Author's response to reviews

Title: Smoking and primary total hip or knee replacement due to osteoarthritis in 54,288 elderly men and women

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Dear Editor and Reviewers,

We are grateful for the comments. The manuscript has been revised and in the following document we provide explanations to each of the raised questions and comments. All changes introduced are highlighted in the manuscript in red font.

Response to Reviewer Jari P Arokoski

Comment 1: “Although the study has several strengths, the study has two limitations.

1. It seems that authors are unable to assess other potential confounders (i.e. joint injuries or past stressful physical work). The effects of these variables are usually taken into account, when examining risk factors for knee and hip OA.”

Response to comment 1:
This limitation is stated in the manuscript. We do not have the information about past injury or past stressful physical work and therefore we cannot account for these factors as stated in the limitation section in the Discussion.

The only variable that measured any possible physical stress on the hip or knee joints was the participant-reported weekly physical exercise. Our study did account for this variable and found it to be a risk factor for TJR among males (adjusted sHR: 1.13, 95% CI 1.01 – 1.26) but not among females (adjusted sHR: 1.00 95% CI 0.92 – 1.01) as shown in the multivariable model presented in Table 4.

Comment 2:
2. “Secondly, exclusion of those with definite hip or knee OA at the baseline seems to be impossible. Knee/hip OA may have been present at baseline.”

Response to comment 2:
We could not exclude those with hip or knee OA at baseline. This limitation is stated in the manuscript. Our study endpoint was “undergoing a total joint replacement (TJR) due to severe osteoarthritis (OA)”. This was further clarified in the manuscript. TJR was chosen as a
surrogate indicator of severe osteoarthritis. Since “having a TJR” rather than “having any OA” was our outcome, all those who had had a TJR procedure before our follow-up (i.e., the prevalent cases) were omitted from the analysis.

**Response to Reviewer David Felson**

**Comment 1:**
“The good news is that the authors have addressed the comments we made in review of the initial submission. The bad news is that the responses don't (and perhaps can't) address the substantive and residual concerns about confounding that remain.”

**Response to comment 1:**
As stated earlier, our retrospective cohort study, which is the highest possible level of evidence to study the relationship between smoking and long term outcomes, is not a randomised controlled study and therefore, confounding from unknown factors that cannot be accounted for is always possible. This limitation is stated in the manuscript.

**Comment 2:**
“There have been many studies of smoking and OA, many of which have reported results similar to those in this paper.”

**Response to comment 2:**
We agree that several studies reported an inverse association between smoking and either OA or TJR. The inverse association between smoking and OA was demonstrated in prevalence (a less optimal design) and incidence studies such as the one reported by Felson D et al., 1997 (ref # 8). The findings of our study are consistent with the various reports – some of which have been cited in our paper.

However, our cohort analysis is the first study to show such consistent findings in 1) males and females, 2) older and relatively younger participants, 3) low, middle and high socioeconomic status groups, 4) obese and non-obese participants, 5) and in both total knee and total hip replacements.

**Comment 3:**
“These have been recently reviewed in at least one meta-analysis. As an author of a couple of these studies, the main concern is that obesity is a huge risk factor for disease in the knee (and to a lesser extent in the hip) and that smokers are invariably much thinner on average than nonsmokers. The persistent thinness of smokers makes the independent relation of smoking and OA difficult to determine without adjustment for obesity and weight over time.”

**Response to comment 3:**
As clarified previously, change in weight over the study follow-up time cannot be accounted for. This limitation is clearly stated in the discussion. However, it is noteworthy that mean follow-up time was not too long, mean of 8.6 (SD 3.4) years.

As clarified previously, we accounted for various nurse-measured determinants of baseline obesity such as weight and height, BMI, and arm, waist and hip circumferences. Our models
do validate the Reviewer’s comments that obesity is a risk factor for TKR and THR although the association is stronger for the knee.

As we have clarified previously, the inverse association between smoking and TJR was observed in both the obese and non-obese participants. Smoking was prevalent in all groups, both obese and non-obese. However, this study is the first to demonstrate that this inverse relationship is more prominently observed in the obese.

