Development and validation of a new algorithm for improved cardiovascular risk prediction

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ABSTRACT

QRISK algorithms have been used in millions of people to identify individuals at high risk of cardiovascular disease (CVD). Here, we derive and externally validate a new algorithm, termed QR4, that incorporates novel risk factors to estimate 10-year CVD risk separately for men and women. Health data from 9.98 million and 6.79 million adults from the United Kingdom were used for derivation and validation of the algorithm, respectively. Cause-specific Cox models were used to develop models to predict CVD risk and the performance of QR4 was compared with the QRISK3, SCORE2 and ASCVD risk scores. We identified 7 novel risk factors in models for both men and women (brain cancer, lung cancer, Down's syndrome, blood cancer, COPD, oral cancer and learning disability) and two additional novel risk factors present only in women (pre-eclampsia and post-natal depression). On external validation, QR4 had a higher C statistic than QRISK3 in both women (0.835, 95% confidence interval 0.833-0.837 and 0.831, 0.829-0.832 for QR4 and QRISK3, respectively) and men (0.814 (0.812 -0.816) and 0.812 (0.81-814 for QR4 and QRISK3, respectively). QR4 also had better performance compared to the ASCVD and SCORE2 risk scores in both men and women. The QR4 risk score identifies new risk groups and provides superior CVD risk prediction in the UK compared with other international CVD risk scores.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death globally, responsible for an estimated 17.9 million deaths in 2019(1). International guidelines from the World Health Organization (WHO),(2) United States of America (U.S.),(3) Europe(4) and the United Kingdom (U.K.)(5) all recommend use of CVD risk prediction tools to target those at high risk for interventions to reduce risk. Consequently, the effectiveness of public health policies are reliant on risk prediction tools that identify all the important risk groups in the population, with validated risk estimates across the full range of population characteristics. The U.S. recommends the Atherosclerotic Cardiovascular Disease (ASCVD) score based on the Pooled Cohort Equation developed in 20,338 non-Hispanics and 1,647 African-Americans.(3, 6) European guidelines recommend SCORE2 developed in 677,684 volunteers.(4, 7) The U.K. recommends QRISK3, developed in a large diverse community population of 7.9 million people.(5, 8)

Recent research has highlighted conditions associated with increased CVD risk that are not captured by any of the three most widely used CVD equations globally(9)[9], ASCVD, (3) QRISK3(8) and SCORE2.(4, 7) These include chronic obstructive pulmonary disease (COPD),(10) learning disability,(11) Down's syndrome,(9, 12) cancer,(13) and reproductive health conditions(14). If these conditions are independently associated with increased CVD risk, then current CVD risk scores will under-estimate risk in these groups and people with these diagnoses may not be offered the opportunity for beneficial interventions to improve survival. Equally, if risks are over-estimated, then individuals may receive unnecessary interventions.(15) Furthermore, more accurate CVD risk tools are useful for identifying those at higher CVD risk for recruitment into clinical trials, especially for primary prevention.

We sought to derive a new population-based CVD risk score (QR4) to include novel risk factors and account for competing risks, and externally evaluate its performance compared

with three widely used internationally CVD risk scores (i.e., ASCVD, QRISK3 and SCORE2), in large and diverse populations of over 16 million people drawn from across the U.K. We used two established electronic record research databases (QResearch and CPRD Gold) both of which contain anonymised data collected during routine NHS clinical care.

RESULTS

STUDY POPULATION

There were 9,976,306 people aged 18 to 84 in the QResearch English derivation cohort, 3,246,602 in the QResearch English validation cohort and 3,542,007 in the CPRD validation cohort of the other three U.K. nations. Extended Table 1 shows the flow of subjects and the relevant exclusions. Extended Table 2 shows the new predictors under consideration.

Table 1 shows the baseline characteristics of each cohort and completeness of recording of data for predictors with missing data. The cohorts were broadly similar except both English cohorts had more complete data for ethnicity, smoking, cholesterol and body mass index (BMI) than the CPRD cohort from the other three nations. Supplementary Table 4 shows the characteristics of participants with complete vs missing data, showing those with complete data tended to be older, with a higher proportion of females and with clinical conditions.

There were 202,424 incident CVD cases (based on primary outcome definition) from 49.1 million person-years in the derivation cohort. Extended Table 1 shows the types of CVD events in each cohort for each of the three outcome definitions.

Extended Table 3 shows the crude CVD incidence rates for the primary CVD outcome by age, sex, ethnicity and calendar year in the English derivation cohort and CPRD validation cohort. CVD Rates using linked data were higher in the English cohort, which was largely explained by the additional data linkage to hospital and mortality data. Extended Figure 1 shows both CVD incidence and non-CVD mortality rates by calendar year and month for the whole study period. CVD rates per 1000 person years were lower in 2020, the first year of the COVID-19 pandemic, when the overall rate was 4.03 (3.97-4.08) but returned to pre-pandemic values in 2021 (4.31, 4.25-4.37). Non-CVD mortality rates increased from 3.45 (3.40-3.50) in 2019 to 3.84 (3.79-3.89) in 2020 and remained elevated in 2021.

