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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Response to Reviewers

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BMC Medicine

Dear Editor and Reviewers,

We are grateful for the comments and suggestions. 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 Jeffrey Katz

Comment 1: “Explain the components of the SES indicator so the reader can better understand what it means and how it is derived.”

Response to comment 1: As suggested, we explained the socioeconomic status indicator included in the Socioeconomic Index For Areas (SEIFA). The following was added to the Methods:

“The socioeconomic status (SES) was measured by an ecological measure, the Socioeconomic Index For Areas (SEIFA) which is based on data from the 1996 census for residential postcodes [23]. SEIFA is a composite index that ranks geographic areas across Australia in terms of their relative socio-economic advantage and disadvantage based on census data, where lower scores indicate more disadvantaged areas and higher scores indicate more advantaged areas. The score is constructed using a number of different variables that indicate both advantage (i.e. high income, having a degree qualification) and disadvantage (i.e. unemployment status, low income, not enough bedrooms). For example, an area could have a low score if there are, among other things, many households with low
incomes, or many people in unskilled occupations. This index is frequently used in Australian epidemiological studies where individual measures of socioeconomic status are not available.” (Methods, pages 5-6)

Comment 2: “Provide the interested reader with an explanation of how the competing risk regression works. Not in mathematical terms but conceptually how does the regression calculate a hazard for smoking that takes into account mortality risks?”

Response to comment 2: As suggested, we have added the sentence below to further explain the subhazard that takes into account the presence of a competing risk.

“The regression model for competing risks of Fine and Gray estimates the ratios of the hazards of the subdistributions, a natural extension of Cox modelling for hazards in the non-competing risks situation. The hazard of the subdistribution [for the event of interest, that is TJR] can be interpreted as the probability of observing the event of interest in the next time interval while knowing that either the event did not happen until then or the competing event did happen.” (Methods, page 7)

Response to Reviewer Jari P Arokoski

Comment 1: “This study evaluates the association between smoking and risk of undergoing primary total joint replacement (TJR) in a large national cohort of men and women. The aim of the study is important as the authors indicate that the reported association of smoking with OA or total joint replacement has not been consistent. The one strength of this study is that the study sample represents family medical practices throughout Australia well. However, I would like to suggest some points for revision.

1. One possible limitation or confounding factor is that if participant already had clinical knee or hip OA at baseline. You asked several co-morbidities at baseline (please explain shortly the Charlson Co-morbidity Index). Although TJR subject were excluded from the analysis, did you ask separately the clinical hip and/or knee OA at baseline?”

Response to comment 1: We have added the following limitation to address this comment.
“Our study considered TJR as a surrogate indicator of severe osteoarthritis (OA); however, OA status was not ascertained at baseline among study participants. Thus in our relatively older cohort (mean age 73 [SD 5] years), OA may have been present at baseline. It was also not possible to identify OA cases through the Charlson co-morbidity index since OA is not a component of this score.” (Discussion, page 13)

Comment 2: “Secondly, two important possible confounding risk factors were not taken account in this study. It is known that heavy physical stress at work and traumatic joint injuries are well known risk factors predisposing to OA particularly in the knee joint. Is it possible to take into account these confounding factors afterwards?”

Response to comment 2: As the Reviewer has previously commented, the study sample represented Australian family medical practices. The 54,288 men and women came from all walks of life and all types of work. We had no information about the participants’ level of physical intensity at work nor their history of past traumatic injuries. Although our study only considered elective TJR procedures due to OA, we agree that a proportion of the individuals with OA reflect past injury that was not accounted for. This limitation was also added. (Discussion, page 13)

Response to Reviewer David Felson

Comment 1: “The failure to count TJR’s just after the blood pressure exam is a potentially major source of bias. For example, there could have been a higher rate of TJR’s among smokers just after the blood pressure exam that would have been missed, leaving fewer smokers to get TKR’s thereafter.”

Response to comment 1: The paper addresses the above potential limitation. However, as we have also stated, there is no evidence to suggest that, during the 2.3 years from baseline to complete national capture of all lower limb joint replacements by the Australian National Joint Replacement Registry, the missed procedures were more likely to be among smokers. The original ANBP2 study was not related to the objectives of this current analysis and the participants were not screened for the presence of any joint disease requiring a replacement. All 54,288 participants were hypertensive, and those eligible to take part in the then planned RCT had to be either untreated or previously treated (for their
hypertension) with no history of recent cardiovascular morbidity or serious intercurrent illness.\(^1\)


**Comment 2**: It appears that the smoking analysis presented in tables 4 and 5 were carried out adjusting for ordinal categories of body mass index, but this leaves room for residual confounding by bmi.

