Hippisley-Cox, Julia and Coupland, Carol and Brindle, Peter (2017) Authors' response to letters on QRISK3 regarding the definition of severe mental illness and analysis of systolic blood pressure variability. BMJ, 357 . j2099. ISSN 1756-1833

Authors' response published in the BMJ

Published online: 19 June 2017

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British Medical Journal 2017;357:j2099 doi: https://doi.org/10.1136/bmj.j2099

URL: http://www.bmj.com/content/357/bmj.j2099/rr-2

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Dear Editor

We would like to provide additional information in response to the letter from Professor Osborn and Dr Walters in relation to our recent paper published in the BMJ describing the derivation and validation of QRISK3 [1]. Of the 10,561,100 patients in our QRISK3 derivation and validation cohorts, 593,738 (5.62%) were coded as having severe mental illness. Our definition was based on a combination of the Quality and Outcomes Framework (QOF) definition of severe mental illness plus a subset of the codes from the QOF definition of depression (having excluded those codes indicating mild depression).

Overall across both derivation and validation cohorts, we identified 110,798 patients (1.05% of 10,561,100) with a coded diagnosis of either schizophrenia, bipolar affective disorders or other psychoses, the remaining 482,940 (4.57%) having a coded diagnosis of depression which was either moderate or severe depression or not identified as mild. We based our definition of depression on Read codes indicating moderate or severe depression, for example severe depression, major depression, recurrent depression, psychotic depression, depressive disorder, endogenous depression. We think we should have made this clearer in Box 1 of the original paper.

Overall, across the validation and derivation cohorts, we identified 52,128 patients (0.49% of 10,561,100) who were prescribed atypical antipsychotics at study entry. Of these, 35,452 (68.01%) had a diagnosis of severe mental illness (using the broader definition above) and of these, 24,394 (68.81%) had a diagnosis of bipolar affective disorders or schizophrenia. There were 16,676 (31.99%) of 52,128 patients on atypical antipsychotics, who did not have a recorded diagnosis of schizophrenia, bipolar affective disorders or moderate/severe depression. Most atypical antipsychotic drugs will be initiated in secondary care with the ongoing prescriptions generally issued by primary care.

Stevens et al may have misinterpreted how we calculated the standard deviation of systolic blood pressure so we would like to clarify that. In our Methods section, we stated

the following, "To assess variability in systolic blood pressure, we identified all systolic blood pressure values recorded in the five years before study entry and calculated the standard deviation where there were two or more recorded values". Of those who had a standard deviation calculated, this was based on two values for 33.9% of patients and on three or more values for the remaining 66.1% of patients. So, if there were only two values, these would have been used but if there had been 20 values in the preceding five years for an individual patient, then all 20 would have been used to calculate the standard deviation. In other words, we used all the available values to calculate the standard deviation and in so doing, developed an approach which could be implemented back into the GP computer systems where all such values will be recorded. Regarding the number of imputations, because we calculated variability over 2 or more readings, we feel that 5 imputations remains a pragmatic choice in view of the volume of data (nearly 8 million patients in the derivation cohort). Given the magnitude and significance of the coefficients in our models any imputation variability will have little substantive impact on the precision of estimates and selection of variables based on tests of significance [2].

In our study, we reported an adjusted hazard ratio of 1.08 (95% CI 1.07 to 1.09) in women and 1.11 (1.09 to 1.12) in men associated with a 10-unit increase in standard deviation of systolic blood pressure. This is lower than that reported in the paper by Stevens et al [3] which was 1.18 (95% CI 1.07 to 1.30) but their hazard ratio relates to a standardised measure of systolic blood pressure variability on a different scale to our values ("blood pressure variability divided by its sample standard deviation"). Although Stevens et al undertook a meta-analysis for other outcomes, they were only able to identify a single eligible study for the cardiovascular disease outcome [4]. This study consisted of a highly selected group of 8811 patients with type 2 diabetes recruited to a clinical trial experiencing 404 cardiovascular events who are unlikely to be representative of the general population eligible for cardiovascular disease risk assessment. Their cohort was considerably older (mean age 66 compared with 43 in QRISK3) and had substantially higher systolic blood pressure values compared with the QRISK3 population. For example, the mean systolic blood pressure was 137 mmHg compared with 123 mmHg in women and 129 mmHg in men in our study. Furthermore the blood pressure measurements in the trial were made at specific follow-up times using standardised equipment which does not reflect the situation in a primary care setting where the QRISK3 risk prediction models are intended to be used.

