Author’s response to reviews

Title: Validation of two prediction models of undiagnosed chronic kidney disease in mixed-ancestry South Africans

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Author’s response to reviews:

Re: “Validation of two prediction models of undiagnosed chronic kidney disease in mixed-ancestry South Africans”

Dear Editor,

We are grateful to the Editor and Reviewers for the time spent to provide comments to improve our manuscript. We are glad that the Editor and Reviewers found our paper to be of interest.

We have revised the paper accordingly, as indicated in the format of the manuscript with track changes. We have also provided a point by point response to the comments of the editors and the reviewers. Each of our response is preceded by the expression “Our response”

We appreciate your time and look forward to the outcome of your evaluation.

Yours sincerely,

Andre P. Kengne
On behalf of the co-authors

Editorial Comments:

Thank you for submitting your manuscript to BMC Nephrology.

Two reviewers and an associate editor have assessed your manuscript. We found your manuscript of interest and would like to consider a revised manuscript for publication.

In revising your manuscript, please make sure to address all the points raised by reviewer 2 (Dr. Raji) in the comments.

Our response: As the editor will see below, we have provided a point by point response raised by the second reviewer.

ADDITIONALLY, THE EDITORS WOULD LIKE TO MAKE SURE THAT THE AUTHORS ADDRESS THE VALIDITY OF THE 4 VARIABLE GFR TO DEFINE
CKD AND IF IT IS MORE APPROPRIATE TO USE THE NEWER CKD-EPI EQUATION. MOREOVER, IT IS NOT CLEAR WITH THE KNOWN RISK FACTORS FOR CVD, WHY THE KOREAN AND THAI RISK SCORE WERE USED AS COMPARISON AND DID NOT INCLUDE IMPORTANT FACTORS SUCH AS ELEVATED LDL; HISTORY OF CVD; ETC. THE MODEL BUILDING FOR THE BELLVILLE SOUTH WAS ALSO NOT JUSTIFIED.

Our response: We thank the editor for the suggestions regarding the validity of the four variables included in the glomerular filtration rate (GFR), we have previously explored this in our population through a comparison of various methods of GFR estimation, with ethnicity correction (Matsha TE, et al. Chronic kidney diseases in mixed ancestry South African populations: prevalence, determinants and concordance between kidney function estimators. BMC Nephrol. 2013 Apr 2;14:75). The performance of CKD-EPI equation was close to that of the MDRD equation, but not better. That being said, we do not have enough studies or hindsight to make a unilateral choice in this matter for the type of population explored. In accordance with the Editor's suggestion, we have now presented sensitivity analyses of the performance of the models using the CKD-EPI equation. These are shown presented Tables 3 and 5 and updated figures, as well as on in the new section of the results on pages 9 and 10, lines 235 to 260. We have also included a sentence in the discussion to that effect on page 11 (lines 271 and 272) to indicate that no significant differences were observed with the use of the two eGFR equations.

The Thai models and Korean were chosen for their potential applicability in resource-limited settings. Chronic kidney disease is increasingly common globally, especially in low and middle income countries. In the later settings, measuring lipids levels, urinary albumin excretion, and diagnosis of concurrent cardiovascular disease in everyday clinical or public health practice may not be that obvious. Hence, absolutely relying on these risk factors or conditions to preselect people for further biochemical testing to detect a growing problem such as chronic kidney disease might not be the most appropriate approach from a public health/population perspective. There is always a trade-off between the applicability of a model in a setting and its performance. Hence the adjustment (calibration) and changes made (exclusions) were based on these consideration, as well on the availability of data in our population. It may be better to have an ideal model for predicting prevalent undiagnosed CKD, but we somewhat have to reconcile the ideal with reality.

Regarding the model development, we did not develop new models in our population, we merely validated the models on this populations. The changes/adjustments made, were function of the available variables (predetermined by the original models) and the calibration to our population.

Reviewer 1 - CHARLOTTE OSAFO

Reviewer's report:

This is a well written manuscript by Amelie et al describing the validation of two prediction models of undiagnosed chronic kidney disease in mixed ancestry South Africans.
The question of whether these prediction models of undiagnosed CKD can be used in mixed-ancestry South Africans is well defined and the Methods used are appropriate and well described.

The manuscript adheres to the relevant standards for reporting and data disposition and limitations are clearly stated. The title and abstract accurately convey what has been found.

Our response: We are grateful to the reviewer for their appreciation of our paper. Writing is acceptable however there is the need for a statistician to review the data and figures presented.

