External validation of clinical prediction models using big datasets from e-health records or IPD meta-analysis: opportunities and challenges

Riley RD[1], Ensor J[1], Snell KIE[2], Debray TPA[3,4], Altman DG[5], Moons KGM[3,4], Collins GS[5]

Contact details:

* corresponding author:

Professor of Biostatistics; e- mail: r.riley@keele.ac.uk;

Tel: +44 (0) 1782 733905 Fax: +44 (0) 1782 734719

[1] Research Institute for Primary Care and Health Sciences, Keele University, Staffordshire, UK. ST5 5BG

[2] Institute of Applied Health Research, University of Birmingham, Edgbaston, Birmingham, UK. B15 2TT

[3] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

[4] Cochrane Netherlands, University Medical Center Utrecht, Utrecht, The Netherlands

[5] Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK. OX3 7LD.

Word count: 4960

Standfirst

Access to big datasets from e-health records and individual participant data meta-analysis is signalling a new advent of external validation studies for clinical prediction models. In this article the authors illustrate novel opportunities for external validation in big, combined datasets, whilst drawing attention to methodological challenges and reporting issues.

Introduction

A popular type of clinical research is the development of statistical models that predict disease presence and outcome occurrence in individuals,[1-3] thereby informing clinical diagnosis and prognosis. Such models are referred to here as diagnostic and prognostic *prediction models*, but they have many other names including risk models, risk scores and clinical prediction rules. They are typically developed using a multivariable regression framework, which provides an equation to estimate an individual's risk based on his/her values of multiple predictors (such as age and smoking, or biomarkers and genetic information). Box 1 gives the format of equations based on logistic or Cox regression, which involve an intercept or baseline hazard term combined with multiple predictor effects (corresponding to odds or hazard ratios). Well-known examples are the Framingham risk score and QRISK2,[4 5] which estimate the 10-year risk of developing cardiovascular disease; the Nottingham Prognostic Index, which predicts the 5-year survival probability of a woman with newly diagnosed breast cancer;[6 7] and the Wells score for predicting the presence of a pulmonary embolism.[8 9]

In 2009 the *BMJ* published a series of four articles to guide those undertaking prediction model research,[2 10-12] and further recommendations were made in the 2013 PROGRESS series.[3 13-15] These articles all emphasised three fundamental components of prediction model research: *model development*, *external validation*, and *impact evaluation*. Model development is the process that leads to the final prediction equation, and involves many aspects detailed elsewhere.[2 16-18] Impact studies evaluate, ideally in a randomised trial, whether implementing a prediction model in clinical practice actually improves patient outcomes by informing treatment decisions according to the model's predicted risk. However, impact studies should not be considered until the robustness and generalisability of a developed model is verified in one or more external validation studies.[3 19] External validation uses new participant-level data, external to that used for model development, to examine whether the model's predictions are reliable (i.e. accurate enough) in individuals from potential population(s) for clinical use.[20] Unfortunately, most prediction research focuses on model development and

there are relatively few external validation studies.[3 21-23] This leads to a plethora of proposed models, with very little evidence about which are reliable and under what circumstances. Confusion then ensues: promising models are often quickly forgotten,[24] and, of more concern, many models may be used or advocated without appropriate examination of their performance.[25]

A shortage of external validation studies is often attributed to the lack of data available besides that used for model development. Data from a single study (e.g. a cohort study) usually has a limited number of events. Hence all data are best retained for model development, rather than splitting the data so that part is used for development and the remainder for validation.[26] However, increasingly researchers have access to 'big' data as evident by meta-analyses using individual participant data (IPD) from multiple studies,[27-30] and by analyses of registry databases containing e-health records for thousands or even millions of patients from multiple practices, hospitals, or countries.[31] For example, QRISK2 was developed using e-health data from the QRESEARCH database using over 1.5 million patients (with over 95000 new cardiovascular events) from 355 randomly selected general practices [5], with external validation carried out by independent investigators in an additional 1.6 million patients from a further 365 practices [32]. In the IPD meta-analysis setting, an example is the IMPACT consortium which developed a prediction model for mortality and unfavourable outcome in traumatic brain injury by sharing IPD from 11 studies (8509 patients), with external validation then performed using IPD from another large study (6681 patients).[33]

Such big, combined datasets heralds an exciting opportunity to improve the uptake of external validation research. Here, we describe the additional opportunities, challenges and reporting issues involved in prediction research in this situation. We begin by introducing two key performance measures (calibration and discrimination) and a review of current practice in external validation research. Then, using five empirical examples, we show how big datasets allow a model's predictive performance to be more fully interrogated across different populations, subgroups and settings. We conclude by signposting methodological challenges and reporting criteria, which build upon the recent TRIPOD Statement.[34 35]

Summarising predictive performance of a model via discrimination and calibration

External validation of a prediction model typically involves quantifying a model's discrimination and calibration performance in data that were not used to develop the model.

To be useful, a model's predicted risks must discriminate (separate) well between those participants who do and do not have the outcome (disease or event) of interest. Discrimination is usually measured by the c-statistic,[18] and for survival outcomes also the D-statistic (Box 2).[36] Calibration examines the agreement between predicted and observed risks, and can be quantified by measures such as the calibration slope and the Expected/Observed (E/O) statistic (Box 2). Calibration can also be visualised graphically, for example by plotting observed versus predicted risks across tenths of predicted risk,[10] or by using a flexible calibration plot with a smoothed non-linear curve generated using a loess smoother or splines,[10 37] or by displaying observed and predicted survival curves over time for different risk groups.[38]

Current shortcomings of external validation studies

A systematic review of 78 external validation studies published in 2010 concluded that 'there is a dearth of well-conducted and clearly reported external validation studies'.[39] Although model discrimination was usually reported, 68% of studies did not report evaluating model calibration and only 11 (14%) presented a calibration plot. It was also often unclear how missing data were handled and even which model (the original model or some simplified version of it) was being evaluated. Further, sample size was often small with 46% having fewer than 100 events, which is a suggested minimum effective sample size suggested for external validation[40 41] (though an increase to 200 was recently proposed for assessing calibration[37 41]). Other reviews have identified similar problems.[21 23]

A major problem of external validation studies is that they are often based on small and local datasets. For this reason, most external validation studies can, at best, assess the performance of a prediction model in a specific setting or population. However, it is increasingly recognised that the predictive performance of a model tends to vary across settings, populations and periods.[20 30 42 43] This implies that there is often *heterogeneity* in model performance and that *multiple* external validation studies are needed to fully appreciate the generalisability of a prediction model.[20] Although multiple datasets are increasingly available for this purpose,[29] studies with access to such data mainly focus on model development and often ignore external validation.[28] Hence, heterogeneity in model performance across populations, settings and periods is rarely assessed. Similar deficiencies are apparent in external validation studies using big datasets from e-health records or disease registries. For example, after development of the QRISK2 model using routinely collected data from 355 primary care practices, Hippisley-Cox et al.[5] immediately evaluated the model's performance

using further data from an additional 176 practices. However, potential heterogeneity in model performance across these 176 practices was ignored, with calibration and discrimination only summarised across all practices combined. Similarly, the independent external validation of QRISK2 by Collins and Altman[44] ignored between-practice heterogeneity. Therefore, it remains unclear whether QRISK2 performs better or worse in some practices, regions or (sub)populations than in others, and we return to this issue in examples 2 and 4 below.

