PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A population-based survival analysis describing the association of body mass index on time to revision for total hip and knee replacements: Results from the UK General Practice Research Database
AUTHORS	Arden, Nigel; Culliford, David; Maskell, Joe; Judge, Andrew

VERSION 1 - REVIEW

REVIEWER	Jessica L. Maxwell, PT, DPT, OCS Clinical Assistant Professor of Physical Therapy and Athletic Training Boston University, USA There are no competing interests.
REVIEW RETURNED	26-Aug-2013

THE STUDY	More information on validation of GPRD data is needed.
RESULTS & CONCLUSIONS	Focus on categorical data would be clearer to a clinical audience.
GENERAL COMMENTS	This is a well-written and well-executed paper. The knowledge you are disseminating is important and exciting, and the methods, including the thoughtful sensitivity analyses, are thorough and clear. My comments are mainly few suggestions to perhaps improve the accessibility of the results to clinicians. Overall comment: Please be clear about the time frame to revision for each analysis/result. I found myself repeatedly going back to see if results were for the first year post-op, or what the time frame was. Abstract: Results: Perhaps highlighting some of the results with your exposures as categorical variables, rather than continuous, would make the results more clinically interpretable. The result with morbidly obese may be qualified by “in the first year” if this is the case. Conclusions: Page 3, Line 6: may wish to add the term “statistically” to phrase “significant association”. “What this study adds”: Page 3, Line 50. The number needed to treat is interesting from a public health perspective, however I don’t remember reading this in the main results. Main Body: Intro: Page 5, Line 51. Revisions also have increased risk to the patient, in addition to cost. Line 12- It is unclear why you mention the National Joint Registry. If it is to highlight the reasons why you selected the CPRD instead, more transition may be needed.

	Methods: Please describe methods to validate Read codes selected for use in the study, such as review of patient profiles. Results: Pg 9, Line 12. You discuss missing data percentages, but I do not see them in the tables? Please again be clear of time frames for each analysis. A table of results of the categorical variables at different time points would clarify the results from a clinical standpoint and may be more useful than Table 4.

REVIEWER	Hilal Maradit Kremers Associate Professor of Epidemiology Mayo Clinic, USA
REVIEW RETURNED	17-Sep-2013

GENERAL COMMENTS	Thank you for the opportunity to review this interesting article on the role of obesity on time to revision surgery in THA and TKA. As underscored by the authors, there is a paucity of literature on this topic and the authors rely on data from a large, strong general practice database in the UK. As predicted, the findings indicate a small significant effect of BMI but the absolute numbers are small because revision is a relatively uncommon outcome. Adjusting for the competing risk of death is also important because typically, most THA-TKA patients are deceased before their implants wear out. 1. BMI FOCUS: I suggest that the authors focus exclusively on their results with BMI since the association with age and sex are well-established. This would reduce the number of tables and figures (e.g., Figure 2a/2b not needed) 2. BMI unit: Would be preferable to express risk ratios per 5 or 10 kg/m2 units. Risks per 1 unit increase are not clinically intuitive. 3. CAUSE of revision: As the authors highlight, in the absence of information on the causes of revision, it is very difficult to interpret how obesity influences revision risk in THA and TKA. Yet, this can be done indirectly by examining when revisions occurred: if early, most likely instability-fractures or possibly infections and if beyond 5 years, then most likely aseptic loosening, wear related. 4. LIMITATIONS are not adequately highlighted. First, GPRD is possibly not reliable to distinguish primary and revision procedures, or whether a revision is a first or a subsequent revision. This is evident with revision rates lower than the registry estimates. Second, it is unclear how complete the BMI data are, and the time window when BMI data were ascertained. Since these are the main exposure and outcome variables, I suggest that the authors acknowledge measurement limitations, and if possible, include more information in the methods how they worked with the data to overcome these limitations. Apart from these issues, I think this is a valuable addition to the literature on this topic..