Our response: We thank the reviewer for bringing this up. We are confident that our presentation of the data is appropriate, but we defer to the Editor to make this judgment.

Needs some language corrections before being published

Our response: We appreciate the reviewer taking time to point out the omissions and typos. We made the indicated changes, which are shown in the revised manuscript with track changes.

Examples:

Line 236 should read “… our study suggests…”

Our response: We made the suggested change.

Line 247 reads “… across subgroups in our study may simply differences in the distribution of the disease. There is a word missing between ….’Simply’ and ‘differences’

Our response: We inserted the work reflect between simply and differences.

Line 258 …. Unacceptable rates of rate referral … should read ‘unacceptable rates of referral’

Our response: We made the suggested change.

Line 261…. Africa therefore is therefore broad should be Africa therefore is broad

Our response: We made the suggested change.

Line 273 …early diagnostic should be … early diagnosis

Our response: We made the suggested change.

Line 283 should read “the limitations of this study need to be mentioned

Our response: We made the suggested change.

Level of interest: An article of importance in its field

Our response: Thanks

Quality of written English: Needs some language corrections before being published

Our response: We have made corrections (as requested by the reviewer) to improve the flow of the text.

Statistical review: Yes, but I do not feel adequately qualified to assess the
Our response: We think that our presentation of the data is appropriate; however, we defer to the Editor to make this judgment.

Declaration of competing interests: I declare that I have no competing interest.

Reviewer 1: Yemi Raji

Reviewer's report:

General comment: Thank you for the opportunity given to me to review this manuscript. The article is highly relevant to the practice of nephrology in the sub-Saharan African population where preventive nephrology is needed more than anywhere else at this point in time. Designing or validation of a chronic kidney disease prediction model will go along way in early identification of previously undiagnosed case.

Major Compulsory Revision None

Our response: We are grateful to the reviewer for their appreciation of our paper.

Minor Essential Revision

1. Why was anaemia excluded in the prediction model? Could this have added value to the model since anaemia is a universal finding among subjects with CKD.

Our response: We agree with the reviewer that this should be addressed. In the methods section (Handling of missing data) on page 6 (last paragraph, lines 130-138), we clearly specified why we did not include anemia. It is simply because this information was not available in our database. This was indicated as follows: “Some of the predictors included in the tested models were not evaluated in the South Belleville study. These include anemia (included in the Korean model) and kidney stones (component of the Thai model), which were consequently excluded from the validation.”

Though this omission is a limitation that we acknowledge (on page 13 and 14, lines 326-332), such an occurrence is not uncommon in validations studies. It so happen that some of the variables used for prediction in original model(s) are not available in the validation populations. It is even sometimes the case that some of the predictors used in the original models though available in the validation populations, are finally removed from the validated models to account for the distribution of risk factors for the disease (chronic kidney disease here) in the validation population (Moons KG1, Kengne AP, et al. Risk prediction models: II. External validation, model updating, and impact assessment. Heart. 2012 May;98(9):691-8.)

Without the original data to evaluate the added value of including anemia, any attempt to assess this would only be speculative. One can only surmise that this would have improved the performance in the validation population, but it needs to be proven.

2. Both Thai and Korean CKD risk prediction models overestimate the risk in male and underestimate the risk in female in the Bellville cohort, could this be
due to the fact that there are more females than male in the total population eventually included in the analysis? More so that those with missing data that were not included in the analysis were more likely to be male. These issues should be highlighted in the discussion section.

Our response: We are agree with the reviewer, and we have therefore include the following sentence on page 12 (paragraph 2, lines 287 and 288) to indicate the potential reason for the overestimation as follows: “For instance, overestimation observed among of males and youngsters in our population, may simply reflect the predominance of these groups in our population. Also,....”

Discretionary Revisions
Concerning table 2, the comparison with Thai and Korean Model should be completed by including the section on performance from the index study.

Our response: We have added the c-statistics from the model development sample to Table 2. These were broadly within the range of those obtained in our study. This is in line with our conclusion that CKD models developed in Asian population have acceptable performance in mixed-ancestry Africans.

For table 3, the findings of this study should be included in table 3 for easy comparison.

Our response: Previous studies did not use the same grouping variables, nor did those studies extensively validated models as done in our study. Accordingly there is little ground for comparing the performance of models in subgroups.

Level of interest: An article of importance in its field Quality of written
Our response: Thank you

English: Acceptable
Our response: We made appropriate changes as suggested by the first reviewer to improve this.

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Our response: We defer to the Editor regarding this.

Declaration of competing interests: NONE