What causes heterogeneity in model performance?

There are a number of potential causes of heterogeneous model performance across different settings and populations,[29 43 45] which may occur in isolation or in combination. A major reason is different case-mix variation, which is similar to the 'spectrum effect',[46 47] a term used to describe variation in test accuracy performance across different populations and subgroups. Here "case-mix" refers to the distribution of predictor values, other relevant participant or setting characteristics (such as treatment received), and the outcome prevalence (diagnosis) or incidence (prognosis). Case-mix variation across different settings or populations can lead to genuine differences in the performance of a prediction model, even when the true (underlying) predictor effects are consistent (that is, when the effect of a particular predictor on outcome risk is the same regardless of the study population).[43] It is, for instance, well known that the performance of models developed in secondary care is usually different when they are applied in a primary care setting, as the outcome prevalence and/or distribution of predictor values will be different.[48] For example, the Wells score is a diagnostic prediction model for deep vein thrombosis (DVT), which was developed in secondary care outpatients. However, Oudega et al.[49] show that it does not adequately rule out DVT in primary care patients, as 12% of patients in the low risk group had DVT compared to 3% in the original secondary care setting. The higher prevalence is due to a change in the selection and definition of patients with suspected DVT, leading to a different distribution of predictor values and case-mix variation in primary care compared to secondary care.

The magnitude of predictor effects (denoted by β in Box 1) may also depend on the case-mix itself. For example, in the cancer field the effect of a biomarker may vary (interact) with particular subgroups, such as the stage of disease or the treatment received, and its relationship with outcome risk may be non-linear. However, such interactions and non-linear trends are often missed (or mis-specified) when developing a model. Further, a biomarker is

often measured differently (e.g. using equipment from different manufacturers, or using a different assay or technique), recorded at a different time-point (e.g. before or after surgery), or quantified differently (e.g. using a different cut-point to define high and low values) across settings. Many other clinical, laboratory and methodological differences may also exist, including differences in: treatment strategies, clinical guidelines and experience, disease and outcome definitions, and follow-up lengths, amongst others. All these problems may lead to heterogeneity in predictor effects.[14 50] Subsequently, a developed model including predictor effects from one population may not perform well in a different population where the magnitude of predictor effects are different due to the change in case-mix, and use of different clinical, laboratory and methodological standards.

Another key reason is heterogeneity in the average prevalence (incidence rate) of the disease (outcome) to be predicted. This is caused, for example, by different standards of care and administered treatment strategies across regions and countries, and different starting points (e.g. earlier diagnosis of disease in some populations due to a screening programme).[13] This leads to differences across populations in the baseline risk, and thus the intercept (or baseline hazard rate; see Box 1) of a developed model may not be transportable from one population to another, leading to predicted risks that are systematically too low or too high. This is one reason for so-called 'model updating',[51] where the intercept (baseline hazard) or predictor effects of a previous model are updated to recalibrate predictive performance to the new population.

Opportunities to improve external validation using big data

We now use five empirical examples to demonstrate how big datasets from e-health records or IPD meta-analysis allows researchers to examine heterogeneity and (if necessary) improve the predictive performance of a model across different populations, settings and subgroups. Examples 1 and 2 consider ways to investigate the extent of heterogeneity, whereas examples 3 to 5 examine the sources of heterogeneity and how to tailor (recalibrate) the model to the new circumstances.

Example 1: Examining consistency in a model's predictive performance across multiple studies

When data from multiple studies are available for external validation, meta-analysis techniques (such as a random effects meta-analysis[52]) can be used to quantify and summarise between-study heterogeneity in model performance.[30 53 54] For example, Debray et al. developed a prediction model for the diagnosis of DVT in patients suspected of having the

condition.[45] External validation was performed using 12 studies containing a total of 10014 patients (with study sample sizes ranging from 153 to 1768 patients) and 1897 (19%) patients with DVT, with study differences in case-mix and DVT prevalence. On average across the 12 studies, the overall calibration was excellent, with the summary E/O of 1.02 (95% CI: 0.79 to 1.32) revealing that total number of predicted and true DVT cases was almost in perfect agreement (i.e. an E/O close to 1). However, a random effects meta-analysis revealed considerable between-study heterogeneity. I^2 was 97%, which indicated that 97% of the total variation in the study estimates was due to between-study heterogeneity. The large heterogeneity is also evident in the forest plot (Figure 1), with large variation in study estimates and many non-overlapping confidence intervals. The summary E/O estimate was therefore an incomplete picture, as performance in particular populations could vary considerably from the average.

Rather than focusing on I^2, which may be misleading when the study sample sizes are large[55], the extent of heterogeneity in model performance is better quantified by a 95% prediction interval.[52] Debray et al. calculated an approximate 95% prediction interval for E/O in a new population, which was wide (0.38 to 2.72), indicating potentially large under-prediction (E/O < 1) or over-prediction (E/O >1) of DVT risk in some populations, a finding that was masked by focusing solely on the excellent summary performance. Similarly the approximate 95% prediction interval for the c-statistic was 0.64 to 0.73, indicating heterogeneous (and often only moderate) discrimination performance. The model was therefore deemed inadequate: it requires improvements (e.g. recalibration and/or additional predictors) to reduce heterogeneity and improve discrimination to be clinically useful toward an accurate diagnosis of DVT. Indeed, other models for diagnosis of DVT containing more predictors already exist, and appear to perform well across different subgroups and settings.[56]

Example 2: Examining consistency in performance across multiple practices

Given big datasets from e-health records or disease registries, external validation can also utilise meta-analysis techniques to examine heterogeneity in model performance across different clusters, such as practices, hospitals, or countries where case-mix and outcome prevalence (incidence rate) are likely to vary. Indeed, each cluster might be viewed as a different external validation study. For example, we extended Collins and Altman's external validation of QRISK2 using data from 364 general practice,[44] by performing a random-effects meta-analysis to summarise the c-statistic. The summary (average) c-statistic was 0.83 (95% CI: 0.826 to 0.833). However, there was high between-practice heterogeneity in the c-

statistic (I^2=80.9%) and the approximate 95% prediction interval for the true c-statistic in a new practice was wide (0.76 to 0.88), although containing values that would typically be considered moderate or high discrimination.

