Author's response to reviews

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

Authors:

Andrew J Metcalfe (ametcalfe@doctors.org.uk)
Maria L E Andersson (maria.andersson@spenshult.se)
Rhian Goodfellow (goodfellow@Cardiff.ac.uk)
Carina A Thorstensson (carina.thorstensson@spenshult.se)

Version: 3 Date: 28 March 2012

Author's response to reviews: see over
Response to reviewers

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

Manuscript number: 1048016250629862

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

Thank you for the opportunity to further improve our manuscript. Please find enclosed the revised version of “Is Knee Osteoarthritis a Symmetrical Disease? Analysis of a 12 Year Prospective Cohort Study”.

We are grateful to both of the reviewers for their kind and constructive feedback about our paper. We have answered every comment and have revised the manuscript as requested to address the issues which were raised. The specific points raised in their reviews have been dealt with as described below.

Reviewer’s report

Version: 2 Date: 16 January 2012

Reviewer: Michael Anthony Hunt

Reviewer’s report:
The authors have conducted a longitudinal study evaluating radiographic changes bilaterally in people at risk for knee OA. They should be commended for a relatively large sample size and valid outcome measures. While I feel that this study has important findings and can potentially contribute to the current literature, I believe that overall, more justification is needed as to how these data are novel. In particular, the introduction is very short, in my opinion, and does not provide a sufficient overview of the current literature (note that some of the important papers have been discussed in the Discussion instead). Indeed, the authors state that 87% of patients awaiting TKA have bilateral knee OA. Some would argue that this is evidence that the majority of those with unilateral OA at a given point in time will most likely progress to bilateral signs/symptoms at some point. As is, the current data simply confirm these findings and lend support to other previously published studies.

Authors’ response: The introduction has now been expanded to contain significantly more detail and background to the study, as well as the value of the study in comparison to the present literature. Some of the discussion has been moved forward into the introduction and the benefits of the longitudinal cohort study design in terms of the ability to understand timescales and knowledge of the baseline population has been emphasised.

Major Compulsory Revisions:
1. In general, based on the data reported and the discussion of previous findings and knowledge in the Discussion, I am unclear what new information this paper provides. We know that people who have OA in one knee are at risk for developing OA in the other knee. We also know that bilateral OA is a common clinical presentation. All of the potential systemic mechanisms that the authors describe (e.g. genetics, malalignment, obesity, gait mechanics) are well-known
risk factors for OA development and progression. A stronger case needs to be made regarding the novelty of these findings.

Authors’ response: The study used a longitudinal cohort design with community recruitment, and serial radiographs. This has many advantages as it defines the development of bilateral ‘structural’ knee OA over a set time period, with a known baseline population who are representative of community knee pain/early osteoarthritis sufferers (rather than the small proportion of sufferers who go on to require arthroplasty). The argument for the novelty and value of the study has been expanded and enhanced in the introduction as suggested.

Authors’ changes:
The introduction now reads (added paragraphs in yellow):

Knee osteoarthritis was historically considered an ‘asymmetric’ disease and most research continues to focus on each joint as a single entity. Cross sectional studies have shown that bilateral knee pain is a frequent problem in the community [1-3]. Each additional joint affected by osteoarthritis results in a decrease in physical function and an increase in overall pain [1-3]. A recent study demonstrated that bilateral knee pain was an independent risk factor for poor physical function [4]. However, there have been very few studies which have addressed the prevalence or natural history of bilateral disease radiologically.

Whereas joint injury (bony or soft tissue) usually affects one joint alone, there are many reasons why knee osteoarthritis would tend to progress to bilateral disease. Genetic influences and inherent mal-alignment would be expected to lead to bilateral disease [5-6]. A recent gait analysis study found abnormal loading in the unaffected knee of patients with unilateral knee osteoarthritis, implying that patients with a painful joint may accelerate disease in other joints due to changes in gait [7].

We do know that bilateral knee osteoarthritis is particularly common in people with advanced disease, with a previous study finding that eighty-seven percent of patients awaiting total knee replacement (TKR) have radiological evidence of osteoarthritis on the other side [8]. Despite this information, we do not know the timescales involved in this process, or whether this is a common problem in community arthritis sufferers, or just the subset who develop disease severe enough to require arthroplasty.

