# Authors response to reviewers and editors’ comments

We are very thankful for the opportunity to revise and improve the manuscript according to the suggestions made by the reviewers. Their input has been very helpful, and we feel that the manuscript has been improved thanks to their suggestions! We hope that we have satisfactorily addressed all points raised in the editorial and peer review.

In addition to the revised manuscript, we are also happy to submit a video abstract (2 min 44 sec), which we hope is suitable for the publication. We might note that the background sound is from the public domain (no copyright), and that photos are taken by the corresponding author and approved by the persons depicted.

## Reviewer 1

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| **Comment** | **Authors response** | **Changes made** |
| title is too long (176 characters, 27 words). Please shorten. | We agree and have shortened the title | Title changed to “Prediction of Early Periprosthetic Joint Infection after Total Hip Arthroplasty” |
| Abstract: doubled "the" in line 39/40 | Thank you! | We have omitted the repeated word |
| Abstract Results: How about above 10%? How was the respective AUC? | PJI is a rare event (< 3 % within 90 days) for patients operated with THA. Thus, most patients had covariate patterns leading to modest risk estimates (close to the crude rate of < 3 %; Figure 5). Hence, only very few patients were high risk patients with > 10 % risk (such patients might not have been operated and where therefore not available in the sample). Few events among the high-risk patients, implies an underpower sample in this interval. Hence, the estimated probability in this stratum gets unreliable and uninformative. This was seen by the calibration curve/fig 6 (before axis were truncated), which heavily deviated from the diagonal line at about 10 %. Hence, even if it would be theoretically possible to assign predicted values above 10 %, those values would not accurately represent the “truth” due to heavy extrapolation outside the observed range. AUC values, however, as indication of discriminatory ability alone, might be less influenced by the inferior calibration. It is thus still possible that, for two randomly selected patients, one with and one without PJI, the one with PJI might get a higher predicted probability for such event. But this is equally true for a 0 vs 1 probability or a .49 vs .51 probability. Hence, the AUC would be the same, but the clinical utility of the model would be very different. Therefore, we prefer to abstain from presenting the AUC values stratified to the high-risk interval above 10 %.  In the web calculator, we also choose to not show any estimated probabilities above 10 % (see additional comment below). |  |
| INTRO: "The most devastating" might be misleading. Cardiac complications, thromboembolism and sepsis might be worse. | We are thankful for the comment and have adjusted the intro. | We have changed “the most” to “one of the most” |
| INTRO: There are more tools to predict PJI. Just recently, some algorithms have been developed. | We welcome this news and have (2022-01-07) performed an ad hoc Google scholar search for “prediction pji tha” including new publications since 2020. We got 511 items and performed a manual screening based on titles to include only papers describing preoperative and non-laboratory predictive factors of PJI after elective THA. We read 12 abstracts and found 4 relevant papers, now cited in the manuscript. | We have included four new references.  Lespasio M et al. Identifying Risk Factors Associated With Postoperative Infection Following Elective Lower-Extremity Total Joint Arthroplasty. *Perm J*. 2020;24:20.013. doi:[10.7812/TPP/20.013](https://doi.org/10.7812/TPP/20.013)  Ren X et al. Patients’ risk factors for periprosthetic joint infection in primary total hip arthroplasty: a meta-analysis of 40 studies. *BMC Musculoskeletal Disorders*. 2021;22(1):776. doi:[10.1186/s12891-021-04647-1](https://doi.org/10.1186/s12891-021-04647-1)  Resende VAC et al. Higher age, female gender, osteoarthritis and blood transfusion protect against periprosthetic joint infection in total hip or knee arthroplasties: a systematic review and meta-analysis. *Knee Surg Sports Traumatol Arthrosc*. 2021;29(1):8-43. doi:[10.1007/s00167-018-5231-9](https://doi.org/10.1007/s00167-018-5231-9)    Sodhi N et al. What Are Risk Factors for Infection after Primary or Revision Total Joint Arthroplasty in Patients Older Than 80 Years? *Clinical Orthopaedics and Related Research®*. 2020;478(8):1741-1751. doi:[10.1097/CORR.0000000000001389](https://doi.org/10.1097/CORR.0000000000001389) |
| INTRO: It is not sufficiently developed why 90 days post operation were chosen? From a clinical perspective, this makes a lot of sense, but should nonetheless be further pointed out. | In an earlier version of the manuscript, we looked at both 90 days and 2 years, as potentially interesting periods. We found, however, that the results were very similar for both periods. Since most PJI:s occurred within the first 90 days of surgery, we decided to focus on this period only. This is also a commonly used time interval in similar studies. | We have added a motivation: “[…] PJI within 90 days after THA, a commonly used period to clinically define early PJI.” with a reference to the review article by Leaspasio et al. (see above). |
| INTRO: The socioeconomic impact of PJI should also be stated. Here, Swedish and Danish data would be preferred. | Thank you for this suggestion! We agree that this is an important aspect of PJI. Unfortunately, we did not have any specific data for our cohort regarding this aspect available for this study. We were also not able to find any external studies quantifying the social impact for this group of patients. The reverse relation, hence, the impact of socioeconomics on the risk of revision, has been studied in Denmark, but was considered to be out of scope for the current manuscript (<https://pubmed.ncbi.nlm.nih.gov/34085592/>). | We have added “socioeconomic consequences” to the list of negative side effects following PJI, as well as a reference to a book chapter by Malizos et al. 2016. |