Following such a meta-analysis, the use of forest plots to display cluster-specific and meta-analysis results is often impractical given the number of clusters, such as the hundreds of practices observed within e- health records (such as the Clinical Practice Research Datalink (CPRD) and The Health Improvement Network (THIN)). A useful alternative approach to visualise any variability in model performance at the cluster-level is to present plots of performance estimates versus their precision (or sample size). Figure 2 shows a plot of the c-statistic for QRISK2, for each of the 364 included general practices, versus either the number of outcome events in the practice (panel (a)) or the standard error of the c-statistic on the scale used in the meta-analysis (panel (b))[57]. Such plots are often call funnel plots, and indeed in panel (a) the distinctive funnel shape is reasonably well observed, where small practices (in this instance, defined on the *x*-axis by the number of outcome events) exhibit a wider variation in the c-statistic than larger clusters. The extremes of the funnel help reveal particular general practices where the model is performing much better, or much worse, than on average. A formal statistical way to identify practices with 'extreme' predictive performance is shown in panel (b), where an approximate 95% interval is added to reveal where c-statistic estimates are predicted to lie, given the standard error observed. Those points in red denote practices that fall outside the predicted range, with those below the lower boundary of particular interest. Of course, as this is a 95% interval, by definition we expect 5% of all practices to fall out of the region by chance. Nevertheless, we find it a helpful approach to identify, from hundreds of practices, those practices worthy of extra attention. In particular, it motivates enquiry to identify if there are any striking reasons (aside from the play of chance) *why* the model performs so differently in these practices.

Example 3: Examining performance in clinically relevant subgroups

Just as stratified medicine research asks the question 'does a treatment work better or worse for some subgroups than others?',[15] the use of big datasets allows prediction model research to ask 'is the model more accurate for some subgroups than others?'. For example, the performance of QRISK2 has been examined in different ethnic groups[58 59] and in patients with diabetes,[60] the latter in response to a NICE recommendation to not use QRISK2 in patients with type 1 or 2 diabetes.

The recent TRIPOD guideline[34 35] also indicates that a model's predictive performance should be evaluated in relation to key variables, such as age or sex subgroups, rather than just across all individuals combined which can mask any deficiencies in the model. For example, an external validation study of QRISK2 and the Framingham risk score assessed model calibration both in the entire cohort (by tenth of predicted risk) but also by age groups[44]. Over the entire sample of 1.1 million women in the cohort (from the THIN database), both models exhibit good overall calibration between predicted and observed 10-year CVD risk, with an E/O of 1.01 for QRISK2 and 1.03 for the Framingham risk score. This is illustrated in panel A of Figure 3, though there is slight over-prediction observed in women at higher 10-year CVD risk, which is more pronounced for the Framingham risk score.

The big datasets enable further interrogation of predictive performance, for example by five-year age groups (Figure 3, panel B). It is immediately apparent that Framingham over-predicts the 10-year CVD risk in women aged 40 to 64 years and under-predicts risk in women aged 70 to 74 years (Figure 3, panel B); in contrast, QRISK2 appears to accurately predict 10-year CVD risk across all age groups. This was not revealed by the summary calibration plot typically used (Figure 3, panel A). Further work could also examine between-practice heterogeneity in the calibration performance for each age group, and similarly look at performance within categories of other important subgroups (e.g. ethnicity).

Example 4: Examining sources of heterogeneity in model performance

Where model performance is heterogeneous, the sources of heterogeneity can be investigated. For example, Pennells et al.[30] used IPD from multiple studies to evaluate a prediction model for coronary heart disease, and showed (using meta-regression) that its discrimination performance improved in studies with a larger standard deviation of age; every 5-year increase in standard deviation improved the c-statistic by approximately 0.05. Thus larger case-mix variation (here measured by the variability of age in each population) is related to larger discrimination performance; in other words, populations with a narrower case-mix (more homogeneous predictor values across individuals) tend to have worse discrimination performance. We further extended our investigation of QRISK2, and found that the c-statistic decreases across practices as the population's mean age and percentage smokers increases (Figure 4). This suggests that discrimination as measured by the c-statistic is lower in populations with a higher risk of CVD, which again may be due to narrower case-mix variation, but could alternatively (or additionally) be due to differences in the magnitude of predictor effects in such populations. This is now subject to further research.

Example 5: Examining model recalibration strategies (model updating)

Snell et al.[53] used IPD from eight countries to externally validate a prediction model of mortality risk over time in breast cancer patients. They identified large between-country heterogeneity in calibration performance, as evident by a wide 95% prediction interval for the calibration slope (0.41 to 1.58) (Figure 5(a)). This signals potential differences in the baseline mortality rates across countries, and/or differences in the effects of included predictors. It is also possible that important predictors (such as interactions and non-linear effects) are missing from the model that would otherwise explain such differences.

In such situations, researchers may be tempted to discard the model entirely but this is premature, as performance can often be improved if (simple) recalibration strategies are allowed.[20] Recalibration is a form of model updating, where particular components of the developed model (such as the intercept or baseline hazard rate, or even particular predictor effects) are modified or tailored for each study population of interest. For instance, Snell et al. extend their work by examining if the model's calibration performance improves with recalibration of the baseline hazard function in each country; that is, although the model's predictor effects were not modified, the baseline hazard of the developed model was re-estimated for each country to enhance risk predictions. This is akin to diagnostic test research, where post-test probabilities are best tailored to the disease prevalence of the population at hand.[61-63] There was a dramatic improvement in the breast cancer model performance (Figure 5(b)): I^2 was reduced from 98% without recalibration to 35% with recalibration, and the updated 95% prediction interval for the calibration slope was 0.93 to 1.08, which is now narrow and close to 1. The importance of baseline risk recalibration is also shown elsewhere.[51 64]

Practical and methodological challenges

Though the availability of big datasets offers many opportunities for external validation research, potential methodological challenges also arise.[28 29 65] In particular, missing predictor values are likely in some participants and there may be systematically missing predictors, which occurs when a predictor is not measured for any individuals in one or more studies (clusters). Advanced multiple imputation techniques are then necessary (under a missing at random assumption),[66 67] otherwise the prediction model cannot be validated in the clusters with missing predictors. Further, although exploration of heterogeneity in model performance is an opportunity, the potential causes of heterogeneity should ideally be specified in advance, to avoid data-dredging and spurious (chance) findings.

