Author’s response to reviews

Title: Prevalence and associated factors of subclinical atherosclerosis in rheumatoid arthritis at the university hospital of Kinshasa.

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Detailed answers to the reviewers of manuscript BRHM-D-17-00039

Prevalence and associated factors of subclinical atherosclerosis in rheumatoid arthritis at the university hospital of Kinshasa.

Editor Comments:

As you can see from the reviewer comments there was a general interest in your study, but still several significant points that limit the publication of your manuscript in its current form. In particular I would emphasize, that you address methodological concerns raised by reviewer 1. The small sample size limits the capability of your models to adjust for potential predictors. In this case using too many independent predictors in one model would lead to over adjustment.
A/ we thank the editor for his useful comments. We have tried to address the points raised by reviewer 1 as much as possible below and in the manuscript.

I would very much welcome if you could outline your analyses more detailed and stepwise in the methods section of your manuscript. It is also advisable to explain, why you decided to keep or not keep variables in a model.

A/ as suggested by reviewer 1 we have added a detailed statistical analysis plan, see page 4, statistical section, and line 5.

Since your patients had a wide range of disease duration, a suggestion of mine would be to perform separate analyses, after dividing them in tertiles.

A/ thank you for this suggestion. We looked again at our data taking into account different age groups. No significant differences were found depending on the age group and as the general conclusion was not changed we did not add this information in the text.

Please also consider to use different definitions of severe disease as suggested by reviewer 2.

A/ as suggested by reviewer 2 we did reconsider the definition of severe disease (see section: definitions of some concepts: page 4, line 5).

How do you explain that the majority of your RA patients is seronegative?

A/ as we reported previously, probably as a consequence of a different genetic background compared to the Western World, rheumatoid factor is less prevalent in patients with rheumatoid arthritis in the DRC.


I invite you to address all points raised thoroughly and rework your manuscript accordingly and resubmit a tracked and clean version.

A/ Thank you for giving us the opportunity to resubmit our work in a revised version.

We add a clean version and a version with tracked.

Reviewer reports:

Major comments:

1. Would re-word "determinants" as "associations" in this small cross-sectional study. The study design cannot find determinants. The entire study is limited related to the small sample size and cross-sectional nature. While mostly consistent with prior literature, there is limited novelty.

A/ we agree with the reviewer that our study does not allow us to report a causal link between the different factors studied and the presence of atherosclerosis. Therefore we changed the title of the article

2. There are so few outcomes that the multivariable model in Table 8 is unreliable with extremely wide confidence intervals and very low cell sizes. For example, diabetes has a 95%CI of 0.3 to 180 so they have neither confirmed nor eliminated this as risk factor for atherosclerosis.

A/ we thank the reviewers for this valuable suggestion and have further detailed our statistical analysis plan in the text. Moreover thanks to the remark of the reviewer we discovered a mistake in the text: the 95% confidence interval of diabetes in the predictive model was between 0.3 and 79 and not between 0.3 and 179 as reported (see now table 6).

3. Please eliminate the pie graph since frequency of the outcome is already displayed. Overall, there are too many tables for this relatively straightforward analysis.

A/ as suggested by the reviewers we deleted Figure 1.
Minor comments:

1. The measure and category of disease activity should be mentioned in the abstract rather than the raw score.

A/ as suggested the measure and category of disease activity was mentioned in the abstract instead of the raw score.

2. Similarly, severity of RA should be better defined in the abstract.

A/ as requested we have provided a better definition of RA severity in the abstract.

3. The odds ratios are not precise enough to report to the number of digits. Would round to the tenth digit.

A/ we agree with the reviewer and rounded the odds ratio’s to the tenth digit (see now table 5 and 6).

4. Table 1 can be converted to text.

A/ Table 1 has been converted to text as suggested.

5. Disease activity is not typically part of a disease severity definition since they are different concepts.

A/ we agree with the reviewer and reconsidered the definition of the severity of rheumatoid arthritis; this had no impact on our results.

6. Table 3 can be incorporated in Table 2.

A/ table 3 has been incorporated in Table 2 as suggested (see now table 1).

7. P values can be taken out of Table 4. It is self-defined that those with atherosclerosis will have thicker carotid than those without atherosclerosis.

We agree with the reviewer and removed the p values in table 4 (now table 2).
8. The lack of measurement of ACPA should be noted as a limitation since ACPA may be related to cardiovascular disease.

Indeed, unfortunately ACPA cannot routinely measured in our hospital as a consequence of a lack of resources. As suggested by the reviewer we mentioned the lack of ACPA measurement as a limitation of our study in the discussion (see page 6, line 32).

9. The methods mention linear regression but this analysis is not reported.

We thank the reviewer for this remark. Indeed this was a mistake, as we did not perform a linear regression analysis in our study.

Reviewer 2

The Authors investigated 75 consecutive RA patients from Kinshasa for the prevalence of subclinical atherosclerosis. They point out prevalence similar to that detected in most centers from other countries. Nevertheless, the meaning of the finding would be strengthened by data on the prevalence of subclinical atherosclerosis in subjects from the same area, matched for sex, age and by data on previous CV disease in the same subjects.

A/ we thank the reviewer for this interesting suggestion and agree this information would add valuable reference information for the readers of this article. Unfortunately for practical reasons we were not able to include a control group matched for sex, age and comorbidities in our study.

Minor comments:

1. Early disease is a disease with duration < 6 months. However, < 1 year can be accepted

A/ we agree with the reviewer that the definition of early disease is debated in literature. We considered disease duration of ≤ 2 years as recent disease, as reported by Goekoop-Ruiterman et al. (Ann Intern Med. 2007 Mar 20; 146(6):406-15).

2. CRP cut off value should be 1 mg/dl

A/ we agree with the authors that the cut off value we used is different from cut off values used in Caucasians. For CRP, we considered a value of > 6mg/l to define an inflammatory syndrome, because that is the cut-off of our own laboratory, based on the distribution of CRP values in the population of Kinshasa.
3. ESR cut off value should be 20 for males; 30 for females

A/ we agree with the authors that the cut off value we used is different from cut off values used in Caucasians. Also for ESR, we considered the cut-off of our own laboratory, based on the distribution of ESR values in the population of Kinshasa.

4. Severe disease is better defined by a HAQ value>1

A/ we thank the reviewer for this suggestion. We defined the severity of the disease by a HAQ value of $\geq 0.5$ in reference to recommendations for other African populations: see recommendations of good medical practice, Moroccan Society of Rheumatology, ALD number 26, September 2011; page 19 and line 13. work group: Pr. Abdellah El Maghraoui et al.