| INTRO: In addition, the validation is appreciated, as pointed out by yourself, but the comparability of Swedish and Danish data should be (at least briefly) mentioned. | Thank you very much! We agree that this is an important and relevant aspect. We did strive for a concise introduction, however, and have included a discussion of this topic in the discussion section instead. |  |
| MM: Was the study registered? If so, where and when? | No, it was not pre-registered. |  |
| MM: How could the patients be matched? Are all data assessed with name and date of birth? | We are happy to clarify that in both Sweden and Denmark, all residents are assigned individual personal identification numbers, either at birth or at the time of immigration. Those numbers are always used to uniquely identify each individual and are used in all registers and in all contacts with authorities. It is therefore possible to identify patients uniquely by deterministic data linkage, without the need of probabilistic matching.  The whole linkage procedure was described in an earlier paper by Cnudde et al. in 2016. | In the interest of accommodating suggestions from reviewer 2 below, we have now tried to condense the manuscript as much as possible. Therefore, we do not describe the procedure in detail, but instead refer to Cnudde et al, with all the relevant details. |
| MM: Please more explicitly state inclusion and exclusion criteria. | We are thankful for the suggestion. | All inclusion and exclusion criteria are now listed in the first paragraph of the MM section (it was previously spread between different sub-sections). |
| MM: It is a limitation that the danish patients were taken from 2016-2018, while the Swedish patients were assessed from 2008-2015. An overlap would be favorable. | We agree that this might be a limitation, although most for pedagogical reasons. Comparable inclusion criteria are hygiene factors for inferential studies where the goal is to compare groups without confounding. External validation for prediction models is slightly different. The purpose here is to validate that the model is robust and generalizable to an independent cohort. This might include a different geographical region, a different period, or as in our case, both combined. Admittedly, our different periods were not intentionally chosen to facilitate temporal validation, but the successful results indicates that the model is not only valid for the historical period used for model derivation. As noted in the 2nd paragraph of the MM section, the reason for the later Danish period was that BMI and ASA class was not previously recorded. | We have now highlighted in the “Strength and weakness” section that the external validation was both geographical and temporal. |
| MM: Were the Danish data also matched across the two databases? How (date of birth or name)? | Please see comment above. Hence, personal identity numbers were used in Denmark, as well as in Sweden. | A reference to Schmidt et al. 2014 was added with description of the Danish personal identity numbers. |
| MM: The limtiation to concentrate on years 35-99 should be mentioned right from the beginning. | We understand the concern but want to clarify that this was no formal exclusion criteria. It was merely a fact that the observed Swedish sample did not include any patients with PJI outside this range. It is therefore more of a safety measure to not use the model for other patients since this would imply extrapolation. Therefore, we did not validate the model for such patients, wherefore those were excluded from the Danish validation cohort. It would still be theoretically possible to make such predictions based on the model, but we would consider it bad practice. It would also be possibly to assume that patients outside this range would have no risk of PJI within 90 days (risk = 0 as our best guess), but this also seems hard to motivate. |  |
| MM: Explicitly showing the Charlson and Elixhauser criteria is not needed. | We are thankful for the suggestion and have removed the table. | The old table 1 has been removed (tables are now renumbered). |
| MM: How did you account for the possibility that further codes might have been used? | This is an important question, which we do not have a perfect solution for. The issue is even more relevant when using data from different countries with possibly different coding practices.  We started with a complex algorithm initially used by the Swedish knee arthroplasty register and later adopted to the Swedish hip arthroplasty register (p. 174 in their annual report: <https://registercentrum.blob.core.windows.net/slr/r/Svenska-Ledprotesregistret-Arsrapport-2021-HJljVnlWvF.pdf>).  We then had extensive discussions among the clinical co-authors to modify the list even further, partially to work in the Danish setting as well, and to work with the available data from the national patient registers. In general, we included codes which might be indicative of PJI, even without guarantees of such event. Hence, we ended up with more cases and a larger proportion of PJI compared to other studies in the field. We then re-run the analysis multiple times using different codes and found that the results were rather stable. Overall, we hope that our quite complex procedure for variable selection did protect the model from too much over-fitting and too much influence from including/excluding individual medical codes etc. We also think that the inclusion of table 1 (previously table 2) is an important attempt to be as transparent as possible with the codes we used. |  |