The quality of e-health records is of particular concern, as they contain data routinely collected which may not be as rigorous as the IPD from a meta-analysis of research studies. A dataset being large does not imply it is of high quality; *indeed, the opposite may be true*. In relation to CPRD, Herrett et al.[68] state: "The quality of primary care data is variable because data are entered by GPs during routine consultations, not for the purpose of research. Researchers must therefore undertake comprehensive data quality checks before undertaking a study." Particular weaknesses include missing data (and the potential for it to be missing not at random); non-standardised definitions of diagnoses and outcomes; the need to interpret an absence of a 'read code' for a disease or outcome as absence of the disease/outcome itself, when sometimes patients with the disease/outcome simply fail to present to the GP; incomplete follow-up times and event dates (such as hospital admission and length of stay); and lack of recording of potentially important and novel predictors. Thus, just as IPD meta-analyses should examine the risk of bias of included studies[69], researchers using e-health or routine care registry databases should examine the quality of their data.

Research using big datasets can also be expensive. For example, according to the general terms and conditions on the CPRD website (https://www.cprd.com/dataAccess/) for "the sum £255,000 per annum the Licensor grants the Licensee a limited, non-exclusive and non-transferable licence on the terms of this Licence for up to 2 Nominated Users to access the Services …". Costs are reduced for certain parties, for example at about £130,000 per annum for academia in our experience. The use of large data from established cohorts (such as UK Biobank) is an alternative and much cheaper option; for example, according to their website (http://www.ukbiobank.ac.uk/scientists-3/) access to UK Biobank data costs "£1,500 + VAT (where applicable) per application that requires access to data only". However, such cohorts often have a narrower case-mix than the wider population, due to specific entry criteria; for example UK Biobank recruited individuals aged between 40 and 69. For IPD meta-analysis situations, it can also be expensive, time-consuming and generally painstaking to obtain and clean the raw data from multiple studies.[70] Further, not all desired studies may provide their IPD, and the available IPD may be from a selective, non-random part of the evidence-base.[71] Another challenge when using IPD from multiple studies, or multiple e-health or registry datasets, is how to identify and deal with individuals who contribute data to more than one dataset.

Researchers may also want to use the large dataset to both develop and externally validate a model. They thus need to decide if and how a subset of the data are excluded for the

validation phase. Big datasets from e-health records often contains hundreds of clusters and thousands of participants and events; in such situations, a sensible approach is to omit 20 or more clusters for external validation, which are chosen in advance (non-random sample) to cover a wide-range of different populations, settings and case-mix variations. In an IPD meta-analysis, where the number of studies (*k*) is typically fewer than 10 studies, 'internal-external cross-validation' has been proposed for combining model development and validation.[42 45] Here, all but one of the studies are used for model development with the remaining study used for external validation; this is repeated a further *k*-1 times, on each occasion omitting a different study to ascertain external validation performance. If performance is always adequate, a final model may be developed using all studies. Otherwise, it flags heterogeneous study populations where a developed model may not perform well, and signals model updating strategies may be needed (such as recalibration). We note, however, that each cycle should ensure an adequate sample size for model development[72-74] and the use of appropriate model derivation techniques (e.g. adjustment for optimism)[16 26]; otherwise, poor performance may simply reflect small sample sizes, overfitting, and sub-standard development techniques.

For model development, the use of big datasets may lead to many candidate predictors being statistically significant, even when they only improve prediction by a small amount. Therefore a more considered predictor selection process (e.g. based on clinical relevance and magnitude of effect, not just statistical significance) will be required to avoid inclusion of a vast number of predictors unnecessarily. It may also be helpful to ascertain which candidate predictors are heterogeneous across clusters, to limit eventual heterogeneity in model performance; Wynants et al. suggest the residual intra-class correlation for this purpose.[75] Further details of the methodological challenges facing IPD meta-analysis of prognosis research are given elsewhere.[28 65]

Reporting of external validation studies that use big datasets

Box 3 provides some initial suggestions to extend the recent TRIPOD Statement for reporting external validation studies that use big datasets.[34 35] Ideally these should be refined and potentially extended in an international consensus process, and work on this has begun by the TRIPOD initiative. Our aim with Box 3 is to provide some interim guidance for researchers, which also draw on the recent PRISMA-IPD guidelines.[76] Graphical displays presenting model performance are particularly important. In particular forest and funnel plots can be used to display meta-analyses as shown above, ideally with calibration plots for the whole dataset and in each cluster separately, as shown elsewhere.[42 45]

Concluding remarks

We have highlighted how big datasets from multiple studies and e-health or registry databases provide novel opportunities for external validation of prediction models, which we hope will encourage researchers to interrogate the adequacy of prediction models more thoroughly. In particular, researchers should use their big datasets to check a model's predictive performance (in terms of discrimination and calibration) across clinical settings, populations, and subgroups: simply reporting a model's overall performance (averaged across all clusters and individuals) is not sufficient as it can mask differences and important deficiencies across these clusters and subgroups. Potential users need to know if a model is reliable or transportable to all the settings, populations and groups represented in the data. If a model does not have consistent predictive performance, users must know the potential magnitude of the inaccuracy to make a better judgement of the model's worth, and in whom. Further, users should be told when, and which type of, model updating or tailoring strategies (such as recalibration) are necessary for particular settings or clusters, and by how much they improve predictive performance.[20] We demonstrated these issues using empirical examples. Sometimes, even with updating or tailoring strategies, a model may not be transportable to particular settings, and an entirely new model may be required. For example, a model that was developed from practices containing predominately one ethic group are unlikely to perform as well in the wider UK population if there is heterogeneity in predictor effects and baseline risks across different ethnic groups. In such situations important predictors are missing from the model. An example is the Cambridge diabetes risk score which was developed from practices in predominately white population areas of the UK, and does not discriminate as well as the QDS score (now known as QDiabetes), which was developed on a wider set of ethnically diverse practices.[77]

Our work agrees with Van Calster et al.[37] who encourage researchers to examine a model's calibration performance to a higher level. They state that "a flexible assessment of calibration in small validation datasets is problematic", but our examples show how big datasets can help address this. Other issues may also benefit from big datasets, such as comparing (and even combining[78]) multiple competing models,[79] and examining the added value of a new predictor,[30] for example in terms of the net-benefit for clinical decision making.[80] A full discussion of the different research questions one may address in big datasets, such as an IPD meta-analysis, for clinical prediction model research is given by Debray et al.[29]

In conclusion, access to big datasets from, for example, e-health records, registry databases, and IPD meta-analyses should signal a new approach to external validation studies in risk prediction research, for either diagnostic or prognostic purposes. Recent articles in the *BMJ* call for data sharing to be 'the expected norm',[81] and for synthesis of IPD to have greater impact upon clinical guidelines.[82] Our examples reinforce why such calls are of utmost relevance for the validation of prediction models, as we strive to ensure developed models are reliable and fit for purpose in all the settings of intended use.