FACTORS ASSOCIATED WITH INCREASED RISK OF CVD

Figure 1 shows the adjusted hazard ratios (aHR) for CVD incidence in the final cause-specific models in men and women (evaluated at the mean age of 39 years for variables with age interactions). Extended Figure 2 shows the aHRs for the fractional polynomial terms for CVD risk for continuous variables and the predictor variables with significant age

interactions for both men and women. Supplementary Figures 1 and 2 show the corresponding results for non-CVD death.

There were seven new CVD predictors in men and women (brain cancer, lung cancer, Down's syndrome, blood cancer, COPD, oral cancer and learning disability) and two additional ones in women (pre-eclampsia and post-natal depression).

We found no association between the following variables and CVD risk in men or women: asthma, hyperthyroidism, hypothyroidism, antiphospholipid antibody syndrome, benign intracranial hypertension, HIV/AIDs, and the remaining cancers. In women, there were no associations with in vitro fertilisation, endometriosis, polycystic ovarian syndrome, gestational diabetes, miscarriage, termination or placental abruption. No violations of the proportional hazards assumptions were detected graphically. The values for the heuristic shrinkage(16) were all very close to one (0.99) indicating no evidence of over-fitting.

NEW CVD PREDICTORS IN WOMEN

The aHR (95% CI) for the nine new independent predictors of CVD risk in women (evaluated at the mean age of 39 years for variables with age interactions) were: brain cancer (4.52, 2.49-8.21); lung cancer (3.50, 1.31-9.38); Down's syndrome (3.18, 2.40-4.22); blood cancer (2.13, 1.71-2.67); COPD (1.85, 1.50-2.29); oral cancer (1.55, 1.27-1.89); learning disability (1.45, 1.29-1.64); pre-eclampsia (1.56, 1.36-1.78) and post-natal depression (1.18, 1.11-1.26).

The aHRs for several of these predictors were higher at younger ages except for lung cancer in women where aHRs were highest for those aged around 40 and then declined gradually with increasing age (Extended Figure 2). The aHRs at age 69 were brain cancer (2.18, 1.29-3.71); lung cancer (1.97, 1.64-2.37); blood cancer (1.39,1.28-1.50); chronic obstructive pulmonary disease (1.38,1.32-1.44); pre-eclampsia (1.12,1.01-1.24).

The magnitude and direction for many of the aHR for the competing outcome of non-CVD death in women were similar to those for CVD except for large aHR (evaluated at age 39) for Down's syndrome (18.32, 16.24-20.66), lung cancer (49.94, 40.61-61.43), brain cancer (33.35, 26.17-42.49). The aHR for family history of coronary heart disease, pre-eclampsia and migraine were significantly less than one (Supplementary Figure 1).

NEW CVD PREDICTORS IN MEN

Figure 1 shows the aHR for the seven new independent predictors of CVD risk in men evaluated at age 39. For CVD the aHR (95% CI) were brain cancer (5.45, 3.49-8.50); Down's syndrome (2.35, 1.84-2.99); blood cancer (2.06, 1.78-2.39); lung cancer (1.66, 1.45 to 1.92); oral cancer (1.49, 1.30-1.70); COPD (1.37, 1.32-1.41) and learning disability (aHR 1.17, 95% CI 1.07-1.29). The aHR in men declined with age, for two of these, for example at age 69 the values were 2.12 (1.25-3.61) for brain cancer and 1.23 (1.15-1.31) for blood cancer. Figure 2 shows an example of how the predicted 10-year CVD risk varies in a White man for each of

the new risk factors by age compared with a similar man with no adverse clinical indicators and a cholesterol/HDL ratio of 4.0, a systolic blood pressure of 125 mm HG and a BMI of 25 kg/m^2. We selected a White as the reference group as it had the largest number of participants.

Supplementary Figures 3-7 show the aHR for the additional models were similar to our final main models in men and women. These were Model A which included the original QRISK3 predictor variables but without competing risks. Model B which was similar to our final model but with follow-up time ending on 29th February 2020, prior to the COVID-19 pandemic. Model C shows that the aHR for CVD risk were similar over periods of time since diagnosis of each of the four cancers (except for oral cancer in women), although the aHR for non-CVD deaths varied with highest values for more recently diagnosed cancers.

PREDICTED RISKS

Figure 2 shows how each of the new risk factors affects the predicted 10-year CVD risk. In this analysis, for both men and women and as stratified by age, CVD risk was compared between an individual with the new risk factor as compared to a reference individual with no adverse clinical indicators (a cholesterol/HDL ratio of 4.0, a systolic blood pressure of 125 mm Hg and a BMI of 25 kg/m2). These data show the impact of the new risk predictors, which result in increased predicted risks as compared with the reference individual at younger ages, and then decreased risk at older ages as competing risks become more pronounced. Using a reference group having various conventional risk factors (light smokers with a cholesterol/HDL ratio of 6.0, a systolic blood pressure of 170 mm Hg and a BMI of 35 kg/mg2), a similar pattern was observed, albeit with overall higher predicted risks (Supplementary Figure 8).