| MM: What AB were used before surgery? | We agree that this is an important aspect and are thankful for the opportunity to add this information to the paper. | We have added a new sub-section to “Strengths and weaknesses in relation to other studies”:  “The standard peri-operative prophylaxis in THA surgery in Sweden is Cloxacillin (2g x 3) on the day of surgery. Those with confirmed or suspected allergy to Cloxacillin (roughly 10% of all patients) receive Clindamycin (600 mg x 2). This treatment might affect the outcome of interest, and therefore the possibility to generalize our results to countries with other treatment procedures.” |
| RES: The results are novel and provide an advance in the field. | Thank you very much! We appreciate this feedback! |  |
| RES: Fig. 3 should be added the ROC or AUC values. Please remove the major and minor grid lines as well | We agree and have changed the figure. | Grid lines have been removed and AUC values for each curve have been stated within parenthesis. In addition, to make the presentation more focused as suggested by reviewer 2, we have also removed the right panel of the figure. |
| RES: How did you make sure that a PJI was detected, especially if AB were applied "over-the-counter"? | AB is not sold over-the-counter in neither Sweden, nor Denmark. Although not included in the final analysis, we did also study prescription data from the Swedish medical prescription register where different medications are identified by their Anatomical Therapeutic Chemical (ATC) code. In the final version of the analysis, PJI was, however, identified either if the hip was reoperated for this reason, or if an associated ICD-10 or NOMESCO code was recorded in the national patient registers of either Sweden or Denmark (see also comment below as well as the code list in table 2). Overall, we think that our identification criteria were broad; most likely, we included too many, rather than too few, potential cases of PJI. |  |
| DISC: Please start the discussion by summarizing your main findings. | We are thankful for the suggestion but would like to clarify that such summary is found as the first subsection entitled “Principal findings” in the discussion section. |  |
| DISC: Please focus more on the comparison of your findings to other models, especially with regards to complexity. | We thank the review for this relevant comment. | A sentence was added to end of the section of “Strengths and weaknesses in relation to other studies”:  “Another strength is the closed form regression formula presented below which is more transparent than a black box model sometimes associated with machine learning and artificial intelligence.” |
| DISC: Did the model include any opportunity for the operating team to reduce the probability of a PJI? | We agree that identification of modifiable risk factors would be beneficial. Unfortunately, the observational study design does not allow to draw causal conclusions. Hence, the identified predictors are not necessarily causing PJI, they are merely indicators of such events (see de Mast et al; DOI: 10.1080/00031305.2021.2023633).  In addition, we consciously strived for predictors available already before surgery. Therefore, we did not include any potential factors related to the surgical procedure, since this would limit the possibility for the patient to make an informed decision prior to surgery.  Also, further prospective studies are needed to test the model in clinical practice in terms of acceptability, appropriateness, adoption, feasibility, and compliance and decrease in PJI incidence. This was not the aim of the current study. | We added the following sentence (last in the section “Unanswered questions and future research”):  “It should also be noticed that our study design was observational, and can only yield (statistical) correlations between PJI and the included variables.  Additional studies are therefore required to establish causal pathways and to identify possible modifiable risk factors.” |
| CONCL: It should be added the immediate clinical benefit. | We agree that this is an important aspect. We are a little hesitant, however, to be perceived as too speculative if we extrapolate and exaggerate the possible benefits too much. It is thus our hope that the current sentences provide a relatively good balance of the perceived possibilities. |  |
| FIGS & TABS: The figures are clear and legible. Some minor corrections should be done: Fig. 3 and 6: remove major and minor grid. | We are grateful for this positive feedback! | We have removed the grid lines from fig 3 and 6. Figures have also been simplified to increase clarity as suggested by reviewer 2 below, and to avoid transparent layers and additional technical requirements specified below. |
| ADDITIONAL: The shiny app provides interesting results, but instead of giving no answer for certain combinations, a confidence interval or range of probability would be preferred. | We agree that a prediction interval could be of relevance. One difficulty, however, is that the actual outcome is binary, thus that patient either gets PJI or not, while the estimated probability is a continuous value between 0 and 1. Hence, this is a different setting compared to inferential studies where the confidence intervals surround the point estimates as an interval of the most likely outcome (loosely speaking). In our setting, the most likely point estimate would be that the patient will not get PJI (a binary outcome). The probability of such event, on the other hand, might already be seen as a measure of uncertainty. It is not clear that the additional complexity of an estimated probability interval would help the patient further in their decision process. This could be compared to weather prediction. The most important prediction is whether it will rain or not (yes or no). The next level is the probability of rain tomorrow. But already this estimate alone, might be rather unintuitive to interpret.  Considering the situation were no prediction is presented, please see additional comment below. |  |

