Author’s response to reviews

Title: Biomarkers of cardiovascular risk across phenotypes of osteoarthritis

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Reviewer reports:

Zoltan Szekanecz (Reviewer 1): This is an interesting piece of work. OA has been associated with increased CV risk. In this study authors assess OA subsets in relation to arterial stiffness. Thank you for these comments.

This is a simple study, only stiffness parameters (AIx, PWV) were evaluated in relation to OA subsets. Some comments
1. Table 1 contains information on smoking and BMI. Stiffness results should be correlated with these lifestyle-related parameters. Thank you, we agree. The association between all variables presented in table 1 and the dependent variables (CVD vascular biomarkers) were explored in age and gender adjusted models. The final multivariate models, presented in figures 1b and 2b were thus adjusted for significant covariates (p <0.05). The AIx models were also adjusted for smoking, the PWV models were also adjusted for BMI and CRP. None of the covariates were associated with ABI. We acknowledge that the statistical methods should be elaborated and we have therefore added this information page 8, line 180.

2. Authors found correlations in hand OA only. Hand OA is sometimes more inflammatory and may resemble RA. Did the authors correlate stiffness with inflammatory markers, such as CRP and ESR? Please refer to the answer above, CRP was added to the models and information regarding the association between CRP and the vascular biomarkers has been added to table 2.

Staja Booker (Reviewer 2): Overall, this study is well-done and due diligence was given to the measurement of study variables and in validating findings. This topic is important given that OA and CVD are two common and potentially debilitating issues. Thank you for these comments With that said, there are several matters that the authors should attend to.

1. The introduction could be strengthened by providing statistics on prevalence rate of OA and CV concurrently. We agree that this is relevant. We have added this information in the background, lines 67-70 and 73-4.

2. Pg 2, line 79- "ankel" is misspelled. Sorry, we have now corrected this, line 86.3.

3. Pg. 7, line 143-144: Please clarify if the statement "258 (70.5%), 257 (70.2%) and 174 (47.5 %) persons respectively" refers to those with OA, Oslo controls, and UK controls respectively. This sentence has now been rewritten and clarified, line 153-155.

4. Please state the design of this study in the methods section- case-control? We agree that this information is important and have added the information under “Statistics” line 161.

5. Authors should provide metrics (range of scores- what is considered normal vs. high) for interpretation of measures (PWV, AIx, ABI) in the methods so that readers can interpret figures 1a-2b. For example, what does an ABI of 1.25 mean? Yes, we agree that this would aid the interpretation of our results. We have now added this information under the introduction, line 83-90.

6. Since missing data were not imputed, were they excluded from analysis? How did this affect power- any power calculations? We acknowledge that missing PWA will have reduced the power in our analyses, we do however believe that the study has sufficient power. It is to our knowledge the largest study of vascular biomarkers in OA.

   AIx was available in 91 patients with hand OA, in 96 with lower limb OA and in 71 patients with general OA. Using the mean AIx values identified, the cohort size was large enough to identify a 10-15% difference in AIx with 80% power and 5% α between each OA phenotype and OPC. For the comparison between OA and UKPC smaller difference could be detected.
PWV was available in 91 patients with hand OA, 96 with lower limb OA and in 70, patients with general OA. Using the mean values found in the study the cohort size should be sufficient to identify a clinically significant difference of 1 m/s between cohorts with a power of 80% and 5% $\alpha$.

ABI was available in 64 patients with hand OA, 57 with lower limb OA and 54 patients with general OA. Using the mean values here the cohort size was sufficient to identify a difference of 0.1 with 80% power and 5% $\alpha$.

7. List age and sex as co-variates in the methods section "Covariates" The covariates paragraph has now been revised, line 162.

8. I appreciate the authors diligence in using objective measures to model arterial stiffening; however, did the authors assess for cardiovascular conditions, such as hypertension, hypercholesterolemia, history of myocardial infarction or other CV issues? It could be that diagnoses of CV conditions are more related to OA than actual arterial stiffening. Thank you for this comment. This information was not available in the data-set used for this study. We also considered the vascular biomarkers to be of interest in their own right.

9. The authors should provide more discussion on the possible mechanistic pathways by which CVD risk is related to hand OA specifically. Currently the authors cite studies to support greater CVD risk in persons with hand OA but stop short of explaining why this is observed in only hand OA vs. knee/hip OA. The purpose of discussion sections are not only to provide supporting evidence but to "explain, expound, and explicate" the findings. Thank you for this challenge. We have added a paragraph which elaborates on the possible mechanistic pathways that may explain why AIx is particularly increased in hand OA, line 243-249.

10. What are the clinical implications of this study? This is indeed important, and we have added more information concerning clinical relevance, line 250-255.

11. Please provide labels for vertical axis for Figures 1a-2b. Also add "unadjusted models" to the figures 1a and 2a title. Thank you for pointing this out. The axes labels have now been added to the figure legends at the end of the manuscript. We have also edited the title of the figures. 1a and 2a are age and gender adjusted models, whereas 1b and 2b are fully adjusted models.

12. The following covariates, Use of NSAIDs and heart rate, are not reported in Table 1 or Supplementary Table 1. Information on all covariates has now been added to all tables.