DISCRIMINATION

Table 2 shows the performance statistics (C statistic, calibration slope and calibration intercept) for QR4 and QRISK3 for validation cohorts in England, Scotland, Wales and Northern Ireland. The C statistic was marginally higher with QR4 than QRISK3 in both validation cohorts. For example, for QR4 it was 0.835 (0.833-0.837) and for QRISK3 was 0.831 (0.829-0.832) in women in the devolved administrations (Scotland, Wales and Northern Ireland). The corresponding values in women in England were 0.864 (0.862-0.866) and 0.862 (0.860-0.864). Values were generally higher in England than the other three nations although all remained within the excellent range (>0.8). The results for men were similar though values were slightly lower.

Extended Table 4 shows discrimination results for QR4, SCORE and ASCVD overall and by ethnic group, restricted to those aged 40 and older in the validation cohort in England. Discrimination was highest for women with QR4 (0.781, 0.778-0.784) followed by ASCVD (0.767, 0.764-0.770) and SCORE2 (0.767, 0.764-0.770). There was a similar pattern for men.

Extended Table 5 shows the C statistic, calibration slope and calibration index for QRISK3 and QR4 in men and women aged 18 to 84 overall and by ethnic group in the English validation cohort. It shows that discrimination varied by ethnic group in England, with the

highest C statistic value for Chinese-origin men (QR4 0.923, 0.906-0.939) and lowest for Caribbean-origin men (QR4 0.825, 0.801-0.841).

Supplementary Table 1 shows the definitions of the CVD outcome used for sensitivity analyses. Supplementary Table 2 shows the performance statistics for QR4, SCORE2, and ASCVD for each outcome measure for each of the four UK nations among those aged 40+. The C statistic values were highest for outcome 3 for all scores, and for all outcome measures, discrimination values were higher for QR4 than SCORE2 and ASCVD, which had similar results.

DECISION CURVE ANALYSIS

The decision curves in Figure 3 indicate a small increased net benefit of using QR4 compared with QRISK3 and Model A which is more marked in the Devolved Administrations than in England.

Extended Figure 3 shows the decision analysis curves for QR4, SCORE2 and ASCVD for the primary outcome in England. Supplementary Figures 9 and 10 show corresponding results for the second and third CVD outcomes.

CALIBRATION

QR4 was well-calibrated in England, with close correspondence of predicted and observed risks whilst QRISK3 over-predicted risk in the higher centiles of predicted risk (Figure 4). Table 2 shows the calibration slope and intercept values for QRISK3 and QR4 by country. There was a degree of miscalibration for QRISK3 and QR4 in each of the Devolved Administrations (Supplementary Figure 11) based on GP data only.

Extended Figure 4 shows calibration results for ASCVD and SCORE2 in the English validation cohort, based on our primary outcome definition. Supplementary Table 2 and Supplementary Figures 12 and 13 shows the corresponding results for the second and third outcomes. Overall, there is a degree of over-prediction for ASCVD and under-prediction for SCORE2 which was improved when comparisons were made with the more specific second and third outcomes.

RECLASSIFICATION

Extended Table 6 shows the characteristics for the 84,700 (2.6%) participants in the English validation cohort reclassified using QR4 instead of QRISK3 at the 10% threshold. Of the 3554 people reclassified from low to high risk by QR4, 1168 (32.9%) had COPD, 57 (1.6%) had learning disability, 72 (2.0%) had Down's syndrome, 72 (2.0%) had a history of pre-eclampsia, 125 (3.5%) had a history of post-natal depression, 90 (2.5%) had oral cancer, 54 (1.5%) had brain cancer, 92 (2.6%) had lung cancer and 322 (9.1%) had blood cancer. Those reclassified as high risk with QR4 tended to be younger (mean age 52.4 years) than the 81,146 people reclassified as low risk (mean age 60.5 years). Supplementary Table 3 shows the corresponding analyses for the 4068 participants reclassified as high risk using

QR4 instead of Model A as well as the 12,791 reclassified as low risk, where the pattern was similar although the total reclassified was much smaller (16,859, 0.52%).

DISCUSSION

We have developed and externally validated a new CVD risk score, QR4, to predict 10-year risk of CVD in a diverse population of men and women, incorporating nine novel predictors all with good face validity and clinical utility. These new predictors are learning disability, Down's syndrome, COPD, lung cancer, oral cancer, blood cancer, brain cancer in men and women, and pre-eclampsia and post-natal depression in women. The performance of QR4 was better than the other widely used CVD risk scores, namely ASCVD, QRISK3 and SCORE2. QR4 is likely to result in clinically important changes in risk leading to different CVD risk reduction advice or interventions, particularly for those with the new predictors, which might lead to interventions at a younger age as in the examples given. Furthermore, QR4 accounts for the competing risk of non-CVD death thereby reducing over-prediction of risk especially among the more elderly populations.(17) Lastly, we have utilised and published the SNOMED-CT clinical code groups used to derive our model, facilitating re-use for further research, and international comparisons.

