Author's response to reviews

Title: Forefoot pathology in rheumatoid arthritis identified with ultrasound may not localise to areas of highest pressure: cohort observations at baseline and twelve months

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Author's response to reviews: see over
Dear, Dr Menz,

Re: "Ultrasound definitions of forefoot pathology in rheumatoid arthritis are out of phase with high pressure areas: cohort observations at baseline and twelve months."

We submitted the above manuscript for consideration of publication within ‘the Journal of Foot and Ankle Research’ as an original article and would like to take this opportunity to thank the reviewers for their continued very helpful and favourable comments. We have addressed the comments and queries raised by the reviewer a follows:

**Major Compulsory Revisions**

1. Control group – the participants were not matched for age, which potentially has a significant impact on the footwear worn and their gait, which may influence peak pressures.

Due to the nature of the large dataset we have sought advice on statistical analyses throughout the study. David Culliford, the second author, is a medical statistician based in the Faculty of Medicine, University of Southampton and the Musculoskeletal Biomedical Research Unit, University of Oxford. We acknowledge the reviewer’s comments that the control participants were not matched for age, however we did perform additional statistical analyses to test this and had added the statement: “to assess whether any differences found could be due to the confounding influences of age and weight, an analysis of variance (ANOVA) was performed. After adjustment for age and weight the results remained significant (p<0.001)”. See pg 15.

We also included the following statement to acknowledge the influence of not controlling for footwear: “As a response to this we performed additional analyses and an analysis of variance to assess the confounding influences of footwear. We found that the location of peak foot pressure remained predominantly medial in all footwear types. However, at twelve months, for the left foot only those wearing..."
unsuitable shoes had higher peak pressure values. In this study therefore, it is possible that for the twelve month left foot data, peak pressures for the whole group may be inflated”. See pg 21.

1. **Justification for inclusion of the control group is required.**

2. **I am unsure of the need to follow-up patients over two time points, what benefit does this add to this observational study?**

To further clarify this within the introduction to the methods section, we have added the statement:

“The optimal research design was considered to be a longitudinal cohort study in which the foot pathology and foot pressure characteristics of a heterogenous group of patients who have RA were assessed at two time points. The use of two cross sectional time points within the same population allows for better understanding of the effect of variability in pathophysiology of RA within the foot over time. Embedded within the design of study was a case reference study, to enable comparisons of baseline demographic and clinical characteristics of the RA study sample with healthy control participants”. See pg 5

And also added within discussion of strengths and limitations:

“There are several strengths within this study that include a longitudinal cohort follow up design, the large sample size, and that it was a pragmatic clinical study representative of secondary care in the UK. A few potential limitations should also be considered”. See pg 21

3. **Footwear – how did you group footwear, what was the criteria? It is also unclear if each patient wore the same pair of shoes at baseline and follow-up, this has the potential to influence peak pressure measurement readings. Further justification is required.**

To clarify this within the methods section we have added:

“Footwear was assessed and categorised as either prescribed therapeutic footwear or retail (shop bought) footwear. Footwear was further noted as being suitable or not suitable according to fit and style (e.g. court styles and high heel/stiletto shoes were deemed unsuitable). Due to the high numbers of participants and the highly emotive factors associated with both prescribed therapeutic and retail footwear [4, 20, 21] it was neither economically feasible nor clinically desirable to standardise footwear between visits. Participants were instructed to attend each visit wearing comfortable flat shoes that they wore the most at the time”. See pgs 7 & 8

Within the discussion we have also expanded our consideration of the influences of footwear against our aim:

“The literature on plantar foot pressure measurement in RA suggests that the methods may be feasible [2] however, their ability to discriminate in clinical practice has yet to be determined. Our aim was to therefore examine the forefoot pathology of patients who had RA at two cross sectional time points relevant to their usual daily activities / habits to mimic routine clinical practice assessments. It was not feasible to control for footwear over such a long period of time and in such a large population which may be controversial”. See pg 21

4. **What impact does the intermetatarsal bursal hypertrophy have on the plantar pressure? It would be interesting to compare jt synovitis, erosions, IM and SM hypertrophy individually against peak pressures which would help us understand the cause and aid treatment interventions.**

We agree with the reviewer that this is indeed an interesting concept that is worthy of further investigation and have included the following statement within our considerations of strengths and limitations:
Finally, for pragmatic analysis we categorised the forefoot nominally into either medial or lateral segments and also amalgamated the foot pathology data due to low counts in these categories, thus caution is required in interpreting this observational data. No further statistical inferences could be made from this current analysis and we recommend that future work in this area would be of value, particularly in the use of US detectable foot pathology and interface foot–shoe pressure pattern identification and cluster analysis [37]. Ideally, future work could focus on whether it is the impact of discrete pathology, such as IM or SM bursal hypertrophy, MTP joint synovial hypertrophy or tenosynovitis that may be associated with high plantar forefoot pressures or whether there is an ‘optimal level’ of forefoot pathology that impacts on plantar foot pressures”. See pg 22.

Minor essential revisions

Background Pg 4
1. In the first sentence more relevant and recent references are available.
Thank you for highlighting this, these have now been updated.

2. End of the first paragraph – where are the US detectable soft tissue pathologies?
This has been amended

Methods pg 7
3. First paragraph – Was DAS28–ESR carried out on the same day as the US, if not how relevant is it?
We chose to use the DAS 28 ESR values as, although they give similar information about non–specific inflammation, CRP appears and disappears more quickly than changes in ESR such that ESR levels may remain elevated for a longer period. Therefore we only included DAS28–ESR scores that had been recorded within one month of the participants’ visit. We have now noted this within the methods section.

4. 2nd paragraph – Could you have used the Platto Structural Index?
The reviewer raises an interesting point here and within the conceptual stages of the study we did consider the use of the foot structural index (FSI) proposed by Platto in 1991 that was advocated as a simple scoring method for clinical practice. However, to date and to our knowledge the FSI has not been robustly validated or extensively used in clinical practice. We therefore decided to use the domains advised by the UK clinical assessment guidelines for the rheumatoid foot (references 5 & 6) that are based on the domains of the FSI for documentation of observations, but not used as a score.

5. Final paragraph – Responses to LFIS are true or not true, minimally important clinical differences scores have not been established for the LFIS yet.
Thank you for highlighting this, the reference has now been altered to the paper by Turner et al 2007 which indicates <4 as an exclusion criteria for an RCT on podiatry interventions in RA.

“Responses to each question are dichotomized as yes or no and scoring is a simple tally for each domain [22] with 4 or less suggested to represent good foot health and scores higher than 4 representing poor foot health [23]”. See pg 8.

Editors comments
All formatting requests have been amended. For point “7. Figures (please crop and remove any excess white space)” we were not sure whether you meant all figures and tried to crop all but they appear in the word document as already cropped?

Thank you, once again, for considering our manuscript and please do not hesitate to contact, should you
require any further detail on this

Yours sincerely

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