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Body:

11-Oct-2017

Dear Dr. Hippisley-Cox

Manuscript ID BMJ.2017.040627.R1 entitled "Development and validation of QDiabetes®-2017 risk prediction algorithm to estimate future risk of type 2 diabetes: cohort study."

Thank you for sending us the revisions to your paper, and for addressing the comments of editors and reviewers. Our statistical consultant still has a few remaining comments and I will ask you to address them before we can make a final decision on the paper.

We are looking forward to reading the revised version and, we hope, reaching a decision.

Yours sincerely,

Jose Merino
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Comments:

Thank you for the details revision and response to comments, which generally seem fine. Some further comments from me at this stage.

1) "We used the regression coefficients for each variable from the final models as weights which we combined with the baseline survivor function estimated from the Cox model" – but the baseline survivor function is not obtainable following a Cox model; another method (non-parametric?) method must have been used. Often this is part of the Cox model package in software, but it would be wrong to say it was obtained from the Cox model itself.

2) It is great to see that the authors have included a decision curve analysis, as requested. When this is introduced they say: "The net benefit of a risk equation at a given risk threshold is given by calculating the difference between the proportion of true positives and the proportion of false positives multiplied by the odds of the risk threshold." I find this explanation slightly confusing, as it would benefit from explaining what the odds means (odds of what?). Perhaps say odds DEFINED by the risk threshold value (i.e. value/(1-value)). And add italics to make distinct the two terms such as: "The net benefit of a risk equation at a given risk threshold is given by calculating the *difference between the proportion of true positives* and *the proportion of false positives multiplied by the odds of the risk threshold*."
I could not actually see the decision curves in Figure 4, as it was not uploaded to the system, so I simply trust that the interpretation was correct.

3) thanks for clarifying that the non-linear trends were identified using the complete data. I think this should be noted as a potential limitation, as by ignoring missing data, the trends identified are more likely to be biased and/or have less power to detect genuine trends than the missing data analysis. This reference may be helpful from Morris et al.
http://onlinelibrary.wiley.com/doi/10.1002/sim.6553/abstract

4) "Although the new models are more complex than the existing models, this is unlikely to affect the take up of the new models as they are all designed to be calculated automatically based on information recorded in the electronic patient record" – can this really be argued when there was only 16% complete data in the registry for blood glucose measurements, smoking and body mass index? i.e. are these variables really routinely recorded?

5) "additional external validation of Models B and C in datasets with more completely collected data would be valuable before the models are used in clinical practice." – thank you for acknowledging this limitation. I wonder if this could also be included in the abstract conclusion, as otherwise the abstract conclusion reads much stronger than this point would warrant.

6) Thank you for adding the calibration slopes, which are reassuringly close to 1 as expected in the overall population. Indeed, they are only very slightly less than 1, which reflects the very small overfitting, a consequence of the huge sample size. Indeed this results formally backs up the low overfitting hypothesised by the authors in their discussion.
Why do the authors think the calibration slopes are generally less than 1 (between 0.7 and 0.9) for subgroups, however? Why is the model not peforming as well in these individuals, and does this suggest there are further improvements warranted in the future?

7) I see another reviewer, whose comments are indeed very insightful, criticised the use of funnel plots. In their defence, they are just used to display the distribution of C statistics; they are not for examining asymmetry as in a meta-analysis. A forest plot would be too long for showing all the C values for each practice. They are calculated on the logit-scale (more symmetric), and then transformed to c scale, and so should be skewed indeed. So I agree that these have been left in.

8) The full model is still not reported in full in the paper. The authors say that "information on estimates for the full models with baseline survival values is published on the qdiabetes.org website." – surely this is a key part of the TRIPOD guidelines, and should also be in the paper? Is the rationale that you may alter the model over time, and thus don't want the model to be set in stone here? If so, the model can still be provided but with a note of the latest version being on-line?

9) I do not agree with competing risk models being difficult to interpret. After all, they again allow an equation to provide risk estimates. But I agree that competing risks is probably best considered in a different paper, specifically in the older age group. Indeed I hope, going forward, the authors look at refining their model in the frail populations where competing risks are likely, such that the risk estimates for diabetes are improved.

Best wishes, Richard Riley

Additional Questions:
Please enter your name: Richard Riley

Job Title: Professor of Biostatistics

Institution: Keele University

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

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