VERSION 1 – AUTHOR RESPONSE

Reviewer: Jessica L. Maxwell, PT, DPT, OCS Clinical Assistant Professor of Physical Therapy and Athletic Training Boston University, USA

There are no competing interests.

More information on validation of GPRD data is needed.
Focus on categorical data would be clearer to a clinical audience.

Dear Authors: This is a well-written and well-executed paper. The knowledge you are disseminating is important and exciting, and the methods, including the thoughtful sensitivity analyses, are thorough and clear. My comments are mainly few suggestions to perhaps improve the accessibility of the results to clinicians.

Overall comment: Please be clear about the time frame to revision for each analysis/result. I found myself repeatedly going back to see if results were for the first year post-op, or what the time frame was.

Abstract:
Results: Perhaps highlighting some of the results with your exposures as categorical variables, rather than continuous, would make the results more clinically interpretable.

The result with morbidly obese may be qualified by “in the first year” if this is the case.
This refers to the overall relative subhazard of revision, not the first year.

Conclusions: Page 3, Line 6: may wish to add the term “statistically” to phrase “significant association”.
We have added the word “statistically”

“What this study adds”: Page 3, Line 50. The number needed to treat is interesting from a public health perspective, however I don’t remember reading this in the main results.
Thank you for highlighting this omission. We have now corrected this so that the NNT numbers are in the main results section.

Main Body:
Intro:
Page 5, Line 51. Revisions also have increased risk to the patient, in addition to cost.
We have made additional comments to reflect this point.

Line 12- It is unclear why you mention the National Joint Registry. If it is to highlight the reasons why you selected the CPRD instead, more transition may be needed.
The National Joint Registry (NJR) is the most complete source of data on hip and knee replacements in England and Wales, and we cite it in order to give an idea of the current magnitude of THR/TKR activity. We partly mention it to explain why the CPRD was used, and we have added sentences to further support our choice of CPRD.

Methods:
Please describe methods to validate Read codes selected for use in the study, such as review of patient profiles.
We did not request patient notes for this study, but we did verify the selection criteria. The list of Read codes used to select primary and revision operations were independently verified by different physicians and then a consensus list was agreed between them. We have added a sentence to reflect this.

Results:
Pg 9, Line 12. You discuss missing data percentages, but I do not see them in the tables?
The only variable where we had missing data was BMI, where for 19% of hips and 14% of knees we did not have a recording of BMI preoperatively, and we quote these rates in the table. All other variables listed in the table (e.g. age, gender) were completely observed.

Please again be clear of time frames for each analysis.
We thank the reviewer for this helpful suggestion. We have been through the manuscript and have tried to be more specific about the timeframes. One example was where the word “overall” was misplaced and now we refer to “differences in the overall cumulative incidence” to make it clear that we are not looking at a timepoint (e.g. 3 years). Also, in the two main paragraphs describing the competing risks results, we have added the phrase “again over the entire period of follow-up” to emphasise the time period being modelled (i.e. all the data).

A table of results of the categorical variables at different time points would clarify the results from a clinical standpoint and may be more useful than Table 4.
We did produce cumulative incidence estimates for revision at different time points (1, 3, 5 10 years), but these are by definition unadjusted, simple statistics. However, all our regression models for both competing risks and Cox proportional hazards were estimated using all the revision events over the entire follow-up, therefore we did not have categorical parameter estimates available for different timepoints to include in a table. The reasoning was to focus the results for the effect of BMI, and to maximise precision by using all the data.

We would like to retain table 4 to enable comparison between the competing risks and the Cox estimates so that the reader can fully appreciate just how similar these parameter estimates are, even though they should be viewed as having subtly different interpretations.

Thank you.

