Author's response to reviews

**Title:** Is Knee Osteoarthritis a Symmetrical Disease? Analysis of a 12 Year Prospective Cohort Study

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**Version:** 4 **Date:** 24 July 2012

**Author's response to reviews:** see over
Response to reviewers, second comments and revision

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Manuscript number: 1048016250629862

Authors: A J Metcalfe, M L E Andersson, R Goodfellow, C A Thorstensson

We would like to thank both of the reviewers again for their helpful comments.

The specific points raised in their reviews have been dealt with as described below.

Reviewer 1

Reviewer's report
Title: Is Knee Osteoarthritis a Symmetrical Disease? Analysis of a 12 Year Prospective Cohort Study
Version: 3 Date: 3 May 2012
Reviewer: Michael Anthony Hunt

Reviewer's report:
Thank you for the revisions to this manuscript, which I feel have enhanced the readability of the paper. I also appreciate the additions to the manuscript (especially within the Introduction) outlining the anticipated novelty of this research. There are still some issues that I feel would improve the relevance of this paper.

Major compulsory revisions:
1. Thank you for expanding on the novelty of this work. The authors indicate that “we do not know the timescales involved in [bilateral OA involvement]”, that the “timing of progression to bilateral disease has not been clarified”, and that the current approach will “allow researchers, clinicians and patients to understand the disease process and the risk of further disease in the future over a known time period”. However, I am not sure that the current study design is able to address these issues given that only 2 time points were assessed – it would have been nice to have annual radiographs to establish a more definitive time scale of development of bilateral disease. Importantly, it is unclear how knowledge that a given % of participants with knee pain will develop unilateral or bilateral disease over a 12 year period will change clinical practice. A clear description of how clinical practice may change (likely in the Discussion) would greatly enhance the applicability of this paper.

Authors’ response: We understand these comments and have worked hard to address this question both in the previous and the current revision. We have utilised a well established cohort study over a prolonged period of time and are not aware of any study of comparable length which has followed up patients annually. Although we accept that this would be an ideal it would practically involve greatly increased radiation exposure over a prolonged period and a very expensive and time consuming study protocol.
We have added substantially to the clinical relevance of the study and we believe that this does add value for both clinicians and researchers (most of the authors are clinicians), especially in light of recent papers emphasising the effect that bilateral disease (as opposed to unilateral) has on function.

Authors’ changes:

The following has been added to the introduction:

Researchers wishing to plan longitudinal studies need to be able to quantify the changes that would be expected on the other side, as the development of bilateral disease has an impact on gait and on overall function, therefore affecting the results of research [4, 11]. Patients frequently ask about the risk of new disease on the contra lateral side and increased knowledge about prognosis for their condition might allow clinicians to offer more specific advice, and to understand the potential benefits of preventative treatments to protect an apparently normal joint on the other side (such as footwear modification, gait retraining, or simply lifestyle advice).

The following has also been added to the discussion:

Certainly, more information would have been gained from yearly radiographs compared to the two time points of follow-up in the study. Whilst this might have been preferable scientifically, it would require a much large research budget, and compliance would be a challenge, as well as the ethical issues of radiation doses and inconvenience to the participants. Yearly radiographic examination might not have influenced the overall conclusion, namely that bilateral osteoarthritis is common in this population over a prolonged period of time.

And:
Studies have demonstrated that the biomechanics of the unaffected limb are not normal in patients with unilateral knee osteoarthritis, and also that gait asymmetries exist in patients with unilateral osteoarthritis that subsequently change when a patient develops bilateral disease [7, 11]. The treatment of the patient may therefore change depending on whether they have unilateral or bilateral disease. It is important to note from our findings that the majority of patients with unilateral disease would potentially benefit from interventions aimed at preventing disease in the other, apparently normal joint. Techniques such as wedged insoles, neuromuscular exercises and gait retraining may be appropriate and further research is warranted to examine ways to protect the ‘joint at risk’.

*Also, in the final paragraph of the discussion we have added:*  
Patients can be given a prognosis which may help motivate them to comply with treatments and address symptoms in the other knee appropriately.

2. It is unfortunate that none of the exploratory variables (age, gender, knee pain, or BMI) were different in the bilateral OA group. There does not appear to be a rationale for this in the Introduction as to why any of these variables should be different. Presumably these data came from a larger cohort study with a number of additional variables. Why were none of these chose (alignment for example)? Identification of explanatory variables would certainly be of interest to the clinical community.

*Authors’ response:* The data represents the full cohort, rather than a sub-set, and the recruitment protocol, flowchart of recruitment, and number of cases involved is described both in this paper but also in previous articles referenced in the paper (Namely Thorstensson et al 2009 Ann Rheum Dis. and Petersson et al 1997 Ann Rheum Dis., references 12 and 13 in the manuscript). As is the nature of all long term follow up studies, this cohort was established a number of years ago with a different dataset then might be used now with our greater understanding of disease pathogenesis. This cohort represents one of the longest running osteoarthritis cohorts in the literature at present.