Stevens et al correctly state that patients using antihypertensive medication were included in the cohort of patients used to develop QRISK3. The use of antihypertensive medication in patients with a diagnosis of hypertension was included as a parameter in the risk equation in a similar way to earlier versions of QRISK [5]. Given the purpose of QRISK3 (which is to assess CVD risk at a point in time based on information which is already available), we decided to assess each predictor at baseline based on information that was already available, not on information which might change at a future point. Whilst it would be possible to model changes in medication during follow up as a time varying exposure, it is conceptually difficult to see how such a risk equation could be used in clinical practice as the information would not be known to either the doctor or the patient at the time of assessment. This is also relevant to the interesting point that Peek et al make regarding interventions which may occur during follow-up.

Stevens et al also highlight the similarities in the validation statistics between the models with and without the standard deviation of blood pressure. Whilst we felt that, on average the models had the same overall performance, for those patients that do have higher levels of blood pressure variability, it seemed reasonable to choose the model that could represent that increased risk to some degree. It is possible that the risk

associated with blood pressure variability has been underestimated, but choosing a model without any variable for this, would lead to even more underestimation of the true risk in people with variable blood pressure. Further versions of QRISK3 could seek to improve how blood pressure variability is represented in the model.

Lastly, whilst independent external validation of risk assessment tools is the gold standard, numerous validation studies of the QRISK2 cardiovascular risk prediction algorithms (including external studies) have shown that the results in our independent validation practices pretty much match the results when tested in other similar databases both in the UK [6-10] and internationally [11] [12]. We have no reason to think this study should be different but also look forward to future validation studies to confirm our results.

References

1. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ 2017;357 doi: 10.1136/bmj.j2099
2. Bodner TE. What Improves with Increased Missing Data Imputations? Structural Equation Modeling: A Multidisciplinary Journal 2008;15(4):651-75. doi: 10.1080/10705510802339072
3. Stevens SL, Wood S, Koshiaris C, et al. Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. BMJ 2016;354
4. Hata J, Arima H, Rothwell PM, et al. Effects of visit-to-visit variability in systolic blood pressure on macrovascular and microvascular complications in patients with type 2 diabetes mellitus: the ADVANCE trial. Circulation 2013;128(12):1325-34. doi: 10.1161/circulationaha.113.002717 [published Online First: 2013/08/09]
5. Hippisley-Cox J, Coupland C, Vinogradova Y, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. BMJ 2008:bmj.39609.449676.25. doi: 10.1136/bmj.39609.449676.25
6. Collins GS, Altman DG. Predicting the 10 year risk of cardiovascular disease in the United Kingdom: independent and external validation of an updated version of QRISK2. BMJ 2012;344:e4181. doi: 10.1136/bmj.e4181
7. Collins GS, Altman DG. An independent and external validation of QRISK2 cardiovascular disease risk score: a prospective open cohort study. BMJ 2010;340:c2442. doi: 10.1136/bmj.c2442
8. Hippisley-Cox J, Coupland C, Brindle P. The performance of seven QPrediction risk scores in an independent external sample of patients from general practice: a validation study. BMJ Open 2014;4(8):e005809. doi: 10.1136/bmjopen-2014-005809
9. Hippisley-Cox J, Coupland C, Vinogradova Y, et al. Performance of the QRISK cardiovascular risk prediction algorithm in an independent UK sample of patients from general practice: a validation study. Heart 2008;94:34-39. doi: 10.1136/hrt.2007.134890
10. Riley RD, Ensor J, Snell KIE, et al. External validation of clinical prediction models using big datasets from e-health records or IPD meta-analysis: opportunities and challenges. BMJ 2016;353 doi: 10.1136/bmj.i3140
11. Arts EEA, Popa C, Den Broeder AA, et al. Performance of four current risk algorithms in predicting cardiovascular events in patients with early rheumatoid arthritis. Annals of the Rheumatic Diseases 2015;74(4):668-74. doi: 10.1136/annrheumdis-2013-204024
12. Pike MM, Decker PA, Larson NB, et al. Improvement in Cardiovascular Risk Prediction with Electronic Health Records. Journal of Cardiovascular Translational Research 2016:1-9. doi: 10.1007/s12265-016-9687-z

Competing interests: see competing interests for the original paper at bmj.com