Author's response to reviews

Title: How age and sex affect the erythrocyte sedimentation rate and C-reactive protein in early rheumatoid arthritis.

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Version: 3 Date: 23 October 2014

Author's response to reviews: see over
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Authors’ response to reviews: see next pages
Dear editor,

Thank you for giving us the opportunity to submit a revised version of our manuscript “How age and sex affect the erythrocyte sedimentation rate and C-reactive protein in early rheumatoid arthritis”.

Please find the revised version of our manuscript enclosed as well as our response to each point raised by the reviewers. We agreed with the suggestions made by the reviewers and modified the manuscript accordingly.

We would like to take this opportunity to thank the reviewers for their constructive and useful comments and suggestions, which have certainly improved the manuscript.

We hope that the revised version will be accepted for publication and look forward to hearing from you.

Also on behalf of the other authors,

Sincerely,

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**Editorial Requirements:**

We strongly urge you to make these changes promptly, as we cannot proceed to the next process until we have received a version containing the changes.

By way of a section Acknowledgements, please acknowledge anyone who contributed towards the article by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include the source(s) of funding for each author, and for the manuscript preparation. Authors must describe the role of the funding body, if any, in design, in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. Please also acknowledge anyone who contributed materials essential for the study. If a language editor has made significant revision of the manuscript, we recommend that you acknowledge the editor by name, where possible.

The role of a scientific (medical) writer must be included in the acknowledgements section, including their source(s) of funding. We suggest wording such as 'We thank Jane Doe who provided medical writing services on behalf of XYZ Pharmaceuticals Ltd.'

Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements section.

- We don't have an acknowledgement section to include. Furthermore, although there was no involvement of study sponsors, and none of the authors have financial, commercial, or other associations that might pose a conflict of interest in connection with the work, we included this information in the article (page 12).
Reviewer’s report - 1

Title: How age and sex affect the erythrocyte sedimentation rate and C-reactive protein in early rheumatoid arthritis.

Version: 2
Date: 4 July 2014

Reviewer: Robert Shmerling

Reviewer's report:
Reviewer number: 1

Referee's comments to the author(s)
This study attempts to determine the impact of age, gender and BMI on the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) in early rheumatoid arthritis. The findings are of interest but such studies are challenging to perform well given all of the potential confounders. Indeed, this study has a number of limitations, listed below. I have previously reviewed this paper - the authors have made a number of revisions that have improved the manuscript. However, a number of major limitations remain.

Major compulsory revisions:
1. The lack of information about medications, especially corticosteroids – the authors state that their “aim here was not to provide an exhaustive list of all possible confounders” – fair enough, but the potential impact of NSAIDs, corticosteroids and other medications is too big to discount. It is good that this is now mentioned as a limitation but it is also a flaw that might invalidate the findings. This should be given more discussion.

- We agree that the potential impact of medications deserves a bit more emphasis and included two phrases:
  1. “A possible limitation of the current study might be the exclusion of other potential confounding variables, such as ...., or medication use (e.g. estrogen, steroids, or NSAIDs) [21-23, 25, 33]. To study the effects of these variables, further research is needed. Till then, the results of this study should be interpreted with caution.” (page 10)
  2. “However, one should keep in mind that there might be other confounding factors that were not included in this study (e.g. NSAIDs or corticosteroids), but which may affect the inflammatory markers as well, potentially making the use of the ESR equally acceptable.” (page 11)

2. Details about how the diagnosis of RA was established are missing – the authors refer to 2 studies, one of which is in press. The one in press should be omitted and, in addition to stating that the diagnosis was established clinically, the readers should be informed whether or not the clinical diagnosis was established by a certified rheumatologist. This is particularly important given the low disease activity and low rates of positive RF and anti-CCP: while this could be due to early disease it could also be due to non-disease.

- We agree that information was missing on whether the diagnosis was established by a certified rheumatologist - which it was - and included this in the article:
  “This observational multicenter cohort included patients that were newly and clinically diagnosed with RA by a certified rheumatologist, …” (page 5)

The study that was still in press has now been published and, as such, was kept in the references.
3. In the result section, the authors state: “At inclusion, patients had active disease as characterized by a DAS28 score > 2.6” – as I read this, the authors continue to conflate lack of remission with active disease – yes, a DAS > 2.6 is an indication of non-remission; but it does not mean they had high disease activity. By virtue of the clinical data presented, these patients had LOW disease activity, so stating that they had active disease is not as accurate as it could be.