The variables chosen were used because they have been implicated in the literature previously as influencing osteoarthritis development and/or progression and were collected at baseline in all patients. We thank you for the suggestion to use alignment as a predictor, and will consider using alignment measures in future publications from this
cohort, however it was not a part of this protocol. Whilst it is unfortunate that none of the variables were different in the analysis between the two groups, we feel that negative findings should still be reported as such and have therefore left it in.

Authors’ changes: We have clarified that this is the full study cohort rather than a sub-set by inserting the following into the methods:

‘and the full cohort was analysed for the purposes of this paper’

3. It would appear that secondary analysis attempting to “understand the effects of these factors on new onset bilateral disease over 12 years)” included all eventual bilateral disease patients with the exception of those with pre-existing bilateral disease at baseline. This suggests that everyone with no OA or just unilateral OA were included in this analysis. What evidence exists to suggest that these 2 groups (no OA vs unilateral OA) should proceed to bilateral OA in the same manner under the same mechanisms. Please elaborate on the appropriateness of including both of these apparently different phenotypes into a single analysis to determine mechanism of bilateral onset.

Authors’ response: We accept that this is a weakness of this analysis however it allowed us to improve on the number of patients in the analysis and increases the generalisability of the findings. Whilst there is no data to suggest the two phenotypes are the same there is equally little to suggest that they might behave differently with this regard. We were advised by the other reviewer to include the full cohort in the regression analysis so clearly a balance needs to be achieved between generalisability and subgrouping to assess every possible factor involved. We feel we have achieved this by using this approach but we have accepted in the discussion that this is a potential weakness.

Authors’ changes: The paragraph describing the weaknesses of the study now contains:

‘The logistic regression analysis was performed on both patients with no disease at baseline and those with unilateral disease at baseline and we accept that these may be two distinct phenotypes which progress differently towards bilateral disease, although we have seen no evidence to either confirm or refute this assertion. The lack of association between bilateral disease and age, gender, BMI and pain should therefore be considered with some caution.’

Minor essential revisions:
1. Was the same radiologist involved in all assessment of radiographs? While inclusion of kappa values outlining the agreement is important, data pertaining to
these actual radiologists would be preferred.

Authors’ response: The same experienced musculoskeletal radiologist read all the radiographs, and this has been clarified in the text.

Authors’ changes: The relevant sentence has been modified to:

All radiographs were assessed by the same experienced radiologist blind to the patient details.

2. As suggested in the previous review, it is unclear what additional information the OARSI-OMERACT criteria add to this study. For example, it would appear that this approach was used as an additional method of classifying OA (see page 10), however no additional analyses were reported on these findings. Further, the breakdown of compartmental involvement in those with bilateral disease does not appear to match the previous numbers (i.e. 73 medial bilateral + 6 medial in one, lateral in the other + 2 lateral bilateral + 25 equal scores = 106 knees, yet page 9 indicates that “At 5 and 12 years the number with bilateral disease had increased to 65 and 100 respectively”).

Authors’ response: The OARSI-OMERACT classification has been included for two reasons. The first is to assist in the determination of which compartment was involved, as described in the methods. This was expanded in the first revision to make the methodology clearer. The second is to provide a secondary measure which allows interested readers to make comparison with their own data, as the classification system has been carefully developed for use in contemporary radiographic studies of osteoarthritis (see Gossec et al 2008 Osteoarthritis and Cartilage, reference 21). Therefore the data has been included in the results as:

Using the OARSI-OMERACT joint space width scoring to classify osteoarthritis, 79 patients (63%) had bilateral disease at 5 year follow up, and 106 patients (74%) with bilateral disease at 12 year follow up.

The ‘...65 and 100 respectively’ are the total numbers for the primary outcome measure of the study (KL≥1), as documented in the methods, whereas the numbers quoted for the OARSI-OMERACT data tally correctly. It is interesting that the OARSI-OMERACT scoring data and the KL≥1 data correspond so well as they are based on different criteria, but we chose to not complicate the issue further by mentioning this in the discussion.

3. The description of pain is inconsistent throughout. For example, the purpose statement indicates the aim to explore whether “baseline bilateral knee pain” explains development of bilateral OA, while in the Methods it is stated that subjects were asked “if they had pain in any of your knees practically daily for the last three months and were subsequently seen by a rheumatologist” to determine how many knees were painful, and in the Results, it simply describes “those who started the study with knee pain”. Indeed, the inclusion criteria only states that
participants had “chronic knee pain”. Thus, it is unclear what relationship between knee pain and eventual OA findings was actually examined. If both unilateral and bilateral pain was allowable, it would be interesting to report the “agreement” between type of pain and eventual OA findings (for example, if pain was only in the right knee but OA developed in the left, or if the pain and OA matched, etc.).