There is a shortage of longitudinal studies examining the natural history of bilateral knee osteoarthritis in the literature, and timing of progression to bilateral disease has not been clarified. In a previous study with 2 year follow-up, 34% of patients with unilateral disease subsequently developed disease in the contra-lateral knee, however follow up was relatively short and the study was restricted to females only [9].

It would appear that community studies of osteoarthritis find lower rates of bilateral disease than studies performed at the time of joint arthroplasty, implying that bilateral disease becomes more common with time [1-3, 8-9]. However, temporal data is absent and definitions of symptomatic or structural osteoarthritis vary widely between studies.
Also, we do not how representative arthroplasty patients are of community-recruited osteoarthritis sufferers, given that those seeking secondary care treatment form a small proportion of community osteoarthritis sufferers [10].

A longitudinal cohort study with community recruitment has a number of advantages for understanding the development of bilateral disease as it allows us to document the change over a set time period, using a standard definition of disease made by the same observers. This approach allows researchers, clinicians and patients to understand the disease process and the risk of further disease in the future over a known time period.

The focus of this study was to determine whether knee osteoarthritis primarily affects both knees over time. The primary aim of this study was therefore to describe the development of bilateral knee osteoarthritis, as opposed to unilateral disease, over a 12 year period using a middle-aged population-based cohort with knee pain at inclusion. A secondary aim of the study was to explore whether the development of bilateral knee OA was related to age, gender, baseline bilateral knee pain or body mass index.

2. While the cohort had a large sample size overall, the actual sizes of those in each cell required for the statistical analysis were small. The authors allude to this, and I feel that this needs to be addressed more in light of the lack of statistically significant findings in the overall results.

Authors’ response: The issues with sample size have been addressed in more detail as a weakness in the discussion.

Authors’ changes:

The following sentence has been added to the discussion (p13-14):

Whilst the sample size used in this study was good overall, some of the numbers in individual cells were relatively small and this may have been a factor in the lack of a significant result. This deficiency is emphasised by the width of the confidence intervals for the odds ratios, which were large.

And later in the paper, as part of a paragraph on strengths and weaknesses, the following has been added (p15):

Therefore the weaknesses of the study are the relatively small sample size, particularly when subgroups were considered or in the logical regression results. The lack of association between bilateral disease and age, gender, BMI and pain should be considered with caution given this weakness.

3. Please explain why 2 definitions of OA were used (KL1 – which is “doubtful OA” and KL2).
Authors’ response: The reasoning behind definitions of osteoarthritis as KL=1 (primary definition) and KL=2 (secondary definition) has been expanded in the text. The authors experience, with radiographs read by the same radiologists who reported all the x-rays in this study, was that KL=1 was a better definition for this population when compared to MRI findings and longitudinal follow up, although we accept that many readers would also like to interpret the data according to their own preferences, so a definition of KL=2 was also included to broaden the scope of the paper for interested readers.

Authors’ change:
The following has been added (methods, p6-7):

Previous studies in Spenshult and elsewhere have found that KL grade 1 represents a genuine early stage in knee osteoarthritis, with detectable cartilage deficits on MRI and likely to progress to more severe disease [12, 15, 17]. The use of KL 2 as the definition of radiographic OA has been preferred by some authors whilst others have found it underestimates the prevalence of disease in many cases [12, 15, 17-18]. Both definitions depend on the radiographic protocol used and have considerable inter-observer variability [19-20]. In the Spenshult-cohort KL grade 1 has previously been used as a primary definition of radiographic tibio-femoral osteoarthritis and was also the primary definition used in this study [12, 15]. A secondary definition of KL grade 2 was also recorded to aid interpretation of the data.

Minor Essential Revisions:
1. It would appear that KL grade was the only benchmark used when reporting radiographic data. Thus, what happened to the joint space width and OARSI-OMERACT classification data? The methods are described, but no data are reported as far as I can tell.

Authors’ response: The OARSI-OMERACT data were used to define compartment involvement, although this has been clarified and expanded in the text. The following can be found in the text (results section, p10):

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%) at 12 year follow up.

Of those patients with bilateral disease at 12 year follow up, 73 patients had predominantly medial compartment disease in both knees, 6 patients had medial compartment disease in one knee and lateral compartment disease in the other knee whereas only 2 had predominantly lateral disease in both knees. Twenty-five patients had equal scores in the medial and lateral compartment of at least one knee.