Widely available CVD risk equations have been used for many millions of CVD health checks worldwide supported by international guidelines(2) (3) (4, 5). However, it is important that guidance is based on the best possible algorithms since it will materially affect which patients are offered risk reducing interventions. Failure to adequately assess CVD risk and offer appropriate risk reducing interventions across all patient groups could further disadvantage vulnerable patients, particularly those with significant co-morbidities (such as COPD or cancer survivors), Down's syndrome or learning disability, or a history of postnatal depression or preeclampsia. Whilst the underlying conditions themselves may not be modifiable, the identification of high-risk people in these groups can lead to targeted interventions to reduce CVD risk.

The findings of QR4 for cancer are particularly striking and confirm associations with CVD risk for four cancers (i.e., blood, brain, lung and oral)(13) despite accounting for reduced life expectancy using a competing risks analysis. The increased risk of CVD for cancer survivors needs to be considered in the context of the prognosis of the cancer itself since it would be inappropriate to prescribe therapies that lower CVD risk for those with a very poor prognosis. Whilst only 15% of people with lung cancer survive more than five years, 90% of people with blood cancers(18) and 55% of people with oral cancers now survive more than five years(19) and hence targeted prevention has a potential clinical net benefit. The use of QR4 in clinical practice will need careful consideration and discussion in patients with cancer and will need to account for patient preferences. There are also opportunities for further research to more finely characterise the association between cancer treatment(s) and subsequent CVD. However, longitudinal data on cancer treatments (such as radiotherapy and chemotherapy) are only just becoming available for this type of

research data in the UK. These data are not yet routinely linked to primary care data for clinical use, so at present could not be used to implement more personalised risk prediction.

The lack of an association between asthma and CVD risk is interesting, especially given a pre-conception that inhaled corticosteroids may increase risk of CVD. In contrast, the 1.4 to 1.9-fold increased risk of CVD is both consistent with the 2-fold increased risk of CVD reported among U.S. patients hospitalized with COPD(10) and clinically very important. COPD is now one of the top three causes of death worldwide resulting in an estimated 3 million deaths annually, 90% of which occur in low and middle-income countries.(20) It is striking that this association was strongest in women with COPD. There are two important responses to this finding. Firstly, clinicians need to actively consider the diagnosis of COPD and confirm it with spirometry, especially in women who are often neglected in this regard.(21, 22) Secondly, therapy to reduce CVD risk should be given, which includes optimizing inhaled therapies as this has now been demonstrated to reduce mortality.(23) (24)

The increased risk associated with pre-eclampsia reduced with age, but the 54% increase evaluated at the mean age of 39 is consistent with other research(25, 26) and may reflect damage to the maternal cardiovascular system.(26) It highlights an important opportunity to systematically target CVD prevention.(14) The 2- to 3-fold increased risk of CVD among those with Down's syndrome is consistent with the limited analyses available,(9) and may reflect premature aging and adverse cardio-metabolic profiles. This underscores U.S. recommendations for continued CVD research and surveillance in people with Down's syndrome, especially given improved life expectancy.(12) Incorporation of post-natal depression and learning disabilities into QR4 will help operationalize policy initiatives to ensure parity of esteem with physical health for these patients.

Our study reports good discrimination for ASCVD and SCORE2. Whilst there was a degree of miscalibration with ASCVD and SCORE2 with the main outcome which used a broader definition of CVD, this improved with endpoint definitions aligned to those for which ASCVD and SCORE2 were developed. Any residual miscalibration compared with the original studies may relate to a combination of (a) different study populations which might have different underlying CVD rates; (b) different cohort selection criteria (e.g. inclusion of statins users in the SCORE2 studies); (c) use of a different study period; (e) use of recalibration measures in SCORE2 including the differential application of multipliers by age and sex which are yet to be validated. This suggests CVD risk equations may be transportable to other geographical settings if recalibrated.

The strengths and limitations of this study are similar to those for other well-established risk prediction tools. They include size, duration of follow up, representativeness, lack of selection, recall and respondent bias, and no evidence of over-fitting.(8) The inclusion of more granular information on predictors is a strength, in that the predictions for individual patients are likely to better reflect their individual risk, although this needs to be balanced against the increased complexity of the algorithm with regards to its implementation. However, this is mitigated in settings where electronic health records are available since most relevant information is already available at the point of care and can be automatically populated.(27) Whilst we report improved discrimination for QR4 compared with QRISK3, the absolute values of the improvement in the C statistics were

small. The C statistic is a familiar but limited measure which does not effectively balance misclassification errors(28). It needs to be interpreted in the context of other relevant measures including decision analysis, reclassification, calibration and clinical utility(28). Our study has good face validity since it was conducted in the setting where most patients are managed and hence QR4 could be implemented in similar clinical settings, subject to local validation or recalibration. Lastly, our results are unlikely to have been affected by the COVID-19 pandemic in 2020 and 2021 as the risk factors were predominantly recorded prior to the pandemic, the CVD incidence rates were temporarily affected in 2020, but have since returned to pre-pandemic levels and Model C showed very similar results to our main model.