**Response to comment 2**: Our analysis has adjusted for various measures of obesity.

1. In Table 3, we stratified TJR procedures by: smoking status, age, socio-economic status and BMI categories. As we have stated in the Results, compared with non-smokers at baseline, current smokers were significantly less likely to undergo a TJR procedure observed in all SES groups, age groups; this was seen in both the obese and non-obese.

2. In Tables 4 and 5, we controlled for BMI categories (as shown in the tables), and also adjusted for BMI as a continuous variable. This did not produce any difference in the results (we preferred to show the results on the BMI categories because these categories are meaningful to clinicians). We have added a sentence in the results stating that we adjusted for BMI as a continuous variable (Results, page 10).

3. As listed in the manuscript, besides BMI, we also controlled for other available measures of obesity including body weight and height, arm, waist and hip circumferences, and in all these analyses, the inverse association between smoking and TJR remained consistent and significant without any difference from what is shown in Tables 4 and 5.

**Comment 3**: Since smokers remain thinner over time, a one time measure of BMI is probably insufficient to examine the confounding effect of BMI on smoking and TJR. Even
more concerning is that the mean subject age at baseline was 72 years and that smokers at that time had worse comorbidity scores than nonsmokers. That would have probably worsened over time (time varying comorbidity in smokers) so that smokers would have gotten sick enough that they might not have been candidates for this elective surgery.

**Response to comment 3:** In response to this comment, we have added the following limitation: “The clinical data presented in the study were collected at baseline screening and, except for age, the study did not account for changes in patient characteristics (e.g., change in body weight or co-morbidity) that could have occurred over time.” (Discussion, page 14)

The smokers may remain thinner over time; however, it is noteworthy that the protective effect of smoking was more prominently seen among obese participants (as indicated in Table 3).

Our study is not a randomised controlled trial, which is not feasible to study this question. In addition it is embedded in a large cohort formed to study a different health issue, thus confounding from unknown variables is hypothetically possible – we have stated this in the revised manuscript. (Discussion, page 14) However, our cohort analysis is the highest level of evidence that can be conducted to investigate such study objectives. This analysis is the first to show such consistent findings between the inverse associations between smoking and lower risk of undergoing a TJR 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 total knee and total hip replacements. These consistencies, and the strength of the associations together with the temporality in the relationships provide additional evidence for a possible causal relationship.

Another interesting finding in our study is the fact that TJR was not associated with socioeconomic class, using an ecological measure of SES. It is well known that the socioeconomically disadvantaged smoke more (as indicated in our study) and are most likely to have more co-morbidities than the less disadvantaged. All these may lead to an inverse association between SES and TJR. But this was not shown in our cohort.
**Comment 4:** Note that a comorbidity of special interest given that the outcome is TJR is lung capacity/pulmonary function. Smokers have much worse pulmonary function and this may have made them ineligible for TJR. A comorbidity index would not have captured this well nor would a competing risk of death analysis.

**Response to Comment 4:** As stated in the manuscript, the Charlson co-morbidity index was constructed from 17 groups of co-morbid conditions. One of these groups relates to chronic pulmonary disease. The following chronic pulmonary diseases are represented in this index:

1. Chronic pulmonary hypertension  
2. Chronic unspecified bronchitis  
3. Chronic obstructive bronchitis  
4. Chronic restrictive bronchitis  
5. Emphysema (all types)  
6. Asthma (all types)  
7. Bronchiectasis  
8. Chronic pneumonitis (all types including chronic diseases due to external agents such as asbestos or other agents such as fumes, radiation, etc)  
9. Chronic fibrosis

In separate analyses (not presented) we did fit the models to each of the 17 co-morbid conditions forming the Charlson index. In those models, the significant inverse associations between smoking and TJR remained.

Fitting a statistical model to the data as a function of every single co-morbid condition together with other study covariates may result in model over-fitting. An over-fitted model will generally have poor predictive performance, as it can exaggerate minor fluctuations in the data.\(^2\) Therefore, we preferred the single Charlson co-morbidity adjustment score especially when the results were consistent (with the index alone or with all co-morbid conditions separately).
Response to Reviewer Peter Lee

Comment 1: “This is a very well written and generally clear paper, with appropriate statistical analysis. The only issue I have is that the sensitivity analyses were not well described.