2. Why were BMI data dichotomized to < 30 and > 30?
Authors’ response: We wanted to examine the role of obesity on disease progression, as
the presence or absence of obesity was more of a relevant question for clinicians rather
than the linear relationship to BMI. The WHO classification was used to define obesity
and this has been referenced.

Authors’ Change: Methods (p8) Added reference 21. Physical status: the use and
interpretation of anthropometry: Meeting: Report. WHO; 1995

3. I did not see any data from the 5-year follow-up visit reported.

Authors’ response: Additional 5 year data has been added to the results and can also be
found in figure 2 a) and b).

Authors change: the following has been added (results p9): at 5 years there were 35
(28%) with unilateral osteoarthritis and 24 (19%) with bilateral osteoarthritis.

Reviewer’s report
Version: 2 Date: 24 January 2012
Reviewer: Kamil Barbour

Reviewer's report:
The authors attempted to answer the question of knee OA as a symmetrical
disease. They conclude that bilateral knee OA is very common over time and
clinicians need to be aware of this phenomenon. This is a well written article
which could potentially be of importance in its field.
I have some concerns that the definition of OA (KL #1) may be too sensitive. I
would recommend the authors use the standard KL#2 as the definition for OA,
which may have more clinical relevance. Given that there is a lot of controversy
about use of osteophytes and the longstanding belief has been that equivocal
osteophytes in KL grade 1 are meaningless.
Kijowski R et al. Arthroscopic validation of radiographic grading scales of
osteoarthritis of the tibiofemoral joint. AJR. 2006 Sep;187(3):794-9

Authors’ response: We understand that the question as to the best definition of OA is
difficult. Whilst KL=1 is sensitive, it has been shown in Spenshult (with the same
radiologist and same protocols) to be a valid definition of osteoarthritis with MRI
detected cartilage deficits (Boegard et al 1998), and highly likely to progress to more
severe disease (Thorstensson et al 2009). Our experience is that a definition of KL=2 is too
coarse in this type of community based study. However we accept that this is not a
universal belief and so more details of the results defined by KL=2 have been included to
allow readers to appreciate the results from either perspective (note the figures are
presented for both definitions). A more detailed discussion about the definition of OA has
been included in the paper.
Author’s change: The following has been added

Previous studies in Spenshult and elsewhere have found that KL grade 1 represents a genuine early stage in knee osteoarthritis, with detectable cartilage deficits on MRI and likely to progress to more severe disease [12, 15, 17]. The use of KL 2 as the definition of radiographic OA has been preferred by some authors whilst others have found it underestimates the prevalence of disease in many cases [15, 17-18]. Both definitions depend on the radiographic protocol used and have considerable inter-observer variability [19-20]. In the Spenshult-cohort KL grade 1 has previously been used as a primary definition of radiographic tibio-femoral osteoarthritis and was also the primary definition used in this study [12, 15]. A secondary definition of KL grade 2 was also recorded to aid interpretation of the data.

Introduction:
Any studies showing the effects of bilateral knee OA on physical function? If so, please add to introduction. This study is focused on incident bilateral knee OA, not bilateral knee pain.

Authors’ response: We are not aware of studies on bilateral radiographic OA other than those reported and the wording of this aspect of the introduction has been corrected in the paper.

Author’s change: The following has been added:

However, there have been very few studies which have addressed the prevalence or natural history of bilateral disease radiologically.

Methods:
Consider limiting the analysis to only an OA definition (KL #2).

Authors’ response: This has been discussed in detail above and the manuscript has been changed as described. The results using a definition of KL2 are included in the paper.

Consider listing other covariates measured (i.e., age, height, weight, baseline bilateral pain,) towards the end of the methods section (since they are covariates in the analysis).

Authors’ response: We have changed the description of the explanatory factors section of the paper as suggested, by moving the list of covariates into the methods.

How might not having 18 patients with radiographic examinations at 5 years
affect your findings at 5 and 12 years? Is this a limitation? Potential for misclassification?

Authors’ response: The 18 patients which were not assessed at the 5 year follow up is a shortcoming, but should not affect the 12 year results as the two sets of results were analysed separately. This has been mentioned in the discussion.