Comment 4:
“Further, the subjects in this study are very old and one worries about specific comorbidities like lung disease that would contraindicate the procedure being studied mostly in smokers. The authors note that specific comorbidities were tested in analyses but they really needed to deal explicitly with targeted comorbidities that might affect the relationship of interest, not all of them.”

Response to comment 4:
We accept that old age can be a limitation in this study. However, we argue that the relatively advanced age of our study participants may also be a strength rather than a limitation for the following reasons:

1. Because the cohort was relatively old, exposure to smoking was longer.
2. At baseline, median age of the participants was 72 years and at this age the participants were screened for the presence of various health conditions. Therefore, most of the co-morbidities present at baseline were detected and accounted for.

We have no information on new co-morbidities that occurred over the 8.6 (SD 3.4) years of follow up and this limitation is stated in the manuscript. However, age, which is often considered the simplest co-morbidity score, was accounted for over the follow-up period. Similarly, death that could have occurred in those who were older and sicker was accounted for as a competing risk.

As stated earlier, we did look at all 17 individual co-morbidity groups that form the Charlson index. We did the analyses on each targeted group separately but also on all these groups as presented in the Charlson index. As we have clarified in our previous response, the inverse association between smoking and TJR did not change when individual targeted co-morbid conditions were assessed.

Response to Reviewer Peter Lee

In this document, we want to address the comments of the Reviewer from this review and also from the previous one. We apologise for not addressing some of the points raised in the previous review.

Comments from 2nd review:
“Looking back at the points I raised earlier, my main problem is that, although I have previously published work on the magnitude of the effect that misclassification of smoking habits might have in biasing relative risks, I simply do not understand the final figure.

I had expected to see details of how the magnitude of the relative risk would change after adjusting for different defined fixed levels of specificity (or of sensitivity - though that is hardly of interest as nonsmokers don’t usually claim to smoke), but here I am not even sure whether the x-axis is relative risk or is specificity/sensitivity.

Can the methods and/or legend be expanded to make it precisely clear what the objective of the method is, and what the figure purports to illustrate. I also note that the figure is not actually cited in the text at all, is shown as being Figure 2 under Figure legends, and is actually labelled as Figure 7 at the bottom of the figure itself.”

Comments from 1st review:
“As regards misclassification of smoking status, all one is told is that adjusted relative risks (RRs) were calculated under a variety of possible sensitivities and specificities, without saying what they were. As generally people do not falsely claim to be smokers, so that the sensitivity can be regarded as essentially zero, it would seem better to simply report how the RRs varied for a range of specificities, or even better (as being more comprehensible to the non-statistician), as to how the RRs varied for different assumed proportions of smokers denying smoking, e.g. 5%, 10% or 20%.”

Our response to the statistical review:

1. In both reviews 1 & 2, the Reviewer states that the main possible misclassification of exposure to smoking relates to the specificity and not the sensitivity. We argue that the opposite is true, that is, the main misclassification relates more to the sensitivity measure and less to the specificity. Using the below 2x2 table, we explain our point:

<table>
<thead>
<tr>
<th></th>
<th>Yes smoking</th>
<th>Not smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>The self-reported</td>
<td>Yes smoking</td>
<td>b</td>
</tr>
<tr>
<td>variable of smoking</td>
<td>Not smoking</td>
<td>c</td>
</tr>
<tr>
<td>The ‘truth’</td>
<td>a</td>
<td>d</td>
</tr>
</tbody>
</table>

Specificity is the probability of someone not smoking is classified as not smoking, that is, the specificity will be: d/(b+d). This will be relatively high based on the Reviewer’s correct assumption that “generally non-smokers don't usually claim to smoke”.
Sensitivity is defined as the probability of someone smoking is classified as smoking, that is, the sensitivity will be: a/(a+c). This measure will most surely be more uncertain than the
previous measure since, as the Reviewer correctly commented, some smokers might “deny or decline to reveal that they smoke”.

Therefore, we argue that the main uncertainties lie in the sensitivity and not the specificity measures.

2. However, we also argue that uncertainty may affect the specificity. At baseline, the study participants were asked if they smoked (yes or no). Some who smoked many years ago and who misunderstood the question could have answered yes, when the correct answer was no.

