New risk score for cardiovascular disease with improved performance

QR4 is a new cardiovascular disease (CVD) risk score developed and evaluated in 16.9 million people that has better performance than other commonly used CVD risk scores. It includes nine new risk factors associated with increased risk of developing CVD (for example, a heart attack or stroke) over the next 10 years.

This is a summary of:
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The problem

Cardiovascular disease (CVD) causes an estimated 17.9 million deaths worldwide annually, according to the World Health Organization. International guidelines recommend the use of CVD risk-prediction tools to determine which people are at high risk and should receive interventions to reduce risk. Consequently, the effectiveness of public health policies relies on risk-prediction tools that identify all important risk groups in the population, with validated risk estimates across the full range of population characteristics (such as age, ethnicity, sex and medical conditions). Previous research has highlighted some conditions associated with increased CVD risk that are not included in any of the three most widely used CVD risk-prediction scores: ASCVD[1], QRISK3 (ref. 2) and SCORE2 (refs. 3,4). These conditions include chronic obstructive pulmonary disease (COPD), learning disability, Down's syndrome, cancer and female reproductive health conditions. If these conditions are independently associated with increased CVD risk, then current CVD risk scores will underestimate CVD risk in affected people. We sought to derive a new population-based CVD risk score to include these factors and validate it compared with three other CVD risk scores.

The solution

We developed and validated QR4, a new algorithm to estimate 10-year CVD risk that accounts for the competing risk of death and incorporates nine risk factors, all with good clinical utility. These additional predictors are learning disability, Down's syndrome, COPD, lung cancer, oral cancer, blood cancer and brain cancer (each in men and women), and pre-eclampsia and postnatal depression (in women only). We used large and diverse populations from across the United Kingdom: over 9.9 million people to develop the algorithm, and 6.9 million people to evaluate the algorithm, with two established research databases (QResearch and Clinical Practice Research Datalink Gold) of anonymized electronic health records collected during routine clinical care from the UK National Health Service (NHS). We used these databases to ensure that our populations were representative and that the results of the study would generalize well. We compared QR4's performance in ranking patients by risk of CVD (discrimination) and predicting risk accurately (calibration) with that of ASCVD, QRISK3 and SCORE2.

The new algorithm was well calibrated, and its overall performance was better than that of the other widely used CVD risk scores. QR4 enabled more-accurate CVD risk estimation, which should lead to improvements in health outcomes, especially for people with the conditions now included as risk predictors (Fig. 1). QR4 is likely to result in clinically important changes in risk estimates; these changes will lead to different CVD risk-reduction advice or interventions, particularly for those with the newly included risk factors, which might lead to interventions at a younger age. Furthermore, the algorithm takes into account the risk of death from other causes and thereby reduces over-prediction of CVD risk, especially among elderly populations.

The implications

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

Our validation population was fully from the United Kingdom; further research to enable international use should evaluate the algorithm in different countries with different CVD rates and risk-factor profiles. This evaluation might be achieved by further validation and recalibration where necessary, using different data sets with appropriate linked data.

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EXPERT OPINION

"This paper describes the development of QR4, the latest of the QRISK algorithms designed to estimate the 10-year risk of cardiovascular disease (CVD). Various improvements over QRISK3 might have implications for CVD prevention in the UK. The data used cover a more recent time period, suggesting that the estimated CVD risks will be more appropriate for the contemporary UK population, and inclusion of various additional health conditions as risk predictors might improve risk estimation for affected individuals." **Lisa Pennells, University of Cambridge, Cambridge, UK.**