Authors’ change: The following has been added

To the results (p9):

Of the 18 patients who were not seen at 5 year follow up, 12 had no changes on x-ray at baseline, 4 had unilateral changes and 2 had bilateral changes. At the 12 year follow up, 4 of the 18 had unilateral changes and 14 of the 18 had bilateral disease.

To the discussion (p14):

The primary time-point of interest was the 12 year follow-up. The loss to follow up at 5 years (18/143) was relatively small and the results between baseline and 12 year follow up for those 18 patients were representative of the results for the whole population. We therefore believe that it is unlikely that the loss of those patients at the 5 year time point had a significant effect on the 5 year findings.

Need a reference for the KL classification system.

Authors’ response: The Kellgren-Lawrence classification has been referenced in the revised manuscript, methods section (p6)


Please clarify how bilateral disease was determined based on JSN criteria.

Authors’ response: The use of JSN in the paper was primarily to define compartment involvement. The use of JSN as a secondary definition of osteoarthritis has been clarified in the methods and the results.

Authors’ change: The following has been added:

Methods (p7): A score above 0 in either compartment defined the presence of osteoarthritis. Findings are reported in the results as a secondary definition of unilateral or bilateral OA.
Results (p10): Using the OARSI-OMERACT joint space width scoring to classify osteoarthritits 79 patients (63%) had bilateral disease at 5 year follow up, and 106 patients (74%) at 12 year follow up.

On page 5 “baseline pain” is not defined previously.

Authors’ response: To clarify, ‘baseline pain’ has been changed to ‘baseline bilateral pain’.

Baseline bilateral pain is defined in the methods (p7)

Authors’ change. The following has been added:

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 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 [11-12].

Odds ratios tend to overestimate the risk of bilateral OA, because bilateral OA is common in this population. Can you please justify the use of odds ratios instead of hazard ratios? Consider performing a survival analysis, or an analysis that can computes risk instead of odds.

Authors’ response: Odds ratios were used in reporting the results of the logistic regression only (not in describing the incidence of bilateral disease over the period of the study), and as they tended to 1 for all of the comparator variables we think it is unlikely that they overestimated the strength of the effect. However we have reported confidence intervals of these as requested, and commented in the discussion about the width of these confidence intervals, which demonstrate the weakness of the study in the size of some of the cells in the logistic regression. The longitudinal results on bilateral disease were reported as proportions with confidence intervals and as such do not represent an overestimate but a description of the findings of the study. Survival analysis was considered but with only two time points of follow up, and a lower follow up at 5 years, it would have been a very limited analysis and prone to error. We therefore chose a simpler descriptive style for the reporting of results, which would be easier for the reader to interpret.

Authors’ change: Confidence intervals for the OR have been added as highlighted in yellow below:

Age, gender, BMI>30 or bilateral knee pain at baseline had no influence on the development of bilateral as opposed to unilateral disease. Mean age without developing bilateral disease 43.8 years, mean age in those who developed bilateral disease 44.8
years, \( p=0.41 \). For gender the odds ratio (OR) was 1.19 [95%CI 0.53-2.67]; for BMI<30 OR 1.09 [95%CI 0.35-3.38]; for bilateral knee pain at baseline OR 1.48 [95% CI 0.69-3.55].

Authors need to justify the logistic regression analysis. How does this analysis help answer your research question? Maybe discuss towards the end of the introduction that this manuscript attempts to identify risk factors for bilateral OA.

*Authors’ response:* *We agree and have added this objective as suggested.*

*Authors’ changes:* The following line was added to the end of the introduction:

A secondary aim of the study was to explore whether the development of bilateral knee OA was related to age, gender, baseline bilateral knee pain or body mass index.

**Results**

Table 1 can be improved. Perhaps, consider looking at gender differences by age, BMI, baseline pain, and K-L grade all knees in Table 1. Please list percentages (not just Ns for categorical variables). The analysis for figure 3 is not mentioned in the methods. Use the same scale for y axis on in 2 graphs in figure 2 for ease of comparison of results for two outcomes (KL grade# 1 and KL grade# 2).