Competing interests: None

Funding: Richard Riley and Doug Altman received funding from an MRC Partnership Grant for the PROGnosis RESearch Strategy (PROGRESS) group (grant reference number: G0902393). Richard Riley also received funding from an MRC Methodology Research grant (grant reference number: MR/J013595/1). Karel G.M. Moons receives funding from the Netherlands Organisation for Scientific Research (project 9120.8004 and 918.10.615). Gary Collins and Doug Altman received funding from the Medical Research Council (grant number G1100513)

Contribution statement: RR, GC, DA and KM conceived the article content and structure. RR and GC provided the examples, with analyses and associated figures produced by RR, GC, JE, KS and TD. RR and GC wrote the first draft, and all authors helped revise the paper. RR revised the article, with feedback from all other authors. RR is the guarantor.

Acknowledgements: The authors would like to thank the Editors and four reviewers for their constructive feedback and suggestions, which helped improve the article upon revision.

Box 1: Format of typical prediction models seen in the medical literature

(i) Diagnostic or short-term prognostic prediction models

Where the disease (for a diagnostic prediction model) or the outcome (for a prognostic prediction model) is truly known for all patients at a particular time-point, then researchers typically use logistic regression to develop their prediction model, which is of the form:

$$ln\left(\frac{p}{1-p}\right) = \alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \cdots$$

Here *p* is the probability of having/developing the disease/outcome, $ln\left(\frac{p}{1-p}\right)$ is the log odds of the disease or outcome, the intercept term α is the baseline log-odds (where 'baseline' refers to individuals whose *X* values are all zero), each *X* term denotes values of included predictors (e.g. X_1 could be the age of the patient in years, X_2 could be 1 for males and 0 for females, and so on), and each β denotes the change in log odds (or the log odds ratio) for each 1-unit increase in the corresponding predictor (e.g. β_1 is the increase in the log odds for each one year increase in age, and β_2 is the increase in the log odds for a male compared to a female, and so on). Absolute risk predictions (denoted by $\hat{p}$) for a new individual can be obtained by inputting their predictor values into the equation and then transforming back to the probability scale:

$$\hat{p} = \frac{exp(\alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \cdots)}{1 + exp(\alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \cdots)}$$

(ii) Prognostic prediction models over time

When risks are predicted over time (or for a time-point before which some individuals in the development data are censored), then researchers typically use a survival model (such as a Cox model or a parametric survival model) to obtain their prediction model, which is typically of the form

$$h(t) = h_0(t)\, exp(\beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \cdots)$$

Here $h(t)$ is the hazard rate of the outcome at time *t*, the intercept term $h_0(t)$ is the baseline hazard rate (where 'baseline' refers to individuals whose *X* values are all zero), the *X* terms denote values of included predictors, and each β denotes the change in log hazard rate (or the log hazard ratio) for each 1-unit increase in the corresponding predictor. Absolute risk predictions at time *t* (denoted by $\hat{S}(t)$) for a new individual can be obtained by inputting their predictor values into the equation and then transforming back to the probability scale:

$$1 - \hat{S}(t) = 1 - S_0(t)^{exp(\beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \cdots)}$$

where $S_0(t)$ is the baseline survival probability at time *t*.

Box 2: Explanation of some key measures for calibration and discrimination

Calibration slope
For a perfectly calibrated model we expect to see that, in 100 individuals with a predicted risk of r% from our model, r of the 100 truly have the disease (for diagnostic prediction) or outcome (for prognostic prediction) of interest. The calibration slope is one measure of agreement between observed and predicted risk of the event (outcome) across the whole range of predicted values,[1 18] and should ideally be 1. A slope < 1 indicates that some predictions are too extreme (e.g. predictions close to 1 are too high, and predictions close to 0 are too low) and a slope > 1 indicates predictions are too narrow. A calibration slope < 1 is often observed in validation studies, consistent with over-fitting in the original model development.

Expected / Observed number of events (E/O)
E/O summarises the overall calibration of risk predictions from the model in the entire validation sample (it is closely related to the so-called "calibration-in-the-large",[1] but more intuitive to interpret). It provides the ratio of the total expected to have disease (outcome) to the total observed with disease (or with outcome by a particular time-point). Thus an ideal value is 1. Values less than 1 indicate the model is under-predicting the total number of events in the population, whilst values above 1 indicate it is over-predicting the total number events in the population. Sometimes, in addition to looking at E/O across the entire dataset, E/O is reported for groups of predicted risk (for example, by tenths of predicted risk). The E/O ratios then describe the shape of the calibration slope. Note also that sometimes the O/E ratio is presented; under-prediction then occurs for values above 1 and over-prediction for values less than 1.

c-statistic
A measure of a prediction model's discrimination (separation) between those with or without the outcome. Also known as the concordance index or, for binary outcomes, the area under the receiver operating characteristic (ROC) curve. It gives the probability that for any randomly selected pair of individuals, one with and one without the disease (outcome), the model assigns a higher probability to the individual with the disease (outcome). A value of 1 indicates the model has perfect discrimination, whilst a value of 0.5 indicates the model discriminates no better than chance.

D-statistic
A measure of discrimination for time-to-event outcomes only.[36] This can be interpreted as the log hazard ratio comparing two equally sized groups defined by dichotomising at the median value of the prognostic index from the developed model (where the prognostic index is defined by the combined predictor effects in the developed model, i.e. $\beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \cdots$). Higher values for the D-statistic indicate greater discrimination. A related statistic is R_D^2.[36]

Box 3: Initial suggestions to build upon the TRIPOD guidelines[34 35] for the reporting of external validation studies that use big datasets, such as those generated from IPD meta-analysis or e-health databases.

