Title: Increased risk for chronic comorbid disorders in patients with inflammatory arthritis: a population based study

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Version: 3 Date: 11 November 2013

Author's response to reviews: see over
Dear editor,

Hereby a point-to-point reply to each of the points raised by the reviewers and a revised version of the paper.
We thank the referee’s for their comments.

**Referee 1:**
This is a well written and focused article.

There are no major compulsory revisions.

Minor essential revision:
(i) Figures 2 and 3 need a little more explanation in the text and the legend.

*The legend and text of figure 2 and 3 have been adjusted.*

(ii) Is there an additional limitation that the outcomes were prevalent as opposed to incident?

*The outcomes of this study were all newly developed diseases, so all outcomes are incident.*

(iii) In the discussion, perhaps there is a case to be made for IA being associated with all cause comorbidity, as opposed to the specific mechanisms for each comorbid condition.

*In the discussion we addressed now more generally how IA may be associated with all comorbidity*

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**Referee 2:**
Reviewer’s report:
This is an interesting study examining the risk of developing new comorbid chronic conditions in patients with inflammatory arthritis by comparison to those without.

Major Compulsory Revisions
- My main concern is with the study design with regard to matching of controls for time of follow up. If there are differences between the two groups with the time of follow up this could potentially bias the results, increased follow up means greater opportunity to develop new conditions. Are the authors able to match on follow up time or conduct a survival analysis that would account for time within the study between the two groups? The sensitivity analysis limiting to at least one year, does not address this given the potential for at least 9 years follow up at maximum. A sense of the time to development of first new condition would also be useful.
We understand that the referee might be concerned about the potential bias of the follow-up. However the mean time of follow-up is similar for cases and controls. Furthermore we used a survival analyses technique, Cox regression that is specifically used for time-to-event data, to determine the risk (hazard ratio) of developing a new disease.

The median time to develop a new chronic disorder was shorter in IA patients compared to control patients: median 9.8 months (95%CI 3.6-20.7 months) for IA patients and 11.4 months (95%CI 4.4-24.1 months) for controls (p<0.001). For clarity of the manuscript, we did not include the time to the first diagnoses.

• I would also like the authors to provide some comment on the increased risk of specific disease groupings, in terms of those conditions that may be considered ‘concordant’ or discordant with inflammatory arthritis. i.e. those with RA are known to have an increased risk of CVD.

We added this point to the discussion section. We now discuss possible reasons for co-occurring of chronic diseases, and that the cumulative incidence rates of one or more new morbidities rapidly increase with the number of morbidities already present. Moreover, the different sequence of additional chronic comorbid disorders may be due to different factors like medication use, one disease or disease combination could be a trigger for another disease or a common underlying mechanism. Unfortunately, we do not have enough power in our study to go in-depth into the topic of concordant and discordant, as one need to take time between the onset of two diseases into account and adjust for all existing comorbidies. This would require a much larger dataset than available as many different combinations exist.

• The increased risk of HF may be attributed to the use of NSAIDs in this population? Some discussion on this is required.

We agree with the reviewer and address this point in the discussion. We discuss that the use of medication, might contribute to the occurrence of chronic comorbidities

Minor Essential Revisions
• Introduction
The second to last paragraph - a lack of optimal preventative care and the subsequent development of comorbid conditions could really be said for any ‘index’ chronic condition, not just IA. You should maybe introduce the concept about the development of new comorbid conditions and their influence on overall care, management of the patient, treatment decisions and complexity and likelihood of treatment prioritization

Indeed lack of optimal preventive care and the subsequent development of comorbid conditions could be said for any index disease, not just for IA. However, we decided not to adjust our introduction section since the focus in our study is purely on patients
with IA. Though the topic is indeed important, we now pay attention on this topic in the discussion section.

• The aim could be clearer. The aim of this study is to determine the risk of development of new comorbid chronic conditions in patients newly diagnosed with IA.....

The aim was adjusted

• Discussion

How do you propose that preventative treatment will stop the development of new conditions. Given the average age is 55 years then this seems unlikely for COPD given its development over time as and example.

Of course, not for all chronic comorbidities preventive treatment will stop or delay the development of a new condition. If a comorbidity is already developing, possibly subclinical, treatment will not stop this process. However preventive treatment might decline the process rate and therefore postpone symptoms or it may result in less disease severity. For instance, stop smoking could even in patients with IA be useful to influence the development rate of COPD. Furthermore, some disease however, e.g. cardiovascular diseases, might be prevented with proper preventive treatment.