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%. As far as I can see, the statement that “the 2.5th and the 97.5th percentiles of the simulated distribution of bias-adjusted RRs were 0.03 and 0.58, and the median estimate was 0.33” will have no meaning to anyone without knowledge of the misclassification rates assumed, and will have little meaning even with knowledge. I also note that the second line of the sensitivity analyses has a statement “assuming trapezoidal distribution between 0.75 and 1” which means nothing to me. Distributions of what?

Response to comment 1: We have clarified the methods we used to run the sensitivity analysis. We simplified the explanation of these methods and the reporting of the results. We referred the reader to the studies whose methods we had adopted. We fully agree that statistical terminology can be hard to comprehend. The “Methods” of this analysis now reads as follows:

“As suggested by Jurek et al [21] and Orsini et al [22], we used probabilistic sensitivity analyses to assess the uncertainty in the association between the exposure (i.e., smoking) and the outcome (i.e., TJR) due to probable misclassifications of the smoking exposure and socioeconomic disadvantage score. Misclassification-bias-adjusted relative risks were calculated under a variety of possible fixed sensitivities and specificities of smoking
classification among those with and without TJR. The assigned fixed sensitivities and specificities (for example 1.0 or 0.9 or 0.8 or 0.75) among those with and without TJR allowed adjustment of the observed data for possible classification error [21]. The possible scenarios of different sensitivity and specificity values were assessed simultaneously using probabilistic sensitivity analysis through Monte Carlo simulations with 20,000 replications. Similarly, 20,000 simulations were run to account for uncertainty in the classification of the SEIFA disadvantage score. A limitation in this analysis is that it assumes fixed values and it fails to discriminate among the different scenarios in terms of their likelihood [22].

All analyses were performed using Stata statistical program (version 11, Stata-Corp.) and the PSA was run using Stata command “episensi.” (Methods, pages 7-8)

**Comment 2:** As regards accounting for unmeasured confounding, neither the methods section nor the results section gives the reader a vague clue as to what has been done. For a start, I do not know which variables the authors are considering that might have been relevant confounders. I also note that Figure 2 is labelled Figure 7.

**Response to comment 2:** Since the main objective of the PSA was to account for possible uncertainties in the classification of both smoking status and socioeconomic disadvantage score, we decided to omit from this study the analysis that accounted for unmeasured confounding. The unaccounted confounder initially considered was “physical activity” because the information we had on baseline physical exercise was self reported and was not validated.

We added the following limitation: “Information on the physical activity of the participants was self-reported and not validated.” (Discussion, page 13)

**Comment 3:** Whilst I applaud the general idea of carrying out tests to show that associations are robust to misclassification of smoking status and unmeasured confounding, one needs to be clear what was done. Given they are only sensitivity analyses, I suggest that the authors use additional files to describe what they have done in more detail, give more results, and cross-refer to these files in the main paper.

As I indicated for the misclassification analyses, a simpler approach would be beneficial also.
Response to comment 3: As suggested, we adopted a simpler approach by leaving out all the hard-to-comprehend statistical terms. We clarified the PSA that accounted for misclassification of two variables (smoking and SEIFA disadvantage score). We focused on the sensitivity analysis that accounted for probable misclassification biases. We omitted additional sensitivity analyses. This in turn made both the methods and results easier to comprehend. As suggested, we added a graph to show the simulations.

Comments 4: p 5 “Study independent variables” line 1 – the word “baseline” appears twice.
Response to comment 4: Mistake corrected.

Comment 5: p 7 “Sensitivity analyses” line 3 – “uncertainty” mistyped.
Response to comment 5: Mistake corrected.

Response to the Editor’s comments

Comment 1: Consent: when outlining the ethical approval for your study in the Methods section, please include details of whether informed consent was obtained or whether the need for consent was waived by the ethical committee due to de-identified data being used.

Response to comment 1: As suggested, we included the following sentence: “The need for informed consent was waived by the ethical committees due to de-identified data being used.” (Methods, page 5)

Comment 2: Keywords: please provide a list of 3-10 keywords after the abstract to describe the main contents of the article.

Response to comment 2: As suggested, we added keywords to describe our study. (Page 2)

Thank you.
Sincerely,
George Mnatzaganian
Corresponding Author