Limitations include the lack of formal adjudication of CVD diagnoses. However, the use of linked hospital and mortality data ensure good ascertainment of CVD outcomes in the English cohorts. The miscalibration for QR4 in the other three U.K. nations reflects the lack of linked hospital and ONS mortality outcome data for these nations in the CPRD validation cohort as this will have resulted in under-ascertainment of CVD outcomes. Whilst there is potential for bias due to missing data, our data are substantially more complete than previous studies(8) with residual biases mitigated by multiple imputation using recommended approaches(29). We expect that in clinical practice any missing data will be collected from the patient/carer during a consultation with their clinician so missing data for implementation of QR4 is unlikely to be a substantial issue. Whilst our validation covers a fully external population, further research should validate QR4 in different countries with different CVD rates. This could be addressed by further validation using different datasets with appropriate data linkages.

In conclusion, these results demonstrate the strength of QR4 in the general UK population and its superior performance compared with three other widely used international CVD risk scores. QR4 enables more accurate CVD risk estimation, which should lead to significant improvements in health outcomes, especially for those with COPD, Down's syndrome, learning disability, cancer survivors and women with pre-eclampsia or post-natal depression.

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AUTHOR CONTRIBUTIONS STATEMENT

JHC initiated the study, development of the research question, undertook the literature review, data extraction, data manipulation and primary data analysis and wrote the first draft of the paper. CC contributed to the refinement of the research question, design, analysis, interpretation and drafting of the paper. MB and RR contributed to the refinement of the research question, data interpretation and drafting of the paper. KC, AS and PB contributed to data interpretation and clinical relevance. JHC undertook final editing of the paper. All authors commented critically on drafts of the manuscript and approved the final submission.

COMPETING INTERESTS STATEMENT

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: JHC reports grants from National Institute for Health Research, John Fell Oxford University Press Research Fund, Cancer Research U.K. (C5255/A18085), Wellcome Institutional Strategic Support Fund (204826/Z/16/Z) and other research councils, during the conduct of the study. JHC is an unpaid director of QResearch, a not-for-profit organisation which is a partnership between the University of Oxford and EMIS Health who supply the QResearch database used for this work. Until 09 Aug 2023, JHC had a 50% shareholding in ClinRisk Ltd, co-owning it with her husband, who was an executive director. On 9th August 2023, 100% of the share capital was donated to Endeavour Health Care Charitable Trust and the company renamed to Endeavour Predict Ltd. JHC is an unpaid consultant to Endeavour Predict Ltd and her husband is a non-executive director to cover the transition. The company licences software both to the private sector and to NHS bodies or bodies that provide services to the NHS (through GP electronic health record providers, pharmacies, hospital providers and other NHS providers). This software implements algorithms (including QRISK3) developed from access to the QResearch database during her time at the University of Nottingham. CC reports receiving personal fees from ClinRisk Ltd, outside this work. KMC reports grant funding from the British Heart Foundation. KMC is an academic co-founder, shareholder and director of Caristo Diagnostics Ltd, a University of Oxford cardiac image analysis spin-out company. MB has received grants paid to her institution from AstraZeneca, Roche, Asthma + lung UK, horizon Europe and consulting fees or Honoria fees paid to her institution from AstraZeneca, Sanofi, GSK, Areteia and support for attending meetings from Chiesi.

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Table 1: Baseline characteristics of participants. Baseline characteristics are shown for individuals aged 18-84 years in the English QResearch derivation and validation cohorts and in the external CPRD validation cohort from Scotland, Wales and Northern Ireland. Participants were those without CVD and not on statins at study entry. Values are numbers (%) of participants unless indicated otherwise

