of being located at the same anatomical points over the set of ankles? Please clarify.

Author response: As shown in Figure 1, where possible, the points were located over identifiable landmarks, such as point 6 which was at the center of the curve of the distal tibia, 3 and 9 which were at the most inferior points of the tibial curve, point 18 which was at the highest point of the talar dome, etc. In locations where no clear landmark exists, the points are placed equidistant (as for points 4,5, 7, and 8 along the distal tibia). A detailed guide was generated prior to reading and reviewed by the readers for clarity; this guide was used to assist with placement of the points.

Changes made: Added to page 5: “The location of these landmark points was detailed in an example image along with descriptive text (e.g. point “18” was to be at the center of the top of the talar dome, see figure 1) which was used during training and reading to standardize point placement.”

6. Page 5, line 45

What was the basis for selecting modes describing (only) 80% of the variability in the set of ankles? Please clarify.

Author response: This is somewhat of an arbitrary choice (not just here, but for PCA in general), which was made to balance the inclusion of appropriate variability and yet maintain a parsimonious model. The 19 modes included together explain 80% of variability in the shape data, and each individually explained at least 1% of the variability, while the higher modes were <1%. Another 14 modes would need to be included to reach 90% of variability, which results in unstable models for analyses. Additionally, examination of the scree plot, where the blue line is cumulative variance and the orange line is individual mode variance, shows a reasonable cut point at 19 modes (vertical black line).

Changes made: Added to methods top of page 6: “The scores for modes which together explained 80% of the shape variance (n=19), and for which each mode individually explained at
least 1% of the variance, were retained for modeling in order to obtain a parsimonious and stable model.”


How would the reported levels of inter- and intra-reader variability affect the result? Please provide context.

Author response/changes made: Please see response to R1 Q4.

8. Page 7, lines 33-37 “Currently, different modes of SSM can only be qualitatively assessed by visualizing variations in the modes as no objective comparison measures exist.”

This phrase is not clear. A google search reveals a number of quantitative measures of variation between surface shape and surface orientation or relative surface orientation. Please clarify.

Author response: We have focused on 2D rather than 3D shape, and thus are not dealing with surfaces or their relative orientation, but rather a representation of the 2D outlines of the bone shape. This sentence is referring to the lack of a standardized reference cohort for these measures, such that mode 2 in this study is very unlikely to be the same as mode 2 in another study.

Changes made: We rewrote this sentence for clarity: “Currently, different modes of SSM can only be qualitatively assessed by visualizing variations in the modes, as there is no standardized reference cohort for joint shape, and thus the variations seen are specific to this population.”

9. Page 7, line 42

Please describe the "global shift."

Author response: This was an attempt to qualitatively describe the visual appearance of mode 1 as shown in Figure 2. As noted in Q8 above, there is no standardized reference cohort or established quantitative way to compare the shapes from SSM. The phrase “global shift” was chosen since all of the bones (tibia, anteriorly; navicular, superiorly, talus, superiorly, and calcaneus, inferiorly) are shifted when comparing the +2SD to the mean shape or the -2SD shape.

Changes made: Sentence re-written as: “In particular, mode 1 demonstrates an apparent shift in relative alignment that affects all 3 (tibiotalar, talonavicular, and subtalar) joints visualized on the lateral ankle radiographs.”

10. Page 8, lines 4-9

Is the work presented in the abstract based on a different cohort than that of the current paper? It is not clear that this sentence adds value to the paper. Please clarify or remove.

Changes made: Reference #3 updated.

11. Page 10, line 36

The meaning of "easier … models" is not clear. Please clarify. Also, it is not clear how predicted stresses obtained from 2D or 3D models would affect clinical practice. Please clarify.

Author response: The sentence has been changed as noted below. We think that it is possible, in a manner analogous to the use of finite element modeling for hip fracture prediction (see a few references below), that shape modeling could be used to identify higher risk groups, either for clinical trials or for early lifestyle interventions, particularly if this could be done from a 2D radiograph rather than a more expensive method requiring 3D imaging such as MR or CT.


Changes made: We replaced “cheaper, easier” in this sentence with “simpler.”

13. Page 10, lines 47-52

This sentence is not useful as a conclusion. Please remove or clarify.

Author response/Changes made: The sentence was divided for clarity: “These novel findings may indicate a change in ankle morphology following injury, or that ankle morphology predisposes to injury. In either case ankle shape could be an important factor in the development of ankle OA.”