3. Since uncertainty can hypothetically be associated with both measures, we chose to run a probabilistic sensitivity analysis that used scenarios of different sensitivities and specificities through Monte Carlo simulations with 20,000 repetitions.

4. To answer the Reviewer’s comments from both reviews, in this revised manuscript as suggested we also ran one-way sensitivity analyses. Our results are shown in the below table that has been added to the revised manuscript as Table 6. We agree with the Reviewer that the requested one-way sensitivity analysis is very informative.

<table>
<thead>
<tr>
<th>Level of uncertainty</th>
<th>Sensitivity</th>
<th>Risk ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed risk ratio</td>
<td>-</td>
<td>0.62 (0.54 – 0.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Expected risk ratios</td>
<td>1%</td>
<td>.99</td>
<td>0.66 (0.58 – 0.75)</td>
</tr>
<tr>
<td></td>
<td>5%</td>
<td>.95</td>
<td>0.76 (0.68 – 0.84)</td>
</tr>
<tr>
<td></td>
<td>10%</td>
<td>.90</td>
<td>0.82 (0.75 – 0.90)</td>
</tr>
<tr>
<td></td>
<td>20%</td>
<td>.80</td>
<td>0.89 (0.82 – 0.95)</td>
</tr>
<tr>
<td></td>
<td>25%</td>
<td>.75</td>
<td>0.90 (0.84 – 0.97)</td>
</tr>
<tr>
<td></td>
<td>30%</td>
<td>.70</td>
<td>0.92 (0.86 – 0.98)</td>
</tr>
<tr>
<td></td>
<td>40%</td>
<td>.60</td>
<td>0.93 (0.88 – 0.99)</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>.50</td>
<td>0.94 (0.89 – 1.01)</td>
</tr>
</tbody>
</table>

Table 6: Observed and expected risk ratios of having a total joint replacement associated with smoking: one-way sensitivity analysis accounting for uncertainty in the classification of smoking exposure

1 Uncertainty in the classification of smoking. The values represent hypothetical percentages of study participants potentially declining to reveal that they indeed did smoke

2 Sensitivity is defined as the probability of someone smoking is classified as smoking

3 The one way sensitivity analysis evaluated the risk ratio under various sensitivity measures while holding the specificity fixed.

Assuming that in general non-smokers do not claim to smoke and under various values of uncertainty in the classification of smoking, the inverse association between smoking and
risk of TJR mostly remained statistically significant (Table 6). Only under the assumption of 50% uncertainty, the risk ratio declined to be statistically significant. Using this high proportion of misclassification would inflate our baseline smoking participants from the study observed 3,535 to 24,075, that is, increasing the observed baseline smokers by nearly 7 times which does not seem likely.

5. Because we argue that uncertainty can also affect the specificity, in this revised version, besides the one-way sensitivity analysis, we also report the risk ratio calculated after conducting the probabilistic sensitivity analysis.²

6. We agree with the Reviewer that the graph depicting 20,000 simulations relating to the probabilistic sensitivity analysis is very hard to comprehend. We agree that reporting one-way sensitivity analyses is much clearer as suggested by the Reviewer. Thus we have made the changes reported above.

7. We chose not to attach to this revised version the graph with the 20,000 simulations. However, if the Reviewer or Editor considers that we need to add it, we will do so and will provide a clearer explanation of the figure.

The methods and results relating to the sensitivity analysis were revised. We provided clearer explanations of our methods and also of the simulated findings. With the Reviewer’s permission, in the revised manuscript we used the explanation the Reviewer provided that “non-smokers do not claim to smoke” in order to better explain our methods.


Response to the Editor’s comments

Comment 1: “It is particularly important that you include a limitations section in the discussion, and provide a more thorough explanation of the figures as requested by the statistical reviewer.”

Response to comment 1: We included a separate section in the discussion discussing both the strengths and the limitations of our study. The comments of the statistical Reviewer were addressed.

We thank you for this review and for considering our study for publication.

Sincerely,
Dr George Mnatzaganian

Corresponding Author