## Reviewer 2

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| **Comment** | **Authors response** | **Changes made** |
| TITLE: The title of the article is too long so it covers the main aspect of the study. | We are happy to hear that the title was informative. We agree, however, that a shorter title is preferable and have removed the second part of it. | New title: “Prediction of Early Periprosthetic Joint Infection after Total Hip Arthroplasty” |
| ABSTRACT: We already know that the data collected in the result part of the summary section of the article is a risk factor for PJJ. | Thank you for the confirmation that the individual factors seem relevant and are in line with previous research. We appreciate the feedback! |  |
| INTRO: First of all, why is this method limited to the first 3 months of the surgery? It is not explained anywhere in this study. | This is a relevant question, raised by both reviewers. Please see the provided answer to reviewer 1 above. | Please see the provided answer to reviewer 1 above. |
| INTRO: The introduction is unnecessarily long, just like the rest of the article. Introduction provides background and information about the study. | Thank you very much! We have tried to shorten the introduction to make it more focused and relevant. | Approximately one third of the introduction’s middle section was removed. |
| INTRO: I made a few attempts at the link given in the introduction. but the result was 'We have too little data from similar patients and are unable to make a reliable prediction'. | We are happy to hear that also the web calculator was examined and evaluated. The stated message is showed if the provided data leads to predicted probabilities above 10 %. This is likely to occur for (hypothetical) patients with very severe conditions. It would still be theoretically possible to present the best possible estimate given by the prediction model. We must remember, however, that the training data contains only relatively healthy patients, for whom elective surgery was a viable option. We do fear then that heavy extrapolation outside this scope, might lead to more harm than good. We are aware that other modelers have chosen a less conservative path, and that some models do present even very high estimated risks for severe events. It must be remembered, however, that such risks can only be estimated accurately if we first operate patients with a low probability of success (which seems unethical).  An additional, more technical, aspect, is that the modelling process did not account for possible interaction effects (PJI is rare, leading to unsatisfactory power for a model with too many variables). Such interaction effects, by definition, are more relevant to (hypothetical) patients with multiple comorbidities, for which the estimates will be even less accurate. Thus, for patients with unusually severe conditions, we would suggest a more in-depth and individualized patient-physician-discussion, rather than relying too much on any standardized prediction model. |  |
| MM: The material section was again very long and I had a hard time reading it to the end. | We apologize for the excessive details. We have tried to shorten the description to increase focus and to make the text more digestible. | Instead of explicit descriptions of the Swedish data sources, we refer readers to a previous publication by Cnudde et al. Similarly, for the variable selection process, we refer to Garland et al. In addition, to not lose the details for any interested reader, we have made the source code publicly available in a Zenodo repository (with a DOI provided in the manuscript). |
| MM: The formulas described by the authors are very difficult to use and I did not understand how they were calculated. | We realize that those technicalities might be out of scope, and of less relevance to most readers. | All formulas have been removed from the MM section. |
| RES: There is a lot of data in the result section. All data cited are data obtained by previous statistical methods. | We agree that some data are better presented in figures and tables (which we also realize is the recommendation from the author guidelines). | We have tried to minimize the duplication of data in the text. |
| RES: I could not find where in the model data described in the article. | We must apologize but are not able to fully comprehend the meaning of this comment. If the revised manuscript is still inferior in this regard, we must ask for additional clarification. |  |
| DISC: On line 314; Meaning of the study  - The calculation method is quite complex. The authors say it's simple. However, I could not find the corresponding results and constant values (eg [1+exp(6.31-60⋅0.02)]≈ ) in Table 5. | We aggrege that such value judgment is unnecessary and should be avoided. | We no longer describe the formula as simple. We have also removed some unnecessary technicalities and mathematical notation. We have also tried to better explain the meaning of the different parts in the formula. |
| CONCL: The authors claim to have found [that conclusions corresponds to the results found]. But there is no way to control | Thank you! We appreciate the trust. As above, we have also made the underlaying source code available to aid possible replication studies. |  |