How data were obtained

- When using data from multiple studies describe:
    - how the studies were identified (e.g. systematic review, collaborative project of selected researchers)
    - which studies were approached for their data, and how (e.g. email, letter)
    - the proportion of identified studies that agreed to provide their data, and the design of these studies (e.g. randomised trials, cohort studies, cross-sectional studies)
    - whether studies providing IPD were similar (e.g. in terms of their populations, design) to studies without IPD
- When using data from e-health records, describe the process toward obtaining the data and whether multiple databases were utilised (for example, for linkage of predictor and outcome information)

Clustering in the data

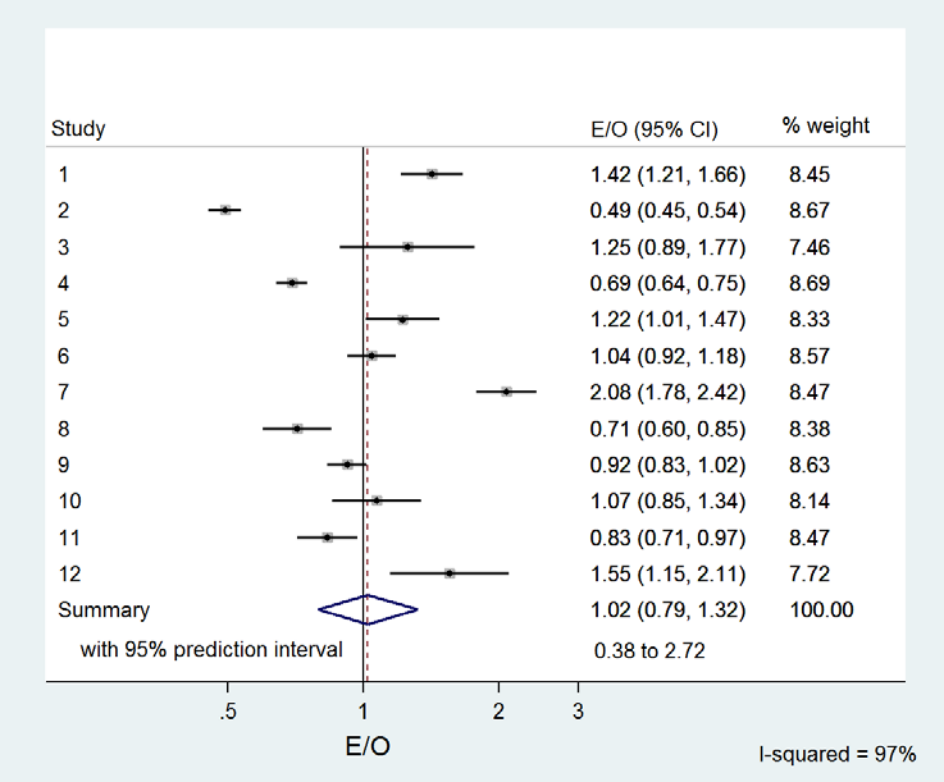
- Summarise the clustering in the data (e.g. due to practices, hospitals, studies) and the different populations each cluster represents (e.g. different regions, countries).
- State the number of clusters in the entire dataset and the number of patients and events in each. If the number of clusters is large then, for ease of presentation, the distribution of patient characteristics and events across clusters might be displayed using histograms and summary measures such as the mean, median, standard deviation, minimum and maximum.
- Report differences in case-mix variation across clusters (e.g. in the mean or standard deviation of predictor values), perhaps with a summary table or graphical display of baseline characteristics in each cluster
- Provide details of any other inconsistencies across clusters, for example in the definition and measurement of predictors, the classification of the disease/outcome to be predicted, the treatment strategies used, etc.

External validation analyses

- For each external validation analysis, state the numbers of patients, events and clusters that were used.
- Explain any methodological challenges in utilising or combining the data across clusters. In particular, state how any missing data were handled in each cluster (especially systematically missing predictors) and how any between-cluster differences in predictor or event definitions were handled.
- Report the external validation performance in the whole dataset, including a weighted (meta-analysis) average across clusters, and in relation to clinically relevant subgroups or important variables
- Summarise the external validation performance in each cluster (e.g. in a forest or funnel plot), and quantify the between-cluster heterogeneity in performance, for example, via a random-effects meta-analysis and deriving 95% prediction intervals for calibration and discrimination performance in a new cluster.
- Explain any model updating (e.g. recalibration) techniques examined, and report how average performance and heterogeneity in performance improves (or worsens) after updating.

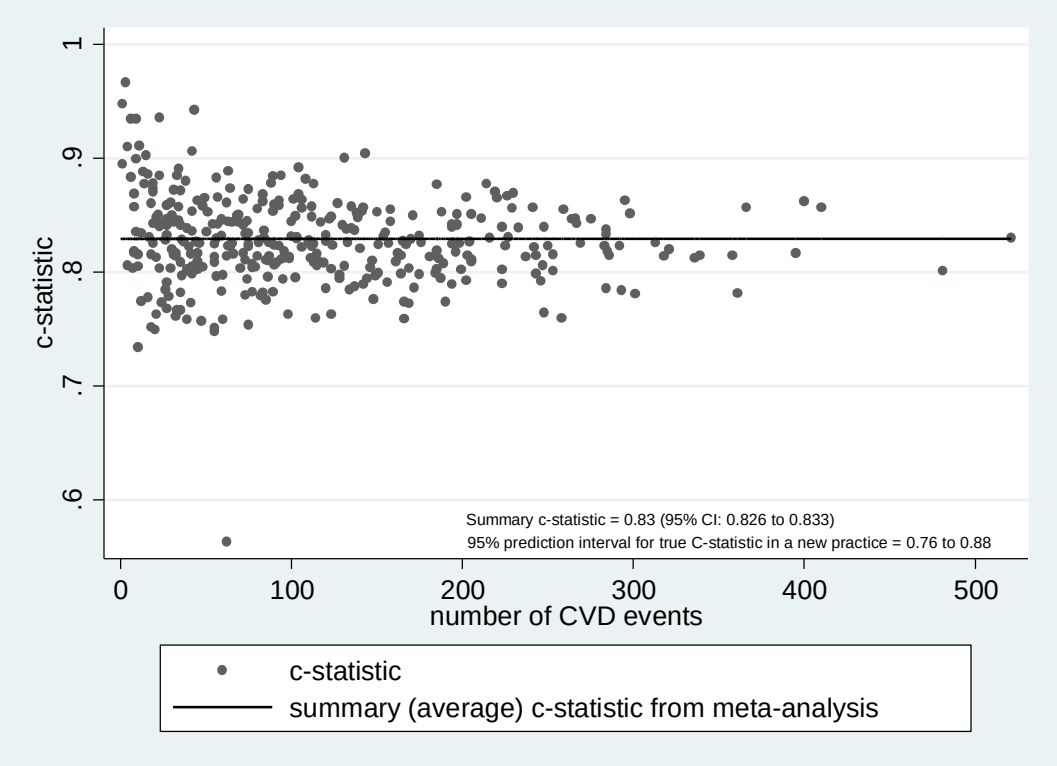
- Provide graphical displays to supplement the results, such as forest (or funnel) plots to display the meta-analyses, and calibration plots covering tenths of predicted risk and relevant subgroups, ideally for the whole dataset and in each cluster separately.