	QResearch Derivation Cohort	QResearch Validation Cohort	CPRD Validation Cohort
Total	9,976,306	3,246,602	3,542,007
Men	4820711 (48.3)	1564545 (48.2)	1698728 (48.0)
Mean age (SD)	39.0 (15.0)	38.9 (14.9)	42.6 (16.4)
Mean Townsend (SD)[Y]	0.7 (3.2)	0.9 (3.2)	0.0 (0.0)
Mean BMI (SD)	25.6 (5.2)	25.6 (5.2)	26.4 (5.0)
Mean Cholesterol/HDL ratio	3.8 (1.2)	3.8 (1.2)	4.0 (1.3)
Mean SBP (SD)	123.6 (15.3)	123.4 (15.3)	125.4 (15.7)
Mean SBP variability (SD) *	9.3 (5.6)	9.3 (5.6)	9.6 (5.9)
Ethnicity recorded	6186167 (62.0)	1972052 (60.7)	1257906 (35.5)
White	4391142 (44.0)	1392310 (42.9)	1155924 (32.6)
Indian	301414 (3.0)	95018 (2.9)	19217 (0.5)
Pakistani	186029 (1.9)	50470 (1.6)	11116 (0.3)
Bangladeshi	115682 (1.2)	42898 (1.3)	3884 (0.1)
Other Asian	218555 (2.2)	67456 (2.1)	10776 (0.3)
Caribbean	103578 (1.0)	34397 (1.1)	1272 (0.0)
Black African	285326 (2.9)	94302 (2.9)	14653 (0.4)
Chinese	148779 (1.5)	47754 (1.5)	12859 (0.4)
Other ethnicity	435662 (4.4)	147447 (4.5)	28205 (0.8)
Smoking recorded	9426326 (94.5)	3056793 (94.2)	2825315 (79.8)
Non-smoker	5764142 (57.8)	1872638 (57.7)	1598409 (45.1)
Ex-smoker	1600361 (16.0)	511647 (15.8)	560550 (15.8)
Light smoker (1-9/day)	1589116 (15.9)	521304 (16.1)	156038 (4.4)
Moderate smoker (10-19/day)	327218 (3.3)	103748 (3.2)	370026 (10.4)
Heavy smoker (20+day)	145489 (1.5)	47456 (1.5)	140292 (4.0)
No learning disability	9936826 (99.6)	3234133 (99.6)	3539790 (99.9)
Other learning disability	34663 (0.3)	10962 (0.3)	335 (0.0)
Down's syndrome	4817 (0.1)	1507 (0.1)	1882 (0.1)
COPD	79991 (0.8)	26156 (0.8)	34909 (1.0)
Lung cancer	4422 (0.0)	1353 (0.0)	1786 (0.1)
Blood cancer	31009 (0.3)	10039 (0.3)	10819 (0.3)
Brain cancer	1245 (0.0)	370 (0.0)	381 (0.0)
Oral/lip/throat cancer	3864 (0.0)	1220 (0.0)	1427 (0.0)
Post-natal depression	96463 (1.0)	29763 (0.9)	32468 (0.9)
Pre-eclampsia or eclampsia	20233 (0.2)	6735 (0.2)	8637 (0.2)

[Y]No practices in the CPRD Gold cohort had Townsend deprivation scores since these data were unavailable, so we assumed a value of zero. *Based on standard deviation of 2 or more values
×schizophrenia, bipolar disorder, severe or recurrent depression (excluding mild depression or where severity not indicated).

Table 2: Evaluation of discrimination and calibration of QR4 compared with QRISK3. The discrimination and calibration of QR4 was compared with QRISK3 in people aged 18-84 years in the internal QResearch (England) and external CPRD (Devolved administrations: Wales, Scotland and Northern Ireland) validation cohorts based on the primary outcome measure.

	Women		Men	
	QRISK3	QR4	QRISK3	QR4
	mean (95% CI)	mean (95% CI)	mean (95% CI)	mean (95% CI)
England				
C Statistic	.862 (.860 to .864)	.864 (.862 to .866)	.848 (.846 to .850)	.849 (.847 to .851)
Calibration slope	1.00 (.994 to 1.01)	.870 (.863 to .878)	1.01 (1.01 to 1.02)	.900 (.894 to .907)
Intercept	.003 (-.006 to .013)	-.130(-.137 to -.122)	.0136 (.006 to .022)	-.100 (-.106 to -.093)
Devolved administrations				
C Statistic	.831 (.829 to .832)	.835 (.833 to .837)	.812 (.81 to .814)	.814 (.812 to .816)
Calibration slope	1.68 (1.66 to 1.69)	1.21 (1.2 to 1.22)	1.61 (1.6 to 1.62)	1.24 (1.23 to 1.25)
Intercept	.676 (.662 to .69)	.211 (.204 to .219)	.608 (.597 to .62)	.238 (.231 to .245)
Wales				
C Statistic	.823 (.82 to .827)	.829 (.825 to .832)	.809 (.806 to .812)	.812 (.809 to .815)
Calibration slope	2.07 (2.04 to 2.11)	1.35 (1.34 to 1.37)	2.06 (2.03 to 2.09)	1.40 (1.39 to 1.42)
Intercept	1.07 (1.04 to 1.11)	.353 (.338 to .368)	1.06 (1.03 to 1.09)	.405 (.391 to .418)
Scotland				
C Statistic	.833 (.83 to .835)	.837 (.834 to .839)	.813 (.811 to .815)	.815 (.812 to .817)
Calibration slope	1.5 (1.48 to 1.51)	1.14 (1.13 to 1.15)	1.44 (1.43 to 1.46)	1.16 (1.15 to 1.17)
Intercept	.496 (.48 to .512)	.136 (.126 to .145)	.444 (.431 to .457)	.162 (.154 to .171)
Northern Ireland				
C Statistic	.844 (.838 to .85)	.847 (.841 to .853)	.821 (.817 to .826)	.823 (.818 to .828)
Calibration slope	1.53 (1.49 to 1.58)	1.15 (1.13 to 1.18)	1.29 (1.26 to 1.32)	1.09 (1.06 to 1.11)
Intercept	.535 (.49 to .58)	.153 (.127 to .179)	.292 (.262 to .321)	.0855 (.0644 to .107)

Figure 1 Final model adjusted hazard ratios for CVD. Shown are adjusted hazard ratios in 5,155,595 women and 4,820,711 men, presented at the mean age of 39 for variables with age interactions**.** The hazard ratios were adjusted for fractional polynomial terms for age, and BMI (see Supplementary Figure 1 which shows the relevant fractional polynomial terms. Systolic BP is per 20 unit increase.