*Authors’ response:* *Table 1 has been expanded as suggested by dividing the results by gender. Percentages were not added to table 1 as it became very difficult to read and interpret, as standard deviations had already been put in brackets for the means. The figures have been adjusted as recommended.*

*Authors’ change:* *The table now reads (changes in yellow):*

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbers of subjects</td>
<td>80</td>
<td>63</td>
<td>143</td>
</tr>
<tr>
<td>Mean Age</td>
<td>44.8 (5.8)</td>
<td>44.8 (5.9)</td>
<td>44.8 (5.9)</td>
</tr>
<tr>
<td>Mean Body Mass Index (kg/m²)</td>
<td>26.2 (4.6)</td>
<td>26.2 (3.2)</td>
<td>26.2 (3.9)</td>
</tr>
<tr>
<td>Pain at baseline (number of subjects)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>40</td>
<td>24</td>
<td>64</td>
</tr>
<tr>
<td>Bilateral</td>
<td>40</td>
<td>39</td>
<td>79</td>
</tr>
<tr>
<td>KL grade at baseline (all knees, n=286)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>99</td>
<td>83</td>
<td>182</td>
</tr>
</tbody>
</table>
Table 1. Demographics of the study group at baseline divided by gender. Age and body mass index are reported as mean (standard deviation).

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45</td>
<td>28</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

The analysis for bilateral knee pain at baseline is not mentioned in the methods.

Authors’ changes: The following has been added to the methods section (p8)

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 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 [11-12].

Page 8, consider moving the line on 37 patients excluded who bilateral disease at baseline to the methods section.

Authors’ response: This has been addressed in response to a previous question and the suggested change to move the text has been made.

The logistic regression results: it is more meaningful to compare bilateral OA at follow-up to everyone else in the cohort (unilateral and no OA). One would like to know, for instance, how does age impact the risk of bilateral knee OA in the population, and not just comparing unilateral vs. bilateral disease.

Authors’ response: The logistic regression was planned in this way to show how the risk factors affect the development of ‘incident’ bilateral knee OA over the set time period, and as such those that already had bilateral disease at baseline were excluded from the logistic regression (we do not know what their ‘pre-disease’ baseline was, or how long ago). However, a post-hoc analysis was performed with all of the subjects in the study and found almost identical results to those presented in the paper.

Also, please report confidence intervals instead of p-values for the odds ratios. Confidence intervals are more useful, because they provide information about direction and strength of the effect as opposed to p-values.
Authors’ response: Confidence intervals have been included in the results and mentioned in the discussion, as described above.

Discussion
The discussion needs to be augmented. More interpretation of the findings is needed.
There needs to be a discussion of joint space narrowing findings and baseline bilateral knee pain findings.
Limitations and strengths of study need to be listed.

Authors’ response: The discussion has been expanded and augmented as requested and a paragraph summarising the studies strengths and weaknesses has been added.

Author’s changes:
The following has been added to the discussion (p12):
Patients developing osteoarthritis after joint injury might be a different subset with different disease course. As patients with joint injury were excluded from this cohort, it is not possible to tell if individuals who develop unilateral disease as a result of injury also progress towards bilateral disease in the same way. Whilst it would be easy to assume that our results are solely due to genetic pre-disposition, changes in gait, mechanical loading and behaviour also need to be considered as causes for bilateral disease development [7].

Later in the discussion the following paragraph has been added (p13-14):
Whilst the sample size used in this study was good overall, some of the numbers in individual cells were relatively small and this may have been a factor in the lack of a significant result. This deficiency is emphasised by the width of the confidence intervals for the odds ratios, which were large.

The following paragraph has also been added (p14):
The primary time-point of interest was the 12 year follow-up. The loss to follow up at 5 years (18/143) was relatively small and the results between baseline and 12 year follow up for those 18 patients were representative of the results for the whole population. We therefore believe that it is unlikely that the loss of those patients at the 5 year time point had a significant effect on the 5 year findings.

A summary of the strengths and weaknesses has also been added (p15):
Therefore the weaknesses of the study are the relatively small sample size, particularly when subgroups were considered or in the logical regression results. The lack of association between bilateral disease and age, gender, BMI and pain should be considered with caution given this weakness. The strengths of the study are the prospectively collected, community based dataset of early osteoarthritis with radiographic data collected over a long time period and read by the same experienced
radiolo gist. We believe that numbers were more than adequate to draw the primary conclusion of the paper, that bilateral disease is a common outcome in patients who present with knee pain and particularly in those who already have evidence of osteoarthritis in one knee.

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

Yours sincerely,

Andy Metcalfe ametcalfe@doctors.org.uk
Carina Thorstensson [Corresponding Author] carina.thorstensson@spenshult.se