Figure 1: Calibration performance (as measured by the E/O statistic) of a diagnostic prediction model for deep vein thrombosis,[45], over all studies combined and in each of the 12 studies separately

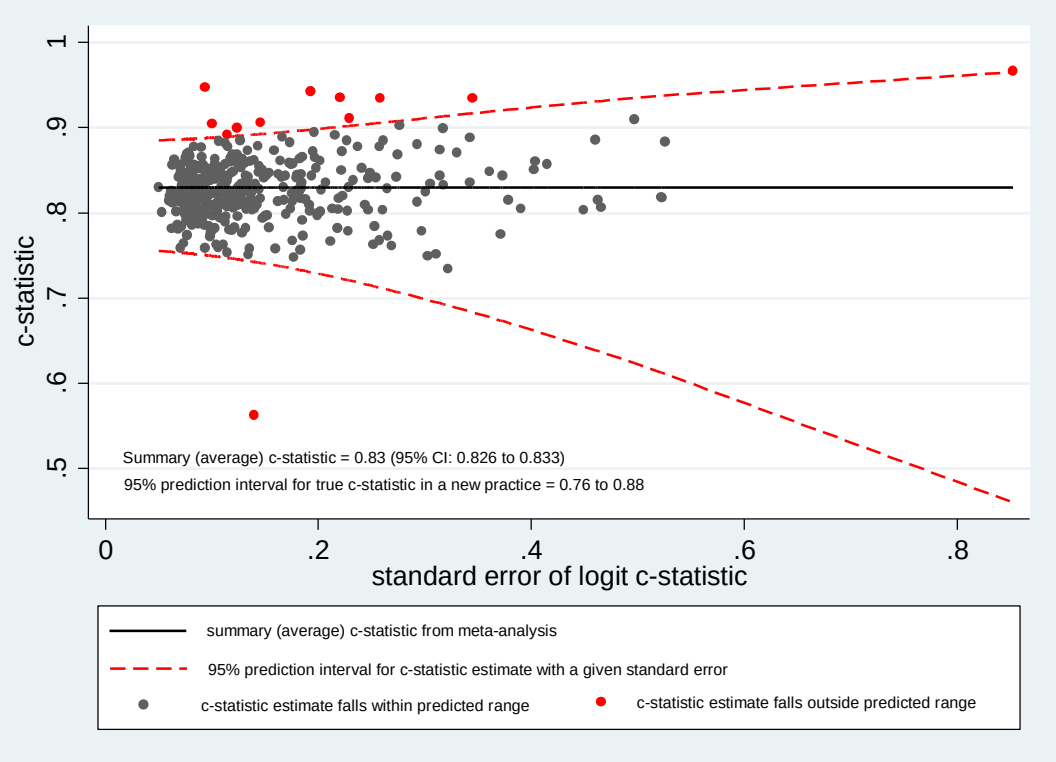


E = total number expected to have deep vein thrombosis according to the prediction model
O = total number observed with deep vein thrombosis;
I-squared is the % of variability in the ln(E/O) estimates in the meta-analysis that is due to between-study variation (genuine differences between studies in the true ln(E/O)), rather than within-study sampling error (chance).

Figure 2: Funnel plots of discrimination performance (as measured by the c-statistic) of QRISK2, across all 364 general practice surgeries in the external validation dataset of Collins and Altman.[44]
(a) c-statistic versus number of events



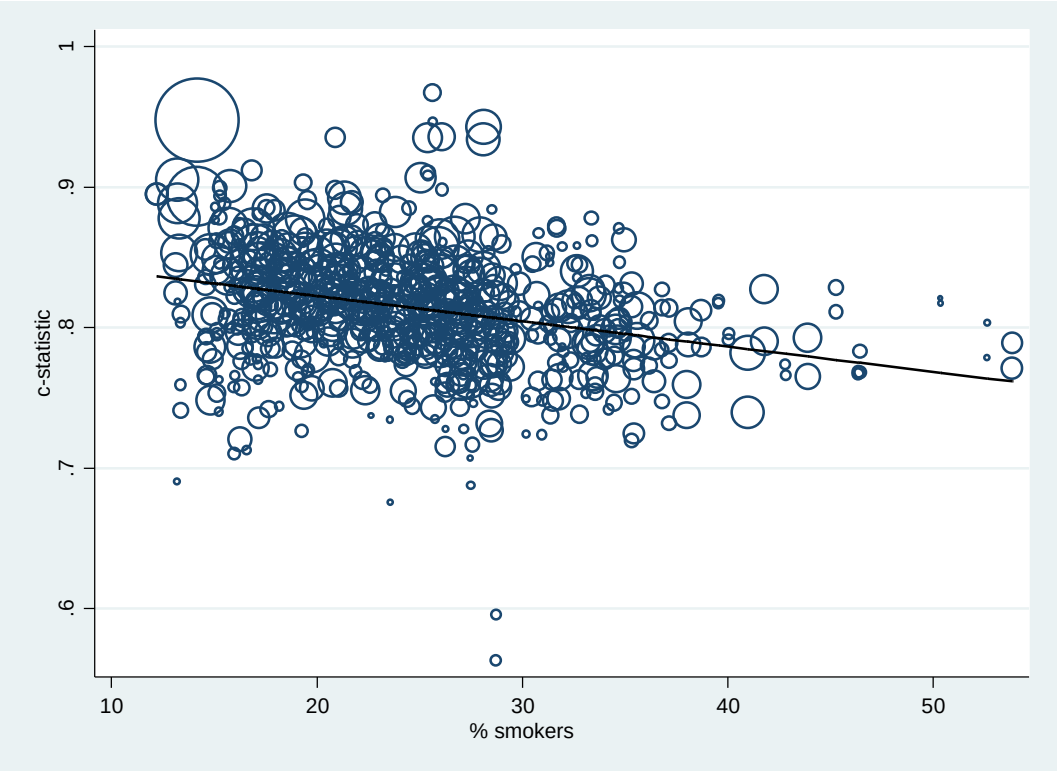
(b) c-statistic versus standard error of logit c-statistic.