- We could indeed state this differently and changed it accordingly:
  “At inclusion, patients were not in remission as characterized by a DAS28 score > 2.6 …” (page 7)

4. The authors state that the study subjects’ relatively low female proportion and older age is typical of a Dutch early RA study – that may be, but it limits the generalizability of the findings. Similarly, the relatively low disease activity scores of these presumably untreated and “active” patients may be due to early presentation but again, this could limit generalizability – other populations with more active disease at presentation could have had different results. These concerns are still not addressed in the discussion of limitations – stating that the findings are not surprising is not enough.

- We agree that we could formulate the limited generalizability more clearly and added the following paragraph:
  “Still, this could limit the generalizability of the results towards other populations with more active disease. Finally, even though the proportion of females in this study (61%) might seem relatively low and the average age of the patients (57 years old) might seem relatively high for the early onset of RA, these numbers do correspond to previous results of (Dutch) early RA populations [34-36]. Nevertheless, the results of this study might not be generalizable to populations with a different composition.”(page 11)

Minor Essential Revisions: None
Discretionary Revisions: None

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests: I declare that I have no competing interests.
Reviewer's report - 2

Title: How age and sex affect the erythrocyte sedimentation rate and C-reactive protein in early rheumatoid arthritis.

Version: 2 Date: 7 July 2014

Reviewer: Cynthia Crowson

Reviewer's report: none

Level of interest: An article whose findings are important to those with closely related research interests.

• Thank you for reviewing our article and for your positive judgment.

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
These authors have recently joined a collaborative group that I am associated with. However, the topic of this paper is different from the topic under study by the collaborative group. I do not feel this emerging relationship has in any way compromised my review of this manuscript.
Reviewer's report - 3

Title: How age and sex affect the erythrocyte sedimentation rate and C-reactive protein in early rheumatoid arthritis.

Version: 2 Date: 28 July 2014

Reviewer: Andrew Wong

Reviewer's report:
Study Summary: This study attempts to examine which inflammatory marker (ESR vs CRP for use in DAS 28 scores) is least affected by age, gender, and BMI in patients with early RA (patients with <1 year symptoms in the multicenter Dutch DREAM registry).

General Comments:
This revised (brief) manuscript is well written, of clinical relevance to practicing rheumatologists, and addressed the major concerns of the reviewers (including study aim, methods, data analysis, and limitations).

Specific Comments:
1. On page 11, Conclusions section, consider revising "but which were not included in this study" to "but which were not included in this study that may make using the ESR equally acceptable."
   • We agree and changed it into: “However, one should keep in mind that there might be other confounding factors that were not included in this study (e.g. NSAIDs or corticosteroids), but which may affect the inflammatory markers as well, potentially making the use of the ESR equally acceptable.” (page 11)

2. On page 21, Table 5, please include or justify why the values for sex in the CRP model was not included in the table.
   • As we explained on page 8 under the heading “After 1 year”: Sex was still significantly associated with ESR levels (showing higher levels in females), but was no longer significantly associated with CRP (p=0.855). That’s the reason why it is not included in table 5. We included this explanation in the note beneath the table to clarify this:
     “After 1 year, sex was no longer significantly associated with CRP levels (p=0.855). Consequently, this factor is no longer included in the CRP model.” (page 22)

3. On page 4, change "complete as possible [7,8] this slow response" to "complete as possible [7,8], this slow response".
   • We changed it accordingly.

4. On page 6, change "were repeated on the 1-years data" to "were repeated on the 1-year's data".
   • We changed it accordingly.

5. On page 12-15, References section, be consistent in the listing of the number of authors before using et al.
   • As stated on the website of the BMC Musculoskeletal Disorders: “Citations in the reference list should include all named authors, up to the first 30 before adding 'et al.'”.
     We changed this accordingly.
**Level of interest:** An article of importance in its field.

**Quality of written English:** Acceptable.

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:** I declare that I have no competing interests.