FIGURE

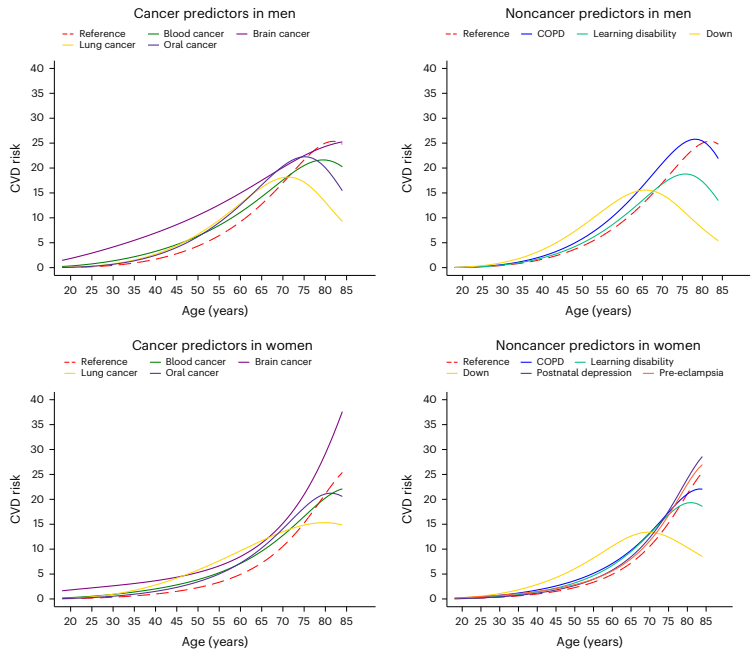

Fig. 1 | Predicted 10-year CVD risk with QR4. Examples of predicted 10-year CVD risk in specific populations (white men and women with healthy levels of modifiable risk factors (systolic blood pressure, cholesterol, body weight index and smoking status) and each of the newly included risk factors), calculated with QR4, presented as predicted risk (%) of CVD at 10 years (vertical axis). Dashed red lines (Reference) indicate the risk for an age-matched person with no adverse health condition. Down, Down's synrome.

BEHIND THE PAPER

In 2007, we published the original version of QRISK, a new CVD risk algorithm for the United Kingdom, given that the NHS needed to identify the patients at highest risk to target them for interventions. In 2008, we published QRISK2, which accounted for ethnicity and several additional co-morbidities. Both algorithms were externally validated and showed better performance than that of other CVD risk tools. By 2014, QRISK2 was recommended for use across the NHS. In 2017, in response to requests from patients, policymakers and clinicians, we developed QRISK3 to include additional conditions, such as severe mental illness. QRISK3 is now recommended for clinical use in the United Kingdom, superseding QRISK2, and has been used many millions of times in the United Kingdom and internationally. This paper presents a new algorithm that supersedes QRISK3 by including additional predictors, new statistical methods and improved underlying linked electronic health care data. **J. H.-C. & C.C.**

REFERENCES

1. Goff, D. C. Jr et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J. Am. Coll. Cardiol.* **63**, 2935–2959 (2014).
   A guideline that recommends the ASCVD score.
2. Hippisley-Cox, J., Coupland, C. & Brindle, P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. *Br. Med. J.* **357**, j2099 (2017).
   An original research paper that presents the derivation and validation of QRISK3.
3. SCORE2 working group & ESC Cardiovascular risk collaboration. Cardiovascular risk collaboration. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. *Eur. Heart J.* **42**, 2439–2454 (2021).
   An original research paper that presents the derivation and validation of SCORE2.
4. SCORE2-OP working group and ESC Cardiovascular risk collaboration. SCORE2-OP risk prediction algorithms: estimating incident cardiovascular event risk in older persons in four geographical risk regions. *Eur. Heart J.* **42**, 2455–2467 (2021).
   An original research paper that presents the derivation and validation of SCORE2 in older people.

FROM THE EDITOR

"Using large data sets from the United Kingdom, this study updates one of the most commonly used risk scores, QRISK3, for predicting the 10-year risk of CVD. The new risk score, called QR4, outperforms standard risk scores and can potentially have a strong clinical impact by changing how CVD risk for patients is calculated." **Editorial Team, *Nature Medicine*.**