Authors’ response: We accept that this was not clear and have adjusted the methods appropriately. Patients were selected using the question above and were only entered into the cohort if they answered ‘yes’, it was then recorded whether the pain was unilateral or bilateral. We have sought to clarify this but more detail can be found in the previous papers on this cohort.

Authors’ changes:
Subjects were asked at the start of the study if they had ‘pain in any of your knees practically daily for the last three months’ and were only included in the cohort if they answered yes. They were subsequently seen by a rheumatologist at the entry to the study, who determined whether the pain was in the right knee, the left knee or both knees. The full protocol for this has been published previously [12-13].

Logistic regression was used to study the effect of age, gender, BMI and baseline pain (unilateral vs. bilateral knee pain) on the likelihood of developing bilateral as opposed to unilateral disease over 12 years.

4. Paragraph 2 of the Discussion indicates that with the exception of previous injury cases, early knee osteoarthritis “in most cases is a bilateral disease”. It is unclear what is meant by this statement. Please elaborate with specific examples from the current dataset – the data would actually suggest that early on most (53%) actually had no radiographic changes.

Authors’ response: We accept that this sentence was not entirely clear and have modified it accordingly.
Authors’ changes: we have modified the sentence so it now finishes:

...in most cases develops into a bilateral disease

5. As above, the exact novelty of the current data is unclear. This comment is supported by a number of comments throughout the Discussion as currently written. For example, “We are unable to comment on the cause for the pattern of
OA progression that we have observed in this paper, although further studies are ongoing” (thus, it may be more prudent to wait on additional data), “the current study did not have sufficient numbers to separate out the effects of these factors properly”, and “further interventions aiming to slow the progression to bilateral disease may well be of benefit to the patient with osteoarthritis” (this is widely accepted and routinely implemented in clinical practice – it would be more beneficial to identify potential strategies or risk factors to target).

Authors’ response: We are clearly disappointed that we have given this impression and have modified the introduction and discussion as described above to clarify this further. We feel we should distinguish between novelty and clinical relevance. We are confident that this study is novel, as the development of bilateral disease has not been well described in a prospective long-term cohort, and certainly not examined in this detail.

We have however, strived to also explain the clinical relevance of this paper. As such, we have modified the discussion to correct some of the sentences quoted above. Clearly an observational cohort study of this design will struggle to establish a clear cause for a complex multi-factorial process such as knee osteoarthritis (has any study to date?), and the purpose for this paper was to define the size of the problem and the potential for treatment of the unaffected joint. What is more, whilst we can always comment that greater numbers would be advantageous, this study has good follow up of a well defined cohort over an unusually long period of time relative to the current literature.

We are clinicians ourselves, with specific interest in knee osteoarthritis, however our experience tells us that it is not common to consciously treat non-diseased joints to prevent future disease. We agree that it might be entirely logical, but still believe that this paper emphasises the importance of such an approach and aim to clarify the potential benefit of doing so in a way that clinicians can understand and researchers can use to assist with planning further studies. We hope that this now comes across clearly in the paper.

We would also like to make one further observation that the study demonstrates that bilateral disease develops in most people in the early stage of the disease (as seen in figure 3, the transition appears to be between KL=1 and KL=2 in the worst knee) and as such a ‘potential strategy’ is evident, namely that targeting treatment at the other joint should be done as early as possible to prevent incident disease.

Authors’ changes:

Aside from the changes made in answer to point 1, most of which also answer this point, we have also amended the quoted paragraph in the discussion to now read:

We are unable to comment on the cause for the pattern of osteoarthritis progression that we have observed in this paper, as this would require much more complicated biological
and biomechanical methods, however at present such studies are not available with the length of follow up achieved in our cohort.

*We have added the following comment to the discussion:*

It can be seen from figure 3 that bilateral knee osteoarthritis becomes much more common as the disease severity increases. This is no surprise, but it is important to note that this happens at an early stage in the disease process, as those with KL=2 in one knee were very likely to have disease present on the other side. Preventive interventions should therefore be instituted early in order to avoid or postpone symptomatic and radiographic knee osteoarthritis on the contra lateral side.

*We have also added:*

Patients can be given a prognosis which may help motivate them to comply with treatments and address symptoms in the other knee appropriately.

*We thank you again for your comments and suggestions to further improve our manuscript, and hope that we have been able to respond and revise satisfactorily.*

**Level of interest:** An article whose findings are important to those with closely related research interests  
**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' below
Reviewer 2

Reviewer's report
Title: Is Knee Osteoarthritis a Symmetrical Disease? Analysis of a 12 Year Prospective Cohort Study
Version: 3 Date: 1 May 2012
Reviewer: Kamil Barbour
Reviewer's report:
I have no further comments. The authors have done a comprehensive job of addressing my concerns.

Many thanks again for your feedback and your time.

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.

Thank you both again for your time and your considerate reviews of our work.

Yours sincerely,

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