Red circles denote extreme c-statistic estimates, i.e. those falling outside the 95% range predicted for the given standard error. Approximate 95% prediction interval obtained by back transforming from the logit-c prediction interval which was derived using:
$\boldsymbol{logit\text{-}c \pm 1.98\sqrt{\tau^2 + var(logit\_c) + var(logit\_c_i)}}$ where $\boldsymbol{logit\_c}$ is the summary c-statistic from the meta-analysis and $\boldsymbol{var(logit\_c)}$ its variance; $\boldsymbol{\tau^2}$ is the estimated between-study variance; $\boldsymbol{var(logit_c_i)}$is the variance of the logit-c estimate in cluster *i* (as obtained from bootstrapping), and 1.98 is the value of the 97.5 percentile of the t-distribution with (364-2) degrees of freedom ($\boldsymbol{t_{362,0.975}}$)

Figure 3: Calibration of QRISK2 and the Framingham risk score in women aged 35 to 74 years: (A) by tenth of predicted risk augmented with a smoothed calibration curve, and (B) within eight age groups; dotted lines denotes perfect calibration.

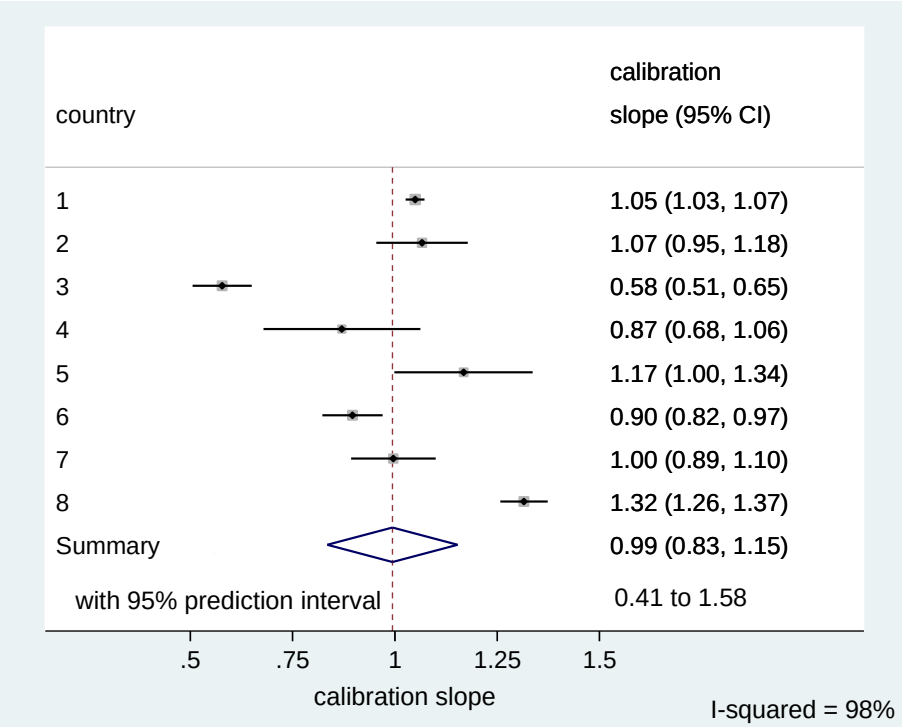
Figure 4: Association between percentage smokers and the c-statistic for QRISK2 across all 364 general practice surgeries in the external validation dataset of Collins and Altman.[44]



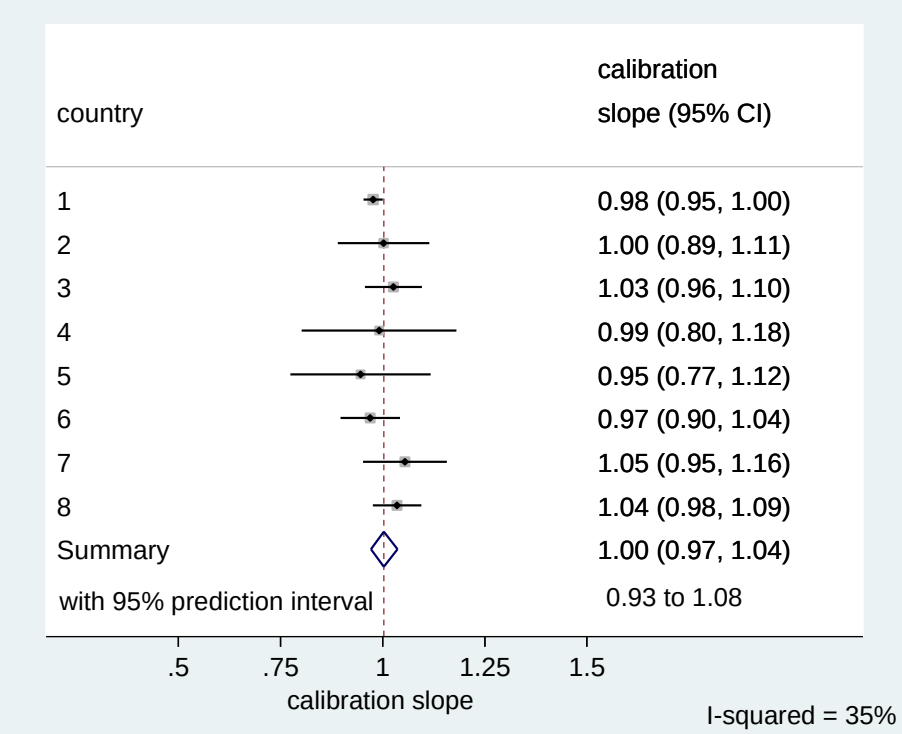
NB Circle size is weighted by the precision of the c-statistic estimate (i.e. larger circles indicate c-statistic estimates with smaller standard errors, and thus more weight in the meta-regression). Solid line shows the meta-regression slope when data are analysed on the c-statistic scale; very similar findings and trend were obtained when re-analysing the logit c-statistic scale.

Figure 5: Calibration performance (as measured by the calibration slope) of the breast cancer model evaluated by Snell et al.,[53] before and after recalibration of the baseline mortality rate in each country.

(a) Assuming the same baseline hazard rate in each country (no recalibration)



(b) Allowing a different baseline hazard rate for each country (recalibration)



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