Figure 2. Effect of the new risk factors on prediction of 10-year CVD risk. Shown are 10-year CVD risk predictions for men and women over different ages, comparing predictions for an individual with each of the new risk factors to a similar individual of the same age but without the new risk factor (reference).In this analysis, the reference indivdual is a White non-smoker and has no adverse health conditions, with a systolic blood pressure of 125 mm Hg, a cholesterol ratio of 4, and a BMI of 25 kg/m^2.

Figure 3 Decision curves for QR4, QRISK3 and Model A. Decision curves showing net benefit in men and women aged 18-84 years in England and the Devolved Administrations are shown. Decision curves for QR4, QRISK3 and Model A are compared to those for "Treat All" (intervention in all individuals irrespective of risk threshold) and "Treat None" (intervention in no individuals).

Figure 4. Calibration of QRISK3 and QR4. Centile calibration plots of the observed and predicted risks for QR4 and QRISK3 in men and women aged 18-84 years in the England validation cohort are shown. The red crosses show the observed risk 10 year risk of CVD at each level of mean predicted risk. The blue line shows perfect calibration where the mean predicted risk is equal to the observed risk.

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METHODS

STUDY DESIGN AND DATA SOURCES

We undertook community-based cohort studies using two large electronic medical records databases, QResearch and the Clinical Practice Research Datalink (CPRD Gold). We randomly allocated three-quarters of QResearch practices in England to the derivation cohort and the remainder to an internal English validation dataset. Both CPRD and QResearch are based on anonymised medical record data collected during the course of clinical care. QResearch is based on a commercial computer system known as EMIS (Egton Medical Information Systems) whilst CPRD (Gold) is based on a different commercial system known as Vision. We used CPRD Gold practices from three U.K. nations (i.e., Northern Ireland, Scotland and Wales) to create a second fully external geographically distinct validation cohort.

We included adults aged 18-84 years between January 1, 2010, and December 31, 2021. The cohort entry date was the latest of the following: 18th birthday, date of registration with the practice plus one year and January 1, 2010. We excluded participants with pre-existing CVD, those prescribed statins and (for QResearch) those with a missing Townsend deprivation score since they often represent temporary or incompletely registered patients with substantial missing data.(30) We followed participants up until the earliest date of the diagnosis of CVD, death, de-registration with the practice or the study end date.

OUTCOME DEFINITIONS

Our primary outcome for model derivation and validation in QResearch was an incident diagnosis of CVD (fatal or non-fatal myocardial infarction, ischaemic heart disease, ischaemic, haemorrhagic or unspecified stroke or transient ischaemic attack (TIA) identified from the general practitioner (GP) record, or linked mortality and hospital records using published clinical codes.(31) Our primary outcome for model validation in CPRD Gold was based on the same diagnoses but recorded solely on the GP data since linked data for deaths and hospital admissions were not available for Scotland, Wales and Northern Ireland.

We had two secondary outcomes for validation comparisons with SCORE2 and ASCVD. Our second outcome, aligned to ASCVD, included non-fatal myocardial infarction or CHD death, or fatal or non-fatal stroke. Our third outcome was similar to our second outcome but additionally included fatal congestive cardiac failure, hypertension and cardiac arrhythmias to align to the SCORE2 outcome definition(4, 7). For more details of the

definitions of the primary and secondary outcomes including the SNOMED-CT and ICD-10 codes used see Supplementary Table 1. We compared performance for all three algorithms (QR4, SCORE2 and ASCVD) using all three outcome definitions in England due to the availability of linked cause of death data, which was not available for the Devolved Administrations.

PREDICTOR VARIABLES

We included established risk factors from ASCVD,(3) QRISK3(8) or SCORE2(4) and new candidate variables highlighted in the literature (see Extended Table 2 which includes more details of the definitions of each predictor considered). (9, 12) (10) (11) (13) (32) . Cholesterol ratio is defined as total serum cholesterol/HDL cholesterol. Ethnicity was based on self-reported ethnicity.

