Reviewer’s report

Title: Predictors for independent external validation of cardiovascular risk clinical prediction rules: Cox proportional hazards regression analyses

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Reviewer: Johanna Damen

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This manuscript describes the analysis of predictors for independent external validation of prediction models in the field of cardiovascular disease. A systematic review describing prediction models for cardiovascular disease was used as a starting point to identify prediction models, and using citation tracking, all external validation studies for these models were identified. Key study characteristics and quality of reporting were extracted, and related to the chance of having an independent external validation (i.e. validation by authors who have no relation to the authors of the development study). The manuscript is well-written, methodology is up to date, and studies were identified in a systematic way. I have a few concerns, which I will describe below, split up in major and minor concerns.

Major

- Although I do believe that a relevant research question is answered in this manuscript, the relevance of studying this is not described in a very convincing way. The authors describe that "CPRs that perform well in these independent external validation studies are much more likely to gain the trust of clinicians." (page 4, line 74) and "These cardiovascular CPRs with no independent external validation may represent research waste because clinicians are unlikely to trust or use CPRs with uncertain generalizability." (page 5, line 80) I believe a reference is necessary for these strong statements. Also, I believe there are other, much stronger, factors that influence the uptake of prediction models in clinical practice, such as the reputation of the researchers developing the model, the extensiveness of the data used to develop the model, and the uptake of the model by clinical guidelines. The pooled cohort equations for example have been introduced in clinical practice, before any independent external validation had been performed.

Furthermore, the authors describe that "Understanding why some cardiovascular CPRs are externally and independently validated and others are not, may help researchers create cardiovascular CPRs that are more likely to get independent external validations." (page 5, line 82). I am not sure if this is what we should aim for, since there are already way to many prediction models out there.

- Flow of articles is not fully described in figure 1. For example, the number of hits from the citation search and the number of articles assessed based on full text have not been reported. Please also correct the typo in the middle lowest box.
- Often, multiple models are derived from the same dataset, such as de Framingham Heart Study. These models are thus developed using a comparable sample size, and also reporting characteristics are comparable because the same authors have published these prediction models. This creates dependency in your data and I believe you should either account for this in your analyses, or discuss the possible impact on your results.

- Cox proportional hazards regression model are normally used in a different context (e.g. predicting patients' outcome). Because of terminology used in this manuscript can cause some confusion. How should terms like 'median follow-up time' and 'median event time' (page 11, line 210, 211 + in the abstract) be interpreted in this specific context?

- The discussion section now contains a lot of repetition from the results, without putting this into a broader context. Please change this.

Minor

- Regarding the systematic review that was used as a starting point in this study: "They excluded a study if it updated an existing CPR" (page 6, line 102). This is not completely true (although I have to admit that this is not clearly reported in the review). Studies that updated an existing model were either categorized as developing a new model, or as external validation + updating. Only studies that added new predictors to a model, to assess the incremental value, were excluded. Please rephrase this in the manuscript.

- "we used a logarithmic transformation to create a continuous variable Log10(sample size)" (page 8, line 155). Strictly spoken, sample size is already a continuous variable, so the logarithmic transformation is not creating a continuous variable. Please rephrase.

- "A post hoc sensitivity analysis showed that the HR for cardiovascular risk CPRs derived in the US (United States) excluding the ones developed by Framingham Heart Study researchers" (page 11, line 228). How many prediction models developed from the Framingham Heart Study were excluded in this analysis?

- I believe the UK is part of Europe as well. Maybe it is better to call it 'continental Europe'.

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