| FIGS & TABS: Too long too much data. Distracted while viewing | We agree that some intermediate results of the variable selection procedure could be omitted for an increase focus. Also some of the figures could be simplified with the same purpose. | We have removed the right panel of figure 3, the left panel of figure 5, the previous table 1 and table 4. We have also omitted two redundant columns from the previous table 2.  Figure 5 and 6 were also simplified to avoid the need of transparent layers (as required by editorial comments below). |
| ADDITIONAL: The article is too long. I had a hard time reading to the end. The formulas given are not simple. They should be reviewed | As described above, we have tried to shorten the article with a hope to increase readability and make it more digestible. As commented above, we have also tried to simplify the mathematical notation. | In addition to what has been mentioned above, we have also removed the supplementary material as well as all references to it from the main text. |

## Editorial corrections

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| **Comment** | **Changes made** |
| Author Affiliations: Please update your author affiliations to the following format: department, institution, city, state (if applicable), country. | X |
| Co-author:  Please remove the co-author's email addresses and authors' qualifications from your title page. We only require the corresponding author's email address(es) to be listed). | X |
| Please provide the institutional details (including department) for the postal address provided and include the corresponding author's full name.  Please also ensure the corresponding author information that should match with the provided author affiliation details. | X |
| Key Words: Please provide three to six keywords as a list within the revised manuscript, following the Abstract. | X |
| Tables: Please remove the tables from amongst the main text - tables should either be supplied in a separate MS Word or MS Excel file, or included following the reference list at the end of the manuscript file. | X |
| Author Contributions: We have noticed that the current Author Contribution statement indicates that not all of your authors meet the Authorship guidelines for Dove Medical Press (<https://www.dovepress.com/author_guidelines.php?content_id=3521>). The problem can be resolved by adding the following sentence (if it is accurate): " All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting,  revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work ".  Alternatively, this section can be removed, please edit prior to resubmission. | X |
| Figure Files: Please supply all figures in high quality.jpg, .tif or .pdf format,  one file for each figure (eg, Fig 1, Fig 2, etc). This should include the figure artwork but not the figure legends. If the figures have also been placed in your manuscript, please remove these. Please note that the figure legends must not be placed within the figure artwork and should instead be listed at the end of the manuscript file. See the figure page on our website for further details (<https://www.dovepress.com/author_guidelines.php?content_id=3511>). | X |
| Please ensure copies of all figures/tables/supplementary material are provided with the revised manuscript, even if these are not altered during the revisions so we can ensure we have the most up to date file for each. | X |
| Figure Presentation: Please carefully revise your figures to ensure they follow our Figure Guidelines regarding accepted fonts, line type, and image sizing. All spelling and grammar should be checked prior to resubmission as the figures supplied at this stage will be the ones sent for publication. See our website for further information: <https://www.dovepress.com/author_guidelines.php?content_id=3511>. | X |
| Table Presentation: Please carefully revise your tables to ensure they follow our Table Guidelines regarding accepted formatting, and ensure that all columns are spaced in a way which makes the table text easy to read. All spelling and grammar should be checked prior to resubmission as the tables supplied at this stage will be the ones sent for publication. See our website for further information: <https://www.dovepress.com/author_guidelines.php?content_id=3511>. |  |
| Figure and Table Legends: Please ensure use of any symbols (eg. \*, \*\*, \*\*\*, #, ##, †, a, b, etc), use of bold or italic font, abbreviations and any subfigures are cited and explained correctly and fully in their respective legends. Do not include explanations for symbols or fonts that are not used in that specific figure or table. | X |
| Figures: Please indicate all the figures in sequential order within the main text of the manuscript. | X |
| Figure Indicators: Explanatory notes or a key should be present if the figure contains patterns, colours, symbols, or other formatting that indicates significant data. A key should be included if any symbols are included in the figure. Please amend your figures and figure legends accordingly. | X |
| Graphical abstract: Graphical abstracts should not be a duplication of any figure (or adaptation of 2 different figures) already included in the paper. Graphical Abstracts do not have a title, a caption or a note section, so should be completely self-explanatory. Before you submit any figures for the Graphical Abstract, please check on the below link to ensure your files meet our criteria. Otherwise, if you are happy to proceed without a graphical abstract, please let me know and I will note this in your submission for you. <https://www.dovepress.com/author-guidelines/graphical-abstracts>. | Our paper does not have a graphical abstract |
| Supplementary figures/tables: Please label the Stable and Sfigures as supplementary figure 1 and supplementary table 1 within the main text of the manuscript and in the supplementary file. | We removed the supplementary material due to comments from reviewer 2. |