MODEL DEVELOPMENT

We used cause-specific Cox models in order to estimate the 10-year risk of CVD accounting for non-CVD death as a competing risk for men and women separately using the biological sex recorded on the electronic health record.(33) This involved fitting two separate Cox models—one for CVD diagnoses and CVD deaths and one for non-CVD deaths with time from cohort entry as the underlying function.(34) We used fractional polynomials(35) to model non-linear risk relationships with continuous variables. We used multiple imputation with chained equations to replace missing values for ethnicity, body mass index (BMI), systolic blood pressure, total cholesterol, HDL cholesterol and smoking status.(36) For binary variables, we coded them as present if there was a recorded diagnosis in the GP medical record and otherwise coded them as absent. We carried out five imputations in the derivation dataset, separately for men and women. We included all predictor variables in the imputation model, along with age interaction terms, the Nelson-Aalen estimator of the CVD baseline cumulative hazard, and the CVD outcome indicator as well as the baseline cumulative hazard, and outcome indicator for non-CVD death(29). We combined results from Cox models using Rubin's rules.(37) We included variables from existing QRISK3 models(8) and retained additional variables with an adjusted hazard ratio (aHR) of <0.90 or >1.10 (for binary variables) and statistically significant at the 0.01 level. We included significant interactions with age in the final model. We assessed model optimism by calculating heuristic shrinkage.(16) We combined estimates from the two cause-specific models to derive risk equations for the predicted risk of CVD at 10 years accounting for competing events in men and women.(34)

We developed three additional models following peer review: Model A included the original QRISK3 parameters but without accounting for competing risks; Model B was similar to our final model but with follow-up time ending on 29th February 2020, prior to the COVID-19 pandemic and Model C which included time since cancer diagnosis as a predictor variable.

MODEL EVALUATION

We also carried out multiple imputation with five imputations in each validation cohort separately for men and women. We applied the risk equations to the internal and external validation cohorts. We evaluated performance by country (England, Wales, Scotland, and Northern Ireland).

We calculated concordance indices, equivalent to the C statistic accounting for competing risks.(33) We assessed model calibration comparing the mean predicted risks at 10 years with the observed risks accounting for competing risks (cumulative incidence) by hundredths of predicted risk. We generated pseudo values accounting for competing risks to calculate the calibration slope and intercept at 10 years.(38)

We compared performance statistics for QR4 with ASCVD,(3, 39) QRISK3,(8) and SCORE2 in England. We used the SCORE2 algorithm for those aged 40-69 years without diabetes(4), SCORE2-OP for those aged 70+ without diabetes(7) and SCORE-2Diabetes(40) for those with diabetes using the authors' published Stata code from July 2023(41). We restricted comparison with ASCVD and SCORE2 to people aged 40 years and older.**(3, 4, 6)** We also evaluated QR4, ASCVD and SCORE2 using our second and third outcomes.

DECISION CURVE ANALYSIS

We used decision curve analysis in both validation cohorts accounting for competing risks to evaluate the net benefits of QR4 compared with QRISK3 and Model A, comparing these with alternative strategies such as assuming all people were treated, or no-one was treated.(42) The strategy with the highest net benefit at any given risk threshold was considered to have the most clinical value.(43) We also used decision curve analyses in people aged 40 and older to compare QR4 with ASCVD and SCORE2 in the English validation cohort using all three outcomes.

RECLASSIFICATION STATISTICS

We classified individuals as "high risk" of CVD if their predicted 10-year risk was ≥10% in line with current U.K. guidelines.(5) We compared predicted risks for QR4 with QRISK3 and Model A, to determine the percentage and characteristics of people reclassified at this high-risk threshold.

We also applied the predicted risk to men and women in the validation group to illustrate how each of the new risk factors affected 10-year CVD risk. In this analysis, for both men and women and as stratified by age, CVD risk was compared between an individual with the new risk factor as compared to a reference individual with no adverse clinical indicators (a cholesterol/HDL ratio of 4.0, a systolic blood pressure of 125 mm Hg and a BMI of 25 kg/m2). For these analyses, the reference group was selected to be White, as this group had the largest number of participants.

We used all eligible individuals to develop and validate the models to maximize the power and generalizability of the results. We used Stata (version 17) for analyses.

INCLUSION AND ETHICS

This study used anonymised data from two electronic health care records databases and hence participant consent was not required. The databases cover a diverse population which is representative of the UK population. The QResearch ethics approval by the East Midlands-Derby Research Ethics Committee [reference 18/EM/0400]. The CPRD ERAP approval reference is 20_000162.

DATA AVAILABILITY

To guarantee the confidentiality of personal and health information only the authors have had access to the data during the study in accordance with the relevant licence agreements. Access to the QResearch data is according to the information on the QResearch website (www.qresearch.org). Access to CPRD data is according to the information on the CPRD website (www.cprd.com).

CODE AVAILABILITY

Clinical codes are published under a creative commons licence here https://www.qresearch.org/data/qcode-group-library/ with accompanying details in the Supplementary Table 1. Software implementing the QR4 algorithm will be made available for research under an academic license via Oxford University Innovations (enquiries@innovation.ox.ac.uk). QRISK3 algorithm is available from the following link https://qrisk.org/src.php. The ASCVD code is available from the following link https://econpapers.repec.org/software/bocbocode/s459162.htm SCORE2 algorithms are available from https://www.phpc.cam.ac.uk/ceu/erfc/programs/.