Reviewer: Hilal Maradit Kremers
Associate Professor of Epidemiology
Mayo Clinic, USA

Thank you for the opportunity to review this interesting article on the role of obesity on time to revision surgery in THA and TKA. As underscored by the authors, there is a paucity of literature on this topic and the authors rely on data from a large, strong general practice database in the UK. As predicted, the findings indicate a small significant effect of BMI but the absolute numbers are small because revision is a relatively uncommon outcome. Adjusting for the competing risk of death is also important because typically, most THA-TKA patients are deceased before their implants wear out.

1. BMI FOCUS: I suggest that the authors focus exclusively on their results with BMI since the association with age and sex are well-established. This would reduce the number of tables and figures (e.g., Figure 2a/2b not needed)
We thank the reviewer for making this point and agree that BMI should be the main focus. We have restructured the tables such that BMI appears first in each table, with age in the middle and gender last. We have also revised the wording and ordering of the results to reflect this. However, we feel that, particularly in the UK, there has not been sufficient coverage of age-specific survival estimates for age within a competing risks framework and would therefore like to retain the graphs with age as of secondary interest.

2. BMI unit: Would be preferable to express risk ratios per 5 or 10 kg/m2 units. Risks per 1 unit increase are not clinically intuitive.
We have added risks per 5 and 10 kg/m2 for THR and TKR in the results section reporting the multivariable model results, to assist with clinical interpretation.

3. CAUSE of revision: As the authors highlight, in the absence of information on the causes of revision, it is very difficult to interpret how obesity influences revision risk in THA and TKA. Yet, this can be done indirectly by examining when revisions occurred: if early, most likely instability-fractures or possibly infections and if beyond 5 years, then most likely aseptic loosening, wear related.
As the reviewer mentions, we acknowledge that we do not have any data on cause of revision within the GPRD. One possibility might have been to look at two-stage revisions (81% of which had infection as primary indication[1]), but we cannot reliably establish linkage of such operations within our GPRD

data - clearly this would be possible within a registry. We have added to the limitations to explain our reasons for not being able to conduct an indication-specific analysis.

What we did do (in terms of looking at a time cutpoint) was to examine whether a single changepoint (at 1 year) showed a difference in the subhazard of revision for the morbidly obese versus non-morbidly obese (see last paragraph of results). Although this seemed to support an elevated risk of early revision for the morbidly obese (as suggested in figure 1a), again we cannot be at all sure whether this is mainly due to infection or other complications. We plan to look at this aspect in our future research.

4. LIMITATIONS are not adequately highlighted. First, GPRD is possibly not reliable to distinguish primary and revision procedures, or whether a revision is a first or a subsequent revision. This is evident with revision rates lower than the registry estimates. Second, it is unclear how complete the BMI data are, and the time window when BMI data were ascertained. Since these are the main exposure and outcome variables, I suggest that the authors acknowledge measurement limitations, and if possible, include more information in the methods how they worked with the data to overcome these limitations.

We fully accept that databases such as GPRD can never be as accurate as registry data, and that coding errors do occur at source. Nevertheless, the Read code system provides offer a range of specific primary and revision codes for hip and knee arthroplasty and the clinicians within our GPRD study team have selected only those codes which they can be fairly confident as to their status (primary total vs. revision). We have excluded any primaries which are unlikely to be total joint replacement.

In terms of the time ordering, we have only taken time from primary THR/TKR to the first revision, thus ruling out double-counting for two-stage revisions for deep infection. We refer to this in the methods section under participants ("the event of interest …was the first recorded revision operation").

We describe the completeness of BMI in terms of how many subjects do not have any pre-operative BMI recorded (19% for THR; 14% for TKR, see table 1). Within the GPRD BMI is usually only available if measured by the GP, and indeed the timing of the most recent pre-operative BMI is variable. As requested by the reviewer, we have included some more information in the Results section under Participant Demographics.

Apart from these issues, I think this is a valuable addition to the literature on this topic..

[1]National Joint Registry for England, Wales and Northern